Substituted Phenylacetic Acids

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims the benefit of Provisional application Ser. No. 60/366,961 filed March 20, 2002, the contents of which are incorporated herein by reference.

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

[0002] NOT APPLICABLE

REFERENCE TO A "SEQUENCE LISTING," A TABLE, OR A COMPUTER PROGRAM LISTING APPENDIX SUBMITTED ON A COMPACT DISK.

[0003] NOT APPLICABLE

BACKGROUND OF THE INVENTION

[0004] Diabetes mellitus, commonly called diabetes, refers to a disease process derived from multiple causative factors and characterized by elevated levels of plasma glucose, referred to as hyperglycemia. *See, e.g.*, LeRoith, D. *et al.*, (eds.), DIABETES MELLITUS (Lippincott-Raven Publishers, Philadelphia, PA U.S.A. 1996), and all references cited therein. According to the American Diabetes Association, diabetes mellitus is estimated to affect approximately 6% of the world population. Uncontrolled hyperglycemia is associated with increased and premature mortality due to an increased risk for microvascular and macrovascular diseases, including nephropathy, neuropathy, retinopathy, hypertension, cerebrovascular disease and coronary heart disease. Therefore, control of glucose homeostasis is a critically important approach for the treatment of diabetes.

[0005] There are two major forms of diabetes: Type 1 diabetes (formerly referred to as insulin-dependent diabetes or IDDM); and Type 2 diabetes (formerly referred to as non-insulin dependent diabetes or NIDDM).

[0006] Type 1 diabetes is the result of an absolute deficiency of insulin, the hormone which regulates glucose utilization. This insulin deficiency is usually characterized by β-cell destruction within the Islets of Langerhans in the pancreas, which usually leads to absolute insulin deficiency. Type 1 diabetes has two forms: Immune-Mediated Diabetes Mellitus, which results from a cellular mediated autoimmune destruction of the β cells of the pancreas;

and Idiopathic Diabetes Mellitus, which refers to forms of the disease that have no known etiologies.

[0007] Type 2 diabetes is a disease characterized by insulin resistance accompanied by relative, rather than absolute, insulin deficiency. Type 2 diabetes can range from predominant insulin resistance with relative insulin deficiency to predominant insulin deficiency with some insulin resistance. Insulin resistance is the diminished ability of insulin to exert its biological action across a broad range of concentrations. In insulin resistant individuals, the body secretes abnormally high amounts of insulin to compensate for this defect. When inadequate amounts of insulin are present to compensate for insulin resistance and adequately control glucose, a state of impaired glucose tolerance develops. In a significant number of individuals, insulin secretion declines further and the plasma glucose level rises, resulting in the clinical state of diabetes. Type 2 diabetes can be due to a profound resistance to insulin stimulating regulatory effects on glucose and lipid metabolism in the main insulin-sensitive tissues: muscle, liver and adipose tissue. This resistance to insulin responsiveness results in insufficient insulin activation of glucose uptake, oxidation and storage in muscle and inadequate insulin repression of lipolysis in adipose tissue and of glucose production and secretion in liver. In Type 2 diabetes, free fatty acid levels are often elevated in obese and some non-obese patients and lipid oxidation is increased.

[0008] Premature development of atherosclerosis and increased rate of cardiovascular and peripheral vascular diseases are characteristic features of patients with diabetes, with hyperlipidemia being an important precipitating factor for these diseases.

[0009] Hyperlipidemia is a condition generally characterized by an abnormal increase in serum lipids in the bloodstream and, as noted above, is an important risk factor in developing atherosclerosis and heart disease. For a review of disorders of lipid metabolism, *see, e.g.*, Wilson, J. *et al.*, (ed.), *Disorders of Lipid Metabolism*, Chapter 23, Textbook of Endocrinology, 9th Edition, (W.B. Sanders Company, Philadelphia, PA U.S.A. 1998; this reference and all references cited therein are herein incorated by reference). Serum lipoproteins are the carriers for lipids in the circulation. They are classified according to their density: chylomicrons; very low-density lipoproteins (VLDL); intermediate density lipoproteins (IDL); low density lipoproteins (LDL); and high density lipoproteins (HDL). Hyperlipidemia is usually classified as primary or secondary hyperlipidemia. Primary hyperlipidemia is generally caused by genetic defects, while secondary hyperlipidemia is generally caused by other factors, such as various disease states, drugs, and dietary factors. Alternatively, hyperlipidemia can result from both a combination of primary and secondary

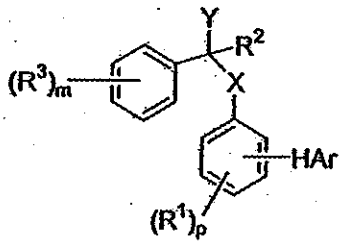
causes of hyperlipidemia. Elevated cholesterol levels are associated with a number of disease states, including coronary artery disease, angina pectoris, carotid artery disease, strokes, cerebral arteriosclerosis, and xanthoma.

[0010] Dyslipidemia, or abnormal levels of lipoproteins in blood plasma, is a frequent occurrence among diabetics, and has been shown to be one of the main contributors to the increased incidence of coronary events and deaths among diabetic subjects (*see, e.g.*, Joslin, E. *Ann. Chim. Med.* (1927) 5: 1061-1079). Epidemiological studies since then have confirmed the association and have shown a several-fold increase in coronary deaths among diabetic subjects when compared with nondiabetic subjects (*see, e.g.*, Garcia, M. J. *et al.*, *Diabetes* (1974) 23: 105-11 (1974); and Laakso, M. and Lehto, S., *Diabetes Reviews* (1997) 5(4): 294-315). Several lipoprotein abnormalities have been described among diabetic subjects (Howard B., *et al., Artherosclerosis* (1978) 30: 153-162).

[0011] What is needed in the art are new compounds and methods useful for the treatment of insulin resistance, Type 2 diabetes, hyperlipidemia and hyperuricemia. The present invention fulfills this and other needs by providing such compounds, compositions and methods for alleviating insulin resistance, Type 2 diabetes, hyperlipidemia and hyperuricemia.

BRIEF SUMMARY OF THE INVENTION

[0011a] In a first aspect of the present invention, there is provided a compound having a formula selected from the group consisting of:



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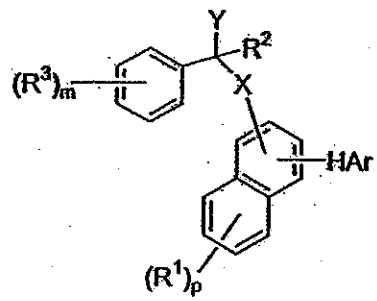


Ib

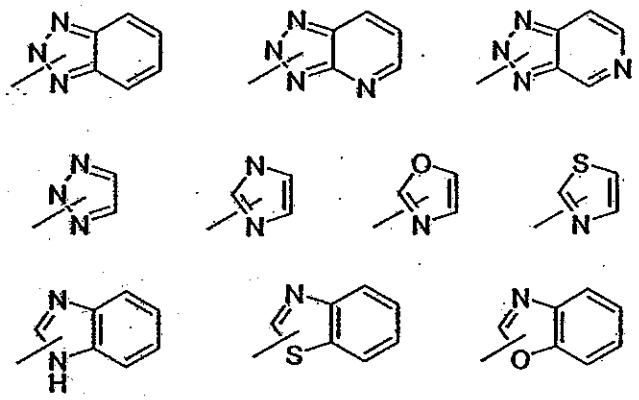
wherein

X is a member selected from the group consisting of O, S, SO and SO_2;

Y is a member selected from the group consisting of CH_2OR^c, CO_2R^c, CHO, $CONR^cR^m$,

$CH(=NR^c)$, $CH(=NOR^c)$, $C(O)NHSO_2R^n$, sulfonic acids, sulfinic acids, phosphonic acids, phosphinic acids, activated carboxamides, hydroxamic acids, tetrazol-5-yl, triazole, hydroxypyrazole, hydroxyoxazole, acidic alcohols and SO_2NHX^1, wherein X^1 is an electron withdrawing group relative to an alkyl group, R^c is a member selected from the group consisting of H, (C_1-C_8)alkyl, (C_3-C_8)alkenyl, (C_3-C_8)alkynyl, (C_3-C_7)cycloalkyl, (C_4-C_8)cycloalkyl-alkyl, aryl, aryl(C_1-C_8)alkyl and (C_1-C_8)alkylene-Z, wherein Z is selected from the group consisting of COR^d, $COOR^d$, NR^dR^e, $NR^dCONR^eR^f$, NR^dCOR^e, NR^dCOOR^e and $CONR^dR^e$ wherein R^d, R^e and R^f are each independently selected from the group consisting of H, (C_1-C_8)alkyl and phenyl, or optionally two of R^d, R^e and R^f when attached to the same nitrogen atom are combined to form a five- or six-membered ring; and wherein R^m is selected from the group consisting of H, (C_1-C_8)alkyl, aryl, OH and SO_2R^n, wherein R^n is selected from the group consisting of (C_1-C_8)alkyl, (C_1-C_8)haloalkyl, aryl(C_1-C_8)alkyl, (C_1-C_8)heteroalkyl, aryl, heteroaryl, (C_1-C_8)alkoxy, aryloxy, alkylamino, dialkylamino, arylamino, diarylamino, haloalkylamino and di(haloalkyl)amino, and R^m and R^c are optionally combined with the nitrogen atom to which each is attached to form a five- or six-membered ring;

HAr is selected from the group consisting of



optionally substituted with from one to three substituents independently selected from the group consisting of halogen, hydroxy, (C_1-C_8)alkyl, aryl(C_1-C_8)alkyl, (C_1-C_8)alkoxy, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_7)cycloalkyl, (C_4-C_8)cycloalkyl-alkyl, (C_1-C_8)heteroalkyl, (C_2-C_5)heterocyclyl, aryl, aryloxy, heterosubstituted(C_3-C_7)cycloalkyl, heteroalkyl substituted (C_3-C_7)cycloalkyl, (C_1-C_8)haloalkyl, O(C_1-C_8)haloalkyl, nitro, cyano, CO_2R^g, COR^g, NR^gR^h, $S(O)_qR^g$, $SO_2NR^gR^h$, $NR^gCONR^hR^i$, NR^gCOR^h, NR^gCOOR^h and $CONR^gR^h$,

wherein R^g, R^h and R^i are each independently selected from the group consisting of H and $(C_1$-$C_8)$alkyl, or optionally two of R^g, R^h and R^i when attached to the same nitrogen atom are combined to form a five- or six-membered ring, and the subscript q is an integer of from 0 to 2;

each R^1 and R^3 is a member independently selected from the group consisting of halogen, hydroxy, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_1$-$C_8)$alkoxy, $(C_3$-$C_7)$cycloalkyl, $(C_4$-$C_8)$cycloalkyl-alkyl, $(C_1$-$C_8)$haloalkyl, $(C_1$-$C_8)$heteroalkyl, $(C_2$-$C_5)$heterocyclyl, heterosubstituted$(C_3$-$C_7)$cycloalkyl, heteroalkyl substituted $(C_3$-$C_7)$cycloalkyl, O$(C_1$-$C_8)$haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl, $S(O)_r$-phenyl, COR^j, $COOR^j$, NR^jR^k, $S(O)_rR^j$, $SO_2NR^jR^k$, $NR^jCONR^kR^l$, NR^jCOR^k, NR^jCOOR^k and $CONR^jR^k$ wherein the phenyl ring is optionally substituted and R^j, R^k and R^l are each independently selected from the group consisting of H, $(C_1$-$C_8)$alkyl and $(C_1$-$C_8)$haloalkyl, or optionally two of R^j, R^k and R^l when attached to the same nitrogen atom are combined to form a five- or six-membered ring, and the subscript r is an integer of from 0 to 2;

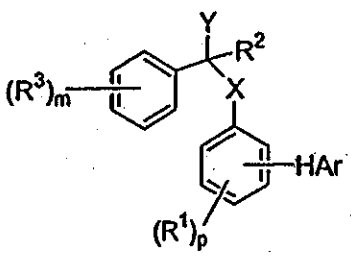
R^2 is a member selected from the group consisting of H, $(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$haloalkyl, aryl$(C_1$-$C_8)$alkyl and $(C_1$-$C_4)$alkylene-Z, wherein Z is as defined above;

the subscript m is an integer of from 0 to 4;

the subscript p is an integer of from 0 to 3; and

pharmaceutically acceptable salts thereof.

[0012] An embodiment may be compounds having the formula:



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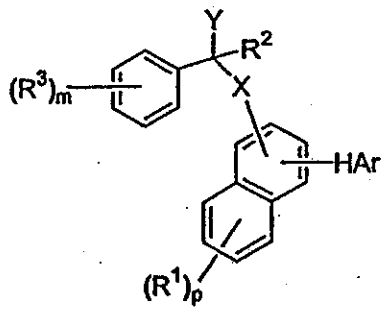


Ib

in which the letter X is selected from O, S, SO, SO_2 and NR, wherein R is H, $(C_1$-$C_8)$alkyl, COR^a, $COOR^a$ and $CONR^aR^b$ wherein R^a and R^b are each independently selected from H and $(C_1$-$C_8)$alkyl; the letter Y represents CH_2OR^c, CO_2R^c, CHO, $CONR^cR^m$, $CH(=NR^c)$, $CH(=NOR^c)$ or a carboxylic acid surrogate, wherein R^c is selected from H, $(C_1$-$C_8)$alkyl, $(C_3$-$C_8)$alkenyl, $(C_3$-$C_8)$alkynyl, $(C_3$-$C_7)$cycloalkyl, $(C_4$-$C_8)$cycloalkyl-alkyl, aryl, aryl$(C_1$-$C_8)$alkyl and $(C_1$-$C_8)$alkylene-Z, wherein Z is selected from COR^d, $COOR^d$, NR^dR^e, $NR^dCONR^eR^f$, NR^dCOR^e, NR^dCOOR^e and $CONR^dR^e$ wherein R^d, R^e and R^f are each independently selected

from H, (C_1-C_8)alkyl and phenyl, or optionally two of R^d, R^e and R^f when attached to the same nitrogen atom are combined to form a five- or six-membered ring; and wherein R^m is selected from H, (C_1-C_8)alkyl, aryl, OH and SO_2R^n, wherein R^n is selected from (C_1-C_8)alkyl, (C_1-C_8)haloalkyl, (C_1-C_8)aralkyl, (C_2-C_8)heteroalkyl, aryl, heteroaryl, (C_1-C_8)alkoxy, aryloxy, alkylamino, dialkylamino, arylamino, diarylamino, haloalkylamino and di(haloalkyl)amino, and R^m and R^c are optionally combined with the nitrogen atom to which each is attached to form a five- or six-membered ring.

[0013] HAr represents a heteroaryl moiety, optionally substituted with from one to three substituents independently selected from halogen, hydroxy, (C_1-C_8)alkyl, aryl(C_1-C_8)alkyl, (C_1-C_8)alkoxy, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_7)cycloalkyl, (C_4-C_8)cycloalkyl-alkyl, (C_1-C_8)heteroalkyl, (C_2-C_5)heterocyclyl, aryl, aryloxy, heterosubstituted(C_3-C_7)cycloalkyl, heteroalkyl substituted (C_3-C_7)cycloalkyl, (C_1-C_8)haloalkyl, O(C_1-C_8)haloalkyl, nitro, cyano, CO_2R^g, COR^g, NR^gR^h, $S(O)_qR^g$, $SO_2NR^gR^h$, $NR^gCONR^hR^i$, NR^gCOR^h, NR^gCOOR^h and $CONR^gR^h$, wherein R^g, R^h and R^i are each independently selected from H and (C_1-C_8)alkyl, or optionally two of R^g, R^h and R^i when attached to the same nitrogen atom are combined to form a five- or six-membered ring, and the subscript q is an integer of from 0 to 2.

[0014] A variety of heteroaryl groups provide compounds having the desired activity. In particular, the heteroaryl groups can be monocyclic or fused bicyclic heteroaryl groups. More particularly, one group of suitable monocyclic heteroaryl groups are provided in Figure 1A. In this Figure, the line extending from the ring indicates the point of attachment to the remainder of the compound and can be made through any available valence on the ring. Other examples of heteroaryl groups are provided in Figure 1B, which illustrates preferred fused-bicyclic heteroaryl groups, wherein attachment to the remainder of the compound can take place through an available valence on either ring.

[0015] Returning to formulae Ia and Ib, the subscripts m and p indicate the presence of substituents on their repective rings, wherein each substituent present can be the same or different from any other substituent. More particularly, the subscript m is an integer of from 0 to 4, and the subscript p is an integer of from 0 to 3. More preferably the subscript m is an integer of from 0 to 3, and the subscript p is an integer of from 0 to 3. Still more preferably, the subscript m is an integer of from 0 to 2, and the subscript p is an integer of from 0 to 2. Most preferably, the subscript m is 0, 1 or 2 and the subscript p is 1 or 2.

[0016] Each R^1 and R^3 represents a substituent independently selected from halogen, hydroxy, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_1-C_8)alkoxy, (C_3-C_7)cycloalkyl, (C_4-C_8)cycloalkyl-alkyl, (C_1-C_8)haloalkyl, (C_1-C_8)heteroalkyl, (C_2-C_5)heterocyclyl,

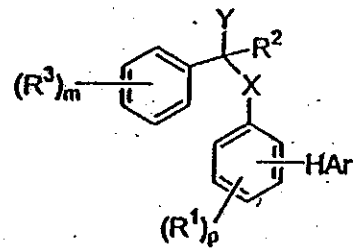
heterosubstituted(C_3-C_7)cycloalkyl, heteroalkyl substituted (C_3-C_7)cycloalkyl, O(C_1-C_8)haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl, $S(O)_r$-phenyl, COR^j, $COOR^j$, NR^jR^k, $S(O)_rR^j$, $SO_2NR^jR^k$, $NR^jCONR^kR^l$, NR^jCOR^k, NR^jCOOR^k and $CONR^jR^k$ wherein the phenyl ring is optionally substituted and R^j, R^k and R^l are each independently selected from H, (C_1-C_8)alkyl and (C_1-C_8)haloalkyl, or optionally two of R^j, R^k and R^l when attached to the same nitrogen atom are combined to form a five- or six-membered ring, and the subscript r is an integer of from 0 to 2. The subscript m is an integer of from 0 to 4 and the subscript p is an integer of from 0 to 3.

[0017] The symbol R^2 represents a member selected from H, (C_1-C_8)alkyl, (C_1-C_8)haloalkyl, (C_1-C_8)aralkyl and (C_1-C_4)alkylene-Z, wherein Z is as defined above.

[0018] In addition to compounds having formula Ia or Ib above, the present invention further includes all salts thereof, and particularly, pharmaceutically acceptable salts thereof. Still further, the invention includes compounds that are single isomers of the above formula (e.g., single enantiomers of compounds having a single chiral center), as well as prodrug forms thereof.

[0018a] In a second aspect of the present invention, there is provided a composition comprising a pharmaceutically acceptable excipient and a compound as defined above.

[0018b] In a third aspect of the present invention, there is provided a use of a compound having the formula:



Ia

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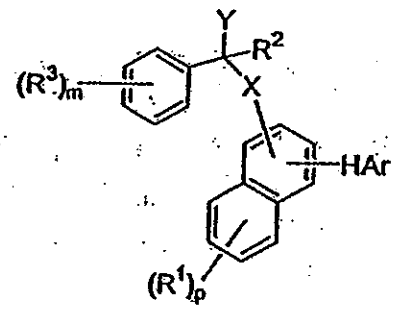


Ib

wherein

X is a member selected from the group consisting of O, S, SO, SO_2 and NR, wherein R is H, (C_1-C_8)alkyl, COR^a, $COOR^a$ and $CONR^aR^b$ wherein R^a and R^b are each independently selected from the group consisting of H and (C_1-C_8)alkyl;

Y is a member selected from the group consisting of CH_2OR^c, CO_2R^c, CHO,

$CONR^cR^m$, $CH(=NR^c)$, $CH(=NOR^c)$ and carboxylic acid surrogates, wherein R^c is a member selected from the group consisting of H, (C_1-C_8)alkyl, (C_3-C_8)alkenyl, (C_3-C_8)alkynyl, (C_3-C_7)cycloalkyl, (C_4-C_8)cycloalkyl-alkyl, aryl, aryl(C_1-C_8)alkyl and (C_1-C_8)alkylene-Z, wherein Z is selected from the group consisting of COR^d, $COOR^d$, NR^dR^e, $NR^dCONR^eR^f$, NR^dCOR^e, NR^dCOOR^e and $CONR^dR^e$ wherein R^d, R^e and R^f are each independently selected from the group consisting of H, (C_1-C_8)alkyl and phenyl, or optionally two of R^d, R^e and R^f when attached to the same nitrogen atom are combined to form a five- or six-membered ring; and wherein R^m is selected from the group consisting of H, (C_1-C_8)alkyl, aryl, OH and SO_2R^n, wherein R^n is selected from the group consisting of (C_1-C_8)alkyl, (C_1-C_8)haloalkyl, aryl(C_1-C_8)alkyl, (C_1-C_8)heteroalkyl, aryl, heteroaryl, (C_1-C_8)alkoxy, aryloxy, alkylamino, dialkylamino, arylamino, diarylamino, haloalkylamino and di(haloalkyl)amino, and R^m and R^c are optionally combined with the nitrogen atom to which each is attached to form a five- or six-membered ring;

HAr is heteroaryl moiety, optionally substituted with from one to three substituents independently selected from the group consisting of halogen, hydroxy, (C_1-C_8)alkyl, aryl(C_1-C_8)alkyl, (C_1-C_8)alkoxy, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_7)cycloalkyl, (C_4-C_8)cycloalkyl-alkyl, (C_1-C_8)heteroalkyl, (C_2-C_5)heterocyclyl, aryl, aryloxy, heterosubstituted(C_3-C_7)cycloalkyl, heteroalkyl substituted (C_3-C_7)cycloalkyl, (C_1-C_8)haloalkyl, O(C_1-C_8)haloalkyl, nitro, cyano, CO_2R^g, COR^g, NR^gR^h, $S(O)_qR^g$, $SO_2NR^gR^h$, $NR^gCONR^hR^i$, NR^gCOR^h, NR^gCOOR^h and $CONR^gR^h$, wherein R^g, R^h and R^i are each independently selected from the group consisting of H and (C_1-C_8)alkyl, or optionally two of R^g, R^h and R^i when attached to the same nitrogen atom are combined to form a five- or six-membered ring; and the subscript q is an integer of from 0 to 2;

each R^1 and R^3 is a member independently selected from the group consisting of halogen, hydroxy, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_1-C_8)alkoxy, (C_3-C_7)cycloalkyl, (C_4-C_8)cycloalkyl-alkyl, (C_1-C_8)haloalkyl, (C_1-C_8)heteroalkyl, (C_2-C_5)heterocyclyl, heterosubstituted(C_3-C_7)cycloalkyl, heteroalkyl substituted (C_3-C_7)cycloalkyl, O(C_1-C_8)haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl, $S(O)_r$-phenyl, COR^j, $COOR^j$, NR^jR^k, $S(O)_rR^j$, $SO_2NR^jR^k$, $NR^jCONR^kR^l$, NR^jCOR^k, NR^jCOOR^k and $CONR^jR^k$ wherein the

phenyl ring is optionally substituted and R^j, R^k and R^l are each independently selected from the group consisting of H, $(C_1$-$C_8)$alkyl and $(C_1$-$C_8)$haloalkyl, or optionally two of R^j, R^k and R^l when attached to the same nitrogen atom are combined to form a five- or six-membered ring, and the subscript r is an integer of from 0 to 2;

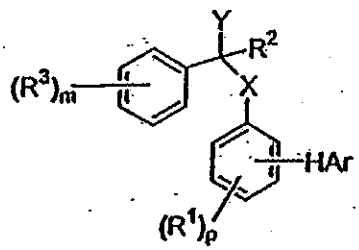
R^2 is a member selected from the group consisting of H, $(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$haloalkyl, aryl$(C_1$-$C_8)$alkyl and $(C_1$-$C_4)$alkylene-Z, wherein Z is as defined above;

the subscript m is an integer of from 0 to 4;

the subscript p is an integer of from 0 to 3; and

pharmaceutically acceptable salts thereof in the manufacture of a medicament for treating Type 2 diabetes.

[0018c] In a fourth aspect of the present invention, there is provided a use of a compound having the formula:



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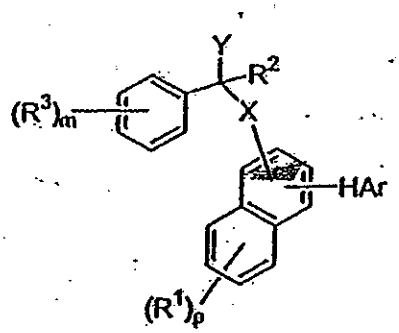


Ib

wherein

X is a member selected from the group consisting of O, S, SO, SO_2 and NR, wherein R is H, $(C_1$-$C_8)$alkyl, COR^a, $COOR^a$ and $CONR^aR^b$ wherein R^a and R^b are each independently selected from the group consisting of H and $(C_1$-$C_8)$alkyl;

Y is a member selected from the group consisting of CH_2OR^c, CO_2R^c, CHO, $CONR^cR^m$, $CH(=NR^c)$, $CH(=NOR^c)$ and carboxylic acid surrogates, wherein R^c is a member selected from the group consisting of H, $(C_1$-$C_8)$alkyl, $(C_3$-$C_8)$alkenyl, $(C_3$-$C_8)$alkynyl, $(C_3$-$C_7)$cycloalkyl, $(C_4$-$C_8)$cycloalkyl-alkyl, aryl, aryl$(C_1$-$C_8)$alkyl and $(C_1$-$C_8)$alkylene-Z, wherein Z is selected from the group consisting of COR^d, $COOR^d$, NR^dR^e, $NR^dCONR^eR^f$, NR^dCOR^e, NR^dCOOR^e and $CONR^dR^e$ wherein R^d, R^e and R^f are each independently selected from the group consisting of H, $(C_1$-$C_8)$alkyl and phenyl, or optionally two of R^d, R^e and R^f when attached to the same nitrogen atom are combined to form a five-

or six-membered ring; and wherein R^m is selected from the group consisting of H, $(C_1$-$C_8)$alkyl, aryl, OH and SO_2R^n, wherein R^n is selected from the group consisting of $(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$haloalkyl, aryl$(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$heteroalkyl, aryl, heteroaryl, $(C_1$-$C_8)$alkoxy, aryloxy, alkylamino, dialkylamino, arylamino, diarylamino, haloalkylamino and di(haloalkyl)amino, and R^m and R^c are optionally combined with the nitrogen atom to which each is attached to form a five- or six-membered ring;

HAr is heteroaryl moiety, optionally substituted with from one to three substituents independently selected from the group consisting of halogen, hydroxy, $(C_1$-$C_8)$alkyl, aryl$(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$alkoxy, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$cycloalkyl, $(C_4$-$C_8)$cycloalkyl-alkyl, $(C_1$-$C_8)$heteroalkyl, $(C_2$-$C_5)$heterocyclyl, aryl, aryloxy, heterosubstituted$(C_3$-$C_7)$cycloalkyl, heteroalkyl substituted $(C_3$-$C_7)$cycloalkyl, $(C_1$-$C_8)$haloalkyl, O$(C_1$-$C_8)$haloalkyl, nitro, cyano, CO_2R^g, COR^g, NR^gR^h, $S(O)_qR^g$, $SO_2NR^gR^h$, $NR^gCONR^hR^i$, NR^gCOR^h, NR^gCOOR^h and $CONR^gR^h$, wherein R^g, R^h and R^i are each independently selected from the group consisting of H and $(C_1$-$C_8)$alkyl, or optionally two of R^g, R^h and R^i when attached to the same nitrogen atom are combined to form a five- or six-membered ring, and the subscript q is an integer of from 0 to 2;

each R^1 and R^3 is a member independently selected from the group consisting of halogen, hydroxy, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_1$-$C_8)$alkoxy, $(C_3$-$C_7)$cycloalkyl, $(C_4$-$C_8)$cycloalkyl-alkyl, $(C_1$-$C_8)$haloalkyl, $(C_1$-$C_8)$heteroalkyl, $(C_2$-$C_5)$heterocyclyl, heterosubstituted$(C_3$-$C_7)$cycloalkyl, heteroalkyl substituted $(C_3$-$C_7)$cycloalkyl, O$(C_1$-$C_8)$haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl, $S(O)_r$-phenyl, COR^j, $COOR^j$, NR^jR^k, $S(O)_rR^j$, $SO_2NR^jR^k$, $NR^jCONR^kR^l$, NR^jCOR^k, NR^jCOOR^k and $CONR^jR^k$ wherein the phenyl ring is optionally substituted and R^j, R^k and R^l are each independently selected from the group consisting of H, $(C_1$-$C_8)$alkyl and $(C_1$-$C_8)$haloalkyl, or optionally two of R^j, R^k and R^l when attached to the same nitrogen atom are combined to form a five- or six-membered ring, and the subscript r is an integer of from 0 to 2;

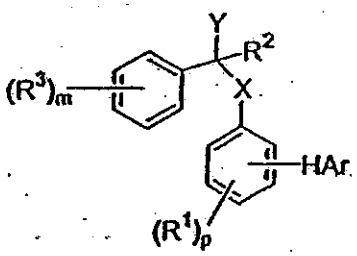
R^2 is a member selected from the group consisting of H, $(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$haloalkyl, aryl$(C_1$-$C_8)$alkyl and $(C_1$-$C_4)$alkylene-Z, wherein Z is as defined above;

the subscript m is an integer of from 0 to 4;

the subscript p is an integer of from 0 to 3; and

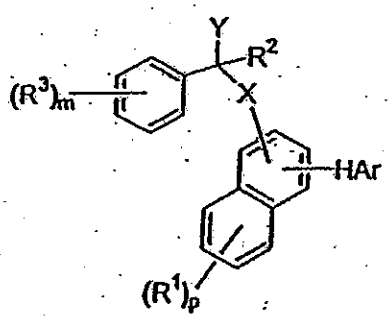
pharmaceutically acceptable salts thereof in the manufacture of a medicament for modulating insulin resistance.

[0018d] In a fifth aspect of the present invention, there is provided a use of a compound having the formula:



Ia

and



Ib

wherein

X is a member selected from the group consisting of O, S, SO, SO_2 and NR, wherein R is H, $(C_1$-$C_8)$alkyl, COR^a, $COOR^a$ and $CONR^aR^b$, wherein R^a and R^b are each independently selected from the group consisting of H and $(C_1$-$C_8)$alkyl;

Y is a member selected from the group consisting of CH_2OR^c, CO_2R^c, CHO, $CONR^cR^m$, $CH(=NR^c)$, $CH(=NOR^c)$ and carboxylic acid surrogates, wherein R^c is a member selected from the group consisting of H, $(C_1$-$C_8)$alkyl, $(C_3$-$C_8)$alkenyl, $(C_3$-$C_8)$alkynyl, $(C_3$-$C_7)$cycloalkyl, $(C_4$-$C_8)$cycloalkyl-alkyl, aryl, aryl$(C_1$-$C_8)$alkyl and $(C_1$-$C_8)$alkylene-Z, wherein Z is selected from the group consisting of COR^d, $COOR^d$, NR^dR^e, $NR^dCONR^eR^f$, NR^dCOR^e, NR^dCOOR^e and $CONR^dR^e$ wherein R^d, R^e and R^f are each independently selected from the group consisting of H, $(C_1$-$C_8)$alkyl and phenyl, or optionally two of R^d, R^e and R^f when attached to the same nitrogen atom are combined to form a five- or six-membered ring; and wherein R^m is selected from the group consisting of H, $(C_1$-$C_8)$alkyl, aryl, OH and SO_2R^n, wherein R^n is selected from the group consisting of $(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$haloalkyl, aryl$(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$heteroalkyl, aryl, heteroaryl, $(C_1$-$C_8)$alkoxy, aryloxy, alkylamino, dialkylamino, arylamino, diarylamino, haloalkylamino and

di(haloalkyl)amino, and R^m and R^c are optionally combined with the nitrogen atom to which each is attached to form a five- or six-membered ring;

HAr is heteroaryl moiety, optionally substituted with from one to three substituents independently selected from the group consisting of halogen, hydroxy, $(C_1$-$C_8)$alkyl, aryl$(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$alkoxy, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$cycloalkyl, $(C_4$-$C_8)$cycloalkyl-alkyl, $(C_1$-$C_8)$heteroalkyl, $(C_2$-$C_5)$heterocyclyl, aryl, aryloxy, heterosubstituted$(C_3$-$C_7)$cycloalkyl, heteroalkyl substituted $(C_3$-$C_7)$cycloalkyl, $(C_1$-$C_8)$haloalkyl, O$(C_1$-$C_8)$haloalkyl, nitro, cyano, CO_2R^g, COR^g, NR^gR^h, $S(O)_qR^g$, $SO_2NR^gR^h$, $NR^gCONR^hR^i$, NR^gCOR^h, NR^gCOOR^h and $CONR^gR^h$, wherein R^g, R^h and R^i are each independently selected from the group consisting of H and $(C_1$-$C_8)$alkyl, or optionally two of R^g, R^h and R^i when attached to the same nitrogen atom are combined to form a five- or six-membered ring, and the subscript q is an integer of from 0 to 2;

each R^1 and R^3 is a member independently selected from the group consisting of halogen, hydroxy, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_1$-$C_8)$alkoxy, $(C_3$-$C_7)$cycloalkyl, $(C_4$-$C_8)$cycloalkyl-alkyl, $(C_1$-$C_8)$haloalkyl, $(C_1$-$C_8)$heteroalkyl, $(C_2$-$C_5)$heterocyclyl, heterosubstituted$(C_3$-$C_7)$cycloalkyl, heteroalkyl substituted $(C_3$-$C_7)$cycloalkyl, O$(C_1$-$C_8)$haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl, $S(O)_r$-phenyl, COR^j, $COOR^j$, NR^jR^k, $S(O)_rR^j$, $SO_2NR^jR^k$, $NR^jCONR^kR^l$, NR^jCOR^k, NR^jCOOR^k and $CONR^jR^k$ wherein the phenyl ring is optionally substituted and R^j, R^k and R^l are each independently selected from the group consisting of H, $(C_1$-$C_8)$alkyl and $(C_1$-$C_8)$haloalkyl, or optionally two of R^j, R^k and R^l when attached to the same nitrogen atom are combined to form a five- or six-membered ring, and the subscript r is an integer of from 0 to 2;

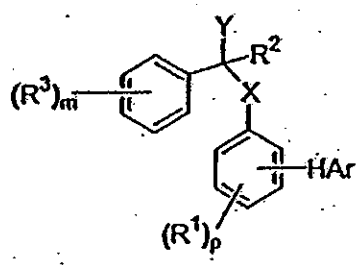
R^2 is a member selected from the group consisting of H, $(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$haloalkyl, aryl$(C_1$-$C_8)$alkyl and $(C_1$-$C_4)$alkylene-Z, wherein Z is as defined above;

the subscript m is an integer of from 0 to 4;

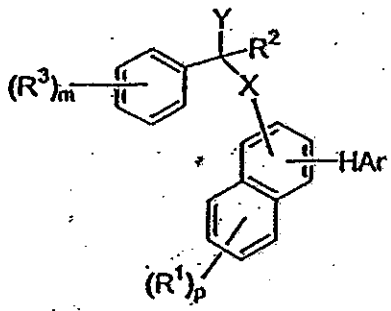
the subscript p is an integer of from 0 to 3; and

pharmaceutically acceptable salts thereof in the manufacture of a medicament for alleviating hyperlipidemia.

[0018e] In a sixth aspect of the present invention, there is provided a use of a compound having the formula:



and



Ia Ib

wherein

X is a member selected from the group consisting of O, S, SO, SO_2 and NR, wherein R is H, $(C_1$-$C_8)$alkyl, COR^a, $COOR^a$ and $CONR^aR^b$ wherein R^a and R^b are each independently selected from the group consisting of H and $(C_1$-$C_8)$alkyl;

Y is a member selected from the group consisting of CH_2OR^c, CO_2R^c, CHO, $CONR^cR^m$, $CH(=NR^c)$, $CH(=NOR^c)$ and carboxylic acid surrogates, wherein R^c is a member selected from the group consisting of H, $(C_1$-$C_8)$alkyl, $(C_3$-$C_8)$alkenyl, $(C_3$-$C_8)$alkynyl, $(C_3$-$C_7)$cycloalkyl, $(C_4$-$C_8)$cycloalkyl-alkyl, aryl, aryl$(C_1$-$C_8)$alkyl and $(C_1$-$C_8)$alkylene-Z, wherein Z is selected from the group consisting of COR^d, $COOR^d$, NR^dR^e, $NR^dCONR^eR^f$, NR^dCOR^e, NR^dCOOR^e and $CONR^dR^e$ wherein R^d, R^e and R^f are each independently selected from the group consisting of H, $(C_1$-$C_8)$alkyl and phenyl, or optionally two of R^d, R^e and R^f when attached to the same nitrogen atom are combined to form a five- or six-membered ring; and wherein R^m is selected from the group consisting of H, $(C_1$-$C_8)$alkyl, aryl, OH and SO_2R^n, wherein R^n is selected from the group consisting of $(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$haloalkyl, aryl$(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$heteroalkyl, aryl, heteroaryl, $(C_1$-$C_8)$alkoxy, aryloxy, alkylamino, dialkylamino, arylamino, diarylamino, haloalkylamino and di(haloalkyl)amino, and R^m and R^c are optionally combined with the nitrogen atom to which each is attached to form a five- or six-membered ring;

HAr is heteroaryl moiety, optionally substituted with from one to three substituents independently selected from the group consisting of halogen, hydroxy, $(C_1$-$C_8)$alkyl, aryl$(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$alkoxy, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$cycloalkyl, $(C_4$-$C_8)$cycloalkyl-alkyl, $(C_1$-$C_8)$heteroalkyl, $(C_2$-$C_5)$heterocyclyl, aryl, aryloxy, heterosubstituted$(C_3$-$C_7)$cycloalkyl, heteroalkyl

substituted (C_3-C_7)cycloalkyl, (C_1-C_8)haloalkyl, O(C_1-C_8)haloalkyl, nitro, cyano, CO_2R^g, COR^g, NR^gR^h, $S(O)_qR^g$, $SO_2NR^gR^h$, $NR^gCONR^hR^i$, NR^gCOR^h, NR^gCOOR^h and $CONR^gR^h$, wherein R^g, R^h and R^i are each independently selected from the group consisting of H and (C_1-C_8)alkyl, or optionally two of R^g, R^h and R^i when attached to the same nitrogen atom are combined to form a five- or six-membered ring, and the subscript q is an integer of from 0 to 2;

each R^1 and R^3 is a member independently selected from the group consisting of halogen, hydroxy, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_1-C_8)alkoxy, (C_3-C_7)cycloalkyl, (C_4-C_8)cycloalkyl-alkyl, (C_1-C_8)haloalkyl, (C_1-C_8)heteroalkyl, (C_2-C_5)heterocyclyl, heterosubstituted(C_3-C_7)cycloalkyl, heteroalkyl substituted (C_3-C_7)cycloalkyl, O(C_1-C_8)haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl, $S(O)_r$-phenyl, COR^j, $COOR^j$, NR^jR^k, $S(O)_rR^j$, $SO_2NR^jR^k$, $NR^jCONR^kR^l$, NR^jCOR^k, NR^jCOOR^k and $CONR^jR^k$ wherein the phenyl ring is optionally substituted and R^j, R^k and R^l are each independently selected from the group consisting of H, (C_1-C_8)alkyl and (C_1-C_8)haloalkyl, or optionally two of R^j, R^k and R^l when attached to the same nitrogen atom are combined to form a five- or six-membered ring, and the subscript r is an integer of from 0 to 2;

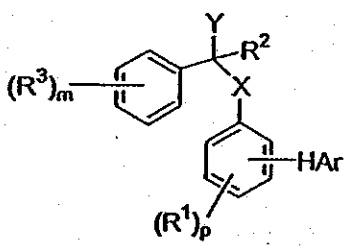
R^2 is a member selected from the group consisting of H, (C_1-C_8)alkyl, (C_1-C_8)haloalkyl, aryl(C_1-C_8)alkyl and (C_1-C_4)alkylene-Z, wherein Z is as defined above;

the subscript m is an integer of from 0 to 4;

the subscript p is an integer of from 0 to 3; and

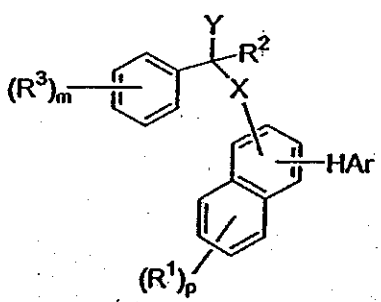
pharmaceutically acceptable salts thereof in the manufacture of a medicament for treating hyperuricemia.

[0018f] In a seventh aspect of the present invention, there is provided a prodrug agent having a formula selected from the group consisting of:



Ia

and



Ib

wherein

X is a member selected from the group consisting of O, S, SO, SO_2 and NR, wherein R is H, $(C_1$-$C_8)$alkyl, COR^a, $COOR^a$ and $CONR^aR^b$ wherein R^a and R^b are each independently selected from the group consisting of H and $(C_1$-$C_8)$alkyl;

Y is CO_2R'', wherein R" is selected from the group consisting of alkyl, heteroalkyl, aryl, heteroaryl, phenyl-lower alkyl, benzamido-lower alkyl, di-lower alkylamino-lower alkyl, ureido-lower alkyl, N'-lower alkyl-ureido-lower alkyl, carbamoyl-lower alkyl, halophenoxy substituted lower alkyl and carbamoyl substituted phenyl;

HAr is benzo-1,2,3-triazole, optionally substituted with from one to three substituents independently selected from the group consisting of halogen, hydroxy, $(C_1$-$C_8)$alkyl, aryl$(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$alkoxy, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$cycloalkyl, $(C_4$-$C_8)$cycloalkyl-alkyl, $(C_1$-$C_8)$heteroalkyl, $(C_2$-$C_5)$heterocyclyl, aryl, aryloxy, heterosubstituted$(C_3$-$C_7)$cycloalkyl, heteroalkyl substituted $(C_3$-$C_7)$cycloalkyl, $(C_1$-$C_8)$haloalkyl, O$(C_1$-$C_8)$haloalkyl, nitro, cyano, CO_2R^g, COR^g, NR^gR^h, $S(O)_qR^g$, $SO_2NR^gR^h$, $NR^gCONR^hR^i$, NR^gCOR^h, NR^gCOOR^h and $CONR^gR^h$, wherein R^g, R^h and R^i are each independently selected from the group consisting of H and $(C_1$-$C_8)$alkyl, or optionally two of R^g, R^h and R^i when attached to the same nitrogen atom are combined to form a five- or six-membered ring, and the subscript q is an integer of from 0 to 2;

each R^1 and R^3 is a member independently selected from the group consisting of halogen, hydroxy, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_1$-$C_8)$alkoxy, $(C_3$-$C_7)$cycloalkyl, $(C_4$-$C_8)$cycloalkyl-alkyl, $(C_1$-$C_8)$haloalkyl, $(C_1$-$C_8)$heteroalkyl, $(C_2$-$C_5)$heterocyclyl, heterosubstituted$(C_3$-$C_7)$cycloalkyl, heteroalkyl substituted $(C_3$-$C_7)$cycloalkyl, O$(C_1$-$C_8)$haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl, $S(O)_r$-phenyl, COR^j, $COOR^j$, NR^jR^k, $S(O)_rR^j$, $SO_2NR^jR^k$, $NR^jCONR^kR^l$,

NR^jCOR^k, NR^jCOOR^k and $CONR^jR^k$ wherein the phenyl ring is optionally substituted and R^j, R^k and R^l are each independently selected from the group consisting of H, $(C_1$-$C_8)$alkyl and $(C_1$-$C_8)$haloalkyl, or optionally two of R^j, R^k and R^l when attached to the same nitrogen atom are combined to form a five- or six-membered ring, and the subscript r is an integer of from 0 to 2;

R^2 is a member selected from the group consisting of H, $(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$haloalkyl, aryl$(C_1$-$C_8)$alkyl and $(C_1$-$C_4)$alkylene-Z, wherein Z is as defined above;

the subscript m is an integer of from 0 to 4;

the subscript p is an integer of from 0 to 3; and

pharmaceutically acceptable salts thereof.

[0019] Another embodiment may be compositions containing one or more compounds of Formula Ia or Ib, as well as methods for the use of such compounds and compositions, either alone or in combination with other pharmaceutical agents as provided in detail below. Yet another embodiment may relate to methods of using the compounds and/or compositions for the treatment of type II diabetes, hyperlipidemia, hyperuricemia, and for the modulation of insulin resistance. Still another embodiment may relate to methods of using the compounds and/or compositions for the treatment of diseases modulated by any of the isoforms of peroxisome proliferation activated receptor (PPAR).

[0020] Still further, embodiment may relate to compositions methods as noted, wherein the compound used is a single isomer of a compound of Formula Ia or Ib, or a prodrug form thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0021] **Figure 1** illustrates a variety of heteroaryl groups (HAr) useful in compounds of formula I. Figure 1A provides selected monocyclic heteroaryl groups while Figure 1B provides selected fused bicyclic heteroaryl groups. Each of the groups is optionally substituted with R^4 substituents that can be the same or different.

[0022] **Figure 2** illustrates a family of preferred sub-generic formulae for compounds of the invention wherein HAr is benzoxazol-2-yl; benzothiazol-2-yl and benzimidazol-2-yl.

[0023] **Figure 3** illustrates another family of preferred sub-generic formulae for compounds of the invention, wherein HAr is a fused bicyclic heteroaryl group.

[0024] **Figure 4** illustrates yet another family of preferred sub-generic formulae for compounds of the invention wherein HAr is benzoxazol-2-yl, benzothiazol-2-yl and benzotriazol-2-yl (see Figure 4A). Figure 4B illustrates other preferred compounds having carboxylic acid surrogates in place of CO_2R^c.

[0025] **Figures 5** illustrates yet another family of preferred sub-generic formulae for compounds of the invention wherein HAr is a monocyclic heteroaryl group selected from oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl and triazolyl (see Figures 5A and 5B). Figure 5C illustrates other preferred compounds having carboxylic acid surrogates in place of CO_2R^c.

[0026] **Figure 6** is a histogram illustrating the glucose lowering effect of selected compounds of the invention in ob/ob mice.

DETAILED DESCRIPTION OF THE INVENTION

Abbreviations and Definitions

[0027] The abbreviations used herein are conventional, unless otherwise defined.

[0028] Unless otherwise stated, the following terms used in the specification and claims have the meanings given below:

[0029] "Alkyl" refers to a linear saturated monovalent hydrocarbon radical or a branched saturated monovalent hydrocarbon radical having the number of carbon atoms indicated in the prefix. For example, $(C_1\text{-}C_6)$alkyl is meant to include methyl, ethyl, *n*-propyl, 2-propyl, *tert*-butyl, pentyl, and the like. For each of the definitions herein (*e.g.*, alkyl, alkenyl, alkoxy, aralkyloxy), when a prefix is not included to indicate the number of main chain carbon atoms in an alkyl portion, the radical or portion thereof will have six or fewer main chain carbon atoms.

[0030] "Alkylene" refers to a linear saturated divalent hydrocarbon radical or a branched saturated divalent hydrocarbon radical having the number of carbon atoms indicated in the prefix. For example, $(C_1\text{-}C_6)$alkylene is meant to include methylene, ethylene, propylene, 2-methylpropylene, pentylene, and the like.

[0031] "Alkenyl" refers to a linear monovalent hydrocarbon radical or a branched monovalent hydrocarbon radical having the number of carbon atoms indicated in the prefix and containing at least one double bond, but no more than three double bonds. For example, $(C_2\text{-}C_6)$alkenyl is meant to include, ethenyl, propenyl, 1,3-butadienyl and the like.

[0032] "Alkynyl" means a linear monovalent hydrocarbon radical or a branched monovalent hydrocarbon radical containing at least one triple bond and having the number of carbon atoms indicated in the prefix. The term "alkynyl" is also meant to include those alkyl groups having one triple bond and one double bond. For example, $(C_2\text{-}C_6)$alkynyl is meant to include ethynyl, propynyl, and the like.

[0033] "Alkoxy", "aryloxy" or "aralkyloxy" refers to a radical -OR wherein R is an alkyl, aryl or arylalkyl, respectively, as defined herein, *e.g.*, methoxy, phenoxy, benzyloxy, and the like.

[0034] "Aryl" refers to a monovalent monocyclic or bicyclic aromatic hydrocarbon radical of 6 to 10 ring atoms which is substituted independently with one to four substituents, preferably one, two, or three substituents selected from alkyl, cycloalkyl, cycloalkyl-alkyl, halo, nitro, cyano, hydroxy, alkoxy, amino, acylamino, mono-alkylamino, di-alkylamino, haloalkyl, haloalkoxy, heteroalkyl, COR (where R is hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, phenyl or phenylalkyl), $-(CR'R'')_n$-COOR (where n is an integer from 0 to 5, R' and R" are independently hydrogen or alkyl, and R is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, phenyl or phenylalkyl) or $-(CR'R'')_n$-$CONR^xR^y$ (where n is an integer from 0 to 5, R' and R" are independently hydrogen or alkyl, and R^x and R^y are independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, phenyl or phenylalkyl). More specifically the term aryl includes, but is not limited to, phenyl, biphenyl, 1-naphthyl, and 2-naphthyl, and the substituted forms thereof.

[0035] "Aralkyl" or "Aryl$(C_1\text{-}C_x)$alkyl" refers to the radical $-R^xR^y$ where R^x is an alkylene group (having eight or fewer main chain carbon atoms) and R^y is an aryl group as defined above. Thus, "aralkyl" refers to groups such as, for example, benzyl, phenylethyl, 3-(4-nitrophenyl)-2-methylbutyl, and the like. Similarly, "Aralkenyl" means a radical $-R^xR^y$ where R^x is an alkenylene group (an alkylene group having one or two double bonds) and R^y is an aryl group as defined above, *e.g.*, styryl, 3-phenyl-2-propenyl, and the like.

[0036] "Cycloalkyl" refers to a monovalent cyclic hydrocarbon radical of three to seven ring carbons. The cycloalkyl group may have one double bond and may also be optionally substituted independently with one, two, or three substituents selected from alkyl, optionally substituted phenyl, or $-C(O)R^z$ (where R^z is hydrogen, alkyl, haloalkyl, amino, mono-alkylamino, di-alkylamino, hydroxy, alkoxy, or optionally substituted phenyl). More specifically, the term cycloalkyl includes, for example, cyclopropyl, cyclohexyl,

cyclohexenyl, phenylcyclohexyl, 4-carboxycyclohexyl, 2-carboxamidocyclohexenyl, 2-dimethylaminocarbonyl-cyclohexyl, and the like.

[0037] "Cycloalkyl-alkyl" means a radical $-R^xR^y$ wherein R^x is an alkylene group and R^y is a cycloalkyl group as defined herein, *e.g.*, cyclopropylmethyl, cyclohexenylpropyl, 3-cyclohexyl-2-methylpropyl, and the like. The prefix indicating the number of carbon atoms (*e.g.*, C_4-C_{10}) refers to the total number of carbon atoms from both the cycloalkyl portion and the alkyl portion.

[0038] "Haloalkyl" refers to an alkyl group which is substituted with one or more same or different halo atoms, *e.g.*, $-CH_2Cl$, $-CF_3$, $-CH_2CF_3$, $-CH_2CCl_3$, and the like, and further includes those alkyl groups such as perfluoroalkyl in which all hydrogen atoms are replaced by fluorine atoms. The prefix "halo" and the term "halogen" when used to describe a substituent, refer to –F, -Cl, -Br and –I.

[0039] "Heteroalkyl" means an alkyl radical as defined herein with one, two or three substituents independently selected from cyano, $-OR^w$, $-NR^xR^y$, and $-S(O)_nR^z$ (where n is an integer from 0 to 2), with the understanding that the point of attachment of the heteroalkyl radical is through a carbon atom of the heteroalkyl radical. R^w is hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, aryl, aralkyl, alkoxycarbonyl, aryloxycarbonyl, carboxamido, or mono- or di-alkylcarbamoyl. R^x is hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, aryl or aralkyl. R^y is hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, aryl, aralkyl, alkoxycarbonyl, aryloxycarbonyl, carboxamido, mono- or di-alkylcarbamoyl or alkylsulfonyl. R^z is hydrogen (provided that n is 0), alkyl, cycloalkyl, cycloalkyl-alkyl, aryl, aralkyl, amino, mono-alkylamino, di-alkylamino, or hydroxyalkyl. Representative examples include, for example, 2-hydroxyethyl, 2,3-dihydroxypropyl, 2-methoxyethyl, benzyloxymethyl, 2-cyanoethyl, and 2-methylsulfonyl-ethyl. For each of the above, R^w, R^x ,R^y, and R^z can be further substituted by amino, fluorine, alkylamino, di-alkylamino, OH or alkoxy. Additionally, the prefix indicating the number of carbon atoms (*e.g.*, C_1-C_{10}) refers to the total number of carbon atoms in the portion of the heteroalkyl group exclusive of the cyano, $-OR^w$, $-NR^xR^y$, or $-S(O)_nR^z$ portions.

[0040] "Heteroaryl" means a monovalent monocyclic or bicyclic radical of 5 to 12 ring atoms having at least one aromatic ring containing one, two, or three ring heteroatoms selected from N, O, or S, the remaining ring atoms being C, with the understanding that the attachment point of the heteroaryl radical will be on an aromatic ring. The heteroaryl ring is optionally substituted independently with one to four substituents, preferably one or two substituents, selected from alkyl, cycloalkyl, cycloalkyl-alkyl, halo, nitro, cyano, hydroxy,

alkoxy, amino, acylamino, mono-alkylamino, di-alkylamino, haloalkyl, haloalkoxy, heteroalkyl, -COR (where R is hydrogen, alkyl, phenyl or phenylalkyl, $-(CR'R'')_n-COOR$ (where n is an integer from 0 to 5, R' and R" are independently hydrogen or alkyl, and R is hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, phenyl or phenylalkyl), or $-(CR'R'')_n-CONR^xR^y$ (where n is an integer from 0 to 5, R' and R" are independently hydrogen or alkyl, and R^x and R^y are, independently of each other, hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, phenyl or phenylalkyl). More specifically the term heteroaryl includes, but is not limited to, pyridyl, furanyl, thienyl, thiazolyl, isothiazolyl, triazolyl, imidazolyl, isoxazolyl, pyrrolyl, pyrazolyl, pyridazinyl, pyrimidinyl, benzofuranyl, tetrahydrobenzofuranyl, isobenzofuranyl, benzothiazolyl, benzoisothiazolyl, benzotriazolyl, indolyl, isoindolyl, benzoxazolyl, quinolyl, tetrahydroquinolinyl, isoquinolyl, benzimidazolyl, benzisoxazolyl or benzothienyl, and the derivatives thereof.

[0041] "Heterocyclyl" or "cycloheteroalkyl" means a saturated or unsaturated non-aromatic cyclic radical of 3 to 8 ring atoms in which one or two ring atoms are heteroatoms selected from O, NR (where R is independently hydrogen or alkyl) or $S(O)_n$ (where n is an integer from 0 to 2), the remaining ring atoms being C, where one or two C atoms may optionally be replaced by a carbonyl group. The heterocyclyl ring may be optionally substituted independently with one, two, or three substituents selected from alkyl, cycloalkyl, cycloalkyl-alkyl, halo, nitro, cyano, hydroxy, alkoxy, amino, mono-alkylamino, di-alkylamino, haloalkyl, haloalkoxy, -COR (where R is hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, phenyl or phenylalkyl), $-(CR'R'')_n-COOR$ (n is an integer from 0 to 5, R' and R" are independently hydrogen or alkyl, and R is hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, phenyl or phenylalkyl), or $-(CR'R'')_n-CONR^xR^y$ (where n is an integer from 0 to 5, R' and R" are independently hydrogen or alkyl, R^x and R^y are, independently of each other, hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, phenyl or phenylalkyl). More specifically the term heterocyclyl includes, but is not limited to, tetrahydropyranyl, piperidino, N-methylpiperidin-3-yl, piperazino, N-methylpyrrolidin-3-yl, 3-pyrrolidino, 2-pyrrolidon-1-yl, morpholino, thiomorpholino, thiomorpholino-1-oxide, thiomorpholino-1,1-dioxide, pyrrolidinyl, and the derivatives thereof. The prefix indicating the number of carbon atoms (*e.g.*, C_3-C_{10}) refers to the total number of carbon atoms in the portion of the cycloheteroalkyl or heterocyclyl group exclusive of the number of heteroatoms.

[0042] "Heterocyclylalkyl" or "Cycloheteroalkyl-alkyl" means a radical $-R^xR^y$ where R^x is an alkylene group and R^y is a heterocyclyl group as defined herein, *e.g.*, tetrahydropyran-2-ylmethyl, 4-methylpiperazin-1-ylethyl, 3-piperidinylmethyl, and the like.

[0043] "Heterosubstituted cycloalkyl" means a cycloalkyl group wherein one, two, or three hydrogen atoms are replaced by substituents independently selected from the group consisting of cyano, hydroxy, alkoxy, amino, acylamino, mono-alkylamino, di-alkylamino, or $-SO_nR$ (where n is an integer from 0 to 2 and when n is 0, R is hydrogen or alkyl and when n is 1 or 2, R is alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, amino, acylamino, mono-alkylamino, di-alkylamino, or hydroxyalkyl). Examples include 4-hydroxycyclohexyl, 2-aminocyclohexyl *etc.*

[0044] "Heteroalkyl substituted cycloalkyl" means a cycloalkyl group wherein one, two, or three hydrogen atoms are replaced independently by heteroalkyl groups, with the understanding that the heteroalkyl group is attached to the cycloalkyl group *via* a carbon-carbon bond. Examples include 1-hydroxymethyl-cyclopent-1-yl, 2-hydroxymethyl-cyclohex-2-yl and the like.

[0045] "Heteroalkyl substituted heterocyclyl" means a heterocyclyl group wherein one, two, or three hydrogen atoms are replaced independently by heteroalkyl groups, with the understanding that the heteroalkyl group is attached to the heterocyclyl group *via* a carbon-carbon bond. Examples include 4-hydroxymethyl-piperidin-1-yl, and the like.

[0046] "Optionally substituted phenyl" means a phenyl ring which is optionally substituted independently with one to four substituents, preferably one or two substituents selected from alkyl, cycloalkyl, cycloalkyl-alkyl, halo, nitro, cyano, hydroxy, alkoxy, amino, acylamino, mono-alkylamino, di-alkylamino, haloalkyl, haloalkoxy, heteroalkyl, -COR (where R is hydrogen, alkyl, phenyl or phenylalkyl, $-(CR'R")_n$-COOR (where n is an integer from 0 to 5, R' and R" are independently hydrogen or alkyl, and R is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, phenyl or phenylalkyl), or $-(CR'R")_n$-$CONR^xR^y$ (where n is an integer from 0 to 5, R' and R" are independently hydrogen or alkyl, and R^x and R^y are, independently of each other, hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, phenyl or phenylalkyl).

[0047] For each of the definitions above, the term "di-alkylamino" refers to an amino moiety bearing two alkyl groups that can be the same, or different.

[0048] As used herein, the term "carboxylic acid surrogate" refers to those moieties that are used as surrogates for a carboxylic acid moiety. Such groups are generally known to one of skill in the art (see, for example, THE PRACTICE OF MEDICINAL CHEMISTRY; Wermuth, C.G.,

ed., Academic Press, New York, 1996, page 203). Suitable isosteres or surrogates include -C(O)NHSO$_2$R wherein R can be alkyl, haloalkyl, heteroalkyl, aralkyl, aryl, heteroaryl, heterocyclyl, alkoxy, haloalkoxy, aryloxy, alkylamino, haloalkylamino, dialkylamino, dihaloalkylamino, arylamino, diarylamino, arakylamino, diarakylamino or other groups to provide an overall acidic character to the moiety; sulfonic acids; sulfinic acids; phosphonic acids; phosphinic acids; activated sulfonamides (e.g., -SO$_2$NHX wherein X is an electron withdrawing group relative to an alkyl group, such as an acyl group or aryl group; activated carboxamides (e.g., -C(O)NHCN); hydroxamic acids (-C(O)NHOH); acidic heterocycles or substituted heterocycles (e.g., tetrazoles, triazoles, hydroxypyrazoles, hydroxyoxazoles, hydroxythiadiazoles); and acidic alcohols (e.g., -C(CF$_3$)$_2$OH or -CH(CF$_3$)OH).

[0049] Compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers". Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers". When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the *R*- and *S*-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (*i.e.*, as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture".

[0050] The compounds of this invention may exist in stereoisomeric form if they possess one or more asymmetric centers or a double bond with asymmetric substitution and, therefore, can be produced as individual stereoisomers or as mixtures. Unless otherwise indicated, the description is intended to include individual stereoisomers as well as mixtures. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (see discussion in Chapter 4 of ADVANCED ORGANIC CHEMISTRY, 4th edition J. March, John Wiley and Sons, New York, 1992).

[0051] "Pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include:

[0052] (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-napthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynapthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or

[0053] (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, trimethylamine, *N*-methylglucamine, and the like.

[0054] "Prodrugs" means any compound which releases an active parent drug according to Formula Ia or Ib *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of a compound of Formula Ia or Ib are prepared by modifying functional groups present in the compound of Formula Ia or Ib in such a way that the modifications may be cleaved *in vivo* to release the parent compound. Prodrugs include compounds of Formula Ia or Ib wherein a hydroxy, amino, or sulfhydryl group in a compound of Formula Ia or Ib is bonded to any group that may be cleaved *in vivo* to regenerate the free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to esters (*e.g.*, acetate, formate, and benzoate derivatives), amides, carbamates (*e.g.*, N,N-dimethylaminocarbonyl) of hydroxy functional groups in compounds of Formula Ia or Ib, and the like.

[0055] "Protecting group" refers to a grouping of atoms that when attached to a reactive group in a molecule masks, reduces or prevents that reactivity. Examples of protecting groups can be found in T.W. Greene and P.G. Wuts, PROTECTIVE GROUPS IN ORGANIC CHEMISTRY, (Wiley, 2nd ed. 1991) and Harrison and Harrison *et al.*, COMPENDIUM OF SYNTHETIC ORGANIC METHODS, Vols. 1-8 (John Wiley and Sons. 1971-1996). Representative amino protecting groups include formyl, acetyl, trifluoroacetyl, benzyl, benzyloxycarbonyl (CBZ), *tert*-butoxycarbonyl (Boc), trimethyl silyl (TMS), 2-

trimethylsilyl-ethanesulfonyl (SES), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl (FMOC), nitro-veratryloxycarbonyl (NVOC) and the like. Representative hydroxy protecting groups include those where the hydroxy group is either acylated or alkylated such as benzyl and trityl ethers as well as alkyl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers and allyl ethers.

[0056] Turning next to the compositions of the invention, the term "pharmaceutically acceptable carrier or excipient" means a carrier or excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes a carrier or excipient that is acceptable for veterinary use as well as human pharmaceutical use. A "pharmaceutically acceptable carrier or excipient" as used in the specification and claims includes both one and more than one such carrier or excipient.

[0057] With reference to the methods of the present invention, the following terms are used with the noted meanings:

[0058] The terms "treating" or "treatment" of a disease includes:

[0059] (1) preventing the disease, *i.e.*, causing the clinical symptoms of the disease not to develop in a mammal that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease,

[0060] (2) inhibiting the disease, *i.e.*, arresting or reducing the development of the disease or its clinical symptoms, or

[0061] (3) relieving the disease, *i.e.*, causing regression of the disease or its clinical symptoms.

[0062] The term "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician. "A therapeutically effective amount" includes the amount of a compound that, when administered to a mammal for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, *etc.*, of the mammal to be treated.

[0063] The term "mammal" includes, without limitation, humans, domestic animals (*e.g.*, dogs or cats), farm animals (cows, horses, or pigs), monkeys, rabbits, mice, and laboratory animals.

[0064] The term "insulin resistance" can be defined generally as a disorder of glucose metabolism. More specifically, insulin resistance can be defined as the diminished ability of

insulin to exert its biological action across a broad range of concentrations producing less than the expected biologic effect. (*see, e.g.*, Reaven, G. M., *J. Basic & Clin. Phys. & Pharm.* (1998) 9: 387-406 and Flier, J. *Ann Rev. Med.* (1983) 34: 145-60). Insulin resistant persons have a diminished ability to properly metabolize glucose and respond poorly, if at all, to insulin therapy. Manifestations of insulin resistance include insufficient insulin activation of glucose uptake, oxidation and storage in muscle and inadequate insulin repression of lipolysis in adipose tissue and of glucose production and secretion in liver. Insulin resistance can cause or contribute to polycystic ovarian syndrome, Impaired Glucose Tolerance (IGT), gestational diabetes, hypertension, obesity, atherosclerosis and a variety of other disorders. Eventually, the insulin resistant individuals can progress to a point where a diabetic state is reached. The association of insulin resistance with glucose intolerance, an increase in plasma triglyceride and a decrease in high-density lipoprotein cholesterol concentrations, high blood pressure, hyperuricemia, smaller denser low-density lipoprotein particles, and higher circulating levels of plaminogen activator inhibitor-1), has been referred to as "Syndrome X" (*see, e.g.*, Reaven, G. M., *Physiol. Rev.* (1995) 75: 473-486).

[0065] The term "diabetes mellitus" or "diabetes" means a disease or condition that is generally characterized by metabolic defects in production and utilization of glucose which result in the failure to maintain appropriate blood sugar levels in the body. The result of these defects is elevated blood glucose, referred to as "hyperglycemia." Two major forms of diabetes are Type 1 diabetes and Type 2 diabetes. As described above, Type 1 diabetes is generally the result of an absolute deficiency of insulin, the hormone which regulates glucose utilization. Type 2 diabetes often occurs in the face of normal, or even elevated levels of insulin and can result from the inability of tissues to respond appropriately to insulin. Most Type 2 diabetic patients are insulin resistant and have a relative deficiency of insulin, in that insulin secretion can not compensate for the resistance of peripheral tissues to respond to insulin. In addition, many Type 2 diabetics are obese. Other types of disorders of glucose homeostasis include Impaired Glucose Tolerance, which is a metabolic stage intermediate between normal glucose homeostasis and diabetes, and Gestational Diabetes Mellitus, which is glucose intolerance in pregnancy in women with no previous history of Type 1 or Type 2 diabetes.

[0066] The term "secondary diabetes" is diabetes resulting from other identifiable etiologies which include: genetic defects of β cell function (*e.g.*, maturity onset-type diabetes of youth, referred to as "MODY," which is an early-onset form of Type 2 diabetes with autosomal inheritance; *see, e.g.*, Fajans S. *et al.*, *Diabet. Med.* (1996) (9 Suppl 6): S90-5 and

Bell, G. *et al.*, *Annu. Rev. Physiol.* (1996) 58: 171-86; genetic defects in insulin action; diseases of the exocrine pancreas (*e.g.*, hemochromatosis, pancreatitis, and cystic fibrosis); certain endocrine diseases in which excess hormones interfere with insulin action (*e.g.*, growth hormone in acromegaly and cortisol in Cushing's syndrome); certain drugs that suppress insulin secretion (*e.g.*, phenytoin) or inhibit insulin action (*e.g.*, estrogens and glucocorticoids); and diabetes caused by infection (*e.g.*, rubella, Coxsackie, and CMV); as well as other genetic syndromes.

[0067] The guidelines for diagnosis for Type 2 diabetes, impaired glucose tolerance, and gestational diabetes have been outlined by the American Diabetes Association (*see, e.g.*, The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, *Diabetes Care*, (1999) Vol 2 (Suppl 1): S5-19).

[0068] The term "hyperinsulinemia" refers to the presence of an abnormally elevated level of insulin in the blood. Similarly, the term "hyperuricemia" refers to the presence of an abnormally elevated level of uric acid in the blood. The term "hyperlipidemia" refers to the presence of an abnormally elevated level of lipids in the blood. Hyperlipidemia can appear in at least three forms: (1) hypercholesterolemia, *i.e.*, an elevated cholesterol level; (2) hypertriglyceridemia, *i.e.*, an elevated triglyceride level; and (3) combined hyperlipidemia, *i.e.*, a combination of hypercholesterolemia and hypertriglyceridemia.

[0069] The term "secretagogue" means a substance or compound that stimulates secretion. For example, an insulin secretagogue is a substance or compound that stimulates secretion of insulin.

[0070] The term "hemoglobin" or "Hb" refers to a respiratory pigment present in erythrocytes, which is largely responsible for oxygen transport. A hemoglobin molecule comprises four polypeptide subunits (two α chain systems and two β chain systems, respectively). Each subunit is formed by association of one globin protein and one heme molecule which is an iron-protoporphyrin complex. The major class of hemoglobin found in normal adult hemolysate is adult hemoglobin (referred to as "HbA"; also referred to HbA_0 for distinguishing it from glycated hemoglobin, which is referred to as "HbA_1," described *infra*) having $\alpha_2\beta_2$ subunits. Trace components such as HbA_2 ($\alpha_2\delta_2$) can also be found in normal adult hemolysate.

[0071] Among classes of adult hemoglobin HbAs, there is a glycated hemoglobin (referred to as "HbA_1," or "glycosylated hemoglobin"), which may be further fractionated into HbA_{1a1}, HbA_{1a2}, HbA_{1b}, and HbA_{1c} with an ion exchange resin fractionation. All of these subclasses have the same primary structure, which is stabilized by formation of an aldimine (Schiff

base) by the amino group of N-terminal valine in the β subunit chain of normal hemoglobin HbA and glucose (or, glucose-6-phosphate or fructose) followed by formation of ketoamine by Amadori rearrangement.

[0072] The term "glycosylated hemoglobin" (also referred to as "HbA_{1c},", "GHb", "hemoglobin - glycosylated", "diabetic control index" and "glycohemoglobin"; hereinafter referred to as "hemoglobin A_{1c}") refers to a stable product of the nonenzymatic glycosylation of the β-chain of hemoglobin by plasma glucose. Hemoglobin A_{1c} comprises the main portion of glycated hemoglobins in the blood. The ratio of glycosylated hemoglobin is proportional to blood glucose level. Therefore, hemoglobin A_{1c} rate of formation directly increases with increasing plasma glucose levels. Since glycosylation occurs at a constant rate during the 120-day lifespan of an erythrocyte, measurement of glycosylated hemoglobin levels reflect the average blood glucose level for an individual during the preceding two to three months. Therefore determination of the amount of glycosylated hemoglobin HbA_{1c} can be a good index for carbohydrate metabolism control. Accordingly, blood glucose levels of the last two months can be estimated on the basis of the ratio of HbA_{1c} to total hemoglobin Hb. The analysis of the hemoglobin A_{1c} in blood is used as a measurement enabling long-term control of blood glucose level (*see, e.g.*, Jain, S., *et al.*, *Diabetes* (1989) 38: 1539-1543; Peters A., *et al.*, *JAMA* (1996) 276: 1246-1252).

[0073] The term "symptom" of diabetes, includes, but is not limited to, polyuria, polydipsia, and polyphagia, as used herein, incorporating their common usage. For example, "polyuria" means the passage of a large volume of urine during a given period; "polydipsia" means chronic, excessive thirst; and "polyphagia" means excessive eating. Other symptoms of diabetes include, *e.g.*, increased susceptibility to certain infections (especially fungal and staphylococcal infections), nausea, and ketoacidosis (enhanced production of ketone bodies in the blood).

[0074] The term "complication" of diabetes includes, but is not limited to, microvascular complications and macrovascular complications. Microvascular complications are those complications which generally result in small blood vessel damage. These complications include, *e.g.*, retinopathy (the impairment or loss of vision due to blood vessel damage in the eyes); neuropathy (nerve damage and foot problems due to blood vessel damage to the nervous system); and nephropathy (kidney disease due to blood vessel damage in the kidneys). Macrovascular complications are those complications which generally result from large blood vessel damage. These complications include, *e.g.*, cardiovascular disease and peripheral vascular disease. Cardiovascular disease refers to diseases of blood vessels of the

heart. *See. e.g.*, Kaplan, R. M., *et al.*, "Cardiovascular diseases" in HEALTH AND HUMAN BEHAVIOR, pp. 206-242 (McGraw-Hill, New York 1993). Cardiovascular disease is generally one of several forms, including, *e.g.*, hypertension (also referred to as high blood pressure), coronary heart disease, stroke, and rheumatic heart disease. Peripheral vascular disease refers to diseases of any of the blood vessels outside of the heart. It is often a narrowing of the blood vessels that carry blood to leg and arm muscles.

[0075] The term "atherosclerosis" encompasses vascular diseases and conditions that are recognized and understood by physicians practicing in the relevant fields of medicine. Atherosclerotic cardiovascular disease, coronary heart disease (also known as coronary artery disease or ischemic heart disease), cerebrovascular disease and peripheral vessel disease are all clinical manifestations of atherosclerosis and are therefore encompassed by the terms "atherosclerosis" and "atherosclerotic disease".

[0076] The term "antihyperlipidemic" refers to the lowering of excessive lipid concentrations in blood to desired levels. Similarly, the term "antiuricemic" refers to the lowering of excessive uric acid concentrations in blood to desired levels.

[0077] The term "modulate" refers to the treating, prevention, suppression, enhancement or induction of a function or condition. For example, the compounds of the present invention can modulate hyperlipidemia by lowering cholesterol in a human, thereby suppressing hyperlipidemia.

[0078] The term "triglyceride(s)" ("TGs"), as used herein, incorporates its common usage. TGs consist of three fatty acid molecules esterified to a glycerol molecule and serve to store fatty acids which are used by muscle cells for energy production or are taken up and stored in adipose tissue.

[0079] Because cholesterol and TGs are water insoluble, they must be packaged in special molecular complexes known as "lipoproteins" in order to be transported in the plasma. Lipoproteins can accumulate in the plasma due to overproduction and/or deficient removal. There are at least five distinct lipoproteins differing in size, composition, density, and function. In the cells of the small of the intestine, dietary lipids are packaged into large lipoprotein complexes called "chylomicrons", which have a high TG and low-cholesterol content. In the liver, TG and cholesterol esters are packaged and released into plasma as TG-rich lipoprotein called very low density lipoprotein ("VLDL"), whose primary function is the endogenous transport of TGs made in the liver or released by adipose tissue. Through enzymatic action, VLDL can be either reduced and taken up by the liver, or transformed into intermediate density lipoprotein ("IDL"). IDL, is in turn, either taken up by the liver, or is

further modified to form the low density lipoprotein ("LDL"). LDL is either taken up and broken down by the liver, or is taken up by extrahepatic tissue. High density lipoprotein ("HDL") helps remove cholesterol from peripheral tissues in a process called reverse cholesterol transport.

[0080] The term "dyslipidemia" refers to abnormal levels of lipoproteins in blood plasma including both depressed and/or elevated levels of lipoproteins (*e.g.*, elevated levels of LDL, VLDL and depressed levels of HDL).

[0081] Exemplary Primary Hyperlipidemia include, but are not limited to, the following:

[0082] (1) *Familial Hyperchylomicronemia*, a rare genetic disorder which causes a deficiency in an enzyme, LP lipase, that breaks down fat molecules. The LP lipase deficiency can cause the accumulation of large quantities of fat or lipoproteins in the blood;

[0083] (2) *Familial Hypercholesterolemia*, a relatively common genetic disorder caused where the underlying defect is a series of mutations in the LDL receptor gene that result in malfunctioning LDL receptors and/or absence of the LDL receptors. This brings about ineffective clearance of LDL by the LDL receptors resulting in elevated LDL and total cholesterol levels in the plasma;

[0084] (3) *Familial Combined Hyperlipidemia*, also known as multiple lipoprotein-type hyperlipidemia; an inherited disorder where patients and their affected first-degree relatives can at various times manifest high cholesterol and high triglycerides. Levels of HDL cholesterol are often moderately decreased;

[0085] (4) *Familial Defective Apolipoprotein B-100* is a relatively common autosomal dominant genetic abnormality. The defect is caused by a single nucleotide mutation that produces a substitution of glutamine for arginine which can cause reduced affinity of LDL particles for the LDL receptor. Consequently, this can cause high plasma LDL and total cholesterol levels;

[0086] (5) *Familial Dysbetaliproteinemia*, also referred to as Type III Hyperlipoproteinemia, is an uncommon inherited disorder resulting in moderate to severe elevations of serum TG and cholesterol levels with abnormal apolipoprotein E function. HDL levels are usually normal; and

[0087] (6) *Familial Hypertriglyceridemia*, is a common inherited disorder in which the concentration of plasma VLDL is elevated. This can cause mild to moderately elevated triglyceride levels (and usually not cholesterol levels) and can often be associated with low plasma HDL levels.

[0088] Risk factors in exemplary Secondary Hyperlipidemia include, but are not limited to, the following: (1) disease risk factors, such as a history of Type 1 diabetes, Type 2 diabetes, Cushing's syndrome, hypothroidism and certain types of renal failure; (2) drug risk factors, which include, birth control pills; hormones, such as estrogen, and corticosteroids; certain diuretics; and various β blockers; (3) dietary risk factors include dietary fat intake per total calories greater than 40%; saturated fat intake per total calories greater than 10%; cholesterol intake greater than 300 mg per day; habitual and excessive alcohol use; and obesity.

[0089] The terms "obese" and "obesity" refers to, according to the World Health Organization, a Body Mass Index (BMI) greater than 27.8 kg/m^2 for men and 27.3 kg/m^2 for women (BMI equals weight (kg)/height (m^2). Obesity is linked to a variety of medical conditions including diabetes and hyperlipidemia. Obesity is also a known risk factor for the development of Type 2 diabetes (*See, e.g.*, Barrett-Conner, E., *Epidemol. Rev.* (1989) 11: 172-181; and Knowler, et al., *Am. J. Clin. Nutr.* (1991) 53:1543-1551).

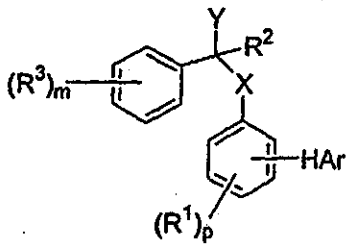
[0090] The terms "optional" or "optionally" as used throughout the specification means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "heterocyclo group optionally mono- or di- substituted with an alkyl group" means that the alkyl may but need not be present, and the description includes situations where the heterocyclo group is mono- or disubstituted with an alkyl group and situations where the heterocyclo group is not substituted with the alkyl group.

General

[0091] The present invention derives from the discovery that compounds of Formula Ia or Ib are useful in treating or controlling a number of diseases associated with glucose metabolism, lipid metabolism and insulin secretion. More particularly, the compounds of the invention are useful in treating insulin resistance, diabetes, hyperinsulinemia, hyperlipidemia, hyperuricemia and obesity. Without intending to be bound by theory, it is considered that the compounds of Formula Ia or Ib operate via modulation of receptor interactions associated with one or more isoforms of PPAR. As a result, the compounds will likely have utility in treating other diseases states or conditions associated with PPAR.

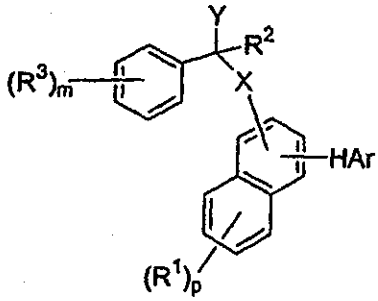
Compounds

[0092] In one aspect, the present invention provides compounds having the formula:



Ia

and



Ib

in which the letter X is selected from O, S, SO, SO_2 and NR, wherein R is H, $(C_1$-$C_8)$alkyl, COR^a, $COOR^a$ and $CONR^aR^b$ wherein R^a and R^b are each independently selected from H and $(C_1$-$C_8)$alkyl; the letter Y represents CH_2OR^c, CO_2R^c, CHO, $CONR^cR^m$, $CH(=NR^c)$, $CH(=NOR^c)$ or a carboxylic acid surrogate, wherein R^c is selected from H, $(C_1$-$C_8)$alkyl, $(C_3$-$C_8)$alkenyl, $(C_3$-$C_8)$alkynyl, $(C_3$-$C_7)$cycloalkyl, $(C_4$-$C_8)$cycloalkyl-alkyl, aryl, aryl$(C_1$-$C_8)$alkyl and $(C_1$-$C_8)$alkylene-Z, wherein Z is selected from COR^d, $COOR^d$, NR^dR^e, $NR^dCONR^eR^f$, NR^dCOR^e, NR^dCOOR^e and $CONR^dR^e$ wherein R^d, R^e and R^f are each independently selected from H, $(C_1$-$C_8)$alkyl and phenyl, or optionally two of R^d, R^e and R^f when attached to the same nitrogen atom are combined to form a five- or six-membered ring; and wherein R^m is selected from H, $(C_1$-$C_8)$alkyl, aryl, OH and SO_2R^n, wherein R^n is selected from $(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$haloalkyl, aryl$(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$heteroalkyl, aryl, heteroaryl, $(C_1$-$C_8)$alkoxy, aryloxy, alkylamino, dialkylamino, arylamino, diarylamino, haloalkylamino and di(haloalkyl)amino, and R^m and R^c are optionally combined with the nitrogen atom to which each is attached to form a five- or six-membered ring.

[0093] HAr represents a heteroaryl moiety, optionally substituted with from one to three substituents independently selected from halogen, hydroxy, $(C_1$-$C_8)$alkyl, aryl$(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$alkoxy, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_7)$cycloalkyl, $(C_4$-$C_8)$cycloalkyl-alkyl, $(C_1$-$C_8)$heteroalkyl, $(C_2$-$C_5)$heterocyclyl, aryl, heteroaryl, aryloxy, heterosubstituted$(C_3$-$C_7)$cycloalkyl, heteroalkyl substituted $(C_3$-$C_7)$cycloalkyl, $(C_1$-$C_8)$haloalkyl, O$(C_1$-$C_8)$haloalkyl, nitro, cyano, CO_2R^g, COR^g, NR^gR^h, $S(O)_qR^g$, $SO_2NR^gR^h$, $NR^gCONR^hR^i$, NR^gCOR^h, NR^gCOOR^h and $CONR^gR^h$, wherein R^g, R^h and R^i are each independently selected from H and $(C_1$-$C_8)$alkyl, or optionally two of R^g, R^h and R^i when attached to the same nitrogen atom are combined to form a five- or six-membered ring, and the subscript q is an integer of from 0 to 2.

[0094] A variety of heteroaryl groups provide compounds having the desired activity. In particular, the heteroaryl groups can be monocyclic or fused bicyclic heteroaryl groups. More particularly, one group of suitable monocyclic heteroaryl groups are provided in Figure

1A. In this Figure, the line extending from the ring indicates the point of attachment to the remainder of the compound and can be made through any available valence on the ring. Other examples of heteroaryl groups are provided in Figure 1B, which illustrates preferred fused-bicyclic heteroaryl groups, wherein attachment to the remainder of the compound can take place through an available valence on either ring.

[0095] Returning to Formula Ia or Ib, the subscripts m and p indicate the presence of substituents on their repective rings, wherein each substituted present can be the same or different from any other substituent. More particularly, the subscript m is an integer of from 0 to 4, and the subscript p is an integer of from 0 to 3. More preferably the subscript m is an integer of from 0 to 3, and the subscript p is an integer of from 1 to 3. Still more preferably, the subscript m is 0, 1, 2 or 3 and the subscript p is 1 or 2.

[0096] Each R^1 and R^3 represents a substituent independently selected from halogen, hydroxy, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $(C_1\text{-}C_8)$alkoxy, $(C_3\text{-}C_7)$cycloalkyl, $(C_4\text{-}C_8)$cycloalkyl-alkyl, $(C_1\text{-}C_8)$haloalkyl, $(C_1\text{-}C_8)$heteroalkyl, $(C_2\text{-}C_5)$heterocyclyl, heterosubstituted$(C_3\text{-}C_7)$cycloalkyl, heteroalkyl substituted $(C_3\text{-}C_7)$cycloalkyl, $O(C_1\text{-}C_8)$haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl, $S(O)_r$-phenyl, COR^j, $COOR^j$, NR^jR^k, $S(O)_rR^j$, $SO_2NR^jR^k$, $NR^jCONR^kR^l$, NR^jCOR^k, NR^jCOOR^k and $CONR^jR^k$ wherein the phenyl ring is optionally substituted and R^j, R^k and R^l are each independently selected from H, $(C_1\text{-}C_8)$alkyl and $(C_1\text{-}C_8)$haloalkyl, or optionally two of R^j, R^k and R^l when attached to the same nitrogen atom are combined to form a five- or six-membered ring, and the subscript r is an integer of from 0 to 2. The subscript m is an integer of from 0 to 4 and the subscript p is an integer of from 0 to 3.

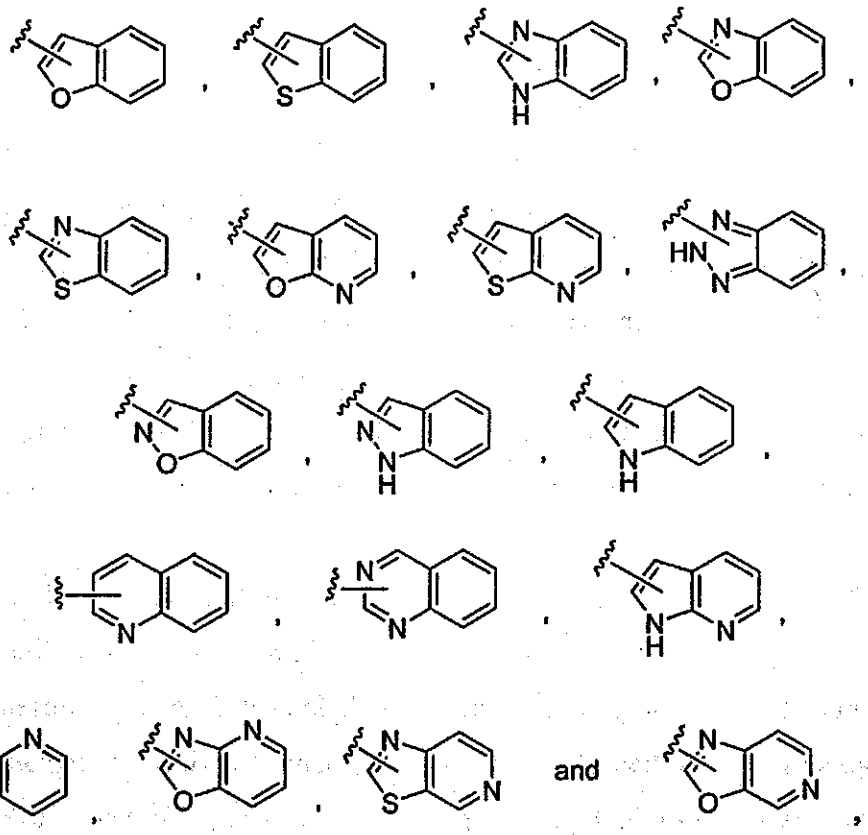
[0097] The symbol R^2 represents a member selected from H, $(C_1\text{-}C_8)$alkyl, $(C_1\text{-}C_8)$haloalkyl, aryl$(C_1\text{-}C_8)$alkyl and $(C_1\text{-}C_4)$alkylene-Z, wherein Z is as defined above.

[0098] In addition to compounds having formula Ia or Ib above, the present invention further includes all salts thereof, and particularly, pharmaceutically acceptable salts thereof. Still further, the invention includes compounds that are single isomers of the above formula (e.g., single enantiomers of compounds having a single chiral center), as well as prodrug forms thereof.

[0099] In certain preferred embodiments, Y is CH_2OR^c, CO_2R^c, a carboxylic acid surrogate or CHO. Preferred carboxylic acid surrogates included tetrazol-5-yl and the group $CONR^cR^m$ wherein R^m is SO_2R^n. Still more preferably, the carboxylic acid surrogate is tetrazol-5-yl or $CONHSO_2R^n$. A further preferred group of embodiments are those in which Y is CO_2R^c, a carboxylic acid surrogate or CH_2OR^c.

[0100] A number of groups of embodiments are preferred and are set forth below.

[0101] In a first group of embodiments, Y is CO_2R^c, a carboxylic acid surrogate (preferably those provided above) or CH_2OR^c; HAr is a fused bicyclic heteroaryl moiety, wherein each of the HAr groups is optionally substituted with from one to three substituents independently selected from the group consisting of halogen, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_8)$heteroalkyl $(C_1\text{-}C_4)$alkoxy, $O(C_1\text{-}C_4)$haloalkyl, aryl$(C_1\text{-}C_4)$alkyl, aryl$(C_1\text{-}C_4)$haloalkyl, aryl, heteroaryl, aryloxy, nitro, cyano, CO_2R^g, COR^g and $CONR^gR^h$. Still further preferred, within this group of embodiments, are compounds wherein X is O, S or NH, with compounds in which R^2 is H, CH_3 or CF_3 being further preferred. Even further preferred are those compounds wherein HAr is attached to the 2- or 3-position of the ring bearing X and is selected from:

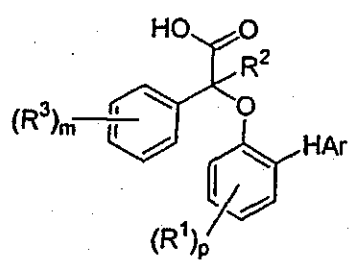


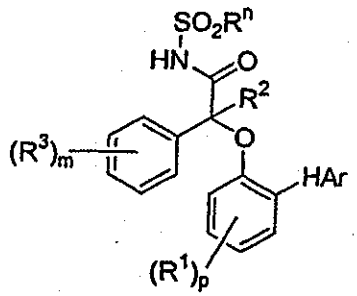
wherein each of the HAr groups is optionally substituted with from one to three substituents independently selected from halogen, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_8)$heteroalkyl $(C_1\text{-}C_4)$alkoxy, $O(C_1\text{-}C_4)$haloalkyl, aryl$(C_1\text{-}C_4)$alkyl, aryl$(C_1\text{-}C_4)$haloalkyl, aryl, heteroaryl, aryloxy, nitro, cyano, CO_2R^g, COR^g and $CONR^gR^h$, and wherein the wavy line indicates the point of attached to the ring bearing X through attachment to any available ring member in either ring of HAr. In preferred embodiments below, these substituents are provided as the group $-(R^4)_s$ wherein each R^4 is halogen, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_8)$heteroalkyl

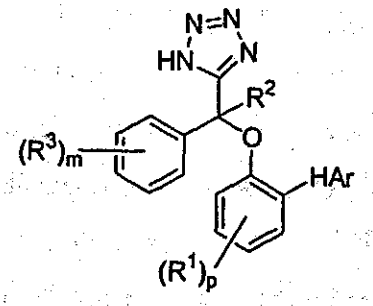
$(C_1$-$C_4)$alkoxy, $O(C_1$-$C_4)$haloalkyl, aryl$(C_1$-$C_4)$alkyl, aryl$(C_1$-$C_4)$haloalkyl, aryl, heteroaryl, aryloxy, nitro, cyano, CO_2R^g, COR^g and $CONR^gR^h$, and the subscipt s is an integer of from 0 to 3, indicating that the substituent is optional (s is 0) or present (s is 1, 2 or 3). When multiple substituents are present, each is selected independently of the others.

[0102] Turning next to other substituents of formula Ia and Ib, each R^3 is preferably, halogen, $(C_1$-$C_4)$alkyl, $O(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$haloalkyl, $O(C_1$-$C_4)$haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl or $S(O)_r$-phenyl and each R^1 is preferably halogen, $(C_1$-$C_4)$alkyl, $O(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$haloalkyl, $O(C_1$-$C_4)$haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl or $S(O)_r$-phenyl. More preferably, the subscript m is is an integer of from 0 to 2; each R^3 is independently selected from halogen, $(C_1$-$C_4)$alkyl, $O(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$haloalkyl, $O(C_1$-$C_4)$haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl or $S(O)_r$-phenyl; and the subscript p is an integer of from 0 to 2, with R^1 being independently selected from halogen, $(C_1$-$C_4)$alkyl, $O(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$haloalkyl, $O(C_1$-$C_4)$haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl or $S(O)_r$-phenyl.

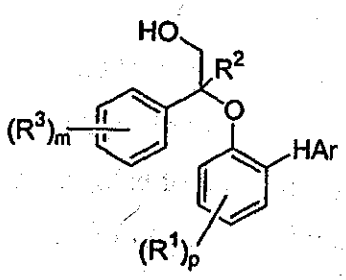
[0103] In a particularly preferred group of embodiments, the compounds have a formula selected from:





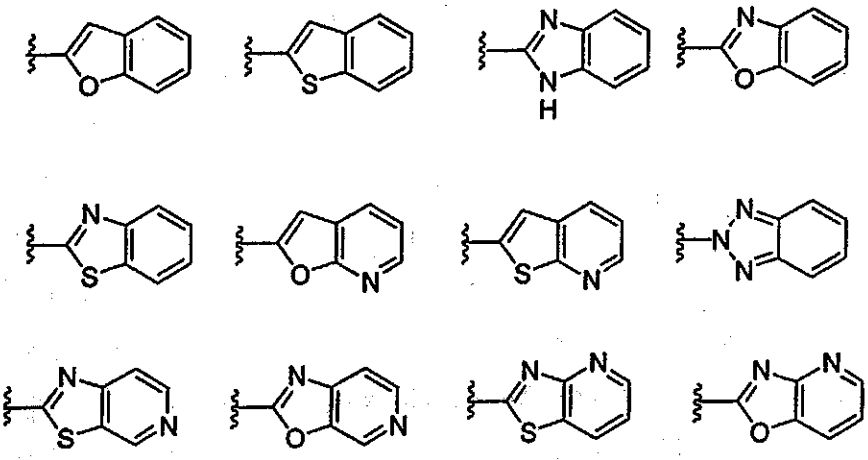


and



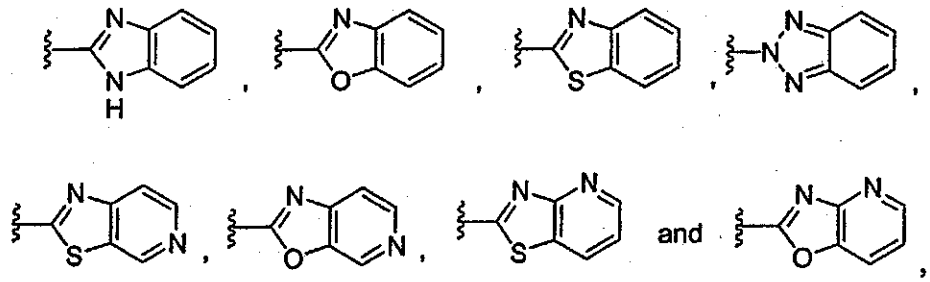
wherein the subscript m is an integer of from 0 to 2, the subscript p is an integer of from 0 to 2, and R^1 and R^3 are each independently selected from the group consisting of halogen, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$haloalkyl, $O(C_1$-$C_4)$haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl and $S(O)_r$-phenyl; and R^n is $(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$haloalkyl, aryl$(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$heteroalkyl, aryl, heteroaryl, $(C_1$-$C_8)$alkoxy, aryloxy, alkylamino, dialkylamino, arylamino, diarylamino, haloalkylamino and di(haloalkyl)amino.

[0104] Still further preferred are those embodiments in which HAr is selected from



wherein each of the HAr groups is optionally substituted with from one to three substituents independently selected from halogen, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_4)$haloalkyl, $O(C_1\text{-}C_4)$haloalkyl, nitro, cyano, CO_2R^g, COR^g and $CONR^gR^h$.

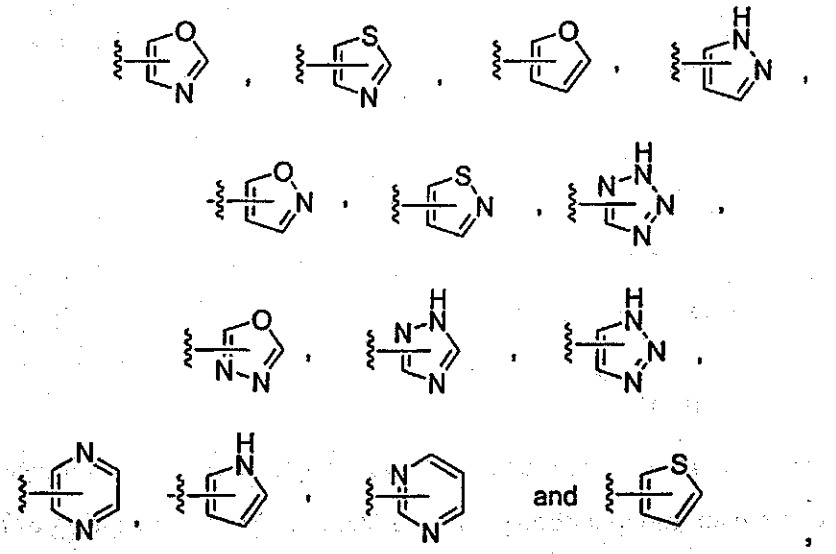
[0105] Even further preferred are those embodiments in which HAr is selected from



wherein each of the HAr groups is optionally substituted with from one to three substituents independently selected from the group consisting of halogen, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_4)$haloalkyl, $O(C_1\text{-}C_4)$haloalkyl, nitro, cyano, CO_2R^g, COR^g and $CONR^gR^h$. In certain most preferred embodiments, HAr is an optionally substituted 2-benzoxazolyl; R^2 is H or CH_3; the subscript m is 0 or 1, and p is 1 or 2; and R^1 and R^3 are each independently selected from the group consisting of halogen, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_4)$haloalkyl, $O(C_1\text{-}C_4)$haloalkyl, nitro, cyano, CO_2R^g, COR^g and $CONR^gR^h$. In other most preferred embodiments, HAr is an optionally substituted 2-benzothiazolyl; R^2 is H or CH_3; the subscript m is 0 or 1, and p is 1 or 2; and R^1 and R^3 are each independently selected from the group consisting of halogen, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_4)$haloalkyl, $O(C_1\text{-}C_4)$haloalkyl, nitro, cyano, CO_2R^g, COR^g and $CONR^gR^h$. In still other most preferred embodiments, HAr is an optionally substituted 2-benzotriazolyl; R^2 is H or CH_3; the subscript m is 0 or 1, and p is 1 or 2; and R^1 and R^3 are each independently selected from the group

consisting of halogen, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)haloalkyl, $O(C_1-C_4)$haloalkyl, nitro, cyano, CO_2R^g, COR^g and $CONR^gR^h$.

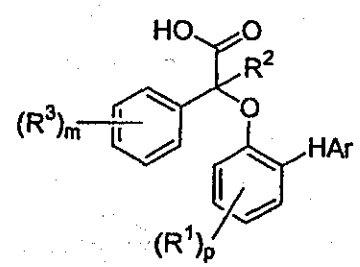
[0106] In a second group of embodiments, Y is CO_2R^c, a carboxylic acid surrogate or CH_2OR^c; HAr is a monocyclic heteroaryl moiety, wherein each of the HAr groups is optionally substituted with from one to three substituents independently selected from halogen, (C_1-C_4)alkyl, (C_1-C_8)heteroalkyl, (C_1-C_4)alkoxy, (C_1-C_4)haloalkyl, $O(C_1-C_4)$haloalkyl, aryl(C_1-C_4)alkyl, aryl, heteroaryl, nitro, cyano, CO_2R^g, COR^g and $CONR^gR^h$. In preferred embodiments below, these substituents are provided as the group $-(R^4)_s$ wherein each R^4 is selected from the group of substituents provided above, and the subscript s is an integer of from 0 to 3, indicating that the substituent is absent (s is 0) or present (s is 1, 2 or 3). When multiple substituents are present, each is selected independently of the others. Still further preferred, within this group of embodiments, are compounds wherein X is O, S or NH, with compounds in which R^2 is H, CH_3 or CF_3 being further preferred. Even further preferred are those compounds wherein HAr is attached to the 2- or 3-position of the phenyl ring bearing X and is selected from the group consisting of

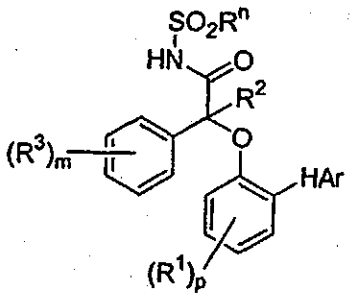


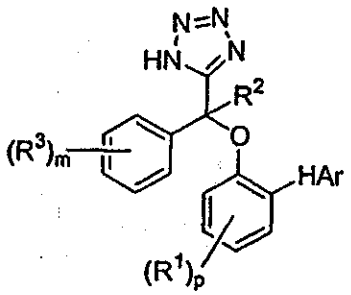
wherein each of said HAr groups is optionally substituted with from one to three substituents independently selected from the group consisting of halogen, (C_1-C_4)alkyl, (C_1-C_8)heteroalkyl, (C_1-C_4)alkoxy, (C_1-C_4)haloalkyl, $O(C_1-C_4)$haloalkyl, aryl(C_1-C_4)alkyl, aryl, heteroaryl, nitro, cyano, CO_2R^g, COR^g and $CONR^gR^h$, and the wavy line indicates the attachment to the ring bearing X. That is, HAr is preferably attached to a carbon atom directly adjacent to the sp^2-carbon bearing X (an *ortho*-position), or is attached to a carbon atom one place removed from the sp^2-carbon bearing X (a *meta*-position).

[0107] Turning next to other substituents of formula Ia and Ib, each R^3 is preferably, halogen, $(C_1\text{-}C_4)$alkyl, $O(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $O(C_1\text{-}C_4)$haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl or $S(O)_r$-phenyl and each R^1 is preferably halogen, $(C_1\text{-}C_4)$alkyl, $O(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $O(C_1\text{-}C_4)$haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl or $S(O)_r$-phenyl. More preferably, the subscript m is is an integer of from 0 to 2; each R^3 is independently selected from halogen, $(C_1\text{-}C_4)$alkyl, $O(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $O(C_1\text{-}C_4)$haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl or $S(O)_r$-phenyl; and the subscript p is an integer of from 0 to 2, with R^1 being independently selected from halogen, $(C_1\text{-}C_4)$alkyl, $O(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $O(C_1\text{-}C_4)$haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl or $S(O)_r$-phenyl.

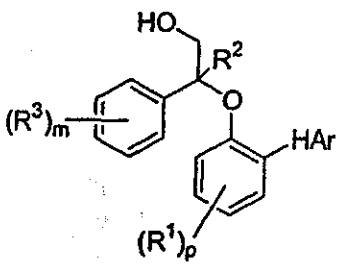
[0108] In a particularly preferred group of embodiments, the compounds have a formula selected from:





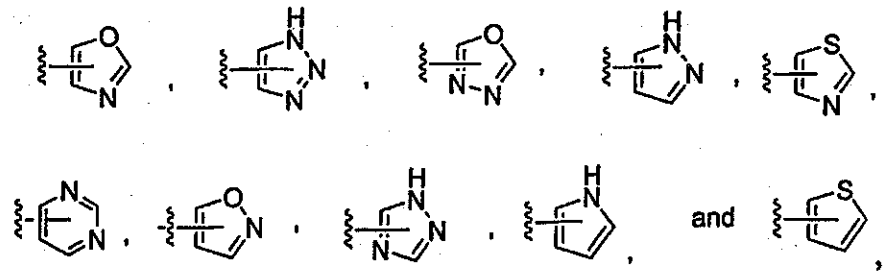


and



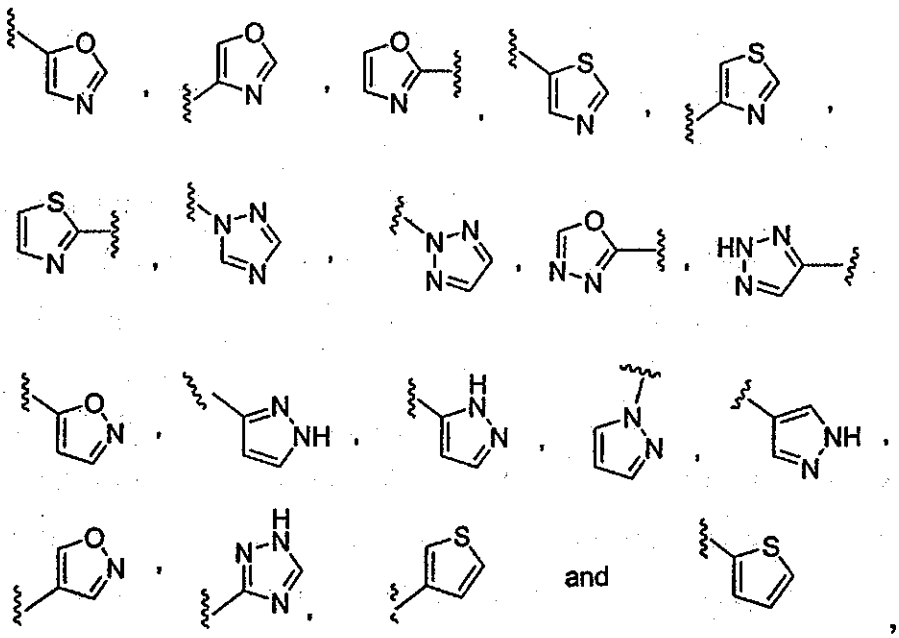
wherein the subscript m is an integer of from 0 to 2, the subscript p is an integer of from 0 to 2, and R^1 and R^3 are each independently selected from the group consisting of halogen, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_4)$haloalkyl, $O(C_1\text{-}C_4)$haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl and $S(O)_r$-phenyl; and R^n is $(C_1\text{-}C_8)$alkyl, $(C_1\text{-}C_8)$haloalkyl, aryl$(C_1\text{-}C_8)$alkyl, $(C_1\text{-}C_8)$heteroalkyl, aryl, heteroaryl, $(C_1\text{-}C_8)$alkoxy, aryloxy, alkylamino, dialkylamino, arylamino, diarylamino, haloalkylamino and di(haloalkyl)amino.

[0109] Still further preferred are those embodiments in which HAr is selected from



wherein each of the HAr groups is optionally substituted with from one to three substituents independently selected from halogen, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_8)$heteroalkyl, $(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_4)$haloalkyl, $O(C_1\text{-}C_4)$haloalkyl, aryl$(C_1\text{-}C_4)$alkyl, aryl, heteroaryl, nitro, cyano, CO_2R^g, COR^g and $CONR^gR^h$.

[0110] Even further preferred are those embodiments in which HAr is selected from the group consisting of



wherein each of the HAr groups is optionally substituted with from one to three substituents independently selected from halogen, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_8)$heteroalkyl, $(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_4)$haloalkyl, $O(C_1\text{-}C_4)$haloalkyl, aryl$(C_1\text{-}C_4)$alkyl, aryl, heteroaryl, nitro, cyano, CO_2R^g, COR^g and $CONR^gR^h$. In the most preferred embodiments, R^1 and R^3 are each independently selected from F, Cl, Br, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_4)$haloalkyl, $O(C_1\text{-}C_4)$haloalkyl, CN, NO_2 and phenyl. Within this most preferred group of embodiments, certain optionally substituted HAr groups are further preferred. In one of these groups HAr is optionally substituted 2-, 4- or 5-thiazolyl wherein the thiazolyl is optionally substituted with from one to two substituents selected from the group consisting of F, Cl, Br, $(C_1\text{-}C_4)$alkyl, aryl$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_4)$haloalkyl, $O(C_1\text{-}C_4)$haloalkyl, CN and phenyl; R^2 is H or

CH_3; the subscript m is 0 or 1 and p is 1 or 2; and R^1 and R^3 are each independently selected from the group consisting of F, Cl, Br, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)haloalkyl, O(C_1-C_4)haloalkyl, CN, NO_2 and phenyl. In another of these groups, HAr is selected from the group consisting of optionally substituted 1, 3, 4 or 5-pyrazolyl wherein the pyrazolyl is optionally substituted with from one to two substituents selected from the group consisting of F, Cl, Br, (C_1-C_4)alkyl, aryl(C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)haloalkyl, O(C_1-C_4)haloalkyl, CN and phenyl; R^2 is H or CH_3; the subscript m is 0 or 1 and p is 1 or 2; and R^1 and R^3 are each independently selected from the group consisting of F, Cl, Br, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)haloalkyl, O(C_1-C_4)haloalkyl, CN, NO_2 and phenyl. In still other groups, HAr is optionally substituted 2-, 4- or 5-oxazolyl wherein the oxazolyl is optionally substituted with from one to two substituents selected from the group consisting of F, Cl, Br, (C_1-C_4)alkyl, aryl(C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)haloalkyl, O(C_1-C_4)haloalkyl, CN and phenyl; R^2 is H or CH_3; the subscript m is 0 or 1 and p is 1 or 2; and R^1 and R^3 are each independently selected from the group consisting of F, Cl, Br, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)haloalkyl, O(C_1-C_4)haloalkyl, CN, NO_2 and phenyl.

[0111] Other preferred groups of embodiments are provided by each of formula IIa through IIam, in Figures 2, 3, and 4A, wherein each of R^c, R^1, R^2, R^3, R^4, R^5 and the subscripts m, p and s have the meanings provided above with regard to their most general embodiments. The group provided as R which is attached to nitrogen in certain formulae is intended to be H or another R^4 moiety that can be the same or different from the remaining R^4 moieties. Preferred members of R^c, R^1, R^3, R^4, and the subscripts m, p and s are those that are provided above as preferred for each of these groups with respect to the fused bicyclic HAr moieties. Further preferred for each of IIa through IIam are those compounds in which p is 0, 1 or 2; m is 0, 1, or 2; each R^1 and R^3 when present is selected from F, Cl, Br, (C_1-C_4)alkoxy, (C_1-C_4)alkyl, (C_1-C_4)haloalkyl, O(C_1-C_4)haloalkyl, CN and NO_2; s is 0 or 1; R^c is H or (C_1-C_4)alkyl; R^2 is H, CH_3 or CF_3. In the most preferred embodiments for each of IIa through IIam, p is 1 or 2, more preferably 1; m is 0, 1, or 2, more preferably 0 or 1; each R^1 and R^3 when present is selected from F, Cl, Br, CF_3 and OCH_3; s is 0 or 1; R^c is H; R^2 is H or CH_3.

[0112] Still other preferred groups of embodiments are provided by each of formula IIan through IIaz, in Figure 4B, wherein each of R^1, R^2, R^3, R^4 R^n and the subscripts m, p and s have the meanings provided above with regard to their most general embodiments. Preferred members of R^1, R^2, R^3, R^4, R^n and the subscripts m, p and s are those that are provided above for each of these groups with respect to the fused bicyclic HAr moieties. Further preferred for each of IIan through IIaz are those compounds in which p is 0, 1 or 2; m is 0, 1, or 2; each

R^1 and R^3 when present is selected from F, Cl, Br, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$alkyl, $O(C_1$-$C_4)$haloalkyl, $(C_1$-$C_4)$haloalkyl ,CN and NO_2; R^n is $(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$haloalkyl, aryl, alkylamino, dialkylamino or arylamino; s is 0 or 1; R^2 is H, CH_3 or CF_3. In the most preferred embodiments for each of IIan through IIaz, p is 1 or 2, more preferably 1; m is 0, 1, or 2, more preferably 0 or 1; each R^1 and R^3 when present is selected from F, Cl, Br, CF_3 and OCH_3; s is 0 or 1; R^2 is H or CH_3.

[0113] Still other preferred groups of embodiments are those having attached monocyclic heteroaryl groups as HAr in formula Ia and Ib and are provided by each of formula IIIa through IIIx, in Figures 5A and 5B, wherein each of R^c, R^1, R^2, R^3, R^4, and the subscripts m, p and s have the meanings provided above with regard to their most general embodiments. The group provided as R which is attached to nitrogen in certain formulae is intended to be H or another R^4 moiety that can be the same or different from the remaining R^4 moieties. Preferred members of R^c, R^1, R^2, R^3, R^4, and the subscripts m, p and s are those that are provided above for each of these groups with respect to monocyclic HAr moieties. Further preferred for each of IIIa through IIIx are those compounds in which p is 0, 1 or 2; m is 0, 1, or 2; each R^1 and R^3 when present is selected from F, Cl, Br, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$alkyl, $O(C_1$-$C_4)$haloalkyl, $(C_1$-$C_4)$haloalkyl, CN and NO_2; s is 0, 1 or 2; R^c is H or $(C_1$-$C_4)$alkyl; R^2 is H, CH_3 or CF_3. In the most preferred embodiments for each of IIIa through IIIx, p is 1 or 2, more preferably 1; m is 0, 1, or 2, more preferably 0 or 1; each R^1 and R^3 when present is selected from F, Cl, Br, CF_3 and OCH_3; s is 0, 1 or 2; R^c is H; R^2 is H or CH_3.

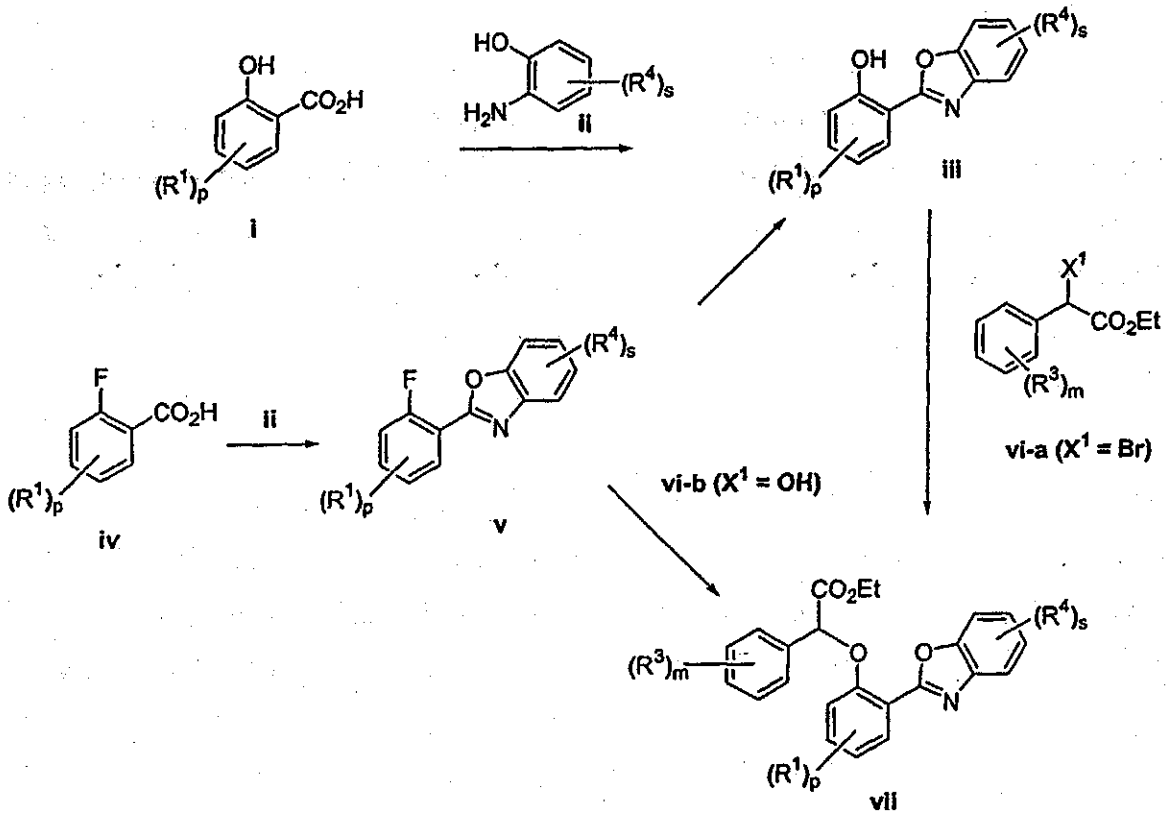
[0114] Still other preferred groups of embodiments are provided by each of formula IIIaa through IIIah in Figure 5C, wherein each of R^1, R^2, R^3, R^4 R^n and the subscripts m, p and s have the meanings provided above with regard to their most general embodiments. Preferred members of R^1, R^2, R^3, R^4, R^n and the subscripts m, p and s are those that are provided above for each of these groups with respect to the monocyclic HAr moieties. Further preferred for each of IIIaa through IIIah are those compounds in which p is 0, 1 or 2; m is 0, 1, or 2; each R^1 and R^3 when present is selected from F, Cl, Br, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$alkyl, $O(C_1$-$C_4)$haloalkyl, $(C_1$-$C_4)$haloalkyl, CN and NO_2; R^n is $(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$haloalkyl, aryl, alkylamino, dialkylamino, arylamino and diarylamino; s is 0, 1 or 2; and R^2 is H, CH_3 or CF_3. In the most preferred embodiments for each of IIIaa through IIIah, p is 1 or 2, more preferably 1; m is 0, 1, or 2, more preferably 0 or 1; each R^1 and R^3 when present is selected from F, Cl, Br, CF_3 and OCH_3; s is 0, 1 or 2; and R^2 is H or CH_3.

[0115] Still other preferred groups of embodiments are provided in the Examples and Tables below.

General Synthetic Routes to Compounds of the Invention

[0116] The compounds of the present invention can be prepared using methods generally outlined in Schemes 1-5.

Scheme 1

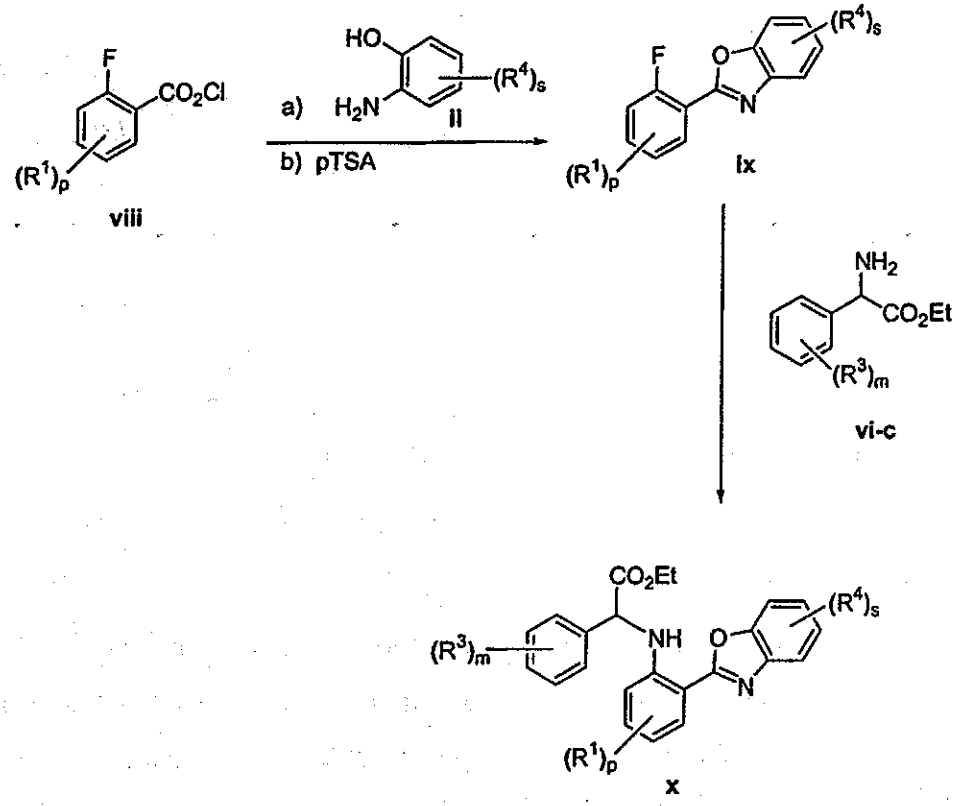


[0117] According to Scheme 1, salicylic acids of formula **i** (either commercially available or prepared according to known methods) are condensed with suitably substituted 2-aminophenols (**ii**) to provide a 2-(benzoxazol-2-yl)phenol (**iii**). Treatment of **iii** with a suitably substituted ethyl 2-bromophenylacetate (**vi-a**), generally in the presence of a base such as potassium carbonate, provides the target compound **vii**. Alternatively, 2-fluorobenzoic acids (**iv**) can be converted to the corresponding derivatives **v** which can then be converted to **iii** and carried on through the scheme as noted, or, in certain embodiments, compounds of formula **v** can be converted directly into target compounds **vii** using 2-hydroxyphenylacetic acid derivatives (**vi-b**). The latter route is particularly useful for the compounds of formula **vii** in which R^1 substituents increase the reactivity of the ring toward fluorine displacement. Additionally, in the above Scheme as well as in Formulae II and III, below, each R^4 (the subscript s being an integer of from 0 to 4), is meant to include any of the HAr substituents provided above.

[0118] Structural isomers, having the benzoxazolyl ring attached at either the 3-position or the 4-position relative to the phenolic hydroxy group in compound **iii** can be prepared from the corresponding 3-hydroxybenzoic acids and 4-hydroxybenzoic acids.

[0119] In a similar manner, compounds of formula Ia wherein X is NH can be prepared as follows.

Scheme 2

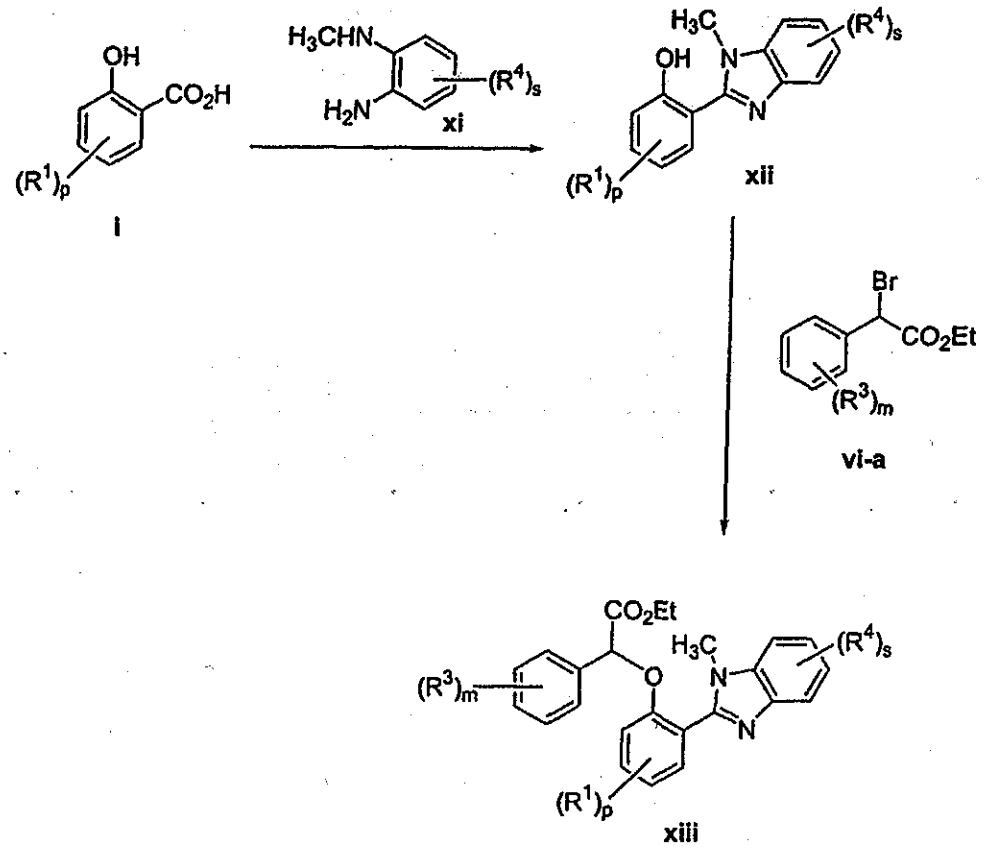


[0120] Here, a 2-fluorobenzoic acid or benzoyl chloride (**viii**) serves as the starting material. The acid chloride is treated with 2-aminophenols (**ii**) to provide substituted aryl fluorides, **ix**. Treatment of **ix** with the suitably substituted ethyl 2-aminophenylacetate (**vi-c**) provides the target compound **x**.

[0121] Still further, the general schemes outlined in Scheme 1 and Scheme 2 can be used to prepare compounds of Formula Ia in which HAr is benzothiazolyl. To obtain these compounds, the 2-aminophenols (**ii**) are replaced by the corresponding 2-aminothiophenols. More specific details are provided in the examples below.

[0122] Preparation of compounds of Formula Ia in which HAr is a suitably substituted benzimidazole can be prepared according to the general methods outlined in Scheme 3.

Scheme 3

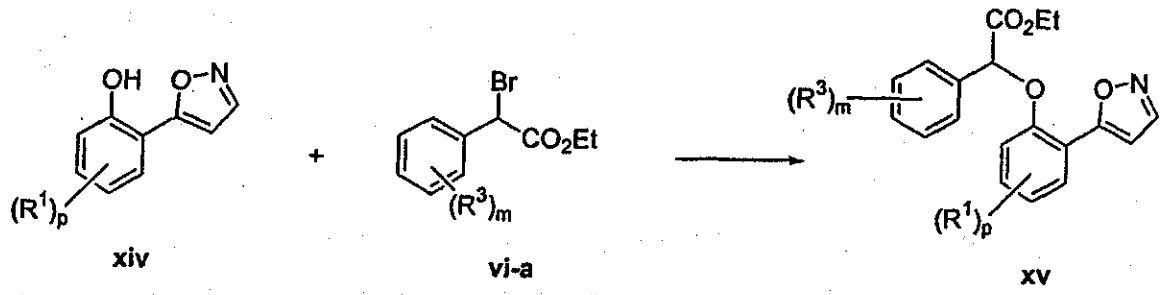


[0123] In Scheme 3, salicylic acid derivatives of formula **i** are condensed with N-methyl-1,2-phenylenediamine derivatives (**xi**) to provide benzimidazolyl-substituted phenols of formula **xii**. Conversion of **xii** to the desired products (**xiii**) can be accomplished using suitably substituted ethyl 2-bromophenylacetate (**vi-a**, in Scheme 1). Additionally, while the synthetic route is illustrated for the preparation of N-methyl benzimidazole compounds, the invention is not so limited and derivatives are contemplated wherein the N-methyl is replaced by hydrogen or by other (C_1-C_8)alkyl groups.

[0124] In each of Schemes 1, 2 and 3, the position of the heteroaryl ring portion can be changed depending on the starting benzoic acids **i** and **viii**.

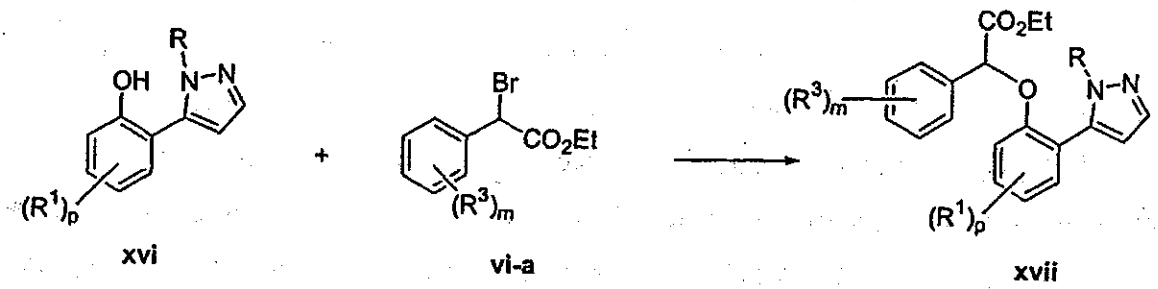
[0125] Related compounds can be prepared in a similar manner beginning with, for example, appropriately substituted 2-(5-isoxazolyl)phenols, many of which are available from commercial sources or can be prepared according to literature methods (see Scheme 4).

Scheme 4



[0126] Similarly, compounds of Formula Ia in which HAr is a pyrazolyl group can be prepared from the corresponding pyrazolylphenols (see Scheme 5).

Scheme 5



[0127] In each of Scheme 1-5, reaction conditions (e.g., amounts of reactants, solvents, temperatures and workup conditions) can be selected using the Examples below as a guide.

Preparation of alcohols, esters and aldehydes

[0128] The above general synthesis schemes are provided to illustrate the prepared of compounds of Formula Ia or Ib in which Y is a carboxylic acid or ester. Conversion of each of these groups into the corresponding alcohols, ethers, or aldehydes can be accomplished using methods generally known to one of skill in the art. Several methods for reduction (and oxidation) are provided below as illustrative of the processess to used in preparing additional compounds of the invention.

Conversion of carboxylic acids into aldehydes, carbinols and carbinol esters.

[0129] The carboxylic acids of this invention can be converted into the corresponding aldehydes, carbinols and carbinol esters by a number of methods, including the routes A-E shown in **Scheme 6**. The method to be used in a given case depends on the nature of R, and

the substituents thereon. A variety of useful methods are described in Larock, COMPREHENSIVE ORGANIC TRANSFORMATIONS, VCH Publishers Inc, New York (1989). In particular, methods are described for converting acyl chlorides **2** to aldehydes **3** (p 620), aldehydes **3** to carbinols **4** (p 528ff), esters **5** to aldehydes **3** (p 621), esters **5** to carbinols **4** (p 549), carboxylic acids **1** to carbinols **4** (p 548), carbinols **4** to aldehydes **3** (p 604) and carbinols **4** to esters **6** (p 966).

[0130] In method A, Scheme 6, the carboxylic acid **1** is first converted into the corresponding acid chloride **2**. This transformation is effected by reacting the acid **1** with oxalyl chloride, phosphorus pentachloride, or, preferably, thionyl chloride. The reaction is conducted in an aprotic solvent such as dichloromethane, tetrahydrofuran or, preferably, 1,2-dichloroethane. The acid chloride **2** is then converted into the aldehyde **3** by chemical reduction, such as by the use of sodium borohydride in DMF at -70°C, as described in *Tetrahedron Lett.* **22**:11 (1981), or, more preferably by hydrogenation using 5% palladium on barium sulfate as catalyst (see, for example, *J. Amer. Chem. Soc.*, **108**:2608 (1986)). The reaction is conducted in an aprotic solvent such as toluene or, preferably, xylene. The aldehyde **3** is converted into the carbinol **4** by reduction, for example by reaction with 9-BBN, lithium aluminum tritertiarybutoxy hydride, or more preferably sodium borohydride, (see, *J. Amer. Chem. Soc.* **71**:122 (1949)). The reaction is conducted in a protic solvent such as ethanol, or preferably, isopropanol.

[0131] In method B, Scheme 6, the carboxylic acid is first converted into an ester **5**, in which R^1 is lower alkyl. This conversion is effected by reacting the acid with a diazoalkane such as diazomethane, or preferably, with a lower alkanol, such as ethanol, in the presence of an acid catalyst. The ester **5** is then converted into the aldehyde **3** by reduction, for example, by the use of sodium aluminum hydride or preferably, diisobutyl aluminum hydride (see, for example, *Synthesis*, 617 (1975)). The reaction is conducted in a non-polar solvent such as benzene or, preferably, toluene.

[0132] The ester **5** is converted into the carbinol **4** by reduction with lithium aluminum hydride or, preferably, with lithium borohydride (see, *J. Amer. Chem. Soc.*, **109**:1186 (1987)). The reaction is conducted in an ethereal solvent such as dioxan or, preferably, tetrahydrofuran.

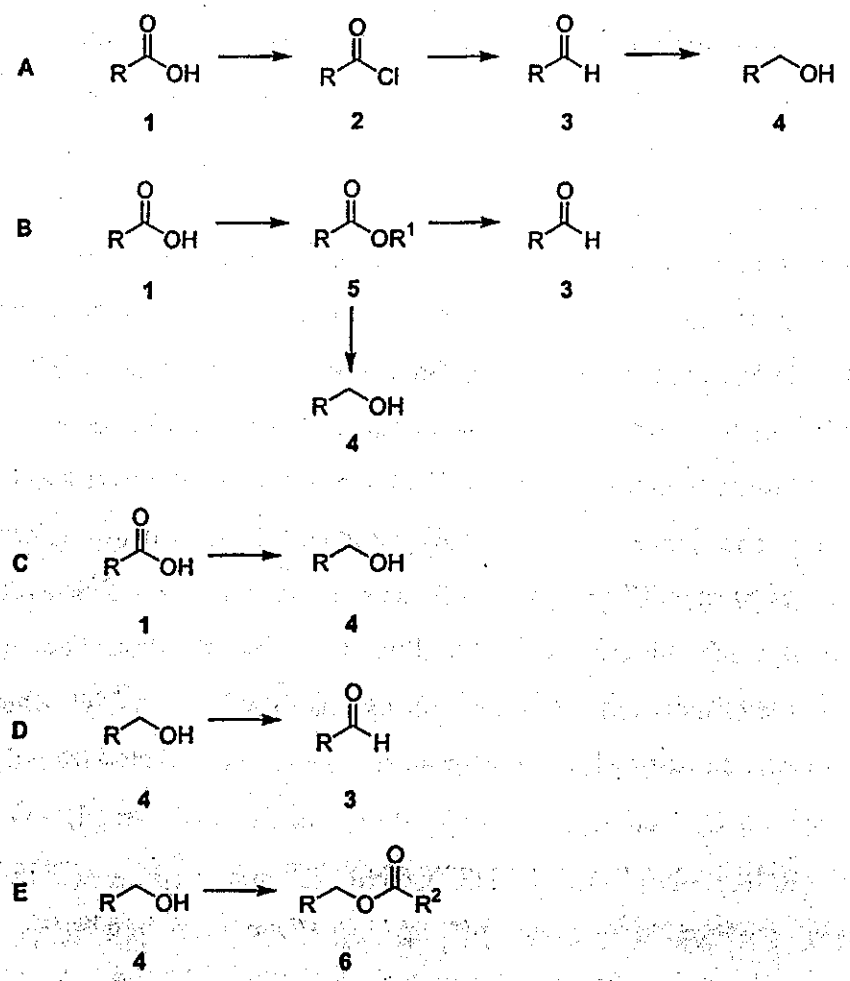
[0133] In method C, Scheme 6, the carboxylic acid **1** is converted into the carbinol **4**. This conversion is effected by reacting the carboxylic acid with a reducing agent such as lithium aluminum hydride or, preferably, with diborane, as described in ORGANIC SYNTHESES,

64:104 (1985). The reaction is conducted in an ethereal solvent such as dioxan or, preferably, tetrahydrofuran.

[0134] In method D, Scheme 6, the carbinol **4** is converted into the aldehyde **3**. This conversion is effected by reacting the carbinol with an oxidizing agent such as dicyclohexylcarbodiimide/dimethylsulfoxide, or, preferably, with pyridinium chlorochromate, as described in *Synthesis*, 245 (1982). The reaction is conducted in an aprotic solvent such as dichloromethane or, preferably, 1,2-dichloroethane, optionally in the presence of celite, as described in J. Org. Chem., 50:2626 (1985).

[0135] In method E, Scheme 6, the carbinol **4** is converted into the ester **6**. This transformation is effected by an esterification reaction, for example by reacting the carbinol **4** with a carboxylic anhydride $(R^2CO)_2O$, or, preferably, with an acyl chloride R^2COCl. The reaction is conducted in an aprotic solvent such as dichloromethane or, preferably, tetrahydrofuran, in the presence of an organic base such as triethylamine or, preferably, pyridine.

Scheme 6



Resolution of isomers (enantiomers)

[0136] For many compounds of the present invention, a single chiral center is present (at the carbon atom bearing R^2), resulting in racemic mixtures of enantiomers. As noted above, the present invention further includes compounds, compositions and methods wherein a single isomer (or single enantiomer) is provided or used. Methods of preparing chiral compounds are provided in the Examples. Alternatively, mixtures of enantiomers can be separated into their individual isomers via methods such as salt formation and crystallization with chiral bases, chiral chromatography (e.g., hplc using commercially available columns for chiral resolution) and via methods such as simulated moving bed chromatography (see, for example, U.S. Patent No. 5,518,625).

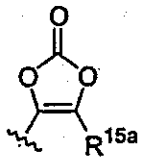
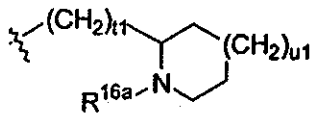
[0137] In certain preferred embodiments of the invention, the (-)-isomer of the compound of formula Ia or Ib is used, which is substantially free of its (+)-isomer. In this context, "substantially free" refers to a compound that is contaminated by less than about 20%, more preferably 10%, still more preferably 5%, even more preferably 2% and most preferably less than about 1% of the undesired isomer. In other preferred embodiments of the invention, the (+)-isomer of the compound of formula Ia or Ib is used, which is substantially free of its (-)-isomer.

Prodrug forms of the Compounds of the Invention

[0138] In some embodiments, the compounds of the invention are present in a prodrug form. In particular, the invention also provides, for example, compounds of Formula Ia or Ib in which Y is $-CO_2H$ which has been esterified to form $-CO_2R''$, wherein R" is selected from alkyl, heteroalkyl, aryl, heteroaryl, phenyl-lower alkyl, benzamido-lower alkyl, di-lower alkylamino-lower alkyl, ureido-lower alkyl, N'-lower alkyl-ureido-lower alkyl, carbamoyl-lower alkyl, halophenoxy substituted lower alkyl and carbamoyl substituted phenyl.

[0139] Examples of such R" groups include, without limitation, the following: C_1-C_5 alkyl, C_1-C_8-cyclic alkyl, C_2-C_5 alkenyl, and C_2-C_5 alkynyl, wherein the groups are optionally substituted with one or more halogen atoms; phenyl, naphthyl and pyridyl, wherein the groups are optionally substituted with one or more substituents selected from the group consisting of halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-NO_2$, $-S(O)_{m1}(C_1$-C_5alkyl), $-OH$, $-NR^{3a}R^{4a}$, $-CO_2R^{5a}$, $-CONR^{3a}R^{4a}$, $-NR^{3a}COR^{4a}$, $-NR^{3a}CONR^{3a}R^{4a}$ and $-C_{v1}F_{w1}$; $-(CHR^{3a})R^{4a}$; $-R^{5a}OR^{3a}$; $-R^{5a}O_2CR^{6a}NR^{3a}R^{4a}$; $-R^{8a}COR^{6a}$; $-R^{7a}NR^{3a}COR^{4a}$; $-R^{7a}NR^{3a}R^{4a}$; $-(CH_2)_{o1}CH(R^{3a})(CH_2)_{q1}O_2CR^{9a}$; $-(CH_2)_{o1}CH(R^{3a})(CH_2)_{q1}NR^{4a}COR^{9a}$;

$-(CH_2)_{o1}CH(R^{3a})(CH_2)_{q1}NR^{4a}CONR^{3a}R^{4a}$; $-(CH_2)_{o1}CH(R^{3a})(CH_2)_{q1}NR^{4a}COOR^{10a}$; $-(CH_2)_{o1}CH(R^{3a})(CH_2)_{q1}NR^{4a}SO_2R^{11a}$; $-(CHR^{3a})_{p1}CO_2R^{12a}$; $-(CHR^{3a})_{p1}NR^{3a}R^{4a}$; $-(CHR^{3a})_{s1}CONR^{13a}R^{14a}$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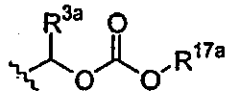
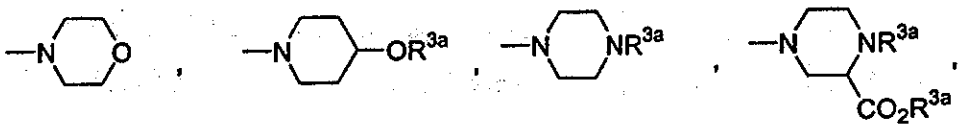
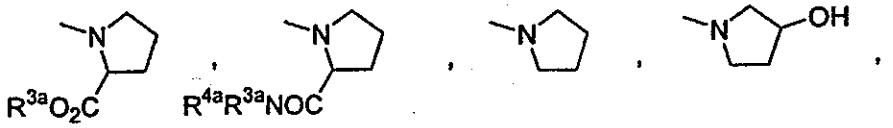
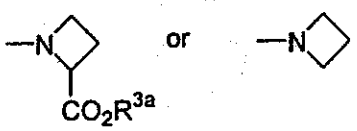


Subscripts m1, o1, q1, s1, t1, u1, v1 and w1 are integers as follows: m1 is 0 to 2; o1 and q1 are 0 to 5; p1 is 1 to 5; s1 is 1 to 3; t1 is 1 to 5; u1 is 0 to 1; v1 is 1 to 3; and w1 is 1 to (2v1 + 1). R^{3a} and R^{4a} are independently H, C_1-C_5 alkyl, phenyl or benzyl. R^{5a} is H, C_1-C_5 alkyl or $NR^{3a}R^{4a}$. R^{6a} is phenyl, naphthyl, pyridyl, imidazolyl, indoxyl, indolizinyl, oxazolyl, thiazolyl, thienyl, pyrimidyl, or 1-pyrazolyl optionally substituted with one or more substituents selected from the group consisting of halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-NO_2$, $-S(O)_{m1}(C_1$-C_5alkyl), $-OH$, $-NR^{3a}R^{4a}$, $-CO_2R^{5a}$, $-CONR^{3a}R^{4a}$, $-NR^{3a}COR^{4a}$, $-NR^{3a}CONR^{3a}R^{4a}$ and $-C_{v1}F_{w1}$. R^{7a} is a C_1-C_8 saturated or unsaturated, straight-chain, branched or cyclic alkylene or alkylidene group optionally substituted with one or more groups selected from halo, hydroxyl, thiol, amino, monoalkyl amino, dialkyl amino, acylamino, carboxyl, alkylcarboxyl, acyl, aryl, aroyl, aralkyl, cyano, nitro, alkoxy, alkenyloxy, alkylcarbonyloxy and arylcarbonyloxy. R^{8a} is a C_1-C_8 straight-chain or branched alkylene or alkylidene optionally substituted with one or more groups selected from amino, monoalkyl amino, dialkyl amino, acylamino, hydroxyl, thiol, methylthiol, carboxyl and phenyl. R^{9a} and R^{10a} are independently H, C_1-C_5 alkyl, optionally substituted with one or more groups consisting of C_1-C_5 alkoxy, aryl and heteroaryl, wherein the aryl is phenyl or naphthyl optionally substituted with one or more substituents selected from the group consisting of halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-NO_2$, $-S(O)_{m1}(C_1$-C_5alkyl), $-OH$, $-NR^{3a}R^{4a}$, $-CO_2R^{5a}$, $-CONR^{3a}R^{4a}$, $-NR^{3a}COR^{4a}$, $-NR^{3a}CONR^{3a}R^{4a}$ and $-C_{v1}F_{w1}$, and wherein the heteroaryl is pyridyl optionally substituted with one or more substituents selected from the group consisting of halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-NO_2$, $-S(O)_{m1}(C_1$-C_5alkyl), $-OH$, $-NR^{3a}R^{4a}$, $-CO_2R^{5a}$, $-CONR^{3a}R^{4a}$, $-NR^{3a}COR^{4a}$, $-NR^{3a}CONR^{3a}R^{4a}$ and $-C_{v1}F_{w1}$. R^{11a} is methyl or phenyl, wherein the phenyl is optionally substituted with methyl and/or $-NO_2$. R^{12a} is H, C_1-C_5 alkyl, phenyl, benzyl, naphthyl or pyridyl, wherein the C_1-C_5 alkyl, phenyl, naphthyl, benzyl and pyridyl are optionally substituted with one or more substituents selected from the group consisting of halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-NO_2$, $-S(O)_{m1}(C_1$-C_5alkyl),

$-OH$, $-NR^{3a}R^{4a}$, $-CO_2R^{5a}$, $-CONR^{3a}R^{4a}$, $-NR^{3a}COR^{4a}$, $-NR^{3a}CONR^{3a}R^{4a}$ and $-C_{v1}F_{w1}$. R^{13a} and R^{14a} are independently the following: alkyl, alkenyl, aryl, aralkyl or cycloalkyl, wherein the groups are optionally substituted with one or more substituents selected from the group consisting of halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-NO_2$, $-S(O)_{m1}(C_1$-C_5alkyl), $-OH$, $-NR^{3a}R^{4a}$, $-CO_2R^{5a}$, $-CONR^{3a}R^{4a}$, $-NR^{3a}COR^{4a}$, $-NR^{3a}CONR^{3a}R^{4a}$, $-CH_2NR^{3a}R^{4a}$, $OOCR^{18a}$ and $-C_{v1}F_{w1}$; and wherein R^{13a} and R^{14a} are included as $-(CHR^{3a})CONR^{13a}R^{14a}$ wherein $NR^{13a}R^{14a}$ is







[0140] R^{15a} is $C_{v1}F_{w1}$ or C_1-C_5 alkyl, wherein C_1-C_5 alkyl is optionally substituted with the following substituents: C_1-C_5 alkoxy; phenyl, optionally substituted with one or more substituents selected from the group consisting of halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-NO_2$, $-S(O)_{m1}(C_1$-C_5alkyl), $-OH$, $-NR^{3a}R^{4a}$, $-CO_2R^{5a}$, $-CONR^{3a}R^{4a}$, $-NR^{3a}COR^{4a}$, $-NR^{3a}CONR^{3a}R^{4a}$ and $-C_{v1}F_{w1}$; benzyl, optionally substituted with one or more substituents selected from the group consisting of halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-NO_2$, $-S(O)_{m1}(C_1$-C_5alkyl), $-OH$, $-NR^{3a}R^{4a}$, $-CO_2R^{5a}$, $-CONR^{3a}R^{4a}$, $-NR^{3a}COR^{4a}$, $-NR^{3a}CONR^{3a}R^{4a}$ and $-C_{v1}F_{w1}$. R^{16a} is H, C_1-C_5 alkyl or benzyl. R^{17a} is C_1-C_5 alkyl, C_3-C_8 cyclic alkyl, phenyl or benzyl. R^{18a} is H, alkyl, aryl, aralkyl or cycloalkyl, where the group is optionally substituted with one or more substituents selected from the group consisting of halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-NO_2$, $-S(O)_{m1}(C_1$-C_5alkyl), $-OH$, $-NR^{3a}R^{4a}$, $-CO_2R^{5a}$, $-CONR^{3a}R^{4a}$, $-NR^{3a}COR^{4a}$, $-NR^{3a}CONR^{3a}R^{4a}$ and $-C_{v1}F_{w1}$.

Pharmaceutical Compositions and Methods of Treating Diseases and Conditions

[0141] In accordance with the present invention, a therapeutically effective amount of a compound of Formula Ia or Ib can be used for the preparation of a pharmaceutical composition useful for treating diabetes, treating hyperlipidemia, treating hyperuricemia, treating obesity, lowering triglyceride levels, lowering cholesterol levels, raising the plasma level of high density lipoprotein, and for treating, preventing or reducing the risk of developing atherosclerosis.

[0142] The compositions of the invention can include compounds of Formula Ia or Ib, pharmaceutically acceptable salts thereof, or a hydrolyzable precursor thereof. In general, the compound is mixed with suitable carriers or excipient(s) in a therapeutically effective amount. By a "therapeutically effective dose", "therapeutically effective amount", or, interchangeably, "pharmacologically acceptable dose" or "pharmacologically acceptable amount", it is meant that a sufficient amount of the compound of the present invention and a pharmaceutically acceptable carrier, will be present in order to achieve a desired result, *e.g.*, alleviating a symptom or complication of Type 2 diabetes.

[0143] The compounds of Formula Ia or Ib that are used in the methods of the present invention can be incorporated into a variety of formulations for therapeutic administration. More particularly, the compounds of Formula Ia or Ib can be formulated into pharmaceutical compositions by combination with appropriate, pharmaceutically acceptable carriers or diluents, and can be formulated into preparations in solid, semi-solid, liquid or gaseous forms, such as tablets, capsules, pills, powders, granules, dragees, gels, slurries, ointments, solutions, suppositories, injections, inhalants and aerosols. As such, administration of the compounds can be achieved in various ways, including oral, buccal, rectal, parenteral, intraperitoneal, intradermal, transdermal, intratracheal administration. Moreover, the compound can be administered in a local rather than systemic manner, in a depot or sustained release formulation. In addition, the compounds can be administered in a liposome.

[0144] The compounds of Formula Ia or Ib can be formulated with common excipients, diluents or carriers, and compressed into tablets, or formulated as elixirs or solutions for convenient oral administration, or administered by the intramuscular or intravenous routes. The compounds can be administered transdermally, and can be formulated as sustained release dosage forms and the like. Compounds of Formula Ia or Ib can be administered alone, in combination with each other, or they can be used in combination with other known compounds (see *Combination Therapy* below).

[0145] Suitable formulations for use in the present invention are found in *Remington's Pharmaceutical Sciences* (Mack Publishing Company (1985) Philadelphia, PA, 17th ed.), which is incorporated herein by reference. Moreover, for a brief review of methods for drug delivery, *see*, Langer, *Science* (1990) 249:1527-1533, which is incorporated herein by reference. The pharmaceutical compositions described herein can be manufactured in a manner that is known to those of skill in the art, *i.e.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes. The following methods and excipients are merely exemplary and are in no way limiting.

[0146] For injection, the compounds can be formulated into preparations by dissolving, suspending or emulsifying them in an aqueous or nonaqueous solvent, such as vegetable or other similar oils, synthetic aliphatic acid glycerides, esters of higher aliphatic acids or propylene glycol; and if desired, with conventional additives such as solubilizers, isotonic agents, suspending agents, emulsifying agents, stabilizers and preservatives. Preferably, the compounds of the present invention can be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

[0147] For oral administration, the compounds of Formula Ia or Ib can be formulated readily by combining with pharmaceutically acceptable carriers that are well known in the art. Such carriers enable the compounds to be formulated as tablets, pills, dragees, capsules, emulsions, lipophilic and hydrophilic suspensions, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by mixing the compounds with a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents can be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[0148] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions can be used, which can optionally contain gum arabic, talc, polyvinyl

pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments can be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0149] Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds can be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers can be added. All formulations for oral administration should be in dosages suitable for such administration.

[0150] For buccal administration, the compositions can take the form of tablets or lozenges formulated in conventional manner.

[0151] For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas, or from propellant-free, dry-powder inhalers. In the case of a pressurized aerosol the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, *e.g.*, gelatin for use in an inhaler or insufflator can be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[0152] The compounds can be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection can be presented in unit dosage form, *e.g.*, in ampules or in multidose containers, with an added preservative. The compositions can take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and can contain formulator agents such as suspending, stabilizing and/or dispersing agents.

[0153] Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds can be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions can contain

substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension can also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, the active ingredient can be in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

[0154] The compounds can also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter, carbowaxes, polyethylene glycols or other glycerides, all of which melt at body temperature, yet are solidified at room temperature.

[0155] In addition to the formulations described previously, the compounds can also be formulated as a depot preparation. Such long acting formulations can be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds can be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[0156] Alternatively, other delivery systems for hydrophobic pharmaceutical compounds can be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. In a presently preferred embodiment, long-circulating, *i.e.*, stealth liposomes can be employed. Such liposomes are generally described in Woodle, *et al.*, U.S. Patent No. 5,013,556. The compounds of the present invention can also be administered by controlled release means and/or delivery devices such as those described in U.S. Pat. Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719.

[0157] Certain organic solvents such as dimethylsulfoxide (DMSO) also can be employed, although usually at the cost of greater toxicity. Additionally, the compounds can be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various types of sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules can, depending on their chemical nature, release the compounds for a few hours up to over 100 days.

[0158] The pharmaceutical compositions also can comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

[0159] Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in a therapeutically effective amount. The amount of composition administered will, of course, be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration and the judgment of the prescribing physician. Determination of an effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

[0160] For any compound used in the method of the present invention, a therapeutically effective dose can be estimated initially from cell culture assays or animal models.

[0161] Moreover, toxicity and therapeutic efficacy of the compounds described herein can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, by determining the LD_{50}, (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effect is the therapeutic index and can be expressed as the ratio between LD_{50} and ED_{50}. Compounds which exhibit high therapeutic indices are preferred. The data obtained from these cell culture assays and animal studies can be used in formulating a dosage range that is not toxic for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage can vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (*See, e.g.*, Fingl *et al.* 1975 In: *The Pharmacological Basis of Therapeutics*, Ch. 1).

[0162] The amount of active compound that can be combined with a carrier material to produce a single dosage form will vary depending upon the disease treated, the mammalian species, and the particular mode of administration. However, as a general guide, suitable unit doses for the compounds of the present invention can, for example, preferably contain between 100 mg to about 3000 mg of the active compound. A preferred unit dose is between 500 mg to about 1500 mg. A more preferred unit dose is between 500 to about 1000 mg. Such unit doses can be administered more than once a day, for example 2, 3, 4, 5 or 6 times a day, but preferably 1 or 2 times per day, so that the total daily dosage for a 70 kg adult is in the range of 0.1 to about 250 mg per kg weight of subject per administration. A preferred dosage is 5 to about 250 mg per kg weight of subject per administration, and such therapy can extend for a number of weeks or months, and in some cases, years. It will be understood, however, that the specific dose level for any particular patient will depend on a variety of

factors including the activity of the specific compound employed; the age, body weight, general health, sex and diet of the individual being treated; the time and route of administration; the rate of excretion; other drugs which have previously been administered; and the severity of the particular disease undergoing therapy, as is well understood by those of skill in the area.

[0163] A typical dosage can be one 10 to about 1500 mg tablet taken once a day, or, multiple times per day, or one time-release capsule or tablet taken once a day and containing a proportionally higher content of active ingredient. The time-release effect can be obtained by capsule materials that dissolve at different pH values, by capsules that release slowly by osmotic pressure, or by any other known means of controlled release.

[0164] It can be necessary to use dosages outside these ranges in some cases as will be apparent to those skilled in the art. Further, it is noted that the clinician or treating physician will know how and when to interrupt, adjust, or terminate therapy in conjunction with individual patient response.

Combination Therapy

[0165] As noted above, the compounds of the present invention will, in some instances, be used in combination with other therapeutic agents to bring about a desired effect. Selection of additional agents will, in large part, depend on the desired target therapy (*see, e.g.*, Turner, N. *et al. Prog. Drug Res.* (1998) 51: 33-94; Haffner, S. *Diabetes Care* (1998) 21: 160-178; and DeFronzo, R. *et al.* (eds.), *Diabetes Reviews* (1997) Vol. 5 No. 4). A number of studies have investigated the benefits of combination therapies with oral agents (*see, e.g.*, Mahler, R., *J. Clin. Endocrinol. Metab.* (1999) 84: 1165-71; United Kingdom Prospective Diabetes Study Group: UKPDS 28, *Diabetes Care* (1998) 21: 87-92; Bardin, C. W.,(ed.), CURRENT THERAPY IN ENDOCRINOLOGY AND METABOLISM, 6th Edition (Mosby - Year Book, Inc., St. Louis, MO 1997); Chiasson, J. *et al.*, *Ann. Intern. Med.* (1994) 121: 928-935; Coniff, R. *et al.*, *Clin. Ther.* (1997) 19: 16-26; Coniff, R. *et al.*, *Am. J. Med.* (1995) 98: 443-451; and Iwamoto, Y. *et al.*, *Diabet. Med.* (1996) 13 365-370; Kwiterovich, P. *Am. J. Cardiol* (1998) 82(12A): 3U-17U). These studies indicate that diabetes and hyperlipidemia modulation can be further improved by the addition of a second agent to the therapeutic regimen. Combination therapy includes administration of a single pharmaceutical dosage formulation which contains a compound having the general structure of Formula Ia or Ib and one or more additional active agents, as well as administration of a compound of Formula Ia or Ib and each active agent in its own separate pharmaceutical dosage formulation. For example, a compound of Formula

Ia or Ib and an HMG-CoA reductase inhibitor can be administered to the human subject together in a single oral dosage composition, such as a tablet or capsule, or each agent can be administered in separate oral dosage formulations. Where separate dosage formulations are used, a compound of Formula Ia or Ib and one or more additional active agents can be administered at essentially the same time (*i.e.*, concurrently), or at separately staggered times (*i.e.*, sequentially). Combination therapy is understood to include all these regimens.

[0166] An example of combination therapy that modulates (prevents the onset of the symptoms or complications associated) atherosclerosis, wherein a compound of Formula Ia or Ib is administered in combination with one or more of the following active agents: an antihyperlipidemic agent; a plasma HDL-raising agent; an antihypercholesterolemic agent, such as a cholesterol biosynthesis inhibitor, *e.g.*, an hydroxymethylglutaryl (HMG) CoA reductase inhibitor (also referred to as statins, such as lovastatin, simvastatin, pravastatin, fluvastatin, and atorvastatin), an HMG-CoA synthase inhibitor, a squalene epoxidase inhibitor, or a squalene synthetase inhibitor (also known as squalene synthase inhibitor); an acyl-coenzyme A cholesterol acyltransferase (ACAT) inhibitor, such as melinamide; probucol; nicotinic acid and the salts thereof and niacinamide; a cholesterol absorption inhibitor, such as β-sitosterol; a bile acid sequestrant anion exchange resin, such as cholestyramine, colestipol or dialkylaminoalkyl derivatives of a cross-linked dextran; an LDL (low density lipoprotein) receptor inducer; fibrates, such as clofibrate, bezafibrate, fenofibrate, and gemfibrizol; vitamin B_6 (also known as pyridoxine) and the pharmaceutically acceptable salts thereof, such as the HCl salt; vitamin B_{12} (also known as cyanocobalamin); vitamin B_3 (also known as nicotinic acid and niacinamide, *supra*); anti-oxidant vitamins, such as vitamin C and E and beta carotene; a beta-blocker; an angiotensin II antagonist; an angiotensin converting enzyme inhibitor; and a platelet aggregation inhibitor, such as fibrinogen receptor antagonists (*i.e.*, glycoprotein IIb/IIIa fibrinogen receptor antagonists) and aspirin. As noted above, the compounds of Formula Ia or Ib can be administered in combination with more than one additional active agent, for example, a combination of a compound of Formula Ia or Ib with an HMG-CoA reductase inhibitor (*e.g.*, lovastatin, simvastatin and pravastatin) and aspirin, or a compound of Formula Ia or Ib with an HMG-CoA reductase inhibitor and a β blocker.

[0167] Another example of combination therapy can be seen in treating obesity or obesity-related disorders, wherein the compounds of Formula Ia or Ib can be effectively used in combination with, for example, phenylpropanolamine, phentermine, diethylpropion, mazindol; fenfluramine, dexfenfluramine, phentiramine, β_3 adrenoceptor agonist agents;

sibutramine, gastrointestinal lipase inhibitors (such as orlistat), and leptins. Other agents used in treating obesity or obesity-related disorders wherein the compounds of Formula Ia or Ib can be effectively used in combination with, for example, neuropeptide Y, enterostatin, cholecytokinin, bombesin, amylin, histamine H_3 receptors, dopamine D_2 receptors, melanocyte stimulating hormone, corticotrophin releasing factor, galanin and gamma amino butyric acid (GABA).

[0168] Still another example of combination therapy can be seen in modulating diabetes (or treating diabetes and its related symptoms, complications, and disorders), wherein the compounds of Formula Ia or Ib can be effectively used in combination with, for example, sulfonylureas (such as chlorpropamide, tolbutamide, acetohexamide, tolazamide, glyburide, gliclazide, glynase, glimepiride, and glipizide), biguanides (such as metformin), thiazolidinediones (such as ciglitazone, pioglitazone, troglitazone, and rosiglitazone); dehydroepiandrosterone (also referred to as DHEA or its conjugated sulphate ester, DHEA-SO_4); antiglucocorticoids; TNFα inhibitors; α-glucosidase inhibitors (such as acarbose, miglitol, and voglibose), pramlintide (a synthetic analog of the human hormone amylin), other insulin secretogogues (such as repaglinide, gliquidone, and nateglinide), insulin, as well as the active agents discussed above for treating atherosclerosis.

[0169] A further example of combination therapy can be seen in modulating hyperlipidemia (treating hyperlipidemia and its related complications), wherein the compounds of Formula Ia or Ib can be effectively used in combination with, for example, statins (such as fluvastatin, lovastatin, pravastatin or simvastatin), bile acid-binding resins (such as colestipol or cholestyramine), nicotinic acid, probucol, betacarotene, vitamin E, or vitamin C.

[0170] Additionally, an effective amount of a compound of Formula Ia or Ib and a therapeutically effective amount of one or more active agents selected from the group consisting of: an antihyperlipidemic agent; a plasma HDL-raising agent; an antihypercholesterolemic agent, such as a cholesterol biosynthesis inhibitor, for example, an HMG-CoA reductase inhibitor, an HMG-CoA synthase inhibitor, a squalene epoxidase inhibitor, or a squalene synthetase inhibitor (also known as squalene synthase inhibitor); an acyl-coenzyme A cholesterol acyltransferase inhibitor; probucol; nicotinic acid and the salts thereof; niacinamide; a cholesterol absorption inhibitor; a bile acid sequestrant anion exchange resin; a low density lipoprotein receptor inducer; clofibrate, fenofibrate, and gemfibrozil; vitamin B_6 and the pharmaceutically acceptable salts thereof; vitamin B_{12}; an anti-oxidant vitamin; a β-blocker; an angiotensin II antagonist; an angiotensin converting

enzyme inhibitor; a platelet aggregation inhibitor; a fibrinogen receptor antagonist; aspirin; phentiramines, β_3 adrenergic receptor agonists; sulfonylureas, biguanides, α-glucosidase inhibitors, other insulin secretogogues, and insulin can be used together for the preparation of a pharmaceutical composition useful for the above-described treatments.

Kits

[0171] In addition, the present invention provides for kits with unit doses of the compounds of Formula Ia or Ib, either in oral or injectable doses. In addition to the containers containing the unit doses will be an informational package insert describing the use and attendant benefits of the drugs in alleviating symptoms and/or complications associated with Type 2 diabetes as well as in alleviating hyperlipidemia and hyperuricemia, or for alleviating conditions dependent on PPAR. Preferred compounds and unit doses are those described herein above.

[0172] For the compositions, methods and kits provided above, one of skill in the art will understand that preferred compounds for use in each are those compounds that are preferred above and particularly those compounds provided in formulae IIa through IIat, and IIIa through IIIt in Figures 2, 3, 4A, 4B, 5A, 5B and 5C. Still further preferred compounds for the compositions, methods and kits are those compounds provided in the Examples below.

EXAMPLES

Experimental Section

[0173] General Methods. All operations involving moisture and/or oxygen sensitive materials were conducted under an atmosphere of dry nitrogen in pre-dried glassware. Unless noted otherwise, materials were obtained from commercially available sources and used without further purification.

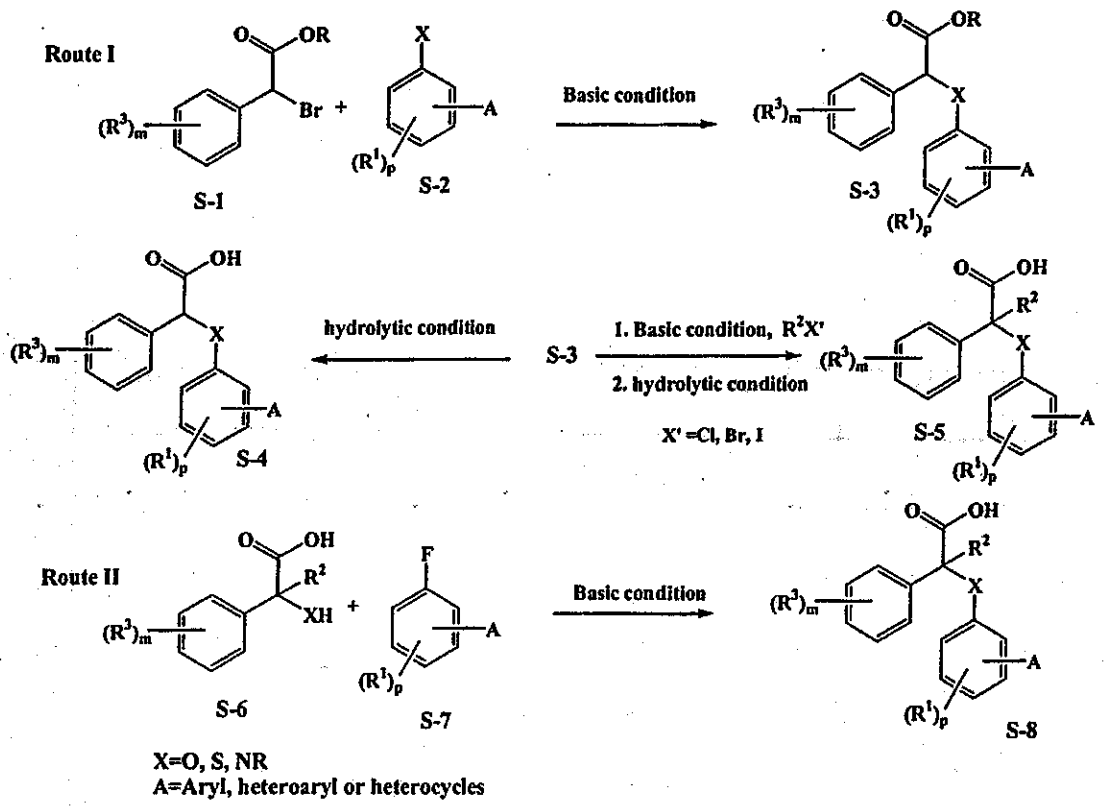
[0174] Flash chromatography was performed on E. Merck silica gel 60 (240-400 mesh) according to the protocol of Still, Kahn, and Mitra (*J. Org. Chem.* **1978**, *43*, 2923). Thin layer chromatography was performed using precoated plates purchased from E. Merck (silica gel 60 PF_{254}, 0.25 mm) and spots were visualized with long-wave ultraviolet light followed by an appropriate staining reagent.

[0175] Nuclear magnetic resonance (NMR) spectra were recorded on a Varian Inova-400 resonance spectrometer. ^1H NMR chemical shifts are given in parts per million (δ) downfield from tetramethylsilane (TMS) using TMS or the residual solvent signal ($CHCl_3$ = δ 7.24, DMSO = δ 2.50) as internal standard. ^1H NMR information is tabulated in the following format: number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant(s) (*J*) in hertz, and, in selected cases, position assignment. The prefix *app* is occasionally applied in cases where the true signal multiplicity was unresolved and *br* indicates the signal in question was broadened.

[0176] Combustion analyses were performed by Robertson Microlit Laboratories, Inc. (Madison, N.J.) and optical rotations were measured on Perkin-Elmer 241 MC polarimeter and reported as: $[\alpha]^T_\lambda$ (*c* = (g/100 mL), solvent).

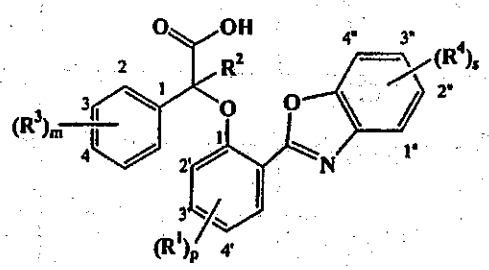
[0177] Two routes are illustrated below which are useful in preparing the coumpounds disclosed in this invention. In **Route I**, α-bromo-phenylacetate **S-1** was treated with a phenol, aniline or benzenethiol **S-2** under basic condition to yield α-phenoxy-, α-phenylamino- or α- phenylsulfanyl-phenylacetate **S-3**. Hydrolysis of **S-3** under basic condition yielded the corresponding acid **S-4**. Alternatively, **S-3** was alkylated with a corresponding alkyl halide followed by basic hydrolysis to afford the alkylated acid **S-5**. In **route B**, intermediates **S-7** with an electron withdrawing R_1 such as 4-CF_3 were treated with α-hydroxy, amino, or mercapto-phenyl acetic acid **S-6** under strongly basic condition to afford phenylacetic acid **S-8** directly.

Figure 1. General Reaction Schemes



[0178] The compounds listed in Tables 1 through Table 12 were either synthesized or can be synthesized by the reaction routes and examples illustrated throughout the experimental section. All the intermediates and final products can be prepared by known procedures or by those skilled in the arts.

Table 1: 2- Benzooxazole analogs



Compound I-X and Ia-X

Compound	R^2	$(R^3)_m$	$(R^1)_p$	$(R^4)_s$	Configuration
I-1	H	4-Cl	H	H	R/S

I-2	H	3-OPh	H	H	R/S
I-3	H	3-CF_3	H	H	R/S
I-4	H	3-Cl	H	H	R/S
I-5	H	4-OMe	H	H	R/S
I-6	H	4-CF_3	H	H	R/S
I-7	H	4-Br	H	H	R/S
I-8	H	H	H	H	R/S
I-9	H	4-F	H	H	R/S
I-10	H	2,3-di-F	H	H	R/S
I-11	H	2,4-di-F	H	H	R/S
I-12	H	2,5-di-F	H	H	R/S
I-13	H	2,6-di-F	H	H	R/S
I-14	H	3,4-di-F	H	H	R/S
I-15	H	3,5-di-F	H	H	R/S
I-16	H	2,3,5-tri-F	H	H	R/S
I-17	H	4-Et	H	H	R/S
I-18	H	4-Cl	H	2"-Me	R/S
I-19	H	3-CF_3	H	2"-Me	R/S
I-20	H	3-OPh	H	2"-Me	R/S
I-21	H	3-Cl	H	2"-Me	R/S
I-22	H	4-OMe	H	2"-Me	R/S
I-23	H	4-CF_3	H	2"-Me	R/S
I-24	H	4-Br	H	2"-Me	R/S
I-25	H	H	H	2"-Me	R/S
I-26	H	4-F	H	2"-Me	R/S
I-27	H	4-Et	H	2"-Me	R/S

I-28	H	4-Cl	H	2"-Ph	R/S
I-29	H	3-CF_3	H	2"-Ph	R/S
I-30	H	3-OPh	H	2"-Ph	R/S
I-31	H	3-Cl	H	2"-Ph	R/S
I-32	H	4-OMe	H	2"-Ph	R/S
I-33	H	4-CF_3	H	2"-Ph	R/S
I-34	H	4-Br	H	2"-Ph	R/S
I-35	H	H	H	2"-Ph	R/S
I-36	H	4-F	H	2"-Ph	R/S
I-37	H	4-Et	H	2"-Ph	R/S
I-38	H	4-Cl	H	2"-Cl	R/S
I-39	H	3-CF_3	H	2"-Cl	R/S
I-40	H	3-OPh	H	2"-Cl	R/S
I-41	H	3-Cl	H	2"-Cl	R/S
I-42	H	4-OMe	H	2"-Cl	R/S
I-43	H	4-CF_3	H	2"-Cl	R/S
I-44	H	4-Br	H	2"-Cl	R/S
I-45	H	H	H	2"-Cl	R/S
I-46	H	4-F	H	2"-Cl	R/S
I-47	H	4-Et	H	2"-Cl	R/S
I-48	H	4-Cl	H	2"-OCF_3	R/S
I-49	H	3-CF_3	H	2"-OCF_3	R/S
I-50	H	3-OPh	H	2"-OCF_3	R/S
I-51	H	3-Cl	H	2"-OCF_3	R/S
I-52	H	4-OMe	H	2"-OCF_3	R/S
I-53	H	4-CF_3	H	2"-OCF_3	R/S

I-54	H	4-Br	H	2"-OCF_3	R/S
I-55	H	H	H	2"-OCF_3	R/S
I-56	H	4-F	H	2"-OCF_3	R/S
I-57	H	4-Et	H	2"-OCF_3	R/S
I-58	H	4-Cl	H	3"-Me	R/S
I-59	H	3-CF_3	H	3"-Me	R/S
I-60	H	3-OPh	H	3"-Me	R/S
I-61	H	3-Cl	H	3"-Me	R/S
I-62	H	4-OMe	H	3"-Me	R/S
I-63	H	4-CF_3	H	3"-Me	R/S
I-64	H	4-Br	H	3"-Me	R/S
I-65	H	H	H	3"-Me	R/S
I-66	H	4-F	H	3"-Me	R/S
I-67	H	4-Et	H	3"-Me	R/S
I-68	H	4-Cl	H	3"-OMe	R/S
I-69	H	3-CF_3	H	3"-OMe	R/S
I-70	H	3-OPh	H	3"-OMe	R/S
I-71	H	3-Cl	H	3"-OMe	R/S
I-72	H	4-OMe	H	3"-OMe	R/S
I-73	H	4-CF_3	H	3"-OMe	R/S
I-74	H	4-Br	H	3"-OMe	R/S
I-75	H	H	H	3"-OMe	R/S
I-76	H	4-F	H	3"-OMe	R/S
I-77	H	4-Et	H	3"-OMe	R/S
I-78	H	4-Cl	H	3"-Cl	R/S
I-79	H	3-CF_3	H	3"-Cl	R/S

I-80	H	3-OPh	H	3"-Cl	R/S
I-81	H	3-Cl	H	3"-Cl	R/S
I-82	H	4-OMe	H	3"-Cl	R/S
I-83	H	4-CF_3	H	3"-Cl	R/S
I-84	H	4-Br	H	3"-Cl	R/S
I-85	H	H	H	3"-Cl	R/S
I-86	H	4-F	H	3"-Cl	R/S
I-87	H	4-Et	H	3"-Cl	R/S
I-88	H	4-Cl	4'-CF_3	H	R/S
I-89	H	3-CF_3	4'-CF_3	H	R/S
I-90	H	3-OPh	4'-CF_3	H	R/S
I-91	H	4-CF_3	4'-CF_3	H	R/S
I-92	H	H	4'-CF_3	H	R/S
I-93	H	4-OMe	4'-CF_3	H	R/S
I-94	H	3-Cl	4'-CF_3	H	R/S
I-95	H	3,4-diF	4'-CF_3	H	R/S
I-96	H	3-OMe	4'-CF_3	H	R/S
I-97	H	2,3,6-tri-F	4'-CF_3	H	R/S
I-98	H	3-Ph	4'-CF_3	H	R/S
I-99	H	4-Br	4'-CF_3	H	R/S
I-100	H	3-NO_2	4'-CF_3	H	R/S
I-101	H	3,4-methylenedioxy	4'-CF_3	H	R/S
I-102	H	4-F	4'-CF_3	H	R/S
I-103	H	2,3-di-F	4'-CF_3	H	R/S
I-104	H	2,4-di-F	4'-CF_3	H	R/S
I-105	H	2,5-di-F	4'-CF_3	H	R/S

I-106	H	2,6-di-F	4'-CF_3	H	R/S
I-107	H	3,4-di-F	4'-CF_3	H	R/S
I-108	H	3,5-di-F	4'-CF_3	H	R/S
I-109	H	2,3,5-tri-F	4'-CF_3	H	R/S
I-110	H	4-Et	4'-CF_3	H	R/S
I-111	H	2-Cl	4'-CF_3	H	R/S
I-112	Et	H	4'-CF_3	H	R/S
I-113	H	4-iPr	4'-CF_3	H	R/S
I-114	H	4-CF_3	4'-CF_3	H	R/S
I-115	H	3-Br	4'-CF_3	H	R/S
I-116	H	4-MeS	4'-CF_3	H	R/S
I-117	H	4-NO_2	4'-CF_3	H	R/S
I-118	H	2,5-di-Me	4'-CF_3	H	R/S
I-119	H	H	4'-CF_3	2"-Me	R/S
I-120	H	3-CF_3	4'-CF_3	2"-Me	R/S
I-121	H	3-OPh	4'-CF_3	2"-Me	R/S
I-122	H	3-Cl	4'-CF_3	2"-Me	R/S
I-123	H	4-OMe	4'-CF_3	2"-Me	R/S
I-124	H	4-CF_3	4'-CF_3	2"-Me	R/S
I-125	H	4-Br	4'-CF_3	2"-Me	R/S
I-126	H	4-Cl	4'-CF_3	2"-Me	R/S
I-127	H	4-F	4'-CF_3	2"-Me	R/S
I-128	H	4-Et	4'-CF_3	2"-Me	R/S
I-129	H	4-Cl	4'-CF_3	2"-Ph	R/S
I-130	H	3-CF_3	4'-CF_3	2"-Ph	R/S
I-131	H	3-OPh	4'-CF_3	2"-Ph	R/S

I-132	H	3-Cl	4'-CF_3	2"-Ph	R/S
I-133	H	4-OMe	4'-CF_3	2"-Ph	R/S
I-134	H	4-CF_3	4'-CF_3	2"-Ph	R/S
I-135	H	4-Br	4'-CF_3	2"-Ph	R/S
I-136	H	H	4'-CF_3	2"-Ph	R/S
I-137	H	4-F	4'-CF_3	2"-Ph	R/S
I-138	H	4-Et	4'-CF_3	2"-Ph	R/S
I-139	H	4-Cl	4'-CF_3	2"-Cl	R/S
I-140	H	3-CF_3	4'-CF_3	2"-Cl	R/S
I-141	H	3-OPh	4'-CF_3	2"-Cl	R/S
I-142	H	3-Cl	4'-CF_3	2"-Cl	R/S
I-143	H	4-OMe	4'-CF_3	2"-Cl	R/S
I-144	H	4-CF_3	4'-CF_3	2"-Cl	R/S
I-145	H	4-Br	4'-CF_3	2"-Cl	R/S
I-146	H	H	4'-CF_3	2"-Cl	R/S
I-147	H	4-F	4'-CF_3	2"-Cl	R/S
I-148	H	4-Et	4'-CF_3	2"-Cl	R/S
I-149	H	4-Cl	4'-CF_3	2"-OCF_3	R/S
I-150	H	3-CF_3	4'-CF_3	2"-OCF_3	R/S
I-151	H	3-OPh	4'-CF_3	2"-OCF_3	R/S
I-152	H	3-Cl	4'-CF_3	2"-OCF_3	R/S
I-153	H	4-OMe	4'-CF_3	2"-OCF_3	R/S
I-154	H	4-CF_3	4'-CF_3	2"-OCF_3	R/S
I-155	H	4-Br	4'-CF_3	2"-OCF_3	R/S
I-156	H	H	4'-CF_3	2"-OCF_3	R/S
I-157	H	4-F	4'-CF_3	2"-OCF_3	R/S

I-158	H	4-Et	4'-CF_3	2"-OCF_3	R/S
I-159	H	4-Cl	4'-CF_3	3"-Me	R/S
I-160	H	3-CF_3	4'-CF_3	3"-Me	R/S
I-161	H	3-OPh	4'-CF_3	3"-Me	R/S
I-162	H	3-Cl	4'-CF_3	3"-Me	R/S
I-163	H	4-OMe	4'-CF_3	3"-Me	R/S
I-164	H	4-CF_3	4'-CF_3	3"-Me	R/S
I-165	H	4-Br	4'-CF_3	3"-Me	R/S
I-166	H	H	4'-CF_3	3"-Me	R/S
I-167	H	4-F	4'-CF_3	3"-Me	R/S
I-168	H	4-Et	4'-CF_3	3"-Me	R/S
I-169	H	4-Cl	4'-CF_3	3"-OMe	R/S
I-170	H	3-CF_3	4'-CF_3	3"-OMe	R/S
I-171	H	3-OPh	4'-CF_3	3"-OMe	R/S
I-172	H	3-Cl	4'-CF_3	3"-OMe	R/S
I-173	H	4-OMe	4'-CF_3	3"-OMe	R/S
I-174	H	4-CF_3	4'-CF_3	3"-OMe	R/S
I-175	H	4-Br	4'-CF_3	3"-OMe	R/S
I-176	H	H	4'-CF_3	3"-OMe	R/S
I-177	H	4-F	4'-CF_3	3"-OMe	R/S
I-178	H	4-Et	4'-CF_3	3"-OMe	R/S
I-179	H	4-Cl	4'-CF_3	3"-Cl	R/S
I-180	H	3-CF_3	4'-CF_3	3"-Cl	R/S
I-181	H	3-OPh	4'-CF_3	3"-Cl	R/S
I-182	H	3-Cl	4'-CF_3	3"-Cl	R/S
I-183	H	4-OMe	4'-CF_3	3"-Cl	R/S

I-184	H	4-CF_3	4'-CF_3	3"-Cl	R/S
I-185	H	4-Br	4'-CF_3	3"-Cl	R/S
I-186	H	H	4'-CF_3	3"-Cl	R/S
I-187	H	4-F	4'-CF_3	3"-Cl	R/S
I-188	H	4-Et	4'-CF_3	3"-Cl	R/S
I-189	H	H	4'-CF_3	4''-CF_3	R/S
I-190	H	4-Cl	4'-Cl	H	R/S
I-191	H	3- CF_3	4'-Cl	H	R/S
I-192	H	H	4'-Cl	H	R/S
I-193	H	4-OMe	4'-Cl	H	R/S
I-194	H	3-Cl	4'-Cl	H	R/S
I-195	H	4-Br	4'-Cl	H	R/S
I-196	H	3-Ph	4'-Cl	H	R/S
I-197	H	4-Cl	4'-Cl	H	R/S
I-198	H	4-CF_3	4'-Cl	H	R/S
I-199	H	4-F	4'-Cl	H	R/S
I-200	H	2,3-di-F	4'-Cl	H	R/S
I-201	H	2,4-di-F	4'-Cl	H	R/S
I-202	H	2,5-di-F	4'-Cl	H	R/S
I-203	H	2,6-di-F	4'-Cl	H	R/S
I-204	H	3,4-di-F	4'-Cl	H	R/S
I-205	H	3,5-di-F	4'-Cl	H	R/S
I-206	H	2,3,5-tri-F	4'-Cl	H	R/S
I-207	H	4-Et	4'-Cl	H	R/S
I-208	H	3-OMe	4'-Cl	4"-Cl	R/S
I-209	H	4-Cl	4'-Cl	2"-Me	R/S

I-210	H	3-CF_3	4'-Cl	2"-Me	R/S
I-211	H	3-OPh	4'-Cl	2"-Me	R/S
I-212	H	3-Cl	4'-Cl	2"-Me	R/S
I-213	H	4-OMe	4'-Cl	2"-Me	R/S
I-214	H	4-CF_3	4'-Cl	2"-Me	R/S
I-215	H	4-Br	4'-Cl	2"-Me	R/S
I-216	H	H	4'-Cl	2"-Me	R/S
I-217	H	4-F	4'-Cl	2"-Me	R/S
I-218	H	4-Et	4'-Cl	2"-Me	R/S
I-219	H	4-Cl	4'-Cl	2"-Ph	R/S
I-220	H	3-CF_3	4'-Cl	2"-Ph	R/S
I-221	H	3-OPh	4'-Cl	2"-Ph	R/S
I-222	H	3-Cl	4'-Cl	2"-Ph	R/S
I-223	H	4-OMe	4'-Cl	2"-Ph	R/S
I-224	H	4-CF_3	4'-Cl	2"-Ph	R/S
I-225	H	4-Br	4'-Cl	2"-Ph	R/S
I-226	H	H	4'-Cl	2"-Ph	R/S
I-227	H	4-F	4'-Cl	2"-Ph	R/S
I-228	H	4-Et	4'-Cl	2"-Ph	R/S
I-229	H	4-Cl	4'-Cl	2"-Cl	R/S
I-230	H	3-CF_3	4'-Cl	2"-Cl	R/S
I-231	H	3-OPh	4'-Cl	2"-Cl	R/S
I-232	H	3-Cl	4'-Cl	2"-Cl	R/S
I-233	H	4-OMe	4'-Cl	2"-Cl	R/S
I-234	H	4-CF_3	4'-Cl	2"-Cl	R/S
I-235	H	4-Br	4'-Cl	2"-Cl	R/S

I-236	H	H	4'-Cl	2"-Cl	R/S
I-237	H	4-F	4'-Cl	2"-Cl	R/S
I-238	H	4-Et	4'-Cl	2"-Cl	R/S
I-239	H	4-Cl	4'-Cl	2"-OCF_3	R/S
I-240	H	3-CF_3	4'-Cl	2"-OCF_3	R/S
I-241	H	3-OPh	4'-Cl	2"-OCF_3	R/S
I-242	H	3-Cl	4'-Cl	2"-OCF_3	R/S
I-243	H	4-OMe	4'-Cl	2"-OCF_3	R/S
I-244	H	4-CF_3	4'-Cl	2"-OCF_3	R/S
I-245	H	4-Br	4'-Cl	2"-OCF_3	R/S
I-246	H	H	4'-Cl	2"-OCF_3	R/S
I-247	H	4-F	4'-Cl	2"-OCF_3	R/S
I-248	H	4-Et	4'-Cl	2"-OCF_3	R/S
I-249	H	4-Cl	4'-Cl	3"-Me	R/S
I-250	H	3-CF_3	4'-Cl	3"-Me	R/S
I-251	H	3-OPh	4'-Cl	3"-Me	R/S
I-252	H	3-Cl	4'-Cl	3"-Me	R/S
I-253	H	4-OMe	4'-Cl	3"-Me	R/S
I-254	H	4-CF_3	4'-Cl	3"-Me	R/S
I-255	H	4-Br	4'-Cl	3"-Me	R/S
I-256	H	H	4'-Cl	3"-Me	R/S
I-257	H	4-F	4'-Cl	3"-Me	R/S
I-258	H	4-Et	4'-Cl	3"-Me	R/S
I-259	H	4-Cl	4'-Cl	3"-OMe	R/S
I-260	H	3-CF_3	4'-Cl	3"-OMe	R/S
I-261	H	3-OPh	4'-Cl	3"-OMe	R/S

I-262	H	3-Cl	4'-Cl	3"-OMe	R/S
I-263	H	4-OMe	4'-Cl	3"-OMe	R/S
I-264	H	4-CF_3	4'-Cl	3"-OMe	R/S
I-265	H	4-Br	4'-Cl	3"-OMe	R/S
I-266	H	H	4'-Cl	3"-OMe	R/S
I-267	H	4-F	4'-Cl	3"-OMe	R/S
I-268	H	4-Et	4'-Cl	3"-OMe	R/S
I-269	H	4-Cl	4'-Cl	3"-Cl	R/S
I-270	H	3-CF_3	4'-Cl	3"-Cl	R/S
I-271	H	3-OPh	4'-Cl	3"-Cl	R/S
I-271	H	3-Cl	4'-Cl	3"-Cl	R/S
I-272	H	4-OMe	4'-Cl	3"-Cl	R/S
I-273	H	4-CF_3	4'-Cl	3"-Cl	R/S
I-274	H	4-Br	4'-Cl	3"-Cl	R/S
I-275	H	H	4'-Cl	3"-Cl	R/S
I-276	H	4-F	4'-Cl	3"-Cl	R/S
I-277	H	4-Et	4'-Cl	3"-Cl	R/S
I-278	H	3-CF_3	4'-CF_3	4"-Cl	R/S
I-279	H	4-OMe	4'-CF_3	4"-Cl	R/S
I-280	H	4-Cl	4'-CF_3	4"-Cl	R/S
I-281	H	4-CF_3	4'-CF_3	4"-Cl	R/S
I-282	H	4-Br	4'-CF_3	4"-Cl	R/S
I-283	H	H	4'-CF_3	4"-Cl	R/S
I-284	H	3-Cl	4'-Me	H	R/S
I-285	H	3-CF_3	4'-Me	H	R/S
I-286	H	3-OPh	4'-Me	H	R/S

I-287	H	4-OMe	4'-Me	H	R/S
I-288	H	4-Cl	4'-Me	H	R/S
I-289	H	4-CF_3	4'-Me	H	R/S
I-290	H	4-Br	4'-Me	H	R/S
I-291	H	H	4'-Me	H	R/S
I-292	H	4-F	4'-Me	H	R/S
I-293	H	2,3-di-F	4'-Me	H	R/S
I-294	H	2,4-di-F	4'-Me	H	R/S
I-295	H	2,5-di-F	4'-Me	H	R/S
I-296	H	2,6-di-F	4'-Me	H	R/S
I-297	H	3,4-di-F	4'-Me	H	R/S
I-298	H	3,5-di-F	4'-Me	H	R/S
I-299	H	2,3,5-tri-F	4'-Me	H	R/S
I-300	H	4-Et	4'-Me	H	R/S
I-301	H	3-Cl	4'-t-Bu	H	R/S
I-302	H	3-CF_3	4'-t-Bu	H	R/S
I-303	H	3-OPh	4'-t-Bu	H	R/S
I-304	H	4-OMe	4'-t-Bu	H	R/S
I-305	H	4-Cl	4'-t-Bu	H	R/S
I-306	H	4-CF_3	4'-t-Bu	H	R/S
I-307	H	4-Br	4'-t-Bu	H	R/S
I-308	H	H	4'-t-Bu	H	R/S
I-309	H	4-F	4'-t-Bu	H	R/S
I-310	H	2,3-di-F	4'-t-Bu	H	R/S
I-311	H	2,4-di-F	4'-t-Bu	H	R/S
I-312	H	2,5-di-F	4'-t-Bu	H	R/S

I-313	H	2,6-di-F	4'-t-Bu	H	R/S
I-314	H	3,4-di-F	4'-t-Bu	H	R/S
I-315	H	3,5-di-F	4'-t-Bu	H	R/S
I-316	H	2,3,5-tri-F	4'-t-Bu	H	R/S
I-317	H	4-Et	4'-t-Bu	H	R/S
I-318	H	3-Cl	4'-Br	H	R/S
I-319	H	3-CF_3	4'-Br	H	R/S
I-320	H	3-OPh	4'-Br	H	R/S
I-321	H	4-OMe	4'-Br	H	R/S
I-322	H	4-Cl	4'-Br	H	R/S
I-323	H	4-CF_3	4'-Br	H	R/S
I-324	H	4-Br	4'-Br	H	R/S
I-325	H	H	4'-Br	H	R/S
I-326	H	4-F	4'-Br	H	R/S
I-327	H	2,3-di-F	4'-Br	H	R/S
I-328	H	2,4-di-F	4'-Br	H	R/S
I-329	H	2,5-di-F	4'-Br	H	R/S
I-330	H	2,6-di-F	4'-Br	H	R/S
I-331	H	3,4-di-F	4'-Br	H	R/S
I-332	H	3,5-di-F	4'-Br	H	R/S
I-333	H	4-Et	4'-Br	H	R/S
I-334	H	2,3,6-tri-F	4'-Br	H	R/S
I-335	H	3-Cl	4',6'-di Cl	H	R/S
I-336	H	3-CF_3	4',6'-di Cl	H	R/S
I-337	H	3-OPh	4',6'-di Cl	H	R/S
I-338	H	4-OMe	4',6'-di Cl	H	R/S

I-339	H	4-Cl	4',6'-di Cl	H	R/S
I-340	H	4-CF_3	4',6'-di Cl	H	R/S
I-341	H	4-Br	4',6'-di Cl	H	R/S
I-342	H	H	4',6'-di Cl	H	R/S
I-343	H	4-F	4',6'-di Cl	H	R/S
I-344	H	4-Et	4',6'-di Cl	H	R/S
I-345	H	3-Cl	4'-(2,4-diF-Ph)	H	R/S
I-346	H	3-CF_3	4'-(2,4-diF-Ph)	H	R/S
I-347	H	3-OPh	4'-(2,4-diF-Ph)	H	R/S
I-348	H	4-OMe	4'-(2,4-diF-Ph)	H	R/S
I-349	H	4-Cl	4'-(2,4-diF-Ph)	H	R/S
I-350	H	4-CF_3	4'-(2,4-diF-Ph)	H	R/S
I-351	H	4-Br	4'-(2,4-diF-Ph)	H	R/S
I-352	H	H	4'-(2,4-diF-Ph)	H	R/S
I-353	H	4-F	4'-(2,4-diF-Ph)	H	R/S
I-354	H	4-Et	4'-(2,4-diF-Ph)	H	R/S
I-355	H	3-Cl	4'-(1H-pyrrol-yl)	H	R/S
I-356	H	3-CF_3	4'-(1H-pyrrol-yl)	H	R/S
I-357	H	3-OPh	4'-(1H-pyrrol-yl)	H	R/S
I-358	H	4-OMe	4'-(1H-pyrrol-yl)	H	R/S
I-359	H	4-Cl	4'-(1H-pyrrol-yl)	H	R/S
I-360	H	4-CF_3	4'-(1H-pyrrol-yl)	H	R/S
I-361	H	4-Br	4'-(1H-pyrrol-yl)	H	R/S
I-362	H	H	4'-(1H-pyrrol-yl)	H	R/S
I-363	H	4-F	4'-(1H-pyrrol-yl)	H	R/S
I-364	H	4-Et	4'-(1H-pyrrol-yl)	H	R/S

I-365	H	3-CF_3	4'-CF_3	H	(+)
I-366	H	3-CF_3	4'-CF_3	H	(-)
I-367	H	3-CF_3	4'-Cl	H	(+)
I-368	H	3-CF_3	4'-Cl	H	(-)
I-369	H	H	4'-CF_3	H	S
I-370	H	H	4'-CF_3	H	R
I-371	H	3-Cl	4'-CF_3	H	S
I-372	H	4-Cl	4'-CF_3	H	(+)
I-373	H	4-Cl	4'-CF_3	H	(-)
I-374	H	3-Cl	4'-Cl	H	(+)
I-375	H	3-Cl	4'-Cl	H	(-)
I-376	H	3-Ph	4'-CF_3	H	R/S
I-377	H	H	4'-Cl	H	(+)
I-378	H	H	4'-Cl	H	(-)
I-379	H	3-F, 5-F	4'-CF_3	H	R/S
I-380	H	3-F, 4-F	4'-CF_3	H	R/S
Ia-1	Me	4-Cl	H	H	R/S
Ia-2	Me	3-CF_3	H	H	R/S
Ia-3	Me	3-OPh	H	H	R/S
Ia-4	Me	3-Cl	H	H	R/S
Ia-5	Me	4-OMe	H	H	R/S
Ia-6	Me	4-CF_3	H	H	R/S
Ia-7	Me	4-Br	H	H	R/S
Ia-8	Me	H	H	H	R/S
Ia-9	Me	4-F	H	H	R/S
Ia-10	Me	2,3-di-F	H	H	R/S

Ia-11	Me	2,4-di-F	H	H	R/S
Ia-12	Me	2,5-di-F	H	H	R/S
Ia-13	Me	2,6-di-F	H	H	R/S
Ia-14	Me	3,4-di-F	H	H	R/S
Ia-15	Me	3,5-di-F	H	H	R/S
Ia-16	Me	2,3,5-tri-F	H	H	R/S
Ia-17	Me	4-Et	H	H	R/S
Ia-18	Me	4-Cl	H	2"-Me	R/S
Ia-19	Me	3-CF_3	H	2"-Me	R/S
Ia-20	Me	3-OPh	H	2"-Me	R/S
Ia-21	Me	3-Cl	H	2"-Me	R/S
Ia-22	Me	4-OMe	H	2"-Me	R/S
Ia-23	Me	4-CF_3	H	2"-Me	R/S
Ia-24	Me	4-Br	H	2"-Me	R/S
Ia-25	Me	H	H	2"-Me	R/S
Ia-26	Me	4-F	H	2"-Me	R/S
Ia-27	Me	4-Et	H	2"-Me	R/S
Ia-28	Me	4-Cl	H	2"-Ph	R/S
Ia-29	Me	3-CF_3	H	2"-Ph	R/S
Ia-30	Me	3-OPh	H	2"-Ph	R/S
Ia-31	Me	3-Cl	H	2"-Ph	R/S
Ia-32	Me	4-OMe	H	2"-Ph	R/S
Ia-33	Me	4-CF_3	H	2"-Ph	R/S
Ia-34	Me	4-Br	H	2"-Ph	R/S
Ia-35	Me	H	H	2"-Ph	R/S
Ia-36	Me	4-F	H	2"-Ph	R/S

Ia-37	Me	4-Et	H	2"-Ph	R/S
Ia-38	Me	4-Cl	H	2"-Cl	R/S
Ia-39	Me	3-CF_3	H	2"-Cl	R/S
Ia-40	Me	3-OPh	H	2"-Cl	R/S
Ia-41	Me	3-Cl	H	2"-Cl	R/S
Ia-42	Me	4-OMe	H	2"-Cl	R/S
Ia-43	Me	4-CF_3	H	2"-Cl	R/S
Ia-44	Me	4-Br	H	2"-Cl	R/S
Ia-45	Me	H	H	2"-Cl	R/S
Ia-46	Me	4-F	H	2"-Cl	R/S
Ia-47	Me	4-Et	H	2"-Cl	R/S
Ia-48	Me	4-Cl	H	2"-OCF_3	R/S
Ia-49	Me	3-CF_3	H	2"-OCF_3	R/S
Ia-50	Me	3-OPh	H	2"-OCF_3	R/S
Ia-51	Me	3-Cl	H	2"-OCF_3	R/S
Ia-52	Me	4-OMe	H	2"-OCF_3	R/S
Ia-53	Me	4-CF_3	H	2"-OCF_3	R/S
Ia-54	Me	4-Br	H	2"-OCF_3	R/S
Ia-55	Me	H	H	2"-OCF_3	R/S
Ia-56	Me	4-F	H	2"-OCF_3	R/S
Ia-57	Me	4-Et	H	2"-OCF_3	R/S
Ia-58	Me	4-Cl	H	3"-Me	R/S
Ia-59	Me	3-CF_3	H	3"-Me	R/S
Ia-60	Me	3-OPh	H	3"-Me	R/S
Ia-61	Me	3-Cl	H	3"-Me	R/S
Ia-62	Me	4-OMe	H	3"-Me	R/S

Ia-63	Me	4-CF_3	H	3"-Me	R/S
Ia-64	Me	4-Br	H	3"-Me	R/S
Ia-65	Me	H	H	3"-Me	R/S
Ia-66	Me	4-F	H	3"-Me	R/S
Ia-67	Me	4-Et	H	3"-Me	R/S
Ia-68	Me	4-Cl	H	3"-OMe	R/S
Ia-69	Me	3-CF_3	H	3"-OMe	R/S
Ia-70	Me	3-OPh	H	3"-OMe	R/S
Ia-71	Me	3-Cl	H	3"-OMe	R/S
Ia-72	Me	4-OMe	H	3"-OMe	R/S
Ia-73	Me	4-CF_3	H	3"-OMe	R/S
Ia-74	Me	4-Br	H	3"-OMe	R/S
Ia-75	Me	H	H	3"-OMe	R/S
Ia-76	Me	4-F	H	3"-OMe	R/S
Ia-77	Me	4-Et	H	3"-OMe	R/S
Ia-78	Me	4-Cl	H	3"-Cl	R/S
Ia-79	Me	3-CF_3	H	3"-Cl	R/S
Ia-80	Me	3-OPh	H	3"-Cl	R/S
Ia-81	Me	3-Cl	H	3"-Cl	R/S
Ia-82	Me	4-OMe	H	3"-Cl	R/S
Ia-83	Me	4-CF_3	H	3"-Cl	R/S
Ia-84	Me	4-Br	H	3"-Cl	R/S
Ia-85	Me	H	H	3"-Cl	R/S
Ia-86	Me	4-F	H	3"-Cl	R/S
Ia-87	Me	4-Et	H	3"-Cl	R/S
Ia-88	Me	4-Cl	4'-CF_3	H	R/S

Ia-89	Me	3-CF_3	4'-CF_3	H	R/S
Ia-90	Me	3-OPh	4'-CF_3	H	R/S
Ia-91	Me	4-CF_3	4'-CF_3	H	R/S
Ia-92	Me	4-iPr	4'-CF_3	H	R/S
Ia-93	Me	H	4'-CF_3	H	R/S
Ia-94	Me	4-OMe	4'-CF_3	H	R/S
Ia-95	Me	3-CF_3	4'-CF_3	H	R/S
Ia-96	Me	3-Cl	4'-CF_3	H	R/S
Ia-97	Me	3-OMe	4'-CF_3	H	R/S
Ia-98	Me	4-Cl	4'-CF_3	H	R/S
Ia-99	Me	4-Br	4'-CF_3	H	R/S
Ia-100	Me	3-NO_2	4'-CF_3	H	R/S
Ia-101	Me	3,4-methylenedioxy	4'-CF_3	H	R/S
Ia-102	Me	4-F	4'-CF_3	H	R/S
Ia-103	Me	2,3-di-F	4'-CF_3	H	R/S
Ia-104	Me	2,4-di-F	4'-CF_3	H	R/S
Ia-105	Me	2,5-di-F	4'-CF_3	H	R/S
Ia-106	Me	2,6-di-F	4'-CF_3	H	R/S
Ia-107	Me	3,4-di-F	4'-CF_3	H	R/S
Ia-108	Me	3,5-di-F	4'-CF_3	H	R/S
Ia-109	Me	2,3,5-tri-F	4'-CF_3	H	R/S
Ia-110	Me	4-Et	4'-CF_3	H	R/S
Ia-111	Me	2-Cl	4'-CF_3	H	R/S
Ia-112	Me	3-Br	4'-CF_3	H	R/S
Ia-113	Me	4-tBu	4'-CF_3	H	R/S
Ia-114	Me	3-F	4'-CF_3	H	R/S

Ia-115	Me	4-Me	4'-CF_3	H	R/S
Ia-116	Me	4-MeS	4'-CF_3	H	R/S
Ia-117	Me	4-NO_2	4'-CF_3	H	R/S
Ia-118	Me	2,5-di-Me	4'-CF_3	H	R/S
Ia-119	Me	4-Cl	4'-CF_3	2"-Me	R/S
Ia-120	Me	3-CF_3	4'-CF_3	2"-Me	R/S
Ia-121	Me	3-OPh	4'-CF_3	2"-Me	R/S
Ia-122	Me	3-Cl	4'-CF_3	2"-Me	R/S
Ia-123	Me	4-OMe	4'-CF_3	2"-Me	R/S
Ia-124	Me	4-CF_3	4'-CF_3	2"-Me	R/S
Ia-125	Me	4-Br	4'-CF_3	2"-Me	R/S
Ia-126	Me	H	4'-CF_3	2"-Me	R/S
Ia-127	Me	4-F	4'-CF_3	2"-Me	R/S
Ia-128	Me	4-Et	4'-CF_3	2"-Me	R/S
Ia-129	Me	4-Cl	4'-CF_3	2"-Ph	R/S
Ia-130	Me	3-CF_3	4'-CF_3	2"-Ph	R/S
Ia-131	Me	3-OPh	4'-CF_3	2"-Ph	R/S
Ia-132	Me	3-Cl	4'-CF_3	2"-Ph	R/S
Ia-133	Me	4-OMe	4'-CF_3	2"-Ph	R/S
Ia-134	Me	4-CF_3	4'-CF_3	2"-Ph	R/S
Ia-135	Me	4-Br	4'-CF_3	2"-Ph	R/S
Ia-136	Me	H	4'-CF_3	2"-Ph	R/S
Ia-137	Me	4-F	4'-CF_3	2"-Ph	R/S
Ia-138	Me	4-Et	4'-CF_3	2"-Ph	R/S
Ia-139	Me	4-Cl	4'-CF_3	2"-Cl	R/S
Ia-140	Me	3-CF_3	4'-CF_3	2"-Cl	R/S

Ia-141	Me	3-OPh	4'-CF_3	2"-Cl	R/S
Ia-142	Me	3-Cl	4'-CF_3	2"-Cl	R/S
Ia-143	Me	4-OMe	4'-CF_3	2"-Cl	R/S
Ia-144	Me	4-CF_3	4'-CF_3	2"-Cl	R/S
Ia-145	Me	4-Br	4'-CF_3	2"-Cl	R/S
Ia-146	Me	H	4'-CF_3	2"-Cl	R/S
Ia-147	Me	4-F	4'-CF_3	2"-Cl	R/S
Ia-148	Me	4-Et	4'-CF_3	2"-Cl	R/S
Ia-149	Me	4-Cl	4'-CF_3	2"-OCF_3	R/S
Ia-150	Me	3-CF_3	4'-CF_3	2"-OCF_3	R/S
Ia-151	Me	3-OPh	4'-CF_3	2"-OCF_3	R/S
Ia-152	Me	3-Cl	4'-CF_3	2"-OCF_3	R/S
Ia-153	Me	4-OMe	4'-CF_3	2"-OCF_3	R/S
Ia-154	Me	4-CF_3	4'-CF_3	2"-OCF_3	R/S
Ia-155	Me	4-Br	4'-CF_3	2"-OCF_3	R/S
Ia-156	Me	H	4'-CF_3	2"-OCF_3	R/S
Ia-157	Me	4-F	4'-CF_3	2"-OCF_3	R/S
Ia-158	Me	4-Et	4'-CF_3	2"-OCF_3	R/S
Ia-159	Me	4-Cl	4'-CF_3	3"-Me	R/S
Ia-160	Me	3-CF_3	4'-CF_3	3"-Me	R/S
Ia-161	Me	3-OPh	4'-CF_3	3"-Me	R/S
Ia-162	Me	3-Cl	4'-CF_3	3"-Me	R/S
Ia-163	Me	4-OMe	4'-CF_3	3"-Me	R/S
Ia-164	Me	4-CF_3	4'-CF_3	3"-Me	R/S
Ia-165	Me	4-Br	4'-CF_3	3"-Me	R/S
Ia-166	Me	H	4'-CF_3	3"-Me	R/S

Ia-167	Me	4-F	4'-CF_3	3"-Me	R/S
Ia-168	Me	4-Et	4'-CF_3	3"-Me	R/S
Ia-169	Me	4-Cl	4'-CF_3	3"-OMe	R/S
Ia-170	Me	3-CF_3	4'-CF_3	3"-OMe	R/S
Ia-171	Me	3-OPh	4'-CF_3	3"-OMe	R/S
Ia-172	Me	3-Cl	4'-CF_3	3"-OMe	R/S
Ia-173	Me	4-OMe	4'-CF_3	3"-OMe	R/S
Ia-174	Me	4-CF_3	4'-CF_3	3"-OMe	R/S
Ia-175	Me	4-Br	4'-CF_3	3"-OMe	R/S
Ia-176	Me	H	4'-CF_3	3"-OMe	R/S
Ia-177	Me	4-F	4'-CF_3	3"-OMe	R/S
Ia-178	Me	4-Et	4'-CF_3	3"-OMe	R/S
Ia-179	Me	4-Cl	4'-CF_3	3"-Cl	R/S
Ia-180	Me	3-CF_3	4'-CF_3	3"-Cl	R/S
Ia-181	Me	3-OPh	4'-CF_3	3"-Cl	R/S
Ia-182	Me	3-Cl	4'-CF_3	3"-Cl	R/S
Ia-183	Me	4-OMe	4'-CF_3	3"-Cl	R/S
Ia-184	Me	4-CF_3	4'-CF_3	3"-Cl	R/S
Ia-185	Me	4-Br	4'-CF_3	3"-Cl	R/S
Ia-186	Me	H	4'-CF_3	3"-Cl	R/S
Ia-187	Me	4-F	4'-CF_3	3"-Cl	R/S
Ia-188	Me	4-Et	4'-CF_3	3"-Cl	R/S
Ia-189	Me	H	4'-CF_3	4''-CF_3	R/S
Ia-190	Me	3-Cl	4'-CF_3	4"-Cl	R/S
Ia-191	Me	3-CF_3	4'-Cl	H	R/S
Ia-192	Me	3-Cl	4'-Cl	H	R/S

Ia-193	Me	H	4'-Cl	H	R/S
Ia-194	Me	4-OMe	4'-Cl	H	R/S
Ia-195	Me	3-OMe	4'-Cl	H	R/S
Ia-196	Me	4-Br	4'-Cl	H	R/S
Ia-197	Me	3-Ph	4'-Cl	H	R/S
Ia-198	Me	4-Cl	4'-Cl	H	R/S
Ia-199	Me	4-CF_3	4'-Cl	H	R/S
Ia-200	Me	4-F	4'-Cl	H	R/S
Ia-201	Me	2,3-di-F	4'-Cl	H	R/S
Ia-202	Me	2,4-di-F	4'-Cl	H	R/S
Ia-203	Me	2,5-di-F	4'-Cl	H	R/S
Ia-204	Me	2,6-di-F	4'-Cl	H	R/S
Ia-205	Me	3,4-di-F	4'-Cl	H	R/S
Ia-206	Me	3,5-di-F	4'-Cl	H	R/S
Ia-207	Me	2,3,5-tri-F	4'-Cl	H	R/S
Ia-208	Me	4-Et	4'-Cl	H	R/S
Ia-209	Me	4-Cl	4'-Cl	2"-Me	R/S
Ia-210	Me	3-CF_3	4'-Cl	2"-Me	R/S
Ia-211	Me	3-OPh	4'-Cl	2"-Me	R/S
Ia-212	Me	3-Cl	4'-Cl	2"-Me	R/S
Ia-213	Me	4-OMe	4'-Cl	2"-Me	R/S
Ia-214	Me	4-CF_3	4'-Cl	2"-Me	R/S
Ia-215	Me	4-Br	4'-Cl	2"-Me	R/S
Ia-216	Me	H	4'-Cl	2"-Me	R/S
Ia-217	Me	4-F	4'-Cl	2"-Me	R/S
Ia-218	Me	4-Et	4'-Cl	2"-Me	R/S

Ia-219	Me	4-Cl	4'-Cl	2"-Ph	R/S
Ia-220	Me	3-CF_3	4'-Cl	2"-Ph	R/S
Ia-221	Me	3-OPh	4'-Cl	2"-Ph	R/S
Ia-222	Me	3-Cl	4'-Cl	2"-Ph	R/S
Ia-223	Me	4-OMe	4'-Cl	2"-Ph	R/S
Ia-224	Me	4-CF_3	4'-Cl	2"-Ph	R/S
Ia-225	Me	4-Br	4'-Cl	2"-Ph	R/S
Ia-226	Me	H	4'-Cl	2"-Ph	R/S
Ia-227	Me	4-F	4'-Cl	2"-Ph	R/S
Ia-228	Me	4-Et	4'-Cl	2"-Ph	R/S
Ia-229	Me	4-Cl	4'-Cl	2"-Cl	R/S
Ia-230	Me	3-CF_3	4'-Cl	2"-Cl	R/S
Ia-231	Me	3-OPh	4'-Cl	2"-Cl	R/S
Ia-232	Me	3-Cl	4'-Cl	2"-Cl	R/S
Ia-233	Me	4-OMe	4'-Cl	2"-Cl	R/S
Ia-234	Me	4-CF_3	4'-Cl	2"-Cl	R/S
Ia-235	Me	4-Br	4'-Cl	2"-Cl	R/S
Ia-236	Me	H	4'-Cl	2"-Cl	R/S
Ia-237	Me	4-F	4'-Cl	2"-Cl	R/S
Ia-238	Me	4-Et	4'-Cl	2"-Cl	R/S
Ia-239	Me	4-Cl	4'-Cl	2"-OCF_3	R/S
Ia-240	Me	3-CF_3	4'-Cl	2"-OCF_3	R/S
Ia-241	Me	3-OPh	4'-Cl	2"-OCF_3	R/S
Ia-242	Me	3-Cl	4'-Cl	2"-OCF_3	R/S
Ia-243	Me	4-OMe	4'-Cl	2"-OCF_3	R/S
Ia-244	Me	4-CF_3	4'-Cl	2"-OCF_3	R/S

Ia-245	Me	4-Br	4'-Cl	2"-OCF_3	R/S
Ia-246	Me	H	4'-Cl	2"-OCF_3	R/S
Ia-247	Me	4-F	4'-Cl	2"-OCF_3	R/S
Ia-248	Me	4-Et	4'-Cl	2"-OCF_3	R/S
Ia-249	Me	4-Cl	4'-Cl	3"-Me	R/S
Ia-250	Me	3-CF_3	4'-Cl	3"-Me	R/S
Ia-251	Me	3-OPh	4'-Cl	3"-Me	R/S
Ia-252	Me	3-Cl	4'-Cl	3"-Me	R/S
Ia-253	Me	4-OMe	4'-Cl	3"-Me	R/S
Ia-254	Me	4-CF_3	4'-Cl	3"-Me	R/S
Ia-255	Me	4-Br	4'-Cl	3"-Me	R/S
Ia-256	Me	H	4'-Cl	3"-Me	R/S
Ia-257	Me	4-F	4'-Cl	3"-Me	R/S
Ia-258	Me	4-Et	4'-Cl	3"-Me	R/S
Ia-259	Me	4-Cl	4'-Cl	3"-OMe	R/S
Ia-260	Me	3-CF_3	4'-Cl	3"-OMe	R/S
Ia-261	Me	3-OPh	4'-Cl	3"-OMe	R/S
Ia-262	Me	3-Cl	4'-Cl	3"-OMe	R/S
Ia-263	Me	4-OMe	4'-Cl	3"-OMe	R/S
Ia-264	Me	4-CF_3	4'-Cl	3"-OMe	R/S
Ia-265	Me	4-Br	4'-Cl	3"-OMe	R/S
Ia-266	Me	H	4'-Cl	3"-OMe	R/S
Ia-267	Me	4-F	4'-Cl	3"-OMe	R/S
Ia-268	Me	4-Et	4'-Cl	3"-OMe	R/S
Ia-269	Me	4-Cl	4'-Cl	3"-Cl	R/S
Ia-270	Me	3-CF_3	4'-Cl	3"-Cl	R/S

Ia-271	Me	3-OPh	4'-Cl	3"-Cl	R/S
Ia-271	Me	3-Cl	4'-Cl	3"-Cl	R/S
Ia-272	Me	4-OMe	4'-Cl	3"-Cl	R/S
Ia-273	Me	4-CF_3	4'-Cl	3"-Cl	R/S
Ia-274	Me	4-Br	4'-Cl	3"-Cl	R/S
Ia-275	Me	H	4'-Cl	3"-Cl	R/S
Ia-276	Me	4-F	4'-Cl	3"-Cl	R/S
Ia-277	Me	4-Et	4'-Cl	3"-Cl	R/S
Ia-278	Me	3-CF_3	4'-CF_3	4"-Cl	R/S
Ia-279	Me	4-OMe	4'-CF_3	4"-Cl	R/S
Ia-280	Me	4-Cl	4'-CF_3	4"-Cl	R/S
Ia-281	Me	4-CF_3	4'-CF_3	4"-Cl	R/S
Ia-282	Me	4-Br	4'-CF_3	4"-Cl	R/S
Ia-283	Me	H	4'-CF_3	4"-Cl	R/S
Ia-284	Me	3-Cl	4'-Me	H	R/S
Ia-285	Me	3-CF_3	4'-Me	H	R/S
Ia-286	Me	3-OPh	4'-Me	H	R/S
Ia-287	Me	4-OMe	4'-Me	H	R/S
Ia-288	Me	4-Cl	4'-Me	H	R/S
Ia-289	Me	4-CF_3	4'-Me	H	R/S
Ia-290	Me	4-Br	4'-Me	H	R/S
Ia-291	Me	H	4'-Me	H	R/S
Ia-292	Me	4-F	4'-Me	H	R/S
Ia-293	Me	2,3-di-F	4'-Me	H	R/S
Ia-294	Me	2,4-di-F	4'-Me	H	R/S
Ia-295	Me	2,5-di-F	4'-Me	H	R/S

Ia-296	Me	2,6-di-F	4'-Me	H	R/S
Ia-297	Me	3,4-di-F	4'-Me	H	R/S
Ia-298	Me	3,5-di-F	4'-Me	H	R/S
Ia-299	Me	2,3,5-tri-F	4'-Me	H	R/S
Ia-300	Me	4-Et	4'-Me	H	R/S
Ia-301	Me	3-Cl	4'-t-Bu	H	R/S
Ia-302	Me	3-CF_3	4'-t-Bu	H	R/S
Ia-303	Me	3-OPh	4'-t-Bu	H	R/S
Ia-304	Me	4-OMe	4'-t-Bu	H	R/S
Ia-305	Me	4-Cl	4'-t-Bu	H	R/S
Ia-306	Me	4-CF_3	4'-t-Bu	H	R/S
Ia-307	Me	4-Br	4'-t-Bu	H	R/S
Ia-308	Me	H	4'-t-Bu	H	R/S
Ia-309	Me	4-F	4'-t-Bu	H	R/S
Ia-310	Me	2,3-di-F	4'-t-Bu	H	R/S
Ia-311	Me	2,4-di-F	4'-t-Bu	H	R/S
Ia-312	Me	2,5-di-F	4'-t-Bu	H	R/S
Ia-313	Me	2,6-di-F	4'-t-Bu	H	R/S
Ia-314	Me	3,4-di-F	4'-t-Bu	H	R/S
Ia-315	Me	3,5-di-F	4'-t-Bu	H	R/S
Ia-316	Me	2,3,5-tri-F	4'-t-Bu	H	R/S
Ia-317	Me	4-Et	4'-t-Bu	H	R/S
Ia-318	Me	3-Cl	4'-Br	H	R/S
Ia-319	Me	3-CF_3	4'-Br	H	R/S
Ia-320	Me	3-OPh	4'-Br	H	R/S
Ia-321	Me	4-OMe	4'-Br	H	R/S

Ia-323	Me	4-CF_3	4'-Br	H	R/S
Ia-324	Me	4-Br	4'-Br	H	R/S
Ia-325	Me	H	4'-Br	H	R/S
Ia-326	Me	4-F	4'-Br	H	R/S
Ia-327	Me	2,3-di-F	4'-Br	H	R/S
Ia-328	Me	2,4-di-F	4'-Br	H	R/S
Ia-329	Me	2,5-di-F	4'-Br	H	R/S
Ia-330	Me	2,6-di-F	4'-Br	H	R/S
Ia-331	Me	3,4-di-F	4'-Br	H	R/S
Ia-332	Me	3,5-di-F	4'-Br	H	R/S
Ia-333	Me	4-Et	4'-Br	H	R/S
Ia-334	Me	2,3,6-tri-F	4'-Br	H	R/S
Ia-335	Me	3-Cl	4',6'-di Cl	H	R/S
Ia-336	Me	3-CF_3	4',6'-di Cl	H	R/S
Ia-337	Me	3-OPh	4',6'-di Cl	H	R/S
Ia-338	Me	4-OMe	4',6'-di Cl	H	R/S
Ia-339	Me	4-Cl	4',6'-di Cl	H	R/S
Ia-340	Me	4-CF_3	4',6'-di Cl	H	R/S
Ia-341	Me	4-Br	4',6'-di Cl	H	R/S
Ia-342	Me	H	4',6'-di Cl	H	R/S
Ia-343	Me	4-F	4',6'-di Cl	H	R/S
Ia-344	Me	4-Et	4',6'-di Cl	H	R/S
Ia-345	Me	3-Cl	4'-(2,4-diF-Ph)	H	R/S
Ia-346	Me	3-CF_3	4'-(2,4-diF-Ph)	H	R/S
Ia-347	Me	3-OPh	4'-(2,4-diF-Ph)	H	R/S

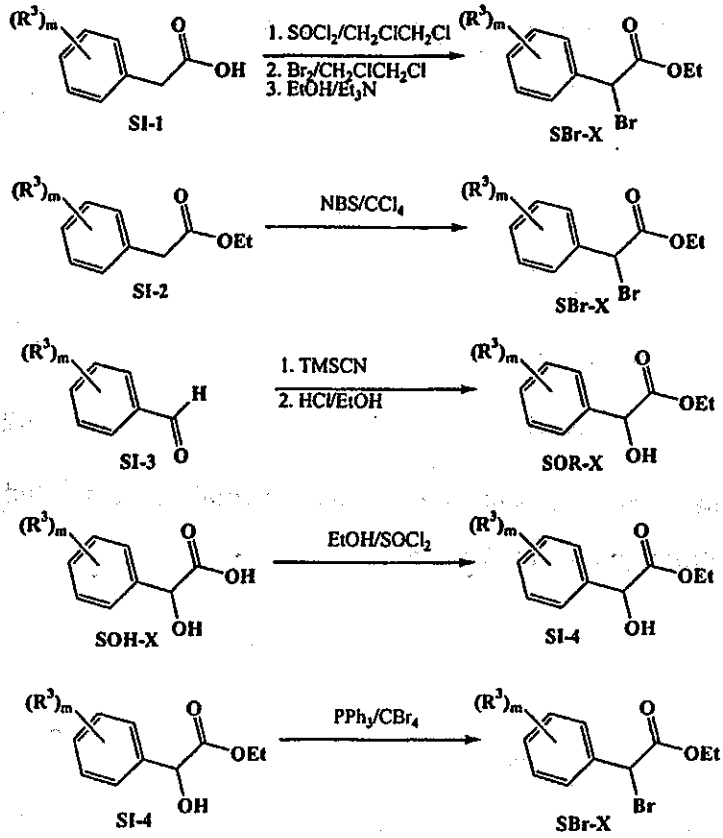
Ia-349	Me	4-Cl	4'-(2,4-diF-Ph)	H	R/S
Ia-350	Me	4-CF_3	4'-(2,4-diF-Ph)	H	R/S
Ia-351	Me	4-Br	4'-(2,4-diF-Ph)	H	R/S
Ia-352	Me	H	4'-(2,4-diF-Ph)	H	R/S
Ia-353	Me	4-F	4'-(2,4-diF-Ph)	H	R/S
Ia-354	Me	4-Et	4'-(2,4-diF-Ph)	H	R/S
Ia-355	Me	3-Cl	4'-(1H-pyrrol-yl)	H	R/S
Ia-356	Me	3-CF_3	4'-(1H-pyrrol-yl)	H	R/S
Ia-357	Me	3-OPh	4'-(1H-pyrrol-yl)	H	R/S
Ia-358	Me	4-OMe	4'-(1H-pyrrol-yl)	H	R/S
Ia-359	Me	4-Cl	4'-(1H-pyrrol-yl)	H	R/S
Ia-360	Me	4-CF_3	4'-(1H-pyrrol-yl)	H	R/S
Ia-361	Me	4-Br	4'-(1H-pyrrol-yl)	H	R/S
Ia-362	Me	H	4'-(1H-pyrrol-yl)	H	R/S
Ia-363	Me	4-F	4'-(1H-pyrrol-yl)	H	R/S
Ia-364	Me	4-Et	4'-(1H-pyrrol-yl)	H	R/S
Ia-365	Me	H	4'-CF_3	H	S
Ia-366	Me	H	4'-CF_3	H	R

1. Synthesis of substituted α-bromo-phenylacetates

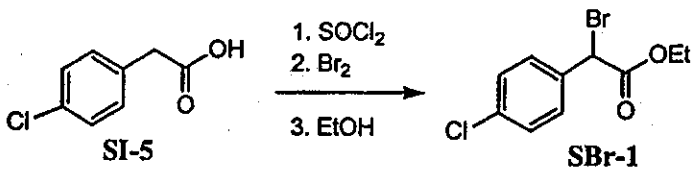
[0179] **Scheme 1** illustrates the general preparative routes for the synthesis of substituted α-bromo-phenylacetates, α-hydroxy-phenylacetic acids and α-hydroxy-phenylacetates. All of the intermediates can be prepared by known procedures or by those skilled in the arts.

Scheme1.

Synthesis of substituted α-bromo-phenylacetate, α-hydroxy-phenylacetic acid and α-hydroxy-phenylacetate



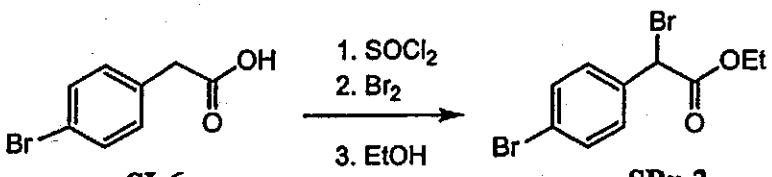
Example 1



[0180] A 2 L three neck roundbottom flask was equipped with an efficient condenser attached to an acid scrubber, a magnetic stir bar, and was placed under nitrogen. 4-Chlorophenylacetic acid (200 g) and 1000 mL of 1,2-dichloroethane were added, followed by thionyl chloride (103.6 mL). The condenser was cooled with 4°C water. The mixture was heated to an internal temperature of 55-60°C. Gas evolution was observed and the solid dissolved as the internal temperature rose to 55-60°C over 45 min. Bromine (66 mL) was added and the mixture was maintained at 55-60°C for 18 h. The internal temperature was then raised to 80-85°C over 1.5 h and heating was continued for 18h. The solution was cooled to room temperature, and 247 mL of ethanol was added slowly at 0 °C. The solution was washed with water and dried over anhydrous sodium sulfate. The solvent was removed

to give 270 g of crude product compound **SBr-1**, which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.33 (dd, 4H), 5.29 (s, 1H), 4.24 (q, 2H), 1.28 (t, 3H).

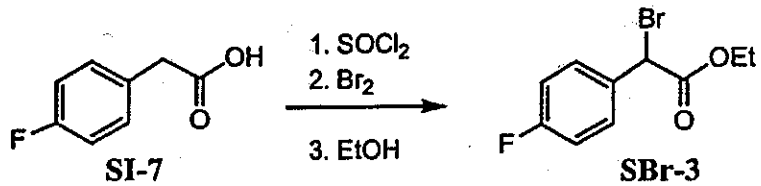
Example 2



SI-6 **SBr-2**

[0181] In the same manner as that described in Example 1, compound **SBr-2** can be prepared from commercially available **SI-6.**

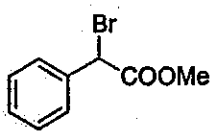
Example 3



SI-7 **SBr-3**

[0182] In the same manner as that described in **Example 1**, compound **SBr-3** can be prepared from commercially available **SI-7.**

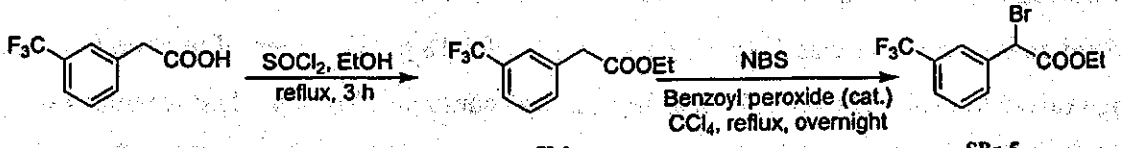
Example 4



SBr-4

[0183] Compound **SBr-4** was purchasd from Aldrich Chemicals Inc., USA

Example 5

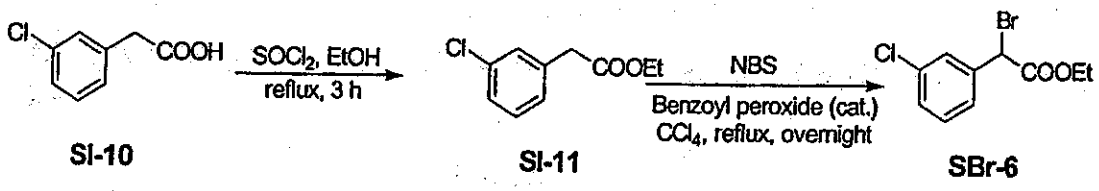


SI-8 **SI-9** **SBr-5**

[0184] To a solution of (α, α, α-trifluoro-*m*-tolyl)acetic acid **SI-8** (202.36 g, 0.99 mol) in absolute ethanol (1.0 L) at 0 °C was added thionyl chloride (79 mL, 1.05 mol), and the

resulting solution was refluxed for 3 h. Concentration *in vacuo* gave a residue which was partitioned between EtOAc and water. The organic layer was washed with sat. $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated *in vacuo* to afford 220.1 g (96%) of crude ethyl ester **SI-9** as a pale yellow liquid. To a mixture of crude ethyl ester **SI-9** (119.15 g, ca. 0.51 mol) and NBS (100.48 g, 0.56 mol) in CCl_4 (1.0 L) was added benzoyl peroxide (1.0 g). The resulting mixture was heated at 75 °C for 20 min. and then refluxed at 90 °C overnight (14 h) until the brown mixture became nearly colorless with white precipitate. The mixture was cooled to 0 °C, filtered through a pad of celite, and concentrated *in vacuo* to afford 151.27 g (95%) of bromide **SBr-5** as a pale brown liquid. The product was sufficiently pure to be used directly in the subsequent substitution reaction. This product was also prepared by refluxing (α, α, α-trifluoro-*m*-tolyl)acetic acid **SI-8** with bromine in the presence of $SOCl_2$, and then quenching with EtOH. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (1H, s), 7.77 (1H, d, J = 7.6 Hz), 7.61 (1H, d, J = 8.0 Hz), 7.51 (1H, t, J = 7.8 Hz), 5.35 (1H, s), 4.26 (2H, q), 1.30 (3H, t).

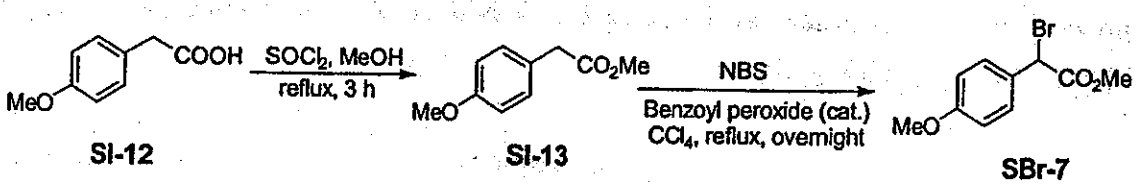
Example 6



SI-10 **SI-11** **SBr-6**

[0185] In the same manner as that described in **Example 5**, compound **SBr-6** was prepared from commercially available **SI-10**. ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.58 (m,1H), 7.42 (m, 2H), 7.30 (m, 2H), 5.29 (s, 1H), 4.26 (m, 2H), 1.30 (t, 3H).

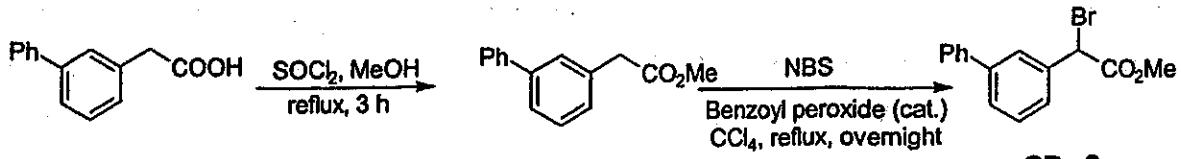
Example 7



SI-12 **SI-13** **SBr-7**

[0186] In the same manner as that described in **Example 5**, compound **SBr-7** was prepared from commercially available **SI-12**. ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.43 (d,2H), 6.88 (d,2H), 5.38 (s,1H), 3.81 (s,3H), 3.79 (s,3H).

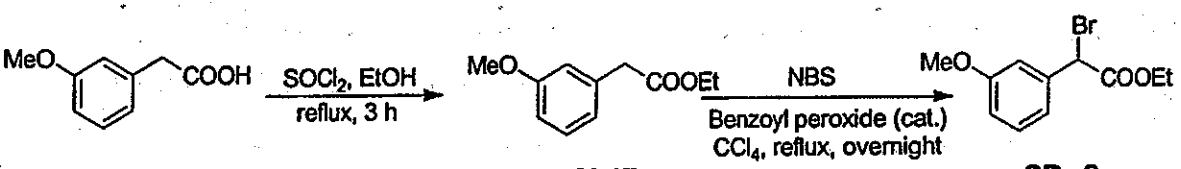
Example 8



SI-14 **SI-15** **SBr-8**

[0187] In the same manner as that described in **Example 5**, compound **SBr-8** was prepared from commercially available **SI-14**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62-7.35 (m, 9H), 5.41 (s, 1H), 3.82 (s, 3H).

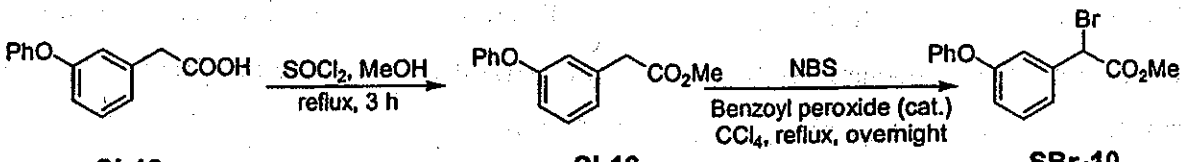
Example 9



SI-16 **SI-17** **SBr-9**

[0188] In the same manner as that described in **Example 5**, compound **SBr-9** was prepared from commercially available **SI-16**. ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.28 (m,1H), 7.09 (m,1H), 6.88 (m,1H), 6.72 (m,1H), 5.33 (s,1H), 4.26 (m,2H), 3.80 (s,3H), 1.29 (t,3H).

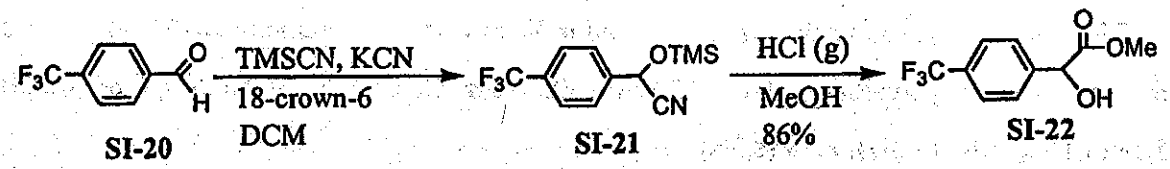
Example 10



SI-18 **SI-19** **SBr-10**

[0189] In the same manner as that described in **Example 5**, compound **SBr-10** was prepared from commercially available **SI-18**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-6.98 (m, 9H), 5.30 (s, 1H), 3.80 (s, 3H).

Example 11



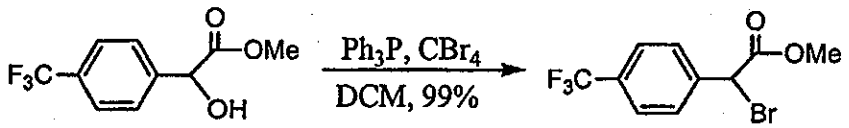
SI-20 **SI-21** **SI-22**

[0190] To a mixture of 4-(trifluoromethyl)-benzaldehyde **SI-20** (25 g), a catalytic amount of KCN and 18-crown-6 in dichloromethane (150 mL) was added slowly TMSCN (21.0 mL)

at 0 °C. The reaction mixture was stirred at room temperature overnight and washed with aqueous sodium bicarbonate solution. The solvent was removed under vacuum to give a crude cyano product.

[0191] The above cyano product was dissolved in methanol, and HCl gas was then bulbed through for several minutes at 0 °C. The solution was stirred overnight at room temperature, neutralized with aqueous NaOH solution, concentrated, and extracted with ethyl acetate. The organic solution was dried over anhydrous sodium sulfate and concentrated. Purification with flash column chromatography (hexanes/ethyl acetate 1/5) gave the desired hydroxyl product **SI-22** (28.75 g, 86%) as a colorless oil. ^{1}H-NMR (DMSO, 400MHz): δ 7.58 (m, 4H), 5.21 (s, 1H), 3.70 (s, 3H).

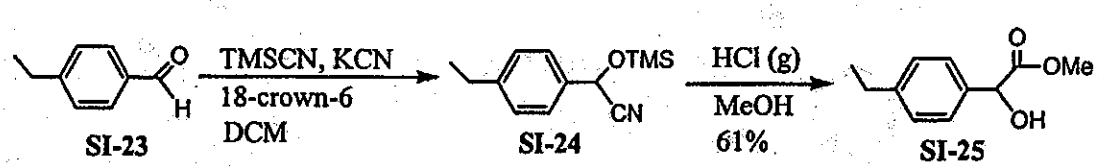
Example 12



SI-22 **SBr-11**

[0192] To a solution of hydroxyl ester **SI-22** (28 g) in dichloromethane (250 mL) containing triphenylphosphine (31.4 g) was slowly added carbon tetrabromide (40 g) at 0 °C, and then the solution was stirred at room temperature overnight. The solution was concentrated and diluted with ethyl acetate/hexanes (2/3, 300 mL). A white precipitate was formed and filtered out. The solvent was removed, and the residue was purified by flash column chromatography (hexane/ethyl acetate 5/1) to give the bromide product **SBr-11** (35 g, 99%) as a colorless oil. ^{1}H-NMR (DMSO, 400MHz): δ 7.78 (m, 4H), 6.10 (s, 1H), 3.68 (s, 3H).

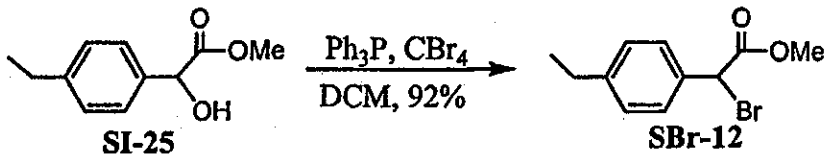
Example 13



SI-23 **SI-24** **SI-25**

[0193] In the same manner as that described in **Example 11**, compound **SI-25** was prepared from commercially available **SI-23** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, 2H), 7.19 (d, 2H), 5.99 (d, 1H), 5.10 (d, 1H), 3.59 (s, 3H), 2.58 (q, 2H), 1.16 (t, 3H).

Example 14



SI-25 SBr-12

[0194] In the same manner as that described in **Example 12**, compound **SBr-12** was prepared from **SI-25**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, 2H), 7.24 (d, 2H), 5.91 (s, 1H), 3.71 (s, 3H), 2.58 (q, 2H), 1.16 (t, 3H).

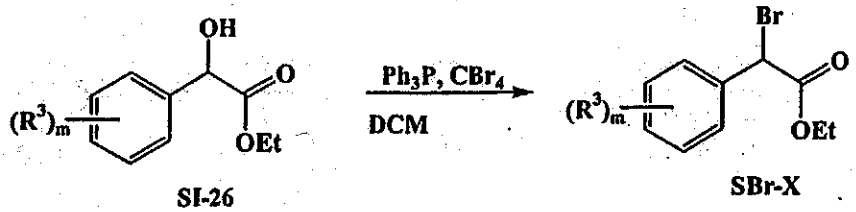
Example 15

SOH-X SI-26

R^3 = H, 4-Cl, 3-CF_3, 3-OPh, 4-CF_3, 4-OMe, 3-CF_3, 3-Cl, 3-OMe, 4-Cl, 4-Br, 3-NO_2, 3,4-methylenedioxy, 4-F, 2,3-di-F, 2,4-di-F, 2,5-di-F, 2,6-di-F, 3,4-di-F, 3,5-di-F, 2,3,5-tri-F, 2,3,6-tri-F, 2-Cl, MeO, 4-Me, 4-MeS, 4-NO_2, 2,5-di-Me

[0195] Differently substituted α-hydroxy phenyl acetic acids **SOH-X** were purchased from a variety of commercial suppliers. The free acids can then be refluxed in absolute ethanol with 1-2 equivalent of thionyl chloride to afford esters **SI-26** after evaporation of the solvent. Alternatively, **SI-26** can be prepared from the corresponding aldehydes as described in **Examples 11** and **13**.

Example 16



SI-26 SBr-X

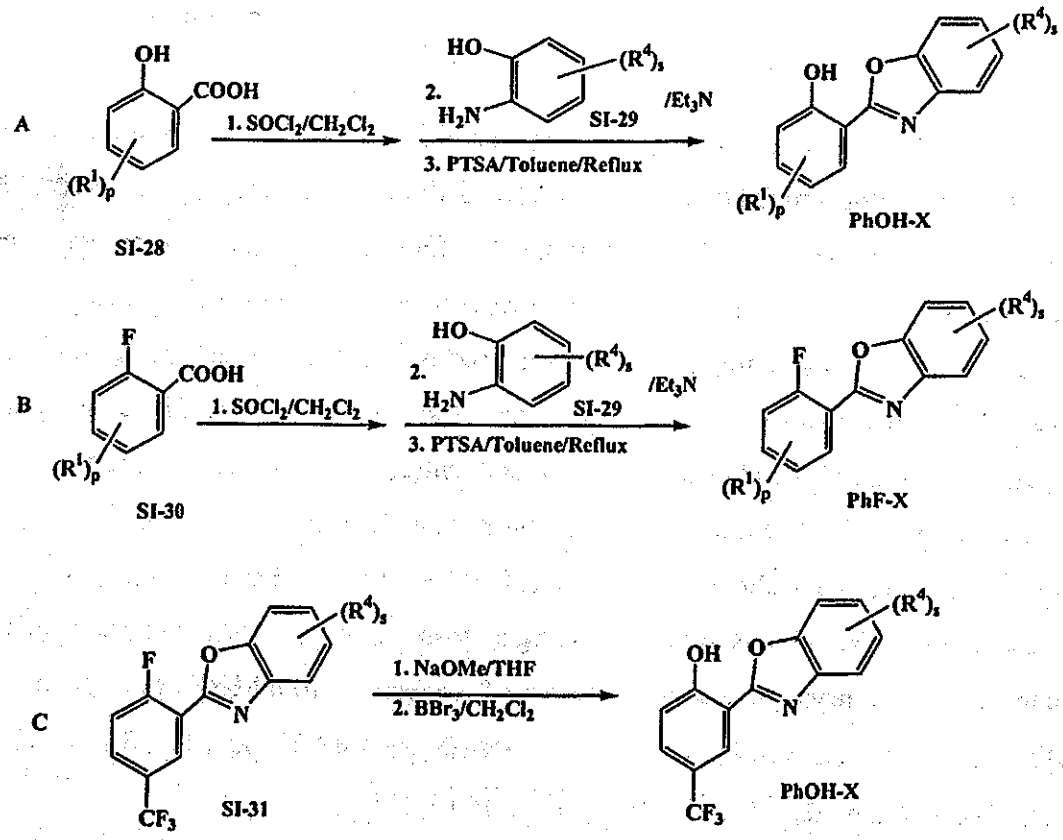
R^3 = H, 4-Cl, 3-CF_3, 3-OPh, 4-OMe, 3-CF_3, 3-Cl, 3-OMe, 4-Cl, 4-Br, 3-NO_2, 3,4-methylenedioxy, 4-F, 2,3-di-F, 2,4-di-F, 2,5-di-F, 2,6-di-F, 3,4-di-F, 3,5-di-F, 2,3,5-tri-F, 2,3,6-tri-F, 2-Cl, MeO, 4-Me, 4-MeS, 4-NO_2, 2,5-di-Me

[0196] In the same manner as that described in **Example 12** and **14**, compound **SBr-X** can be prepared from **SI-26**.

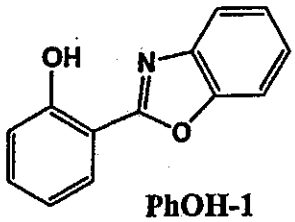
2. Synthesis of 2-benzooxazol-2-yl-phenols

[0197] **Scheme 2** illustrates the general route for preparing 2-benzooxazol-2-yl-phenols or 2-benzooxazol-2-yl- phenylfluorides. Generally, 2-fluoro or 2-hydroxyl benzoic acid was transformed to the corresponding acyl chloride. The acyl chorides were then reacted with aminophenols and were further dehydrated to afford the corresponding 2-benzooxazol-2-yl-phenols or 2-benzooxazol-2-yl-phenylfluorides. 2-benzooxazol-2-yl-phenylfluorides were converted to 2-benzooxazol-2-yl-phenols by reacting with sodium methoxide followed by demethylation. All of the intermediates can be prepared by known procedures or by those skilled in the arts.

Scheme 2
Synthesis of 2-benzoxazoyl phenols and 2-bezoxazoyl florides



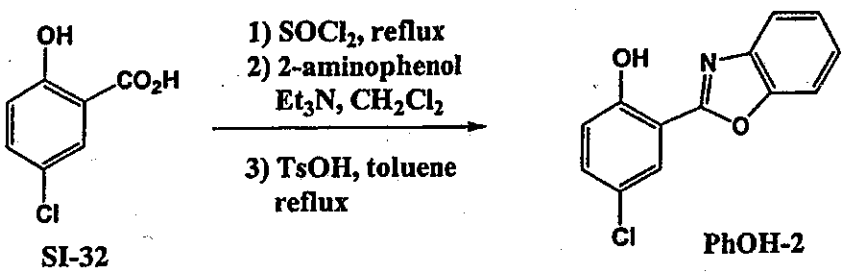
Example 17



PhOH-1

[0198] Compound **PhOH-1** was purchased from Aldrich Chemicals Inc., USA.

Example 18

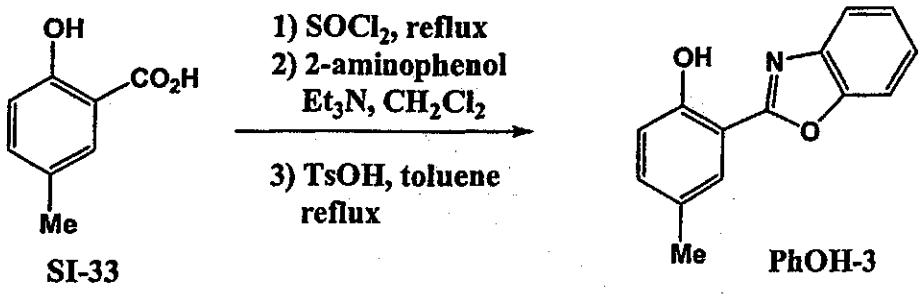


SI-32 **PhOH-2**

[0199] A mixture of **SI-32** (19.24 g, 0.111 mol) and $SOCl_2$ (30 mL) was refluxed for 2h. The mixture was concentrated to dryness and further dried under vaccum. To the residue was added 2-aminophenol (18.2 g, 0.167 mol) in CH_2Cl_2 (500 mL). To the solution was slowly added Et_3N (31 mL, 0.22 mol) at 0°C and the reaction was allowed to warm to room temperature and stirred overnight. The reaction mixture was concentrated to dryness. To the residue was added 1N HCl (400 mL), which was extracted with EtOAc. The organic layer was washed with 1N HCl and brine, dried and concentrated to give a brown solid (28.4 g), which was used for the next reaction without further purification.

[0200] A mixture of the above crude product (28.4 g) and TsOH monohydrate (10 g) in toluene (700 mL) was refluxed overnight using a Dean-Stark apparatus. The reaction mixture was concentrated to dryness. Recrystallization of the residue from MeOH gave phenol **PhOH-2** as an off-white solid (20.9 g, 77%). ^{1}HNMR (d-DMSO, 400 MHz) δ 11.22 (s, 1H), 7.98 (s, 1H), 7.85 (m, 2H), 7.53-7.45 (m, 3H), 7.16 (d, 1H).

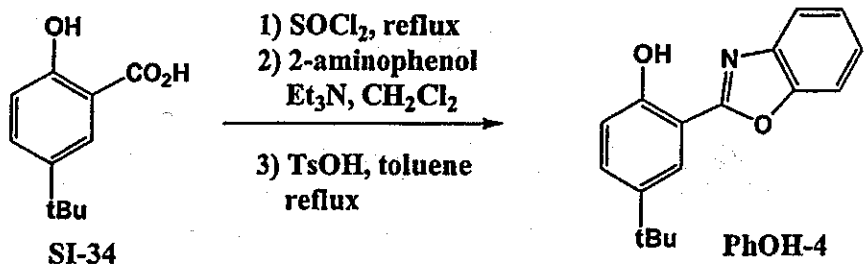
Example 19



SI-33 **PhOH-3**

[0201] In the same manner as that described in **Example 18** compound **PhOH-3** can be prepared from commercially available **SI-33**.

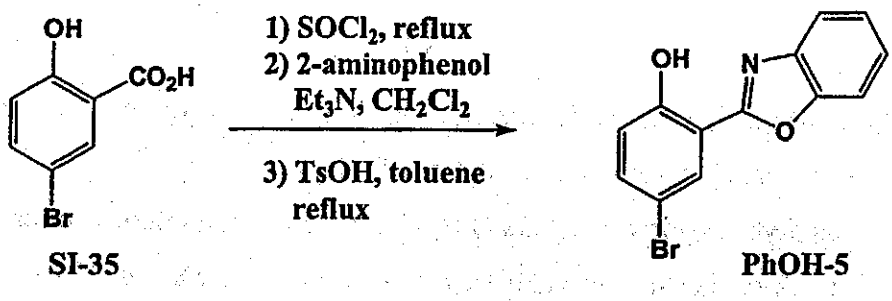
Example 20



SI-34 **PhOH-4**

[0202] In the same manner as that described in **Example 18** compound **PhOH-4** can be prepared from commercially available **SI-34**.

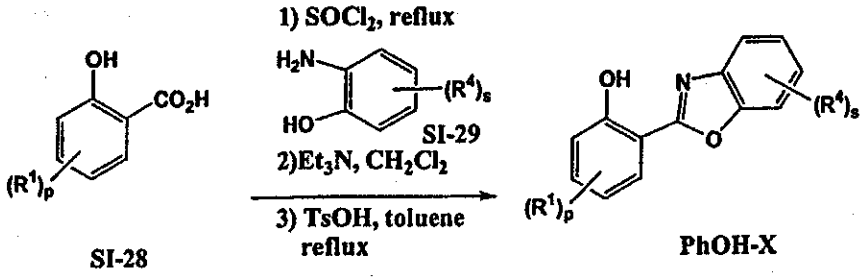
Example 21



SI-35 **PhOH-5**

[0203] In the same manner as that described in **Example 18** compound **PhOH-5** can be prepared from commercially available **SI-35**.

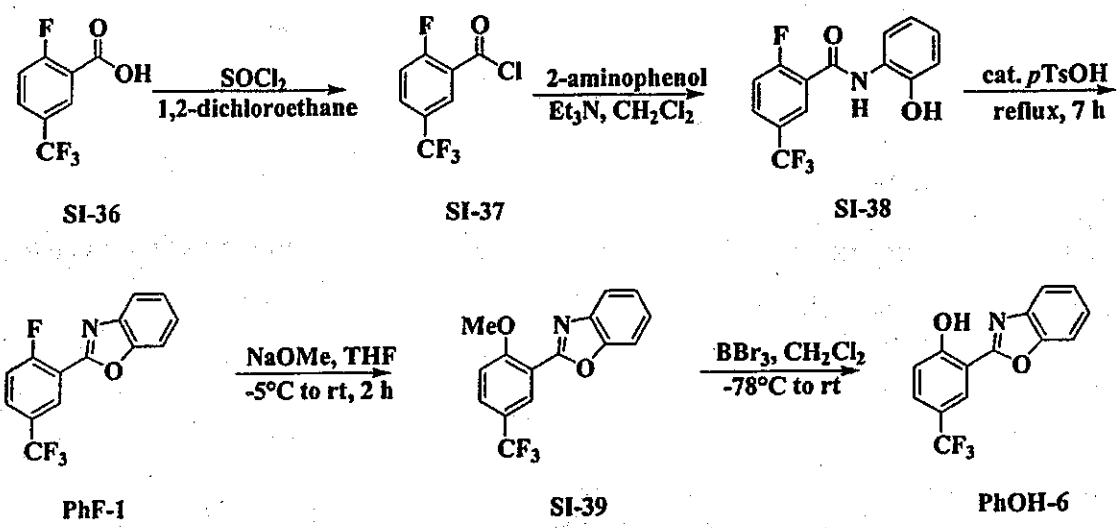
Example 22



R^1 = H, 4'-CF_3, 4'-Cl, 4'-Me, 4'-tBu,4'-Br, 4',6'-diCl, 4'-(1H-pyrrol-yl), 4'-(1H-pyrrol-yl) etc.
R^4 = H, 2"-OCF_3, 2"-Cl, 2"-Me, 2"-Ph, 3"-Me, 3"-OMe, 3"-Cl, etc.

[0204] In the same manner as that described in **Example 18** compound **PhOH-X** can be prepared from commercially available **SI-28**.

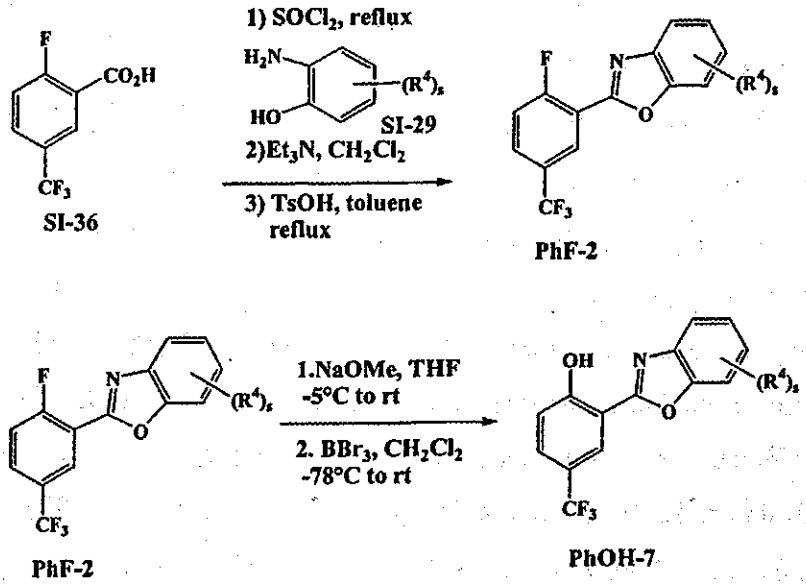
Example 23



[0205] 2-Fluoro-5-(trifluoromethyl)benzoyl chloride **SI-37** was commercially obtained from Aldrich, or prepared by refluxing a solution of 2-fluoro-5-(trifuoromethylmethyl)benzoid acid **SI-36** (116.71 g, 0.56 mol) and thionyl chloride (81.0 mL, 1.11 mol) in 1,2-dichloroethane (250 mL) at 80 °C for 0.5 h. ***Step A.*** To a solution of 2-fluoro-5-(trifluoromethyl)benzoyl chloride **SI-37** (25.7 g, 0.11 mol) and 2-aminophenol (13.87 g, 0.13 mol) in CH_2Cl_2 (350 mL) at 0 °C was added Et_3N (18 mL, 0.13 mol). The resulting mixture was stirred at 0 °C to rt overnight, diluted with EtOAc and washed with water. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo* to afford crude **SI-38** (35 g). ***Step B.*** To a suspension of unpurified **SI-38** (35 g, 0.11 mol) in toluene (500 mL) was added TsOH monohydrate (6.78 g, 0.035 mol). The resulting suspension was refluxed at 80 °C with a Dean-Stork condenser for 7 h. The

reaction mixture was cooled to rt, concentrated *in vacuo*, diluted with EtOAc, washed with H_2O, then washed with sat. $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated *in vacuo* to afford crude **PhF-1** (31.66g, 99% over two steps) as an off-white solid. ^1H NMR (400 MHz, $CDCl_3$): δ 8.56 (1H, d, J = 6.0 Hz), 7.85–7.87 (1H, m), 7.78–7.81 (1H, m), 7.64–7.67 (1H, m), 7.41–7.44 (3H, m) ppm. ***Step C.*** To a solution of unpurified **PhF-1** (31.62 g, 0.11 mol) in THF (200 mL) at –5 °C was added NaOMe (8.95 g, 0.16 mol). The resulting solution was warmed up to rt, and stirred at rt for 1.5 h, quenched with sat. NH_4Cl, and diluted with EtOAc. The organic layer was separated and washed with H_2O and sat. NH_4Cl, dried over Na_2SO_4 and concentrated *in vacuo* to afford crude **SI-39** (31.89 g) as an off-white solid. This product was sufficiently pure to be used directly in the subsequent demethylation reaction, and the analytical pure **SI-39** can be obtained by recrystalization from CH_2Cl_2. ^1H NMR (400 MHz, $CDCl_3$): δ 8.44 (1H, s), 7.84–7.86 (1H, m), 7.77 (1H, d, J = 8.8 Hz), 7.62–7.64 (1H, m), 7.36–7.41 (2H, m), 7.18 (1H, d, J = 8.8 Hz) ppm. ***Step D.*** A solution of unpurified **SI-39** (32.89 g, 0.11 mol) in anhy. CH_2Cl_2 (500 mL) at –78 °C was treated with BBr_3 (17 mL, 0.18 mol). The resultant cloudy solution was warmed to –10 °C over 2 h and stirred at rt for another 2 h. The reaction mixture was cooled to 0 °C and quenched with water. Concentration *in vacuo* gave a residue which was partitioned between EtOAc and water. The organic layer was washed with water, sat. $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated *in vacuo* to afford crude **PhOH-6** (31.31 g, 99.7% over 2 steps) as a white solid. This product was sufficiently pure to be used directly in the subsequent displacement reaction without further purification. ^1H NMR (400 MHz, $CDCl_3$): δ 11.90 (1H, s, ArO*H*), 8.33 (1H, s), 7.75–7.78 (1H, m), 7.64–7.69 (2H, m), 7.42–7.45 (2H, m), 7.22 (1H, d, J = 8.4 Hz).

Example 24



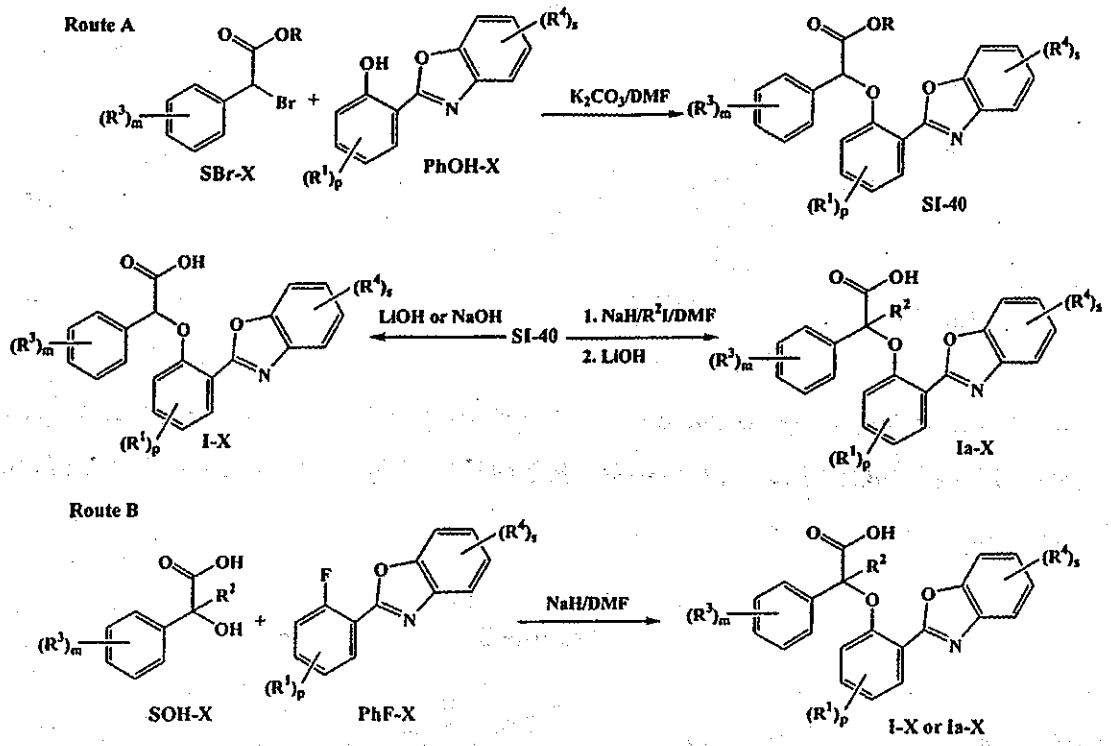
R^4 = H, 2"-OCF_3, 2"-Cl, 2"-Me, 2"-Ph, 3"-Me, 3"-OMe, 3"-Cl, etc.

[0206] In the same manner as that described in **Example 23** compound **PhF-2** and **PhOH-7** can be prepared from commercially available **SI-36** and **SI-29**.

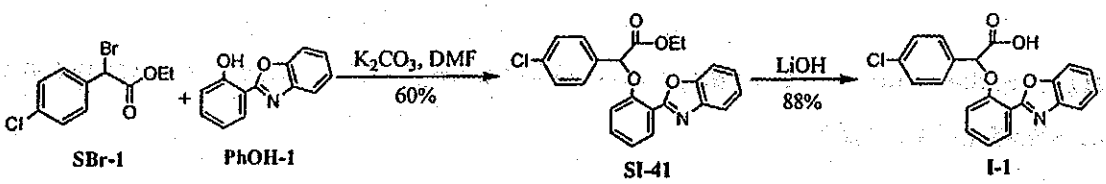
3. Synthesis of Compounds I and Ia in Table 1

[0207] One or two routes illustrated in **Scheme 3** were used to prepare the compounds **I** and **Ia** listed in Table 1. In **route A**, α-bromo-phenylacetate was treated with 2-benzoxazoyl-phenol under basic condition to yield α-phenoxy-phenylacetate **SI-40**. Hydrolysis of **SI-40** under basic condition yielded α-phenoxy-phenylacetic acid **I-X**. Alternatively, **SI-40** was alkylated with a corresponding alkyl halide followed by basic hydrolysis to afford α-phenoxy-phenylacetic acid **Ia-X**. In **route B**, intermediates **PhF-X** with an electron withdrawing R^1 such as a 4-CF_3 group were treated with α-hydroxy-phenyl acetic acid **SOH-X** under strongly basic condition to afford α-phenoxy-phenylacetic acid **I-X** or **Ia-X** directly. All of the intermediates can be prepared by known procedures or by those skilled in the arts.

Scheme 3
Synthesis of compounds I and Ia listed in Table 1.



Example 25

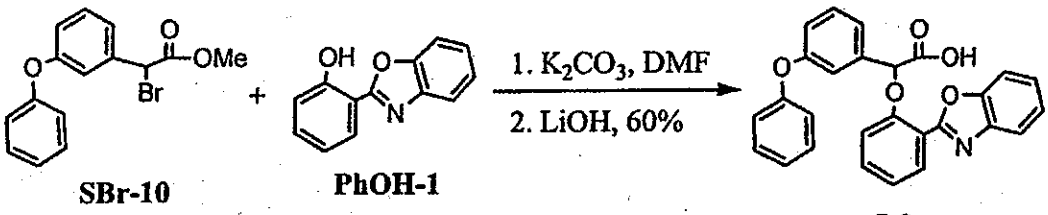


[0208] A mixture of bromo ester **SBr-1** (5.0 g), phenol **PhOH-1** (4.1 g), and K_2CO_3 (3.9 g) in DMF was stirred at room temperature overnight until no starting material was left as judged by TLC. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic solution was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified with flash chromatography (ethyl acetate/hexanes 1:5) to give the desired ester **SI-41** (4.6 g) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 8.22-6.98 (m, 12H), 5.79 (s, 1H), 4.18 (q, 2H), 1.17 (t, 3H).

[0209] The ester (1.0 g) was dissolved in THF (5 mL), and mixed with a LiOH solution (1.0 N, 20 mL). The mixture was stirred at room temperature overnight and extracted with ethyl acetate. The organic solution was washed with 0.1 N HCl, and dried over anhydrous Na_2SO_4 and concentrated. Purification with flash chromatography (ethyl acetate) gave the

desired acid **I-1** (0.82 g) as a white solid. ^{1}H NMR (400 MHz, DMSO): δ 8.10-7.12 (m, 12H), 5.42 (s, 1H).

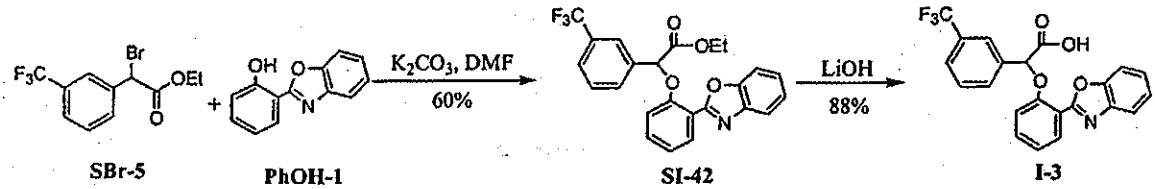
Example 26



SBr-10 **PhOH-1** **I-2**

[0210] In the same manner as that described in **Example 25** compound **I-2** was prepared from **SBr-10** and **PhOH-1** as a white solid. ^{1}H NMR (400 MHz, DMSO): δ 8.24-6.82 (m, 17H), 5.44 (s, 1H).

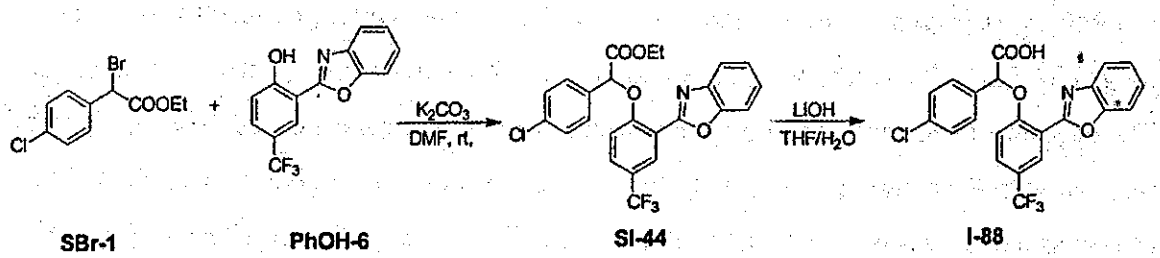
Example 27



SBr-5 **PhOH-1** **SI-42** **I-3**

[0211] In the same manner as that described in **Example 25** compound **I-3** was prepared from **SBr-5** and **PhOH-1**.

Example 28

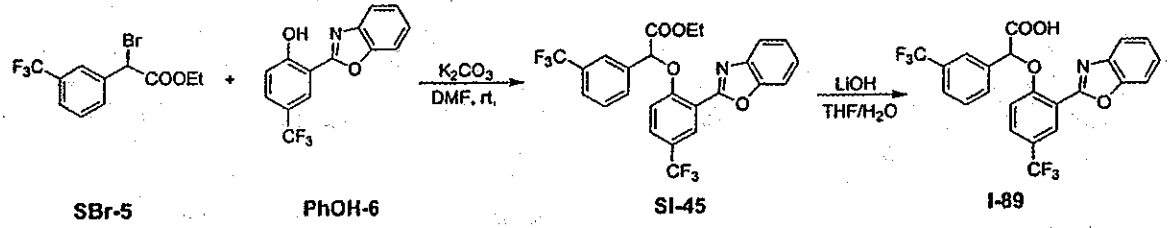


SBr-1 **PhOH-6** **SI-44** **I-88**

[0212] *Step A:*To a solution of phenol **PhOH-6** (0.9882 g, 3.54 mmol) in DMF (10 mL) was added K_2CO_3 (0.92 g, 6.66 mmol) followed by bromide **SBr-1** (1.20 g, 4.57 mmol). After stirring for 0.5 h at rt, the reaction mixture was diluted with EtOAc and water. The organic layer was washed with sat. $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* recrystallization from CH_2Cl_2 afforded ester **SI-44** (1.3698 g) as a snow-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (1H, s), 7.82–7.85 (1H, m), 7.78 (2H,

dd, J = 8.4, 2.0 Hz), 7.71 (1H, d, J = 8.8 Hz), 7.60–7.62 (1H, m), 7.39–7.45 (4H, m), 7.05 (1H, d, J = 8.8 Hz), 5.84 (1H, s), 4.18–4.23 (2H, m), 1.17–1.21 (3H, m). ***Step B.*** To a solution of ester **SI-44** (0.9658 g, 2.03 mmol) in THF / H_2O (20 mL / 5 mL) at rt was added lithium hydroxide monohydrate (0.43 g, 10.25 mmol). The resulting solution was stirred at rt for 1 h, quenched with 1N aqueous HCl and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to afford acid **I-88** (0.8842 g) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.41 (1H, d, J = 2.0 Hz), 7.99 (1H, dd, J = 9.2, 2.0 Hz), 7.89 (1H, dd, J = 6.8, 2.0 Hz), 7.83–7.86 (1H, m), 7.83 (2H, d, J = 8.6 Hz), 7.59 (2H, d, J = 8.6 Hz), 7.43–7.50 (2H, m), 7.40 (1H, d, J = 8.8 Hz), 6.34 (1H, s).

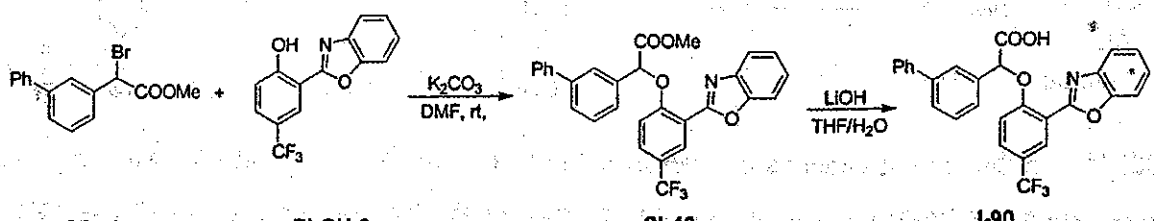
Example 29



SBr-5 PhOH-6 SI-45 I-89

[0213] In the same manner as that described in **Example 28** compound **I-89** was prepared from **SBr-5** and **PhOH-6** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.40 (1H, d, J = 2.0 Hz), 8.35 (1H, s), 8.04 (1H, d, J = 7.6 Hz), 7.97 (1H, dd, J = 8.8, 2.4 Hz), 7.82 (1H, dd, J = 6.8, 2.4 Hz), 7.75–7.77 (1H, m), 7.74 (1H, d, J = 4.4 Hz), 7.69 (2H, t, J = 7.8 Hz), 7.43–7.50 (2H, m), 7.39 (1H, d, J = 9.2 Hz), 6.27 (1H, s) ppm.

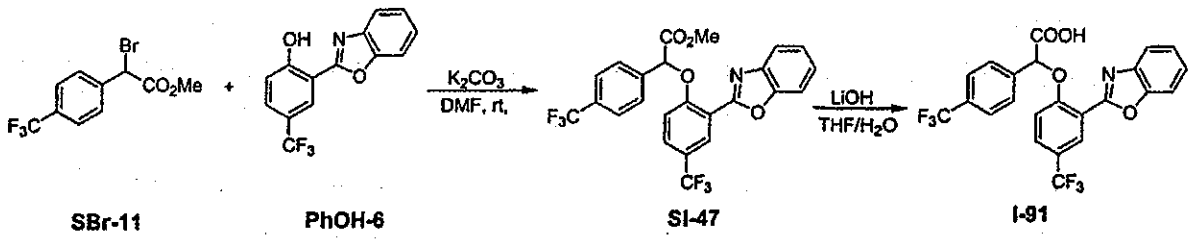
Example 30



SBr-8 PhOH-6 SI-46 I-90

[0214] In the same manner as that described in **Example 28** compound **I-90** was prepared from **SBr-8** and **PhOH-6.** ^{1}H NMR (400 MHz, DMSO): δ 8.40-6.40 (m, 16H), 5.42 (s, 1H).

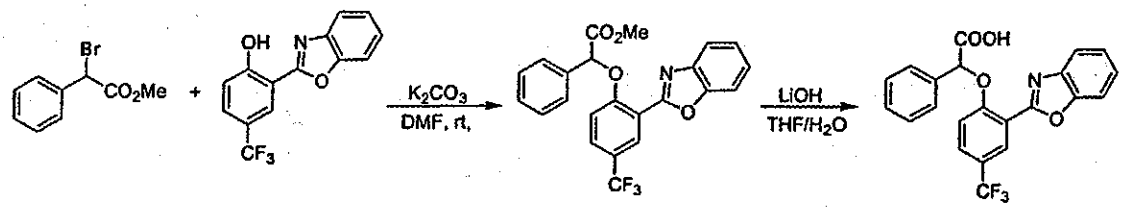
Example 31



SBr-11 PhOH-6 SI-47 I-91

[0215] In the same manner as that described in **Example 28** compound **I-91** was prepared from **SBr-11** and **PhOH-6.** ^{1}H NMR (400 MHz, DMSO): δ 8.42-7.40 (m, 11H), 6.47 (s, 1H).

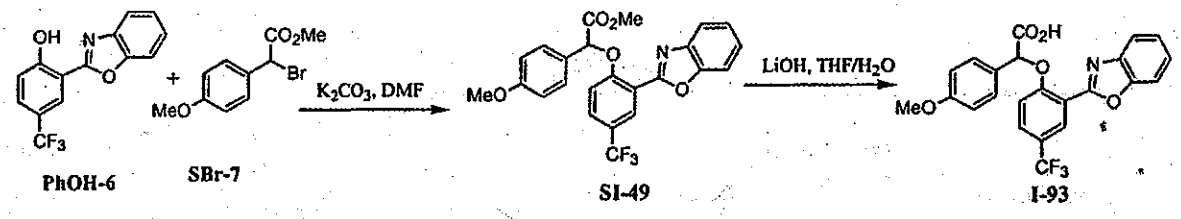
Example 32



SBr-4 PhOH-6 SI-48 I-92

[0216] In the same manner as that described in **Example 28** compound **I-92** was prepared from **SBr-4** and **PhOH-6.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.39 (1H, s), 7.99 (1H, d, J = 8.8 Hz), 7.86 (1H, d, J = 7.2 Hz), 7.77–7.79 (3H, m), 7.40–7.49 (6H, m), 6.27 (1H, s) ppm.

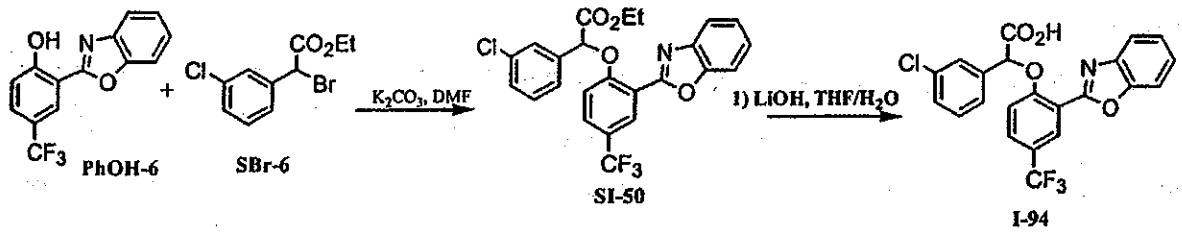
Example 33



PhOH-6 SBr-7 SI-49 I-93

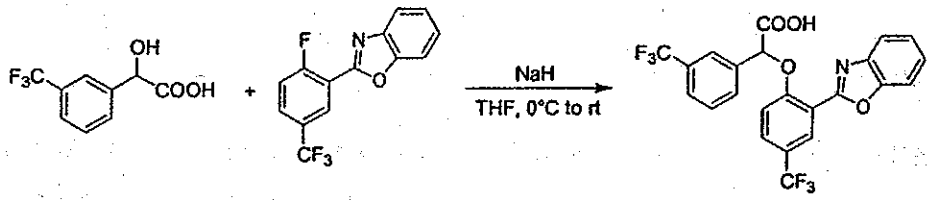
[0217] In the same manner as that described in **Example 28** compound **I-93** was prepared from **SBr-7** and **PhOH-6** as a white solid. ^{1}HNMR (d-DMSO, 400 MHz) δ 13.42 (br, 1H), 8.41 (s, 1H), 8.00 (d, 1H), 7.82 (dd, 2H), 7.70 (d, 2H), 7.42 (m, 3H), 7.05 (d, 2H), 6.22 (s, 1H), 3.79 (s, 3H).

Example 34



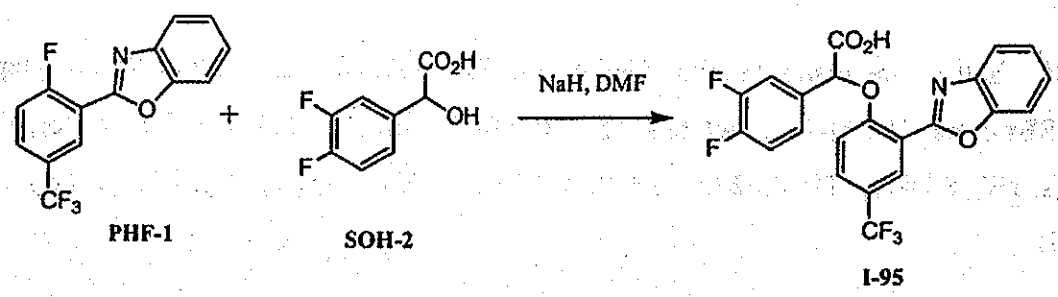
[0218] In the same manner as that described in **Example 28** compound **I-94** was prepared from **SBr-6** and **PhOH-6** as a white solid. ^{1}HNMR (d-DMSO, 400 MHz) δ 13.68 (br, 1H), 8.43 (d, 1H), 8.11 (s, 1H), 8.21 (dd, 1H), 7.89 (m, 1H), 7.83 (m, 1H), 7.70 (d, 1H), 7.50 (m, 4H), 7.42 (d, 1H), 6.40 (s, 1H).

Example 35



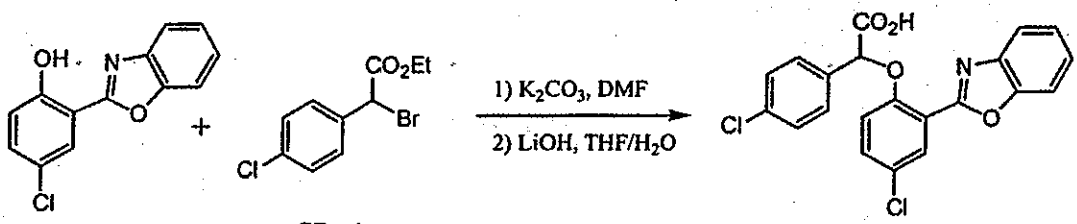
[0219] To a solution of 3-(trifluoromethyl)mandelic acid **SOH-1** (4.8251 g, 0.022 mol) in THF (50 mL) at 0 °C was added NaH (Aldrich, 60%, 4.928 g, 0.055 mol). After stirring for 0.5 h, fluoride **PhF-1** (6.1618 g, 0.022 mol) was added, and then warmed up and stirred at rt overnight. The reaction mixture was cooled to 0 °C and quenched with sat. NH_4Cl (aq.), diluted with EtOAc and water. The organic layer was washed with brine, dried over Na_2SO_4, concentrated *in vacuo*. Purification *via* recrystallization from *i*PrOH (rinsed with 10% EtOAc/hexanes) afforded **I-89** (9.80 g, 92%) as a white solid.

Example 36



[0220] To a solution of **PhF-1** (1.49 g, 5.32 mmol) and **SOH-2** (1 g, 5.32 mmol) in DMF (20 mL) was added NaH (60%, 0.43 g, 10.64 mmol) in one portion at – 10 °C, and the reaction mixture was slowly warmed to room temperature over 0.5 h. After stirring at room temperature for additional 2 h, the mixture was poured into a mixture of ice and 1 N HCl solution, filtered, washed with water and dried. Recrystallization from MeOH gave **I-95** as a white solid (1.94 g). ^{1}HNMR (d-DMSO, 400 MHz) δ 8.42 (d, 1H), 7.99 (m, 2H), 7.85 (m, 1H), 7.79 (d, 1H), 7.58 (m, 2H), 7.49 (m, 2H), 7.44 (d, 1H), 6.38 (s, 1H).

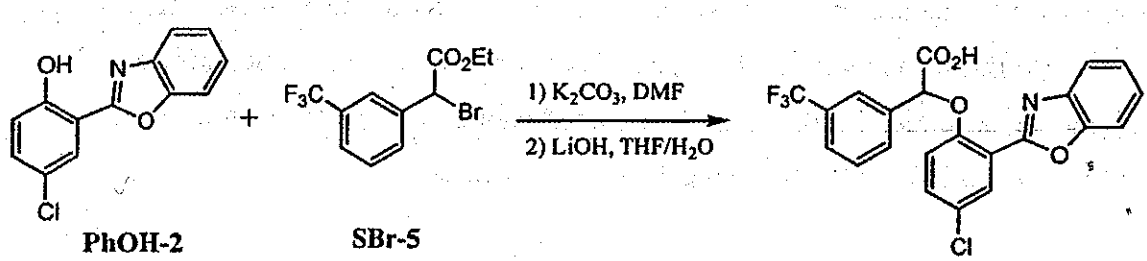
Example 37



PhOH-2 **SBr-1** **I-190**

[0221] In the same manner as that described in **Example 28** compound **I-190** was prepared from **SBr-1** and **PhOH-2** as a white solid. ^{1}HNMR (d-DMSO, 400 MHz) δ 13.6 (br, 1H), 8.10 (d, 1H), 7.84 (m, 4H), 7.66 (dd, 1H), 7.57 (m, 2H), 7.45 (m, 2H), 7.24 (d, 1H), 6.20 (s, 1H).

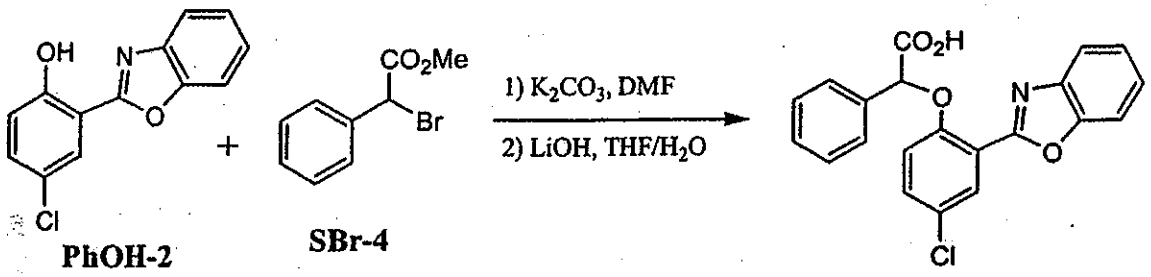
Example 38



PhOH-2 **SBr-5** **I-191**

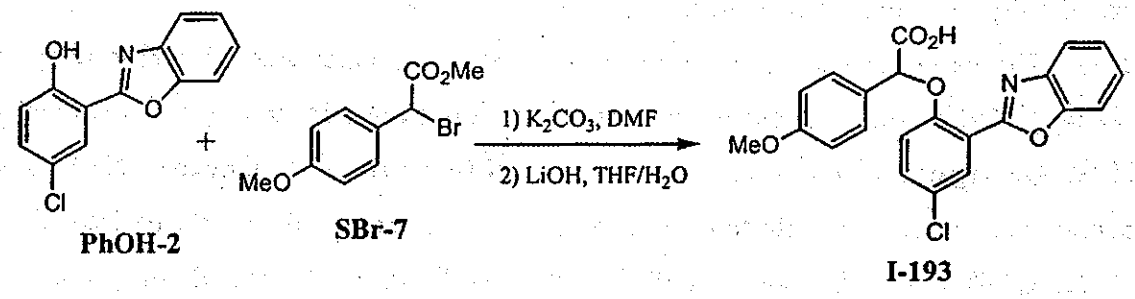
[0222] In the same manner as that described in **Example 28** compound **I-191** was prepared from **SBr-5** and **PhOH-2** as a white solid. ^{1}HNMR (d-DMSO, 400 MHz) δ 13.70 (br, 1H), 8.34 (s, 1H), 8.15 (d, 1H), 8.02 (d, 1H), 7.85-7.71 (m, 5H), 7.50 (m, 2H), 7.29 (d, 1H), 6.40 (s, 1H).

Example 39



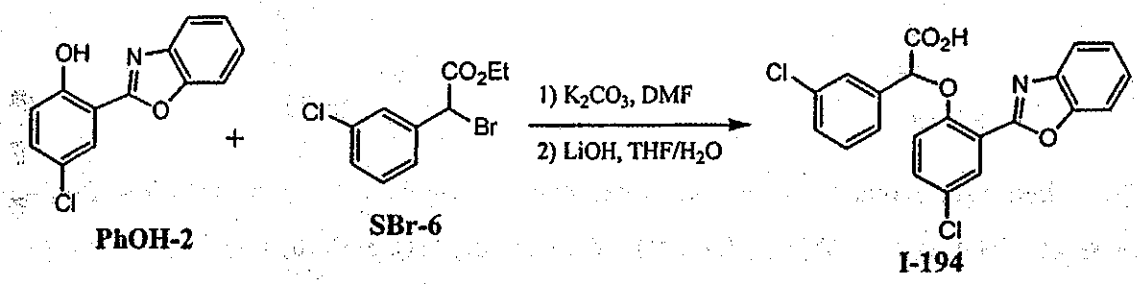
[0223] In the same manner as that described in **Example 28** compound **I-192** was prepared from **SBr-4** and **PhOH-2** as a white solid. ^{1}HNMR (d-DMSO, 400 MHz) δ 13.45 (br, 1H), 8.10 (d, 1H), 7.85 (dd, 1H), 7.75 (m, 3H), 7.67 (dd, 1H), 7.47 (m, 4H), 7.40 (m, 1H), 7.24 (d, 1H), 6.13 (s, 1H).

Example 40



[0224] In the same manner as that described in **Example 28** compound **I-193** was prepared from **SBr-7** and **PhOH-2** as a white solid. ^{1}HNMR (d-DMSO, 400 MHz) δ 13.30 (br, 1H), 8.09 (d, 1H), 7.82 (m, 2H), 7.65 (d, 3H), 7.45 (m, 2H), 7.22 (d, 1H), 7.01 (d, 2H), 6.60 (s, 1H).

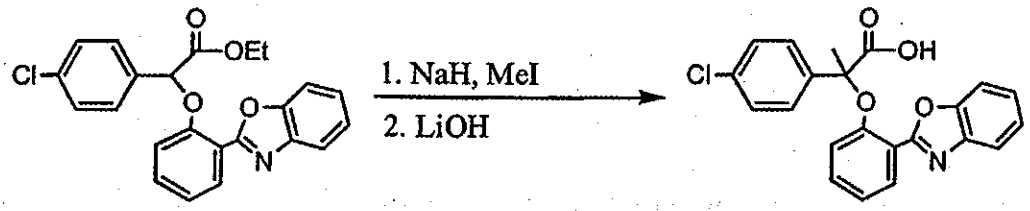
Example 41



[0225] In the same manner as that described in **Example 28** compound **I-194** was prepared from **SBr-6** and **PhOH-2** as a white solid. ^{1}HNMR (d-DMSO, 400 MHz) δ 13.60 (br, 1H),

8.13 (d, 1H), 8.07 (s, 1H), 7.87 (m, 1H), 7.80 (m, 1H), 7.68 (m, 2H), 7.48 (m, 4H), 7.23 (d, 1H), 6.24 (s, 1H).

Example 42

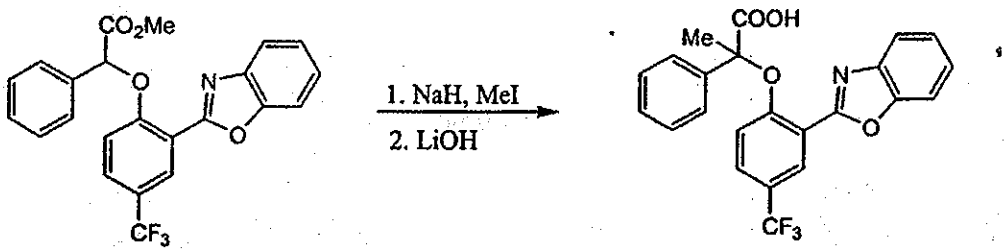


SI-41 **Ia-1**

[0226] To a suspension of NaH (0.44 g) in DMF was added dropwise a solution of ester **SI-41**(3.0 g) in DMF at 0 °C. The reaction mixture was stirred at the same temperature for 30 min, then MeI (0.6 mL) was introduced via syringe. The solution was stirred for one hour, quenched with water, extracted with ethyl acetate. Purification with column chromatography (hexanes/ethyl acetate 5:1) gave the methylated ester (2.1 g).

[0227] The above ester was dissolved in THF (5 mL), and mixed with a LiOH solution (1.0 N, 20 mL). The mixture was stirred at room temperature overnight, and extracted with ethyl acetate. The organic solution was washed with 0.5 N HCl, dried over anhydrous Na_2SO_4, and concentrated. Purification with flash chromatography (ethyl acetate) gave the desired acid **Ia-1** (1.6 g, 80%) as a white solid. ^{1}H NMR (400 MHz, DMSO): δ 7.70-6.61 (m, 12H), 3.30 (s, 3H).

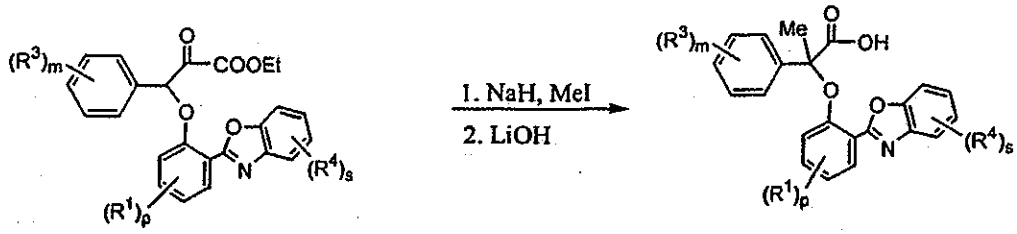
Example 43



SI-48 **Ia-93**

[0228] In the same manner as that described in **Example 42** compound **Ia-93** was prepared from **SI-48.** ^{1}H NMR (d-DMSO, 400 MHz) δ 13.85 (br, 1H), 8.38 (d, 1H), 7.90-7.87 (m, 2H), 7.83-7.79 (m, 3H), 7.52-7.42 (m, 4H), 7.36 (m, 1H), 7.07 (d, 1H), 2.0 (s, 3H).

Example 44



SI-X **Ia-X**

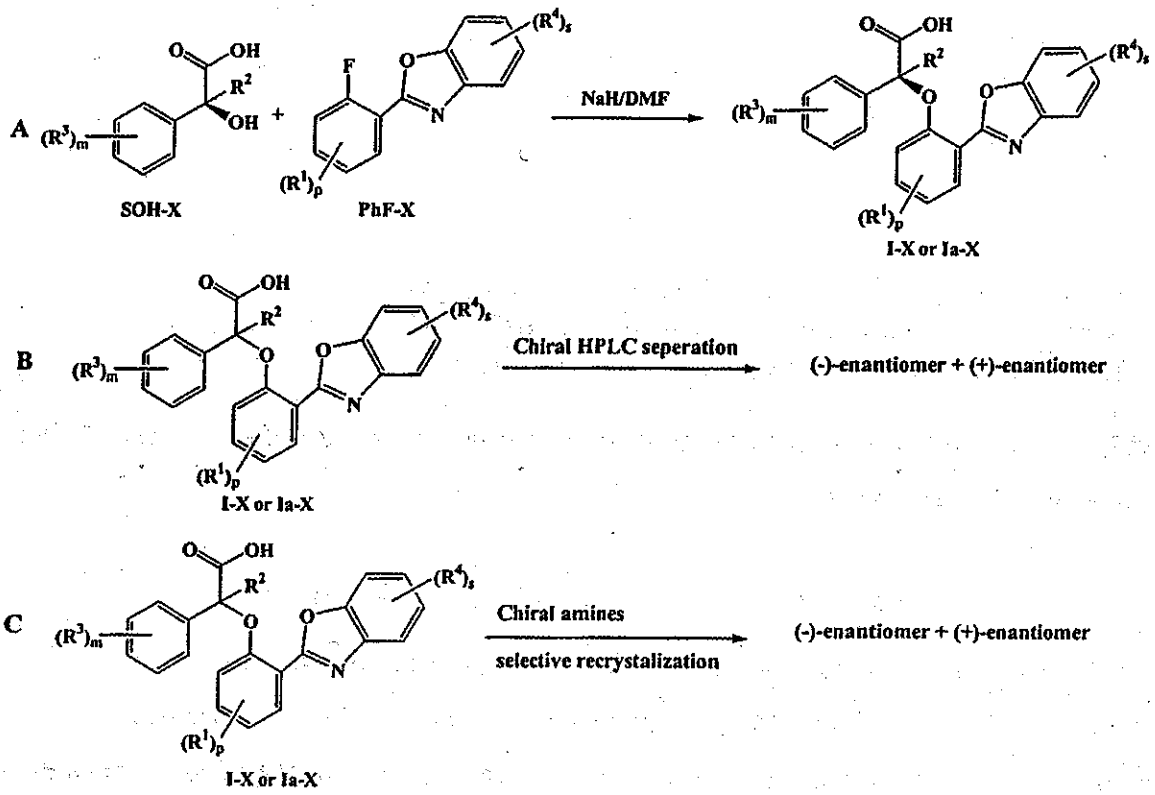
R^3=4-Cl, 3-CF_3, 3-OPh, 3-Cl, 4-OMe, 4-CF_3, 4-Br, H, 4-F, 4-Et
R^1=H, 4'-CF_3, 4'-Cl, 4'-Me, 4'-t-Bu, 4'-Br, 4'6'-di-Cl, 4'-(2,4-diF-Ph), 4'-(1H-pyrrol-yl)
R^4=2"-Me, 2"-Ph, 2"-Cl, 2"OCF_3, 3"-Me, 3"-OMe, 3"-Cl

[0229] In the same manner as that described in **Example 42** the rest of **Ia-X listed in Table 1** can be prepared from **SI-X.**

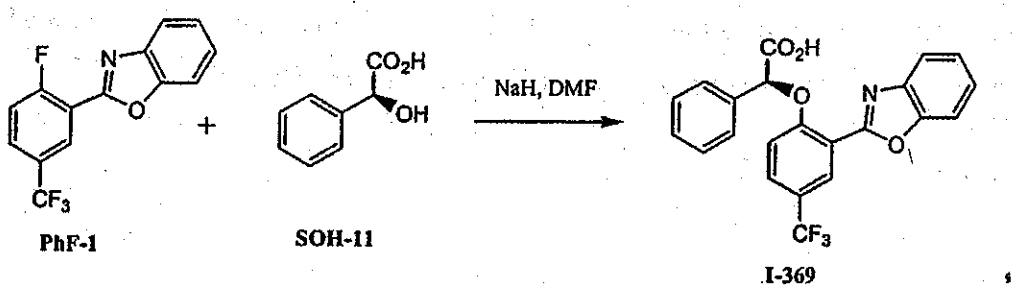
4. Enantioselective synthesis and enantiomer separation

[0230] One or more routes illustrated in **Scheme 4** was or can be used to prepare the individual enantiomers of compound **I-X** and **Ia-X** listed in **Table 1. In route A,** an enantiomerically pure α-hydroxy-phenyl acetic acid was treated with flouro compounds PhF-X with an electron withdrawing group such as CF_3 under strongly basic condition to afford enantiomerically enriched compounds. **In route B,** racemic compounds were resolved into single enantiomers by seperation on a chiral HPLC. **In route C,** racemic compounds were resolved into single enantiomers by recrystalization with a chiral amine.

Scheme 4
Preparation of enantiomerically pure I-X or Ia-X.

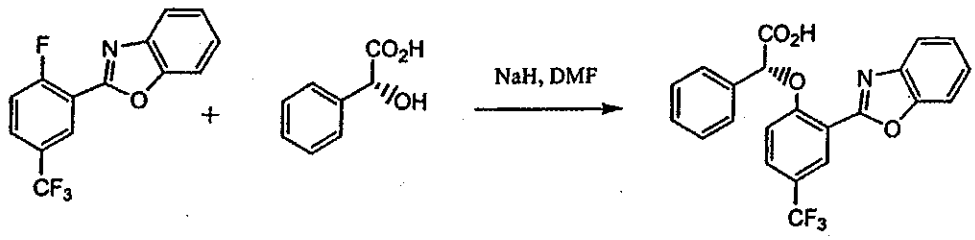


Example 45



[0231] To a solution of **PhF-1** (5.26 g, 0.0187 mol) and **SOH-11** (3.132 g, 0.0206 mol) in DMF (100 mL) was added NaH (60%, 1.484 g, 0.0371 mol) in one portion at – 78 °C, and the reaction mixture was slowly warmed to room temperature over 1 h. After stirring at room temperature for additional 1.5 h, the mixture was poured into a mixture of ice and 1 N HCl solution, filtered, washed with water and dried. Recrystallization from MeOH gave optically pure **I-369** as a white solid (6.56 g). ^{1}H NMR (d-DMSO, 400 MHz) δ 13.48 (br, 1H), 8.41 (d, 1H), 8.0 (dd, 1H), 7.86 (dd, 1H), 7.78 (m, 3H), 7.46 (m, 6H), 6.29 (s, 1H).

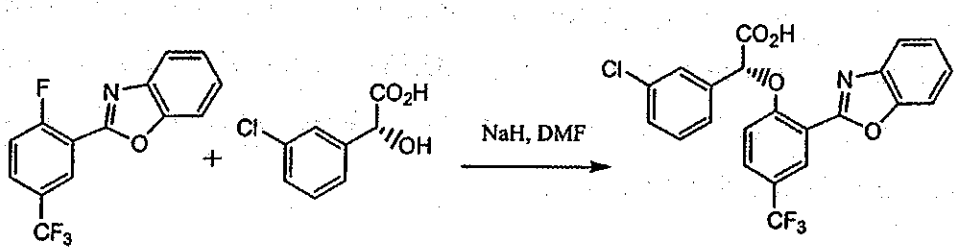
Example 46



PhF-1 SOH-13 I-370

[0232] In the same manner as that described in **Example 45** compound **I-370** was prepared from **PhF-1** and **SOH-13.** ^{1}HNMR (d-DMSO, 400 MHz) δ 13.48 (br, 1H), 8.41 (d, 1H), 8.0 (dd, 1H), 7.86 (dd, 1H), 7.78 (m, 3H), 7.46 (m, 6H), 6.29 (s, 1H).

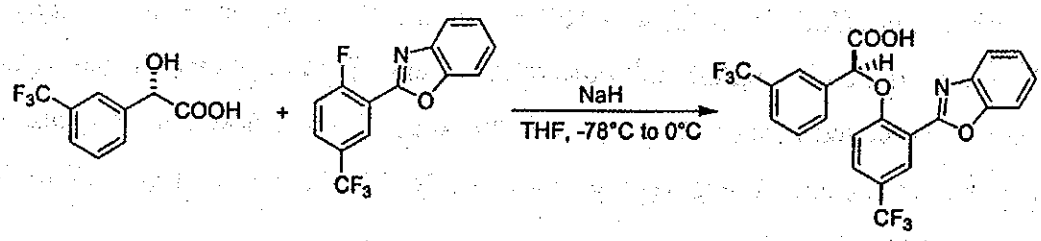
Example 47



PhF-1 SOH-12 I-371

[0233] In the same manner as that described in **Example 45** compound **I-371** was prepared from **PhF-1** and **SOH-12.** ^{1}HNMR (d-DMSO, 400 MHz) δ 13.68 (br, 1H), 8.43 (d, 1H), 8.11 (s, 1H), 8.21 (dd, 1H), 7.89 (m, 1H), 7.83 (m, 1H), 7.70 (d, 1H), 7.50 (m, 4H), 7.42 (d, 1H), 6.40 (s, 1H). **I-367** ee%>20%.

Example 48

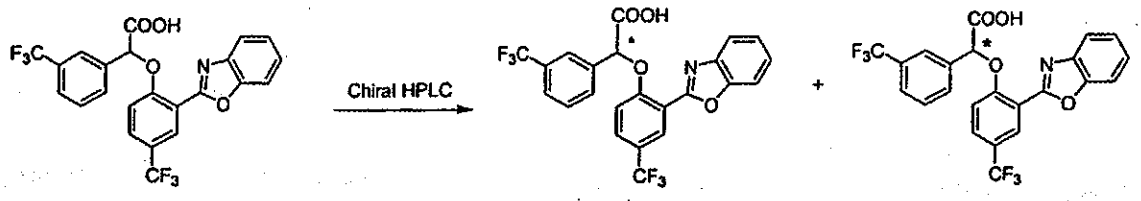


SOH-14 PhF-1 I-89

[0234] To a solution of 3-trifluoromethylmandelic acid **SOH-14** (0.729 g, 3.31 mmol) in THF (20 mL) at -78 °C was added NaH (Aldrich, 60%, 0.594 g, 6.60 mmol). After warming up to -45 °C for 0.5 h, fluoride **PhF-1** (0.9765 g, 3.47 mmol) was added, and then warmed up

to 0 °C overnight. The reaction was checked by chiral HPLC to find that two enantiomers were produced ((+)/(-)-isomer=6:4) with 80% conversion.

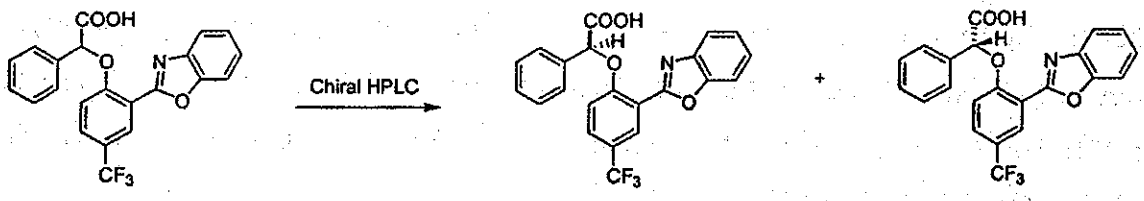
Example 49



I-89 **I-365 (+)-isomer** **I-366 (-)-isomer**

[0235] The two enantiomers were seperated by chiral HPLC using a 25 cm × 21.1 mm Regis Technologies (R,R) WHELK-O 2 10/100 column at ambient temperature. Injected samples were 3.0 mL of 15.5 mg/mL solutions of the racemic **I-89** in *i*PrOH / hexanes (1:1, v/v). The column was eluted with (15/85/0.1) *i*PrOH/hexanes/TFA at a flow rate of 30 mL/min. Detection was at 220 nm. The (+)-enantiomer **I-365** eluted at 6 to 9 min, and the (–)-enantiomer **I-366** at 9.5 to 12 min.

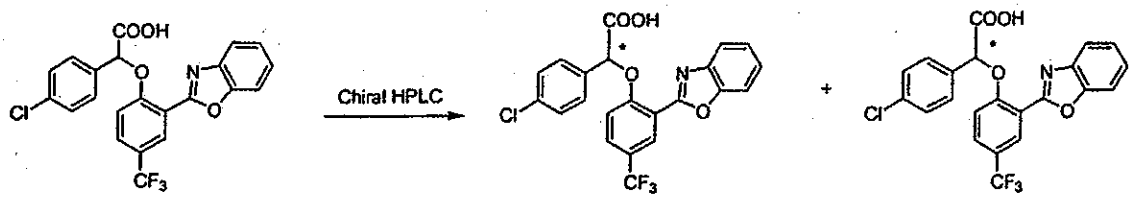
Example 50



I-92 **I-369** **I-370**

[0236] The two enantiomers were seperated by chiral HPLC using a 25 cm × 21.1 mm Regis Technologies (R,R) WHELK-O 2 10/100 column at ambient temperature. Injected samples were 5.0 mL of 7 mg/mL solutions of the racemic **I-92** in *i*PrOH / hexanes (6:4, v/v). The column was eluted with (25/75/0.1) *i*PrOH/hexanes/TFA at a flow rate of 30 mL/min. Detection was at 220 nm. The (*S*)-(+)-enantiomer **I-369** eluted at 5 to 7 min, and the (*R*)-(–)-enantiomer **I-370** at 8 to 10 min.

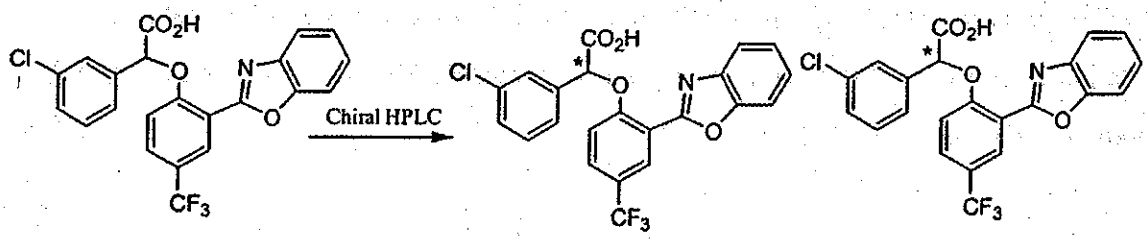
Example 51



I-88 I-372 (+)-isomer I-373 (-)-isomer

[0237] The two enantiomers were seperated by chiral HPLC using a 25 cm x 21.1 mm Regis Technologies (R,R) WHELK-O 2 10/100 column at ambient temperature. Injected samples were 5.0 mL of 7 mg/mL solutions of the racemic **I-88** in *i*PrOH / hexanes (6:4, v/v). The column was eluted with (25/75/0.1) *i*PrOH/hexanes/TFA at a flow rate of 30 mL/min. Detection was at 220 nm. The (+)-enantiomer **I-372** eluted at 6 to 8 min, and the (–)-enantiomer **I-373** at 9 to 11 min.

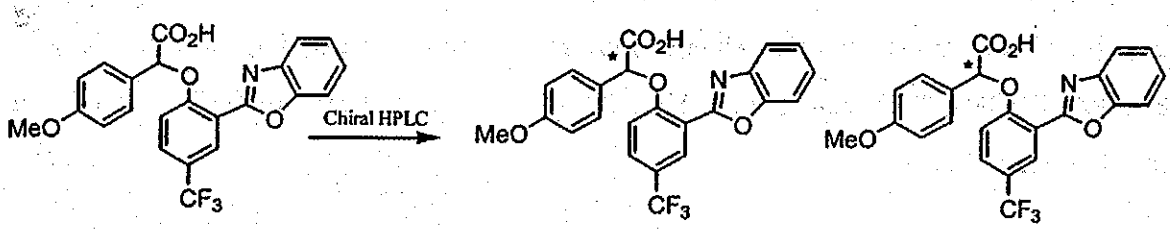
Example 52



I-94 (+)-isomer (-)-isomer

[0238] Racemic **I-94** was resolved by chiral HPLC to give **(+)-I-94** and **(-)-I-94**. HPLC methods and conditions, including eluents used, solvent flow rate and detection wavelength were: 20% iPrOH-80% Hexanes-0.1% TFA, 30 mL/min., λ=220 nm.
For **(+)-I-94**: RT 5.5 min. For **(-)-I-94**: RT 9.5 min.

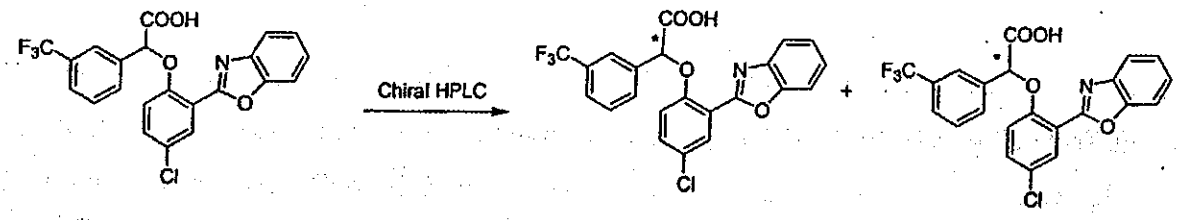
Example 53



I-93 (+)-isomer (-)-isomer

[0239] Racemic **I-93** was resolved by chiral HPLC to give (+)-isomer and (-)-isomer. HPLC methods and conditions, including eluents used, solvent flow rate and detection wavelength were: 50% iPrOH-50% Hexanes-0.1% TFA, 30 mL/min., λ=220 nm. For (+)-isomer: RT 4.7 min. For (-)-isomer: RT 8.75 min.

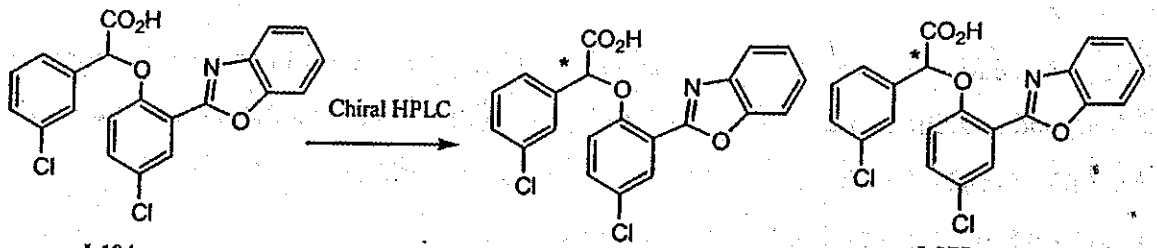
Example 54



I-191 **I-367 (+)-isomer** **I-368 (-)-isomer**

[0240] The two enantiomers were seperated by chiral HPLC using a 25 cm × 21.1 mm Regis Technologies (R,R) WHELK-O 2 10/100 column at ambient temperature. Injected samples were 5.0 mL of 12 mg/mL solutions of the racemic **I-191** in *i*PrOH / hexanes (4:6, v/v). The column was eluted with (15/85/0.1) *i*PrOH/hexanes/TFA at a flow rate of 30 mL/min. Detection was at 220 nm. The (+)-enantiomer **I-367** eluted at 4 to 6 min, and the (–)-enantiomer **I-368** at 7 to 9 min.

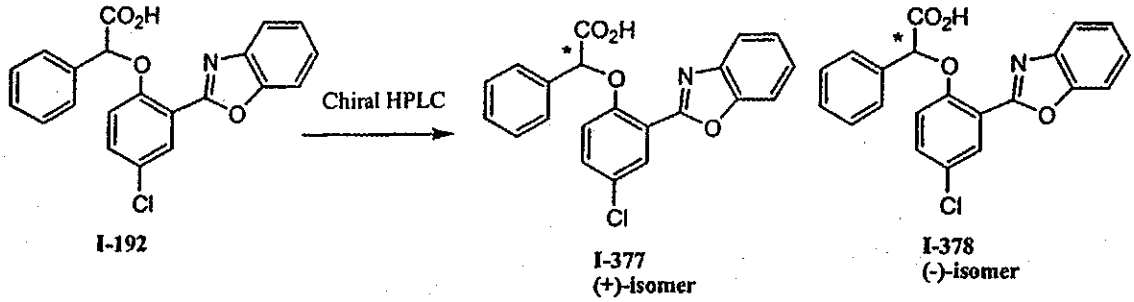
Example 55



I-194 **I-374 (+)-isomer** **I-375 (-)-isomer**

[0241] Racemic **I-194** was resolved by chiral HPLC to give **I-374** and **I-375**. HPLC methods and conditions, including eluents used, solvent flow rate and detection wavelength were: 35% iPrOH-65% Hexanes-0.1% TFA, 30 mL/min., λ=220 nm. For **I-374**: RT 4.7 min. For **I-375**: RT 6.7 min.

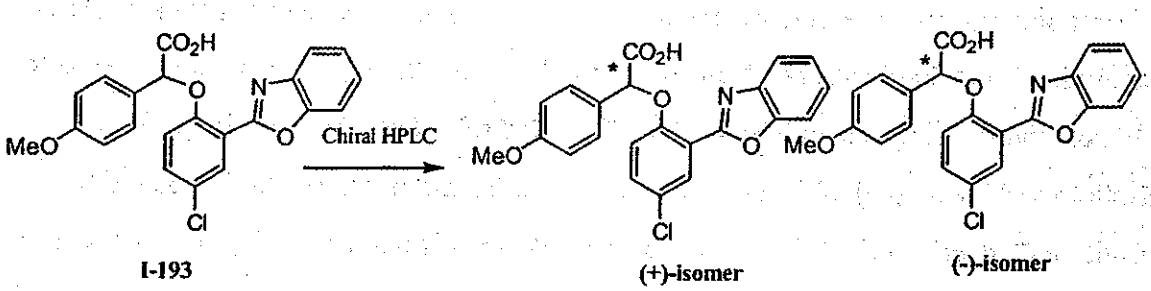
Example 56



I-192 I-377 (+)-isomer I-378 (-)-isomer

[0242] Racemic **I-192** was resolved by chiral HPLC to give **I-377** and **I-378**. HPLC methods and conditions, including eluents used, solvent flow rate and detection wavelength were: 50% iPrOH-50% Hexanes-0.1% TFA, 30 mL/min., λ=220 nm. For **I-377**: RT 5.4 min. For **I-378**: RT 7.8 min.

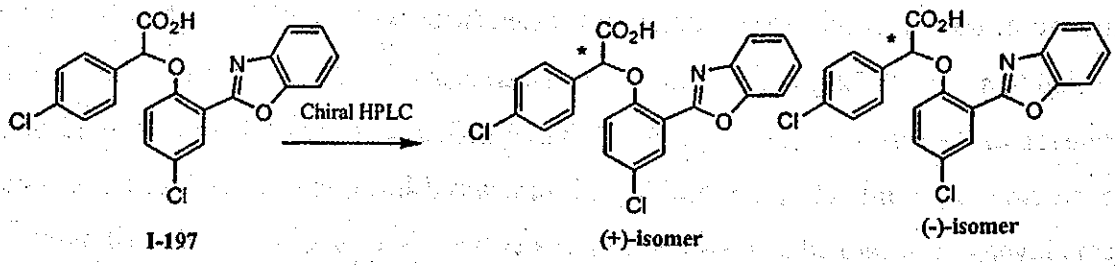
Example 57



I-193 (+)-isomer (-)-isomer

[0243] Racemic **I-193** was resolved by chiral HPLC to give **(+)-I-193** and **(-)-I-193**. HPLC methods and conditions, including eluents used, solvent flow rate and detection wavelength were: 50% iPrOH-50% Hexanes-0.1% TFA, 30 mL/min., λ=220 nm. For **(+)-I-193**: RT 5.5 min. For **(-)-I-193**: RT 11.5 min.

Example 58

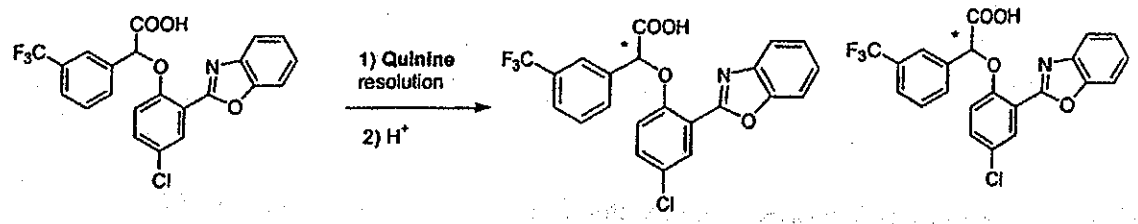


I-197 (+)-isomer (-)-isomer

[0244] Racemic **I-197** was resolved by chiral HPLC to give (+)-isomer and (-)-isomer. HPLC methods and conditions, including eluents used, solvent flow rate and detection

wavelength were: 40% iPrOH-60% Hexanes-0.1% TFA, 30 mL/min., λ=220 nm. For (+)-isomer: RT 4.2 min. For (-)-isomer: RT 7.5 min.

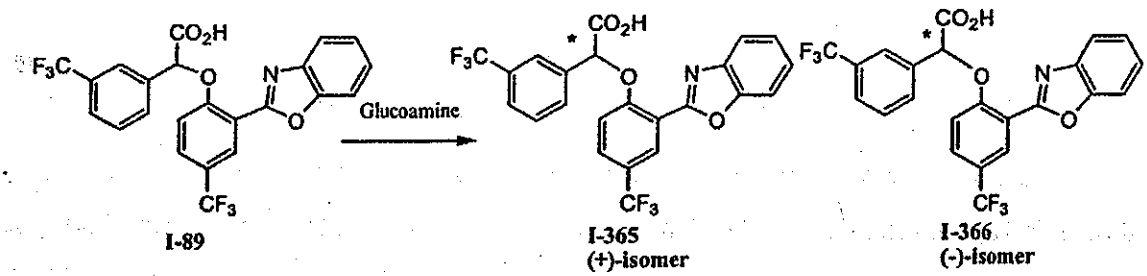
Example 59



[0245] A suspension of **I-191** (37.44 g, 0.084 mol) in 750 mL of EtOH 3A was heated to reflux at 90 °C (water-bath temperature) to give a cloudy solution, then cooled to ca. 80 °C. Quinine (25.34 g, 0.078 mol) was added, and the resulting clear solution was stirred at 70–80 °C. (internal solution temperature) and solid began to crash out of the hot solution. After stirring for 1 h at 70–80 °C, and then cooled to 50°C with stirring. The solid was collected by filtration and rinsed twice with EtOH 3A. The dried solid (ca. 33 g) had an 90–93% enantiomeric excess (ee) of the (+) enantiomer, and the mother liquor had an 85–90% enantiomeric excess (ee) of the (–) enantiomer. When this hot mother liquor was cooled to rt, a second crop solid (17.0g) was obtained. This solid had a 99% ee of the (-)-enatiomer. Chiral HPLC analysis was carried out at λ = 220 nm by injecting 10 μL of an approximately a 0.5 mg/mL solution of the sample dissolved in mobile phase onto a 25 cm × 4.6 mm Regis Technologies (R,R) Whelk-O 1 5 μm column with a 1.5 mL/min flow of (25/75/0.1) *i*PrOH/hexanes/TFA. Under these conditions, (+) enantiomer **I-367** eluted at 4.3 min, and (–) enantiomer at 5.8 min (approximate retention times). To the crude (+) salt (33 g) obtained above was added 520 mL of EtOH 3A, and the suspension was refluxed at 106 °C (oil-bath temperature) for 3 h, cooled to rt, filtered and rinsed twice with EtOH 3A. The white solid was dried to afford 28.32 g of the desired (+) enantiomer salt with an ee of 97–99%. To a suspension of the resolved salt (28 g) in 350 mL of EtOAc was added 45 mL of 2N H_2SO_4. After stirring for 10 min at rt, the resulting mixture was diluted with water (100 mL). The organic layer was separated and washed with water twice and then brine and dried over Na_2SO_4. After removal of solvents *in vacuo* and dried at 40–45 °C / 3 mmHg, 16.26 g of desired (+) enantiomer **I-367** was obtained. Similarly, (+) enantiomer **I-367** was also obtained

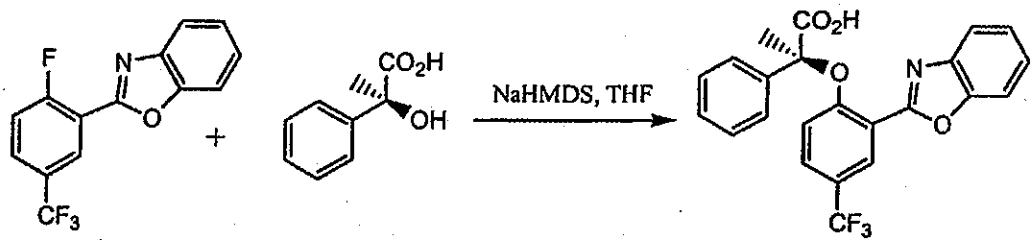
by resolution of racemic **I-191** using cinchonidine (0.9 eq.) in EtOH 3A with 60% recovery of (+) enantiomer with a 97–99% ee.

Example 60



[0246] (+) enantiomer **I-365** and (–) enantiomer **I-366** were obtained by resolution of racemic **I-89** using *N*-methyl-D-glucamine (0.9 eq.) in EtOH 3A by a similar procedure as **Example** 59 above. Chiral HPLC analysis was carried out at $\lambda = 220$ nm by injecting 10 µL of a 0.5 mg/mL solution of the sample dissolved in mobile phase onto a 25 cm × 4.6 mm Regis Technologies (R,R) Whelk-O 1 5 µm column with a 1.5 mL/min flow of (15/85/0.1) *i*PrOH/hexanes/TFA. Under these conditions, (+) enantiomer **I-377** eluted at 4.5 min, and (–) enantiomer at 5.9 min (approximate retention times).

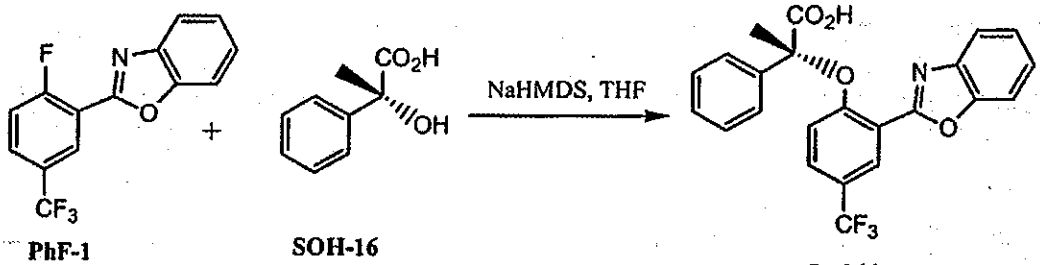
Example 61



PhF-1 SOH-15 Ia-365

[0247] To a solution of **SOH-15** (0.62 g, 3.73 mmol) in THF (10 mL) was added NaHMDS (1.0 M in THF, 7.83 mL) at – 10 °C and the reaction was warmed to room temperature. After stirring at room temperature for 10 min., a solution of **PhF-1** (1.05 g, 3.73 mmol) in THF (10 mL) was added. The reaction mixture was heated at 60°C for 1 h, and then stirred overnight at room temperature. The reaction was quenched with 1 N HCl solution, extracted with EtOAc, washed with brine, dried and concentrated. The residue was purified by flash column (hexane/EtOAc 10:1) to give compound **Ia-365** as a white solid (0.72 g, 45%). ^{1}HNMR (d-DMSO, 400 MHz) δ 8.38 (d, 1H), 7.89 (m, 2H), 7.81 (m, 3H), 7.48 (m, 4H), 7.36 (m, 1H), 7.07 (d, 1H), 2.0 (s, 3H).

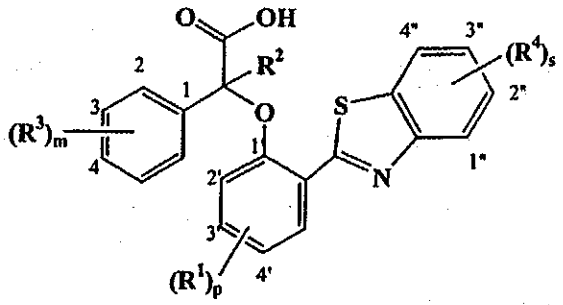
Example 62



PhF-1 SOH-16 Ia-366

[0248] **Ia-366** was obtained as a white solid from **PhF-1** and **SOH-16** in the same manner as that described in **Example 61**. ^{1}HNMR (d-DMSO, 400 MHz) δ 8.38 (d, 1H), 7.89 (m, 2H), 7.81 (m, 3H), 7.48 (m, 4H), 7.36 (m, 1H), 7.07 (d, 1H), 2.0 (s, 3H).

Table 2: 2-benzothiazole analogs



Compounds II and IIa

Compound	R^2	$(R^3)_m$	$(R^1)_p$	$(R^4)_s$	Configuration
II-1	H	4-Cl	H	H	R/S
II-2	H	3-CF_3	H	H	R/S
II-3	H	3-OPh	H	H	R/S
II-4	H	3-Cl	H	H	R/S
II-5	H	4-OMe	H	H	R/S
II-6	H	4-CF_3	H	H	R/S
II-7	H	4-Br	H	H	R/S
II-8	H	H	H	H	R/S
II-9	H	4-F	H	H	R/S
II-10	H	4-Et	H	H	R/S
II-11	H	4-Cl	H	2"-Cl	R/S
II-12	H	3-CF_3	H	2"-Cl	R/S
II-13	H	3-OPh	H	2"-Cl	R/S
II-14	H	3-Cl	H	2"-Cl	R/S
II-15	H	4-OMe	H	2"-Cl	R/S
II-16	H	4-CF_3	H	2"-Cl	R/S
II-17	H	4-Br	H	2"-Cl	R/S

II-18	H	H	H	2"-Cl	R/S
II-19	H	4-F	H	2"-Cl	R/S
II-20	H	4-Et	H	2"-Cl	R/S
II-21	H	H	4'-CF_3	H	R/S
II-22	H	3-CF_3	4'-CF_3	H	R/S
II-23	H	3-OPh	4'-CF_3	H	R/S
II-24	H	4-CF_3	4'-CF_3	H	R/S
II-25	H	4-Et	4'-CF_3	H	R/S
II-26	H	4-Cl	4'-CF_3	H	R/S
II-27	H	4-OMe	4'-CF_3	H	R/S
II-28	H	3-Br	4'-CF_3	H	R/S
II-29	H	3-Cl	4'-CF_3	H	R/S
II-30	H	3-OMe	4'-CF_3	H	R/S
II-31	H	4-Me	4'-CF_3	H	R/S
II-32	H	4-Br	4'-CF_3	H	R/S
II-33	H	3-NO_2	4'-CF_3	H	R/S
II-34	H	3,4-methylenedioxy	4'-CF_3	H	R/S
II-35	H	4-F	4'-CF_3	H	R/S
II-36	H	2,3-di-F	4'-CF_3	H	R/S
II-37	H	2,4-di-F	4'-CF_3	H	R/S
II-38	H	2,5-di-F	4'-CF_3	H	R/S
II-40	H	2,6-di-F	4'-CF_3	H	R/S
II-41	H	3,4-di-F	4'-CF_3	H	R/S
II-42	H	3,5-di-F	4'-CF_3	H	R/S
II-43	H	2,3,5-tri-F	4'-CF_3	H	R/S
II-44	H	4-MeS	4'-CF_3	H	R/S

II-45	H	4-NO_2	4'-CF_3	H	R/S
II-46	H	2,5-di-Me	4'-CF_3	H	R/S
II-47	H	4-Cl	4'-CF_3	2"-Cl	R/S
II-48	H	3-CF_3	4'-CF_3	2"-Cl	R/S
II-49	H	3-OPh	4'-CF_3	2"-Cl	R/S
II-50	H	3-Cl	4'-CF_3	2"-Cl	R/S
II-51	H	4-OMe	4'-CF_3	2"-Cl	R/S
II-52	H	4-CF_3	4'-CF_3	2"-Cl	R/S
II-53	H	4-Br	4'-CF_3	2"-Cl	R/S
II-54	H	H	4'-CF_3	2"-Cl	R/S
II-55	H	4-F	4'-CF_3	2"-Cl	R/S
II-56	H	4-Et	4'-CF_3	2"-Cl	R/S
II-57	H	4-Cl	4'-CF_3	2"- CF_3	R/S
II-58	H	3-CF_3	4'-CF_3	2"- CF_3	R/S
II-59	H	3-OPh	4'-CF_3	2"- CF_3	R/S
II-60	H	3-Cl	4'-CF_3	2"- CF_3	R/S
II-61	H	4-OMe	4'-CF_3	2"- CF_3	R/S
II-62	H	4-CF_3	4'-CF_3	2"- CF_3	R/S
II-63	H	4-Br	4'-CF_3	2"- CF_3	R/S
II-64	H	H	4'-CF_3	2"- CF_3	R/S
II-65	H	4-F	4'-CF_3	2"- CF_3	R/S
II-66	H	4-Et	4'-CF_3	2"- CF_3	R/S
II-67	H	3-Cl	4',6'-di Cl	H	R/S
II-68	H	3-CF_3	4',6'-di Cl	H	R/S
II-69	H	3-OPh	4',6'-di Cl	H	R/S
II-70	H	4-OMe	4',6'-di Cl	H	R/S

II-71	H	4-Cl	4',6'-di Cl	H	R/S
II-72	H	4-CF_3	4',6'-di Cl	H	R/S
II-73	H	4-Br	4',6'-di Cl	H	R/S
II-74	H	H	4',6'-di Cl	H	R/S
II-75	H	4-F	4',6'-di Cl	H	R/S
II-76	H	4-Et	4',6'-di Cl	H	R/S
II-77	H	3-Cl	4'-(2,4-diF-Ph)	H	R/S
II-78	H	3-CF_3	4'-(2,4-diF-Ph)	H	R/S
II-79	H	3-OPh	4'-(2,4-diF-Ph)	H	R/S
II-80	H	4-OMe	4'-(2,4-diF-Ph)	H	R/S
II-81	H	4-Cl	4'-(2,4-diF-Ph)	H	R/S
II-82	H	4-CF_3	4'-(2,4-diF-Ph)	H	R/S
II-83	H	4-Br	4'-(2,4-diF-Ph)	H	R/S
II-84	H	H	4'-(2,4-diF-Ph)	H	R/S
II-85	H	4-F	4'-(2,4-diF-Ph)	H	R/S
II-86	H	4-Et	4'-(2,4-diF-Ph)	H	R/S
II-87	H	3-Cl	4'-(1H-pyrrol-yl)	H	R/S
II-88	H	3-CF_3	4'-(1H-pyrrol-yl)	H	R/S
II-89	H	3-OPh	4'-(1H-pyrrol-yl)	H	R/S
II-90	H	4-OMe	4'-(1H-pyrrol-yl)	H	R/S
II-91	H	4-Cl	4'-(1H-pyrrol-yl)	H	R/S
II-92	H	4-CF_3	4'-(1H-pyrrol-yl)	H	R/S
II-93	H	4-Br	4'-(1H-pyrrol-yl)	H	R/S
II-94	H	H	4'-(1H-pyrrol-yl)	H	R/S
II-95	H	4-F	4'-(1H-pyrrol-yl)	H	R/S
II-96	H	4-Et	4'-(1H-pyrrol-yl)	H	R/S

II-97	H	4-Cl	4'-Cl	H	R/S
II-98	H	3-CF_3	4''-Cl	H	R/S
II-99	H	3-OPh	4'-Cl	H	R/S
II-100	H	3-Cl	4'-Cl	H	R/S
II-101	H	4-OMe	4'-Cl	H	R/S
II-102	H	4-CF_3	4'-Cl	H	R/S
II-103	H	4-Br	4'-Cl	H	R/S
II-104	H	H	4'-Cl	H	R/S
II-105	H	4-F	4'-Cl	H	R/S
II-106	H	4-Et	4'-Cl	H	R/S
II-107	H	4-Cl	4'-Cl	2''-Cl	R/S
II-108	H	3-CF_3	4'-Cl	2''-Cl	R/S
II-109	H	3-OPh	4'-Cl	2''-Cl	R/S
II-110	H	3-Cl	4'-Cl	2''-Cl	R/S
II-112	H	4-OMe	4'-Cl	2''-Cl	R/S
II-113	H	4-CF_3	4'-Cl	2''-Cl	R/S
II-114	H	4-Br	4'-Cl	2''-Cl	R/S
II-115	H	H	4'-Cl	2''-Cl	R/S
II-116	H	4-F	4'-Cl	2''-Cl	R/S
II-117	H	4-Et	4'-Cl	2''-Cl	R/S
II-118	H	4-Cl	4'-Cl	2''- CF_3	R/S
II-119	H	3-CF_3	4'-Cl	2''- CF_3	R/S
II-120	H	3-OPh	4'-Cl	2''- CF_3	R/S
II-121	H	3-Cl	4'-Cl	2''- CF_3	R/S
II-122	H	4-OMe	4'-Cl	2''- CF_3	R/S
II-123	H	4-CF_3	4'-Cl	2''- CF_3	R/S

II-124	H	4-Br	4'-Cl	2"- CF_3	R/S
II-125	H	H	4'-Cl	2"- CF_3	R/S
II-126	H	4-F	4'-Cl	2"- CF_3	R/S
II-127	H	4-Et	4'-Cl	2"- CF_3	R/S
II-128	H	3-Cl	4'-Me	H	R/S
II-129	H	3-CF_3	4'-Me	H	R/S
II-130	H	3-OPh	4'-Me	H	R/S
II-131	H	4-OMe	4'-Me	H	R/S
II-132	H	4-Cl	4'-Me	H	R/S
II-133	H	4-CF_3	4'-Me	H	R/S
II-134	H	4-Br	4'-Me	H	R/S
II-135	H	H	4'-Me	H	R/S
II-136	H	4-F	4'-Me	H	R/S
II-137	H	4-Et	4'-Me	H	R/S
II-138	H	3-Cl	4'-tBu	H	R/S
II-139	H	3-CF_3	4'-tBu	H	R/S
II-140	H	3-OPh	4'-tBu	H	R/S
II-141	H	4-OMe	4'-tBu	H	R/S
II-142	H	4-Cl	4'-tBu	H	R/S
II-143	H	4-CF_3	4'-tBu	H	R/S
II-144	H	4-Br	4'-tBu	H	R/S
II-145	H	H	4'-tBu	H	R/S
II-146	H	4-F	4'-tBu	H	R/S
II-147	H	4-Et	4'-tBu	H	R/S
II-148	H	3-Cl	4'-Br	H	R/S
II-149	H	3-CF_3	4'-Br	H	R/S

II-150	H	3-OPh	4'-Br	H	R/S
II-151	H	4-OMe	4'-Br	H	R/S
II-152	H	4-Cl	4'-Br	H	R/S
II-153	H	4-CF_3	4'-Br	H	R/S
II-154	H	4-Br	4'-Br	H	R/S
II-155	H	H	4'-Br	H	R/S
II-156	H	4-F	4'-Br	H	R/S
II-157	H	4-Et	4'-Br	H	R/S
IIa-1	Me	4-Cl	H	H	R/S
IIa-2	Me	3-CF_3	H	H	R/S
IIa-3	Me	3-OPh	H	H	R/S
IIa-4	Me	3-Cl	H	H	R/S
IIa-5	Me	4-OMe	H	H	R/S
IIa-6	Me	4-CF_3	H	H	R/S
IIa-7	Me	4-Br	H	H	R/S
IIa-8	Me	H	H	H	R/S
IIa-9	Me	4-F	H	H	R/S
IIa-10	Me	4-Et	H	H	R/S
IIa-11	Me	4-Cl	H	2"-Cl	R/S
IIa-12	Me	3-CF_3	H	2"-Cl	R/S
IIa-13	Me	3-OPh	H	2"-Cl	R/S
IIa-14	Me	3-Cl	H	2"-Cl	R/S
IIa-15	Me	4-OMe	H	2"-Cl	R/S
IIa-16	Me	4-CF_3	H	2"-Cl	R/S
IIa-17	Me	4-Br	H	2"-Cl	R/S
IIa-18	Me	H	H	2"-Cl	R/S

IIa-19	Me	4-F	H	2"-Cl	R/S
IIa-20	Me	4-Et	H	2"-Cl	R/S
IIa-21	Me	4-Cl	4'-CF_3	H	R/S
IIa-22	Me	3-OPh	4'-CF_3	H	R/S
IIa-23	Me	3-CF_3	4'-CF_3	H	R/S
IIa-24	Me	H	4'-CF_3	H	R/S
IIa-25	Me	4-OMe	4'-CF_3	H	R/S
IIa-26	Me	4-CF_3	4'-CF_3	H	R/S
IIa-27	Me	3-Cl	4'-CF_3	H	R/S
IIa-28	Me	3-OMe	4'-CF_3	H	R/S
IIa-29	Me	4-Br	4'-CF_3	H	R/S
IIa-30	Me	3-NO_2	4'-CF_3	H	R/S
IIa-31	Me	3,4-methylenedioxy	4'-CF_3	H	R/S
IIa-32	Me	4-F	4'-CF_3	H	R/S
IIa-33	Me	2,3-di-F	4'-CF_3	H	R/S
IIa-34	Me	2,4-di-F	4'-CF_3	H	R/S
IIa-35	Me	2,5-di-F	4'-CF_3	H	R/S
IIa-36	Me	2,6-di-F	4'-CF_3	H	R/S
IIa-37	Me	3,4-di-F	4'-CF_3	H	R/S
IIa-38	Me	3,5-di-F	4'-CF_3	H	R/S
IIa-40	Me	2,3,5-tri-F	4'-CF_3	H	R/S
IIa-41	Me	4-Et	4'-CF_3	H	R/S
IIa-42	Me	H	4'-CF_3	H	R/S
IIa-43	Me	4-Me	4'-CF_3	H	R/S
IIa-44	Me	4-MeS	4'-CF_3	H	R/S
IIa-45	Me	4-NO_2	4'-CF_3	H	R/S

IIa-46	Me	2,5-di-Me	4'-CF_3	H	R/S
IIa-47	Me	4-Cl	4'-CF_3	2"-Cl	R/S
IIa-48	Me	3-CF_3	4'-CF_3	2"-Cl	R/S
IIa-49	Me	3-OPh	4'-CF_3	2"-Cl	R/S
IIa-50	Me	3-Cl	4'-CF_3	2"-Cl	R/S
IIa-51	Me	4-OMe	4'-CF_3	2"-Cl	R/S
IIa-52	Me	4-CF_3	4'-CF_3	2"-Cl	R/S
IIa-53	Me	4-Br	4'-CF_3	2"-Cl	R/S
IIa-54	Me	H	4'-CF_3	2"-Cl	R/S
IIa-55	Me	4-F	4'-CF_3	2"-Cl	R/S
IIa-56	Me	4-Et	4'-CF_3	2"-Cl	R/S
IIa-57	Me	4-Cl	4'-CF_3	2"- CF_3	R/S
IIa-58	Me	3-CF_3	4'-CF_3	2"- CF_3	R/S
IIa-59	Me	3-OPh	4'-CF_3	2"- CF_3	R/S
IIa-60	Me	3-Cl	4'-CF_3	2"- CF_3	R/S
IIa-61	Me	4-OMe	4'-CF_3	2"- CF_3	R/S
IIa-62	Me	4-CF_3	4'-CF_3	2"- CF_3	R/S
IIa-63	Me	4-Br	4'-CF_3	2"- CF_3	R/S
IIa-64	Me	H	4'-CF_3	2"- CF_3	R/S
IIa-65	Me	4-F	4'-CF_3	2"- CF_3	R/S
IIa-66	Me	4-Et	4'-CF_3	2"- CF_3	R/S
IIa-67	Me	3-Cl	4',6'-di Cl	H	R/S
IIa-68	Me	3-CF_3	4',6'-di Cl	H	R/S
IIa-69	Me	3-OPh	4',6'-di Cl	H	R/S
IIa-70	Me	4-OMe	4',6'-di Cl	H	R/S
IIa-71	Me	4-Cl	4',6'-di Cl	H	R/S

IIa-72	Me	4-CF_3	4',6'-di Cl	H	R/S
IIa-73	Me	4-Br	4',6'-di Cl	H	R/S
IIa-74	Me	H	4',6'-di Cl	H	R/S
IIa-75	Me	4-F	4',6'-di Cl	H	R/S
IIa-76	Me	4-Et	4',6'-di Cl	H	R/S
IIa-77	Me	3-Cl	4'-(2,4-diF-Ph)	H	R/S
IIa-78	Me	3-CF_3	4'-(2,4-diF-Ph)	H	R/S
IIa-79	Me	3-OPh	4'-(2,4-diF-Ph)	H	R/S
IIa-80	Me	4-OMe	4'-(2,4-diF-Ph)	H	R/S
IIa-81	Me	4-Cl	4'-(2,4-diF-Ph)	H	R/S
IIa-82	Me	4-CF_3	4'-(2,4-diF-Ph)	H	R/S
IIa-83	Me	4-Br	4'-(2,4-diF-Ph)	H	R/S
IIa-84	Me	H	4'-(2,4-diF-Ph)	H	R/S
IIa-85	Me	4-F	4'-(2,4-diF-Ph)	H	R/S
IIa-86	Me	4-Et	4'-(2,4-diF-Ph)	H	R/S
IIa-87	Me	3-Cl	4'-(1H-pyrrol-yl)	H	R/S
IIa-88	Me	3-CF_3	4'-(1H-pyrrol-yl)	H	R/S
IIa-89	Me	3-OPh	4'-(1H-pyrrol-yl)	H	R/S
IIa-90	Me	4-OMe	4'-(1H-pyrrol-yl)	H	R/S
IIa-91	Me	4-Cl	4'-(1H-pyrrol-yl)	H	R/S
IIa-92	Me	4-CF_3	4'-(1H-pyrrol-yl)	H	R/S
IIa-93	Me	4-Br	4'-(1H-pyrrol-yl)	H	R/S
IIa-94	Me	H	4'-(1H-pyrrol-yl)	H	R/S
IIa-95	Me	4-F	4'-(1H-pyrrol-yl)	H	R/S
IIa-96	Me	4-Et	4'-(1H-pyrrol-yl)	H	R/S
IIa-97	Me	4-Cl	4'-Cl	H	R/S

IIa-98	Me	3-CF_3	4'-Cl	H	R/S
IIa-99	Me	3-OPh	4'-Cl	H	R/S
IIa-100	Me	3-Cl	4'-Cl	H	R/S
IIa-101	Me	4-OMe	4'-Cl	H	R/S
IIa-102	Me	4-CF_3	4'-Cl	H	R/S
IIa-103	Me	4-Br	4'-Cl	H	R/S
IIa-104	Me	H	4'-Cl	H	R/S
IIa-105	Me	4-F	4'-Cl	H	R/S
IIa-106	Me	4-Et	4'-Cl	H	R/S
IIa-107	Me	4-Cl	4'-Cl	2"-Cl	R/S
IIa-108	Me	3-CF_3	4'-Cl	2"-Cl	R/S
IIa-109	Me	3-OPh	4'-Cl	2"-Cl	R/S
IIa-110	Me	3-Cl	4'-Cl	2"-Cl	R/S
IIa-112	Me	4-OMe	4'-Cl	2"-Cl	R/S
IIa-113	Me	4-CF_3	4'-Cl	2"-Cl	R/S
IIa-114	Me	4-Br	4'-Cl	2"-Cl	R/S
IIa-115	Me	H	4'-Cl	2"-Cl	R/S
IIa-116	Me	4-F	4'-Cl	2"-Cl	R/S
IIa-117	Me	4-Et	4'-Cl	2"-Cl	R/S
IIa-118	Me	4-Cl	4'-Cl	2"- CF_3	R/S
IIa-119	Me	3-CF_3	4'-Cl	2"- CF_3	R/S
IIa-120	Me	3-OPh	4'-Cl	2"- CF_3	R/S
IIa-121	Me	3-Cl	4'-Cl	2"- CF_3	R/S
IIa-122	Me	4-OMe	4'-Cl	2"- CF_3	R/S
IIa-123	Me	4-CF_3	4'-Cl	2"- CF_3	R/S
IIa-124	Me	4-Br	4'-Cl	2"- CF_3	R/S

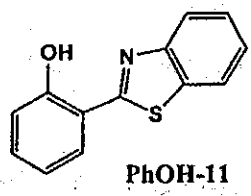
IIa-125	Me	H	4'-Cl	2"- CF_3	R/S
IIa-126	Me	4-F	4'-Cl	2"- CF_3	R/S
IIa-127	Me	4-Et	4'-Cl	2"- CF_3	R/S
IIa-128	Me	3-Cl	4'-Me	H	R/S
IIa-129	Me	3-CF_3	4'-Me	H	R/S
IIa-130	Me	3-OPh	4'-Me	H	R/S
IIa-131	Me	4-OMe	4'-Me	H	R/S
IIa-132	Me	4-Cl	4'-Me	H	R/S
IIa-133	Me	4-CF_3	4'-Me	H	R/S
IIa-134	Me	4-Br	4'-Me	H	R/S
IIa-135	Me	H	4'-Me	H	R/S
IIa-136	Me	4-F	4'-Me	H	R/S
IIa-137	Me	4-Et	4'-Me	H	R/S
IIa-138	Me	3-Cl	4'-tBu	H	R/S
IIa-139	Me	3-CF_3	4'-tBu	H	R/S
IIa-140	Me	3-OPh	4'-tBu	H	R/S
IIa-141	Me	4-OMe	4'-tBu	H	R/S
IIa-142	Me	4-Cl	4'-tBu	H	R/S
IIa-143	Me	4-CF_3	4'-tBu	H	R/S
IIa-144	Me	4-Br	4'-tBu	H	R/S
IIa-145	Me	H	4'-tBu	H	R/S
IIa-146	Me	4-F	4'-tBu	H	R/S
IIa-147	Me	4-Et	4'-tBu	H	R/S
IIa-148	Me	3-Cl	4'-Br	H	R/S
IIa-149	Me	3-CF_3	4'-Br	H	R/S
IIa-150	Me	3-OPh	4'-Br	H	R/S

IIa-151	Me	4-OMe	4'-Br	H	R/S
IIa-152	Me	4-Cl	4'-Br	H	R/S
IIa-153	Me	4-CF_3	4'-Br	H	R/S
IIa-154	Me	4-Br	4'-Br	H	R/S
IIa-155	Me	H	4'-Br	H	R/S
IIa-156	Me	4-F	4'-Br	H	R/S
IIa-157	Me	4-Et	4'-Br	H	R/S

5. Synthesis of 2-benzothiazol-2-yl-phenols

[0249] The 2-benzothiazol-2-yl-phenol or 2-benzothiazol-2-yl-phenylfluorides used for the preparation of compounds **II-X** and **IIa-X** were prepared in the same manner as that described for the synthesis of 2-benzooxazol-2-yl-phenols and 2-benzooxazol-2-yl-phenylfluorides illustrated in **Scheme II** or can be prepared by those skilled in the arts.

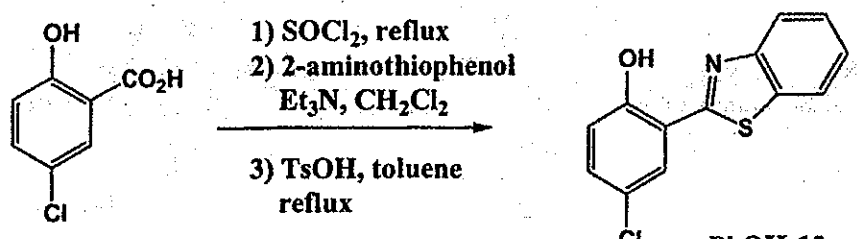
Example 63



PhOH-11

[0250] Compound **PhOH-11** was purchased from Aldrich Chemicals Inc., USA.

Example 64



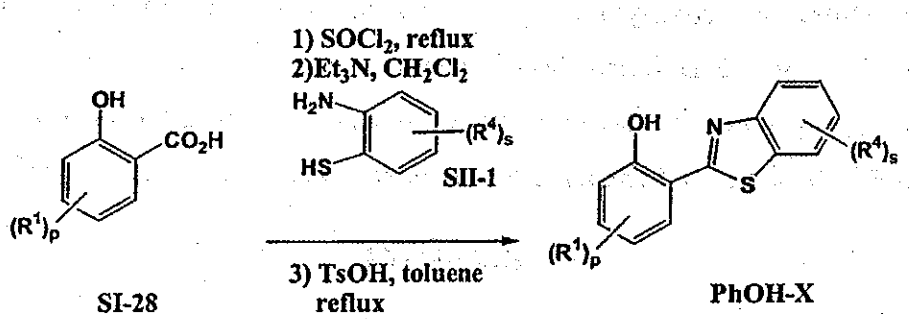
SI-32 **PhOH-12**

[0251] A mixture of **SI-32** (67 g, 0.388 mol) and $SOCl_2$ (42 mL, 0.582) was refluxed for 2h. The mixture was concentrated to dryness and put on high vaccum for a while. To the residue was added THF (700 mL) and then 2-aminothiophenol (53.4 g, 0.427 mol) was added slowly at 0 °C. To the resulted solution was added dropwise Et_3N (82 mL, 0.582 mol) at 0

°C, then warmed to room temperature and stirred overnight. The reaction mixture was acidified by addding 2N HCl and concentrated, to the residue was added water, filtered and washed with water to give a solid (98 g), which was used for the next reaction without further purification.

[0252] A mixture of the above crude product (98 g) and TsOH·H_2O (12.5 g) in toluene (500 mL) was refluxed for 4 hours using Dean-Stark apparatus. The reaction mixture was cooled to room temperature. Filtration and washing with MeOH gave phenol **PhOH-12** as an off-white solid (90 g, 89%). ^{1}HNMR (d-DMSO, 400 MHz) δ 11.69 (s, 1H), 8.20 (d, 1H), 8.08 (d, 1H), 8.04 (d, 1H), 7.53-7.39 (m, 3H), 7.08 (d, 1H).

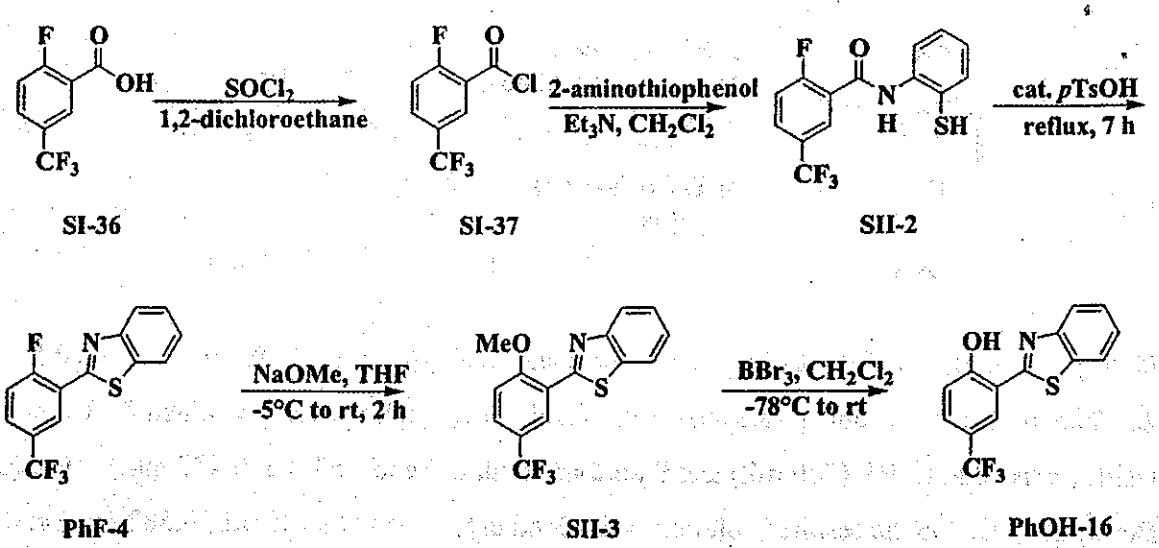
Example 65



R^1 = H, 4'-CF_3, 4'-Cl, 4'-Me, 4'-tBu,4'-Br, 4',6'-diCl, 4'-(1H-pyrrol-yl), 4'-(1H-pyrrol-yl) etc.
R^4 = H, 2"-Cl, 2"-CF_3 etc.

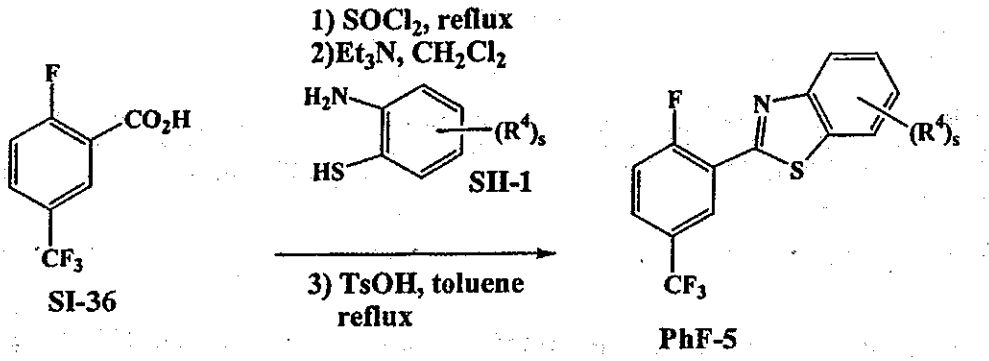
[0253] In the same manner as that described in **Example 64** compound **PhOH-X** can be prepared from commercially available **SI-28**.

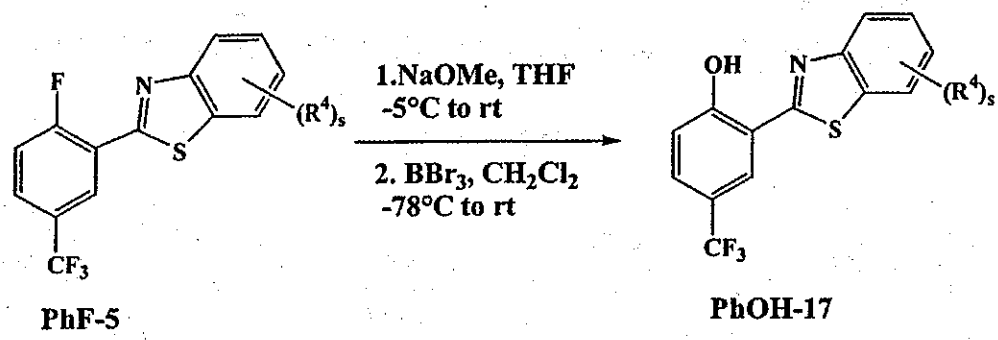
Example 66



[0254] In the same manner as that described in **Example 23** compound **PhF-4** and **PhOH-16** were prepared from commercially available **SI-36** and 2-aminothiophenol.

Example 67





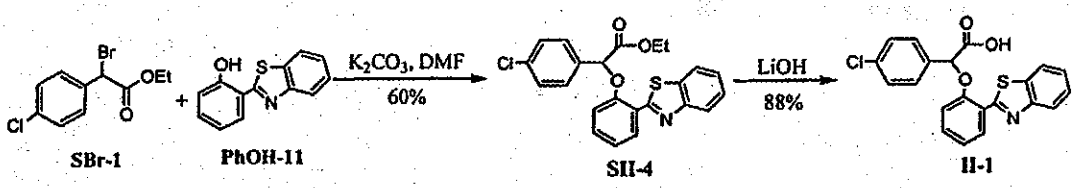
R^4 = H, 2"-Cl, 2"-CF_3,

[0255] In the same manner as that described in **Example 23** compound **PhF-5** and **PhOH-17** can be prepared from commercially available **SI-36** and **SII-1**.

6. Synthesis of Compounds II and IIa in Table 2

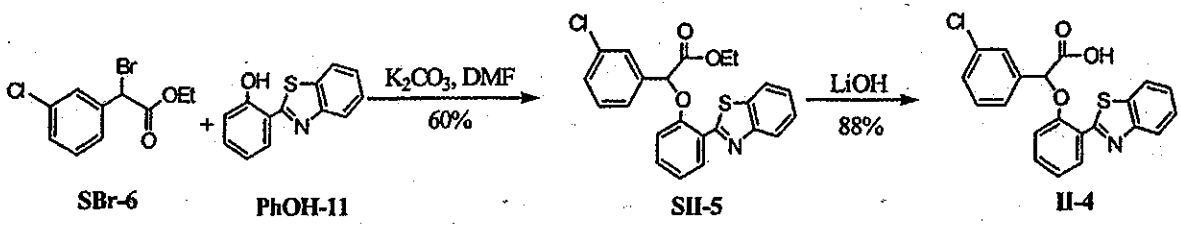
[0256] Compounds **II** and **IIa** were or can be prepared in the same manner as that described for the synthesis of compounds **I** and **Ia**.

Example 68



[0257] In the same manner as that described in **Example 28** compound **II-1** was prepared from **SBr-6** and **PhOH-11**. ^{1}HNMR (d-DMSO, 400 MHz) δ 8.44 (d, 1H), 8.17 (s, 1H), 8.07 (m, 3H), 7.83 (m, 1H), 7.75 (m, 1H), 7.55 (m, 2H), 7.47 (m, 1H), 7.31 (m, 1H), 7.22 (m,1H), 6.51 (s, 1H).

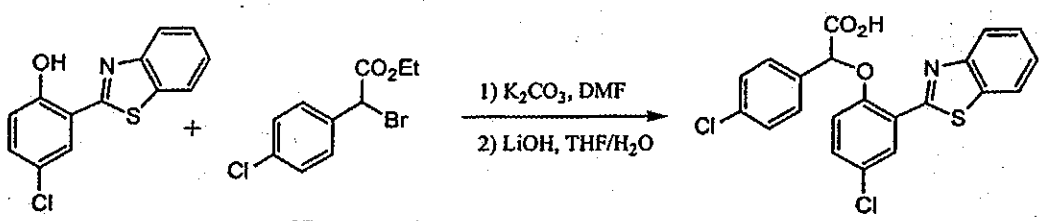
Example 69



SBr-6 **PhOH-11** **SII-5** **II-4**

[0258] In the same manner as that described in **Example 28** compound **II-4** was prepared as a white solid (1.18 g). ^{1}HNMR (d-DMSO, 400 MHz) δ 8.43 (ds, 1H), 8.07 (m, 2H), 7.79 (m, 1H), 7.67 (m, 1H), 7.54-7.41 (m, 5H), 7.26 (d, 1H), 7.19 (m, 1H), 6.35 (s, 1H).

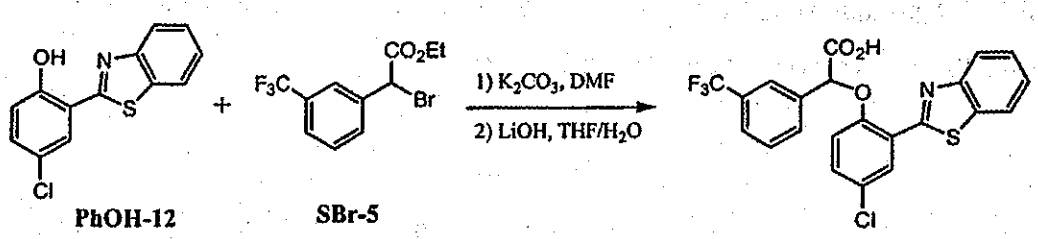
Example 70



PhOH-12 **SBr-1** **II-97**

[0259] In the same manner as that described in **Example 28** compound **II-97** was prepared from **SBr-1** and **PhOH-12**. **II-97**: ^{1}HNMR (d-DMSO, 400 MHz) δ 13.62 (br, 1H), 8.40 (d, 1H), 8.10 (dd, 2H), 7.72 (d, 2H), 7.60-7.53 (m, 5H), 7.45 (m, 1H), 7.31 (d, 1H), 6.38 (s, 1H).

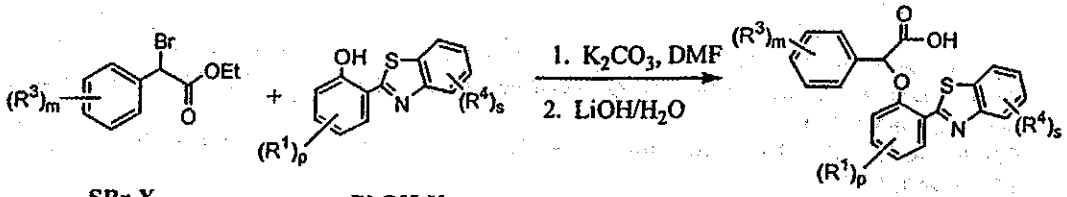
Example 71



PhOH-12 **SBr-5** **II-98**

[0260] In the same manner as that described in **Example 28** compound **II-98** was prepared from **SBr-5** and **PhOH-12**. ^{1}HNMR (400 MHz, DMSO-d6$_1$):δ 8.38 (d, 1H), 8.11-8.00 (m, 4H), 7.83 (d, 1H), 7.73 (m, 1H), 7.63 (dd, 1H), 7.58 (m, 1H), 7.68 (m, 1H), 7.34 (d, 1H), 6.52 (s, 1H).

Example 72

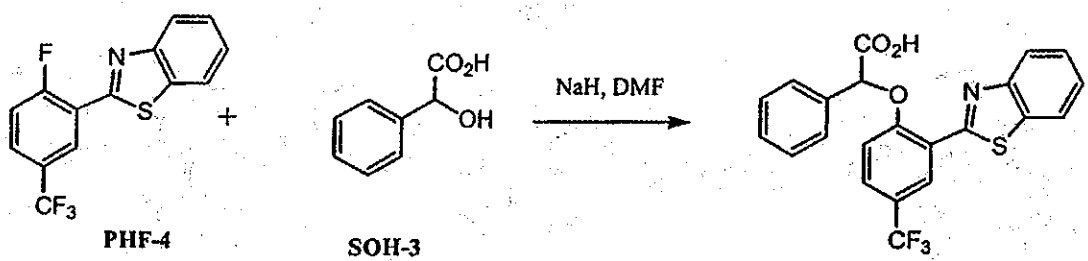


SBr-X **PhOH-X** **II-11 to II-157**

R^3 = 4-Cl, 3-CF_3, 3-OPh, 3-Cl, 4-OMe, 4-CF_3, 4-Br, H, 4-F, 4-Et
R^1 = H, 4'-CF_3, 4', 6', -diCl, 4'-(2,4-diF)Ph, 4'-(1H)-pyrrolyl, 4'-Cl, 4'-Me, 4'-tBu, 4'-Br,
R^4 = 2"-Cl

[0261] In the same manner as that described in **Example 28** the rest of compound **II-X** can be prepared from **SBr-X** and **PhOH-X**.

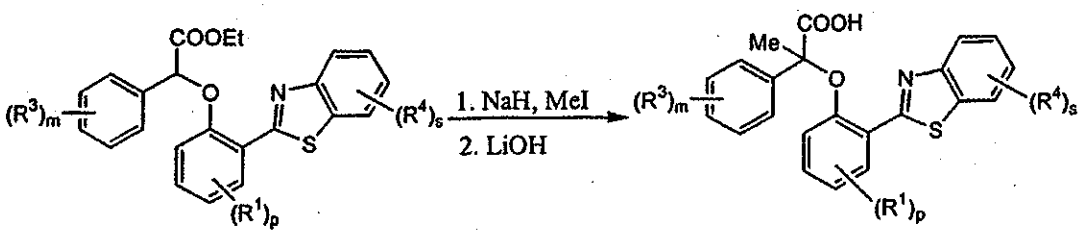
Example 73



PHF-4 **SOH-3** **II-26**

[0262] In the same manner as that described in **Example 35** compound **II-26** was prepared from **SOH-3** and **PhF-4**. **II-26**: ^{1}HNMR (d-DMSO, 400 MHz) δ 13.60 (br, 1H), 8.71 (s, 1H), 8.12 (m, 2H), 7.90 (m, 1H), 7.71 (m, 2H), 7.54 (m, 1H), 7.46 (m, 5H), 6.44 (s, 1H).

Example 74



SII-12 **IIa-1 to IIa-157**

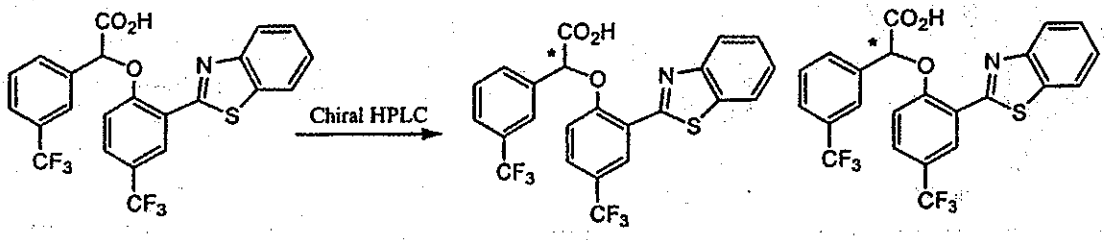
R^3 = 4-Cl, 3-CF_3, 3-OPh, 3-Cl, 4-OMe, 4-CF_3, 4-Br, H, 4-F, 4-Et, 2,3-di-F, 2,4-di-F, 2,5-di-F, 2,6-di-F, 3,4-di-F, 3,5-di-F, 2,3,5-tri-F, 3-OMe, 3-NO_2, 3,4-methylenedioxy, 2,3,6-tri-F, 2-Cl, 4-iPr, 4-Me, 4-MeS, 4-NO_2, 2,5-di-Me, 4-Et.
R^1 = H, 4'-CF_3, 4'-Cl, 4'-Br, 4'-Me, 4'-tBu, 4',6'-diCl, 4'-(1H-pyrrol-yl), 4'-(1H-pyrrol-yl) etc.
R^4 = H, 2-Cl, 2-CF_3

[0263] In the same manner as that described in **Example 42** compound **IIa-1** to **IIa-157** can be prepared from **SI-55.**

7. Enantioselective synthesis and enantiomer separation

[0264] The enantiomers of compounds **II-X** and **IIa-X** were or can be obtained in the same manner as that decribed in **Section 4** and **Example 45** to **Example 62.**

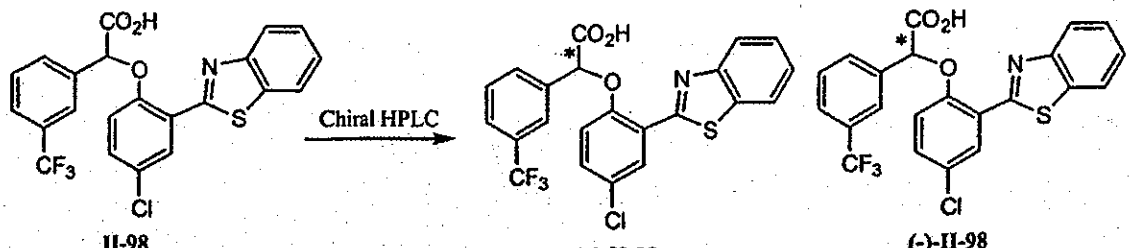
Example 75



II-22 **(+)-II-22** **(-)-II-22**

[0265] (+)-II-22 and (-)-II-22 was separated in the same manner as described in Example 49.

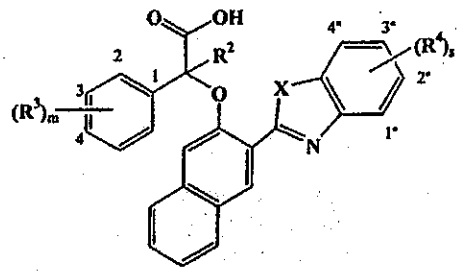
Example 76



II-98 **(+)-II-98** **(-)-II-98**

[0266] (+)-II-98 and (-)-II-98 was separated in the same manner as described in Example 49

Table 3
2-benzooxazole and 2-benzothiazole analogs

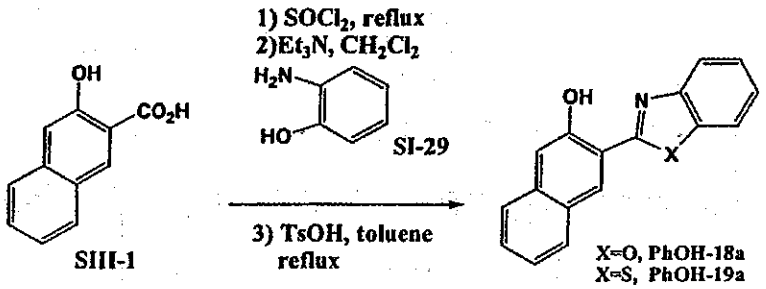


Compounds III

Compound	R^2	$(R^3)_m$	X	$(R^4)_s$	Configuration
III-1	H	4-Cl	O	H	R/S
III-2	H	3-CF_3	O	H	R/S
III-3	H	3-OPh	O	H	R/S
III-4	H	3-Cl	O	H	R/S
III-5	H	4-OMe	O	H	R/S
III-6	H	4-CF_3	O	H	R/S
III-7	H	4-Br	O	H	R/S
III-8	H	H	O	H	R/S
III-9	H	4-F	O	H	R/S
III-10	H	4-Et	O	H	R/S
III-11	H	4-Cl	S	H	R/S
III-12	H	3-CF_3	S	H	R/S
III-13	H	3-OPh	S	H	R/S
III-14	H	3-Cl	S	H	R/S
III-15	H	4-OMe	S	H	R/S
III-16	H	4-CF_3	S	H	R/S

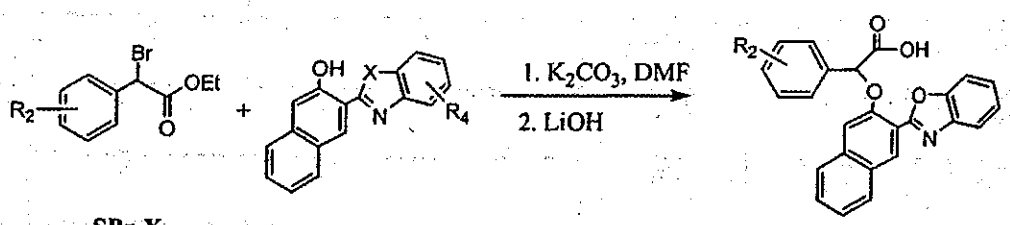
III-17	H	4-Br	S	H	R/S
III-18	H	H	S	H	R/S
III-19	H	4-F	S	H	R/S
III-10	H	4-Et	S	H	R/S

Example 77



[0267] In the same manner as that described in **Example 18** compound **PhOH-18a, 19a** can be prepared from commercially available **SI-29 and SIII-1.**

Example 78

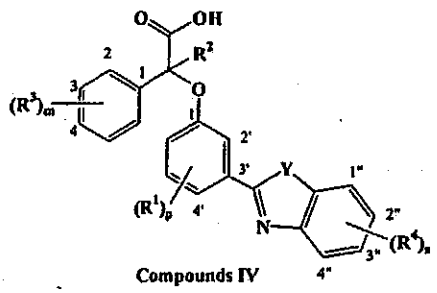


SBr-X **X=O, PhOH-18b** **X=S, PhOH-19b** **III-X**

R_2=4-Cl, 3-CF_3, 3-OPh, 3-Cl, 4-OMe, 4-CF_3, 4-Br, 4-F, 4-Et

[0268] In the same manner as that described in **Example 28** compound **III-X** can be prepared from commercially available **SBr-X** and **PhOH-18a, 19a.**

Table 4
3-benzooxazole and 3-benzothiazole analogs



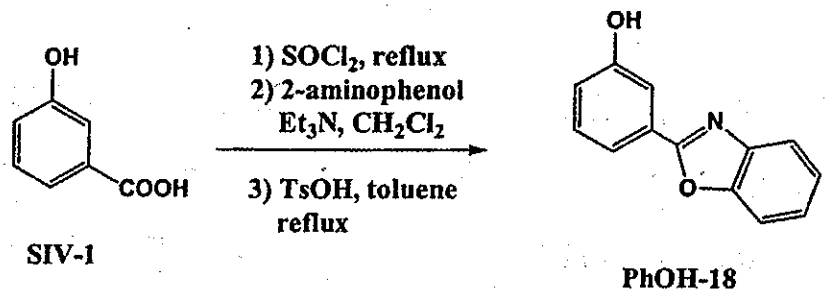
Compounds IV

5

	R^2	$(R^3)_m$	$(R^1)_p$	$(R^4)_s$	Y	Configuration
IV-1	H	4-Cl	H	H	O	R/S
IV-2	H	3-CF_3	H	H	O	R/S
IV-3	H	3-OPh	H	H	O	R/S
IV-4	H	3-Cl	H	H	O	R/S
IV-5	H	4-CF_3	H	H	O	R/S
IV-6	H	3-OMe	H	H	O	R/S
IV-7	H	4-OMe	H	H	O	R/S
IV-8	H	3-F, 5-F	H	H	O	R/S
IV-9	H	2-F, 4-F	H	H	O	
IV-10	H	4-Et	H	H	O	
IV-11	H	4-Cl	2-Me	H	O	R/S
IV-12	H	3-CF_3	2-Me	H	O	R/S
IV-13	H	3-OPh	2-Me	H	O	R/S
IV-14	H	3-Cl	2-Me	H	O	R/S
IV-15	H	4-CF_3	2-Me	H	O	R/S
IV-16	H	3-OMe	2-Me	H	O	R/S
IV-17	H	4-OMe	2-Me	H	O	R/S
IV-18	H	3-F, 5-F	2-Me	H	O	R/S

IV-19	H	2-F, 4-F	2-Me	H	O	
IV-20	H	4-Et	2-Me	H	O	
IV-21	H	4-Cl	H	H	S	
IV-22	H	4-Cl	2-Me	H	S	R/S

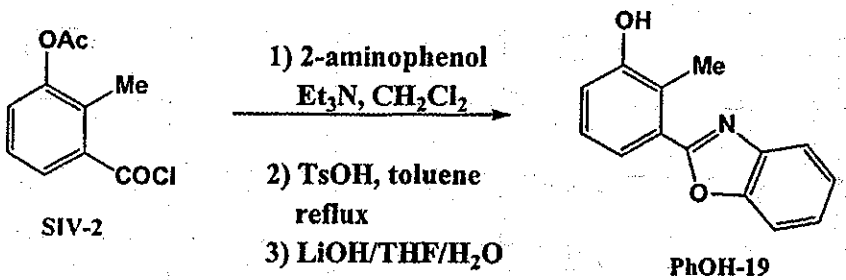
Example 79



SIV-1 PhOH-18

[0269] In the same manner as that described in **Example 18**, **PhOH-18** can be prepared from **SIV-1**.

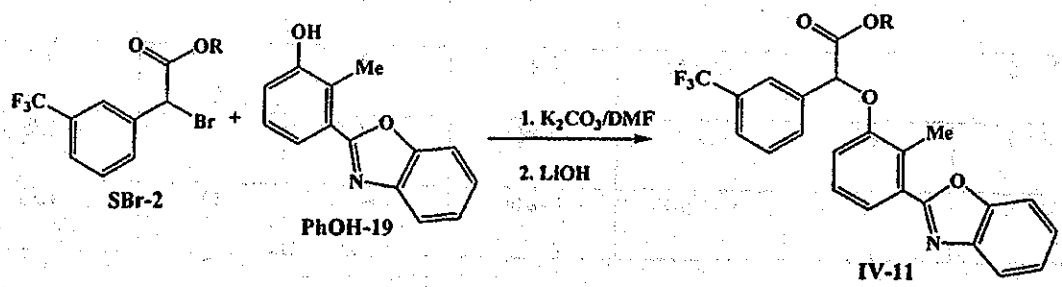
Example 80



SIV-2 PhOH-19

[0270] In the same manner as that described in **Example 18**, **PhOH-19** was prepared from **SIV-2**. **PhOH-19:** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82 (m, 1H), 7.71 (d, 1H), 7.61 (m, 1H), 7.39 (m, 2H), 7.23 (m, 1H), 6.98 (d, 1H), 5.40 (br, 1H), 2.69 (s, 3H).

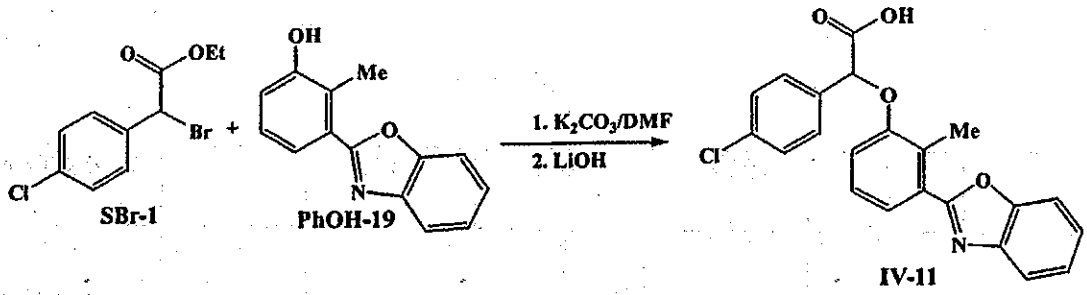
Example 81



SBr-2 PhOH-19 IV-11

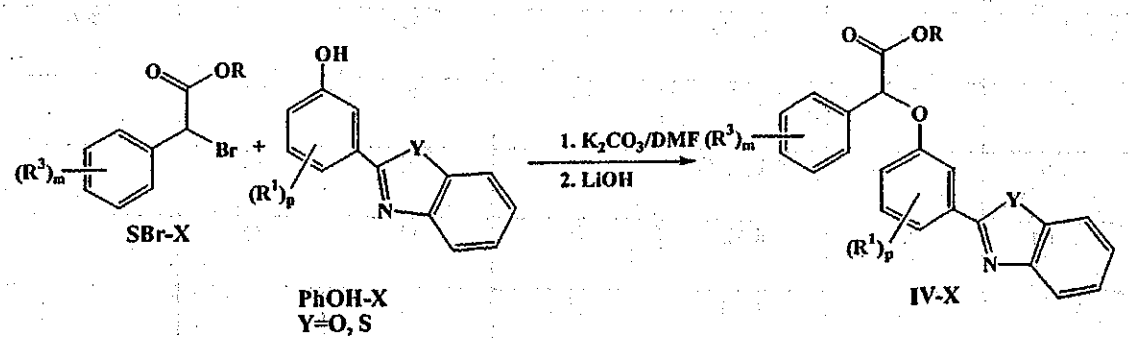
[0271] In the same manner as that described in **Example 28** compound **IV-11** was prepared from **SBr-2** and **PhOH-19**.

Example 82



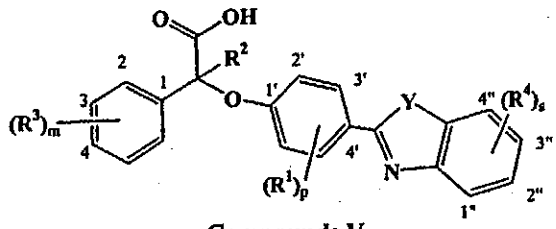
[0272] In the same manner as that described in **Example 28** compound **IV-12** was prepared from **SBr-1** and **PhOH-19**. **IV-11:** ^{1}HNMR (d-DMSO, 400 MHz) δ 13.41 (br, 1H), 7.83 (d, 1H), 7.80 (d, 1H), 7.65 (m, 3H), 7.52 (d, 2H), 7.46-7.39 (m, 2H), 7.35 (m, 1H), 7.16 (d, 1H), 6.05 (s, 1H), 2.69 (s, 3H).

Example 83



[0273] In the same manner as that described in **Example 28** the rest of **IV-X** listed **Table 4** can be prepared.

Table5
4-benzooxazole and 4-benzothiazole analogs

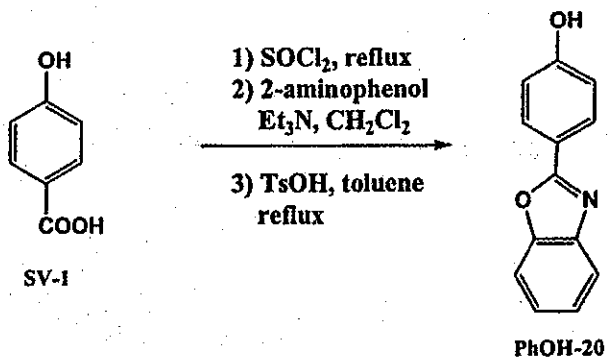


Compounds V

5

	R^2	$(R^3)_m$	$(R^1)_p$	$(R^4)_s$	Y	Configuration
V-1	H	3-CF_3	H	H	O	R/S
V-2	H	4-Cl	H	H	O	R/S
V-3	H	3-OPh	H	H	O	R/S
V-4	H	3-Cl	H	H	O	R/S
V-5	H	4-CF_3	H	H	O	R/S
V-6	H	3-OMe	H	H	O	R/S
V-7	H	4-OMe	H	H	O	R/S
V-8	H	3-F, 5-F	H	H	O	R/S
V-9	H	2-F, 4-F	H	H	O	
V-10	H	4-Et	H	H	O	
V-11	H	4-Cl	H	H	S	

Example 84

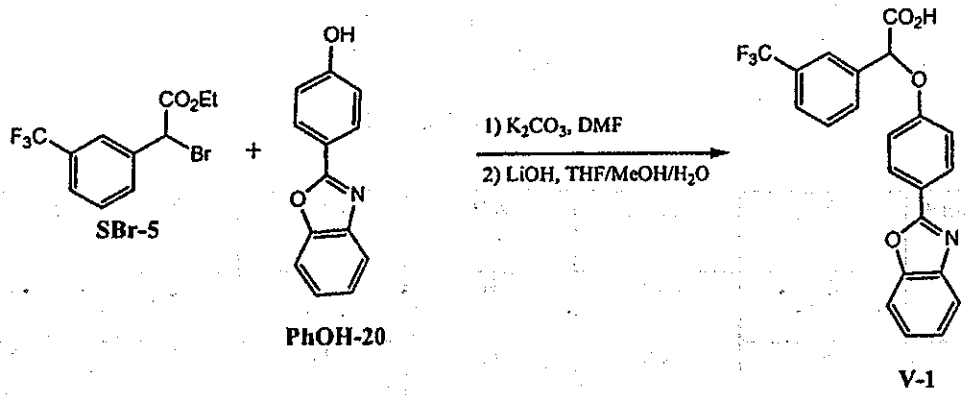


SV-I

PhOH-20

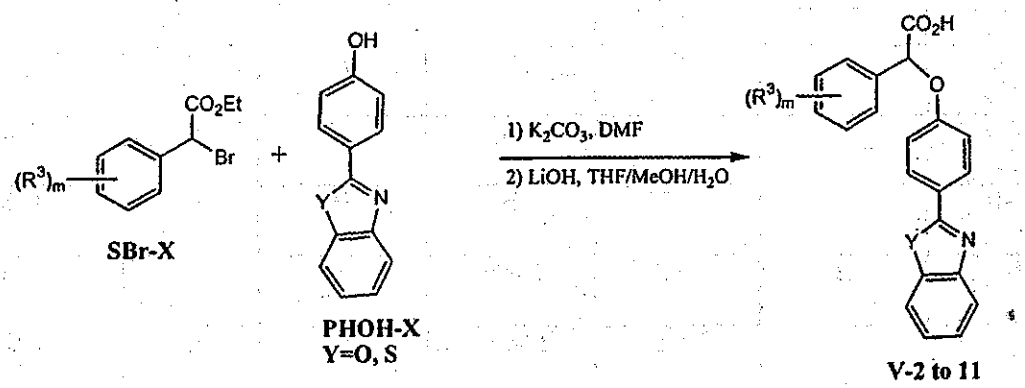
[0274] In the same manner as that described in **Example 18, PhOH-20** was prepared from **SV-1. PhOH-20**: ^{1}H NMR (d-DMSO, 400 MHz) δ 10.36 (br, 1H), 8.05 (d, 2H), 7.75 (m, 2H), 7.38 (d, 2H), 6.97 (d, 2H).

Example 85



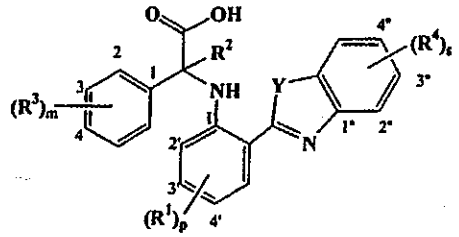
[0275] In the same manner as that described in **Example 28** compound **V-1** was prepared from **SBr-5** and **PhOH-20**. ^{1}H NMR (d-DMSO, 400 MHz) δ 13.60 (br, 1H), 8.19 (d, 2H), 7.90 (m, 2H), 7.75 (m, 4H), 7.40 (m, 2H), 7.22 (d, 2H), 6.22 (s, 1H).

Example 86



[0276] In the same manner as that described in **Example 28** compound **V-2** to **V-11** can be prepared from **SBr-X** and **PhOH-X**.

Table 6
2-benzooxazole and 2-benzothiazole anilino analogs



Compounds VI and VIa

5

Compound	R^2	$(R^3)_m$	$(R^1)_p$	$(R^4)_s$	Y	Configuration
VI-1	H	4-Cl	H	H	O	R/S
VI-2	H	3-CF_3	H	H	O	R/S
VI-3	H	3-OPh	H	H	O	R/S
VI-4	H	3-Cl	H	H	O	R/S
VI-5	H	4-OMe	H	H	O	R/S
VI-6	H	4-CF_3	H	H	O	R/S
VI-7	H	4-Br	H	H	O	R/S
VI-8	H	H	H	H	O	R/S
VI-9	H	4-F	H	H	O	R/S
VI-10	H	4-Et	H	H	O	R/S
VI-11	H	4-Cl	5'-CF_3	H	O	R/S
VI-12	H	3-CF_3	5'-CF_3	H	O	R/S
VI-13	H	3-OPh	5'-CF_3	H	O	R/S
VI-14	H	3-Cl	5'-CF_3	H	O	R/S
VI-15	H	4-OMe	5'-CF_3	H	O	R/S
VI-16	H	4-CF_3	5'-CF_3	H	O	R/S
VI-17	H	4-Br	5'-CF_3	H	O	R/S
VI-18	H	H	5'-CF_3	H	O	R/S

VI-19	H	4-F	5'-CF_3	H	O	R/S
VI-20	H	4-Et	5'-CF_3	H	O	R/S
VI-21	H	3-CF_3	4'-Cl	H	O	R/S
VI-22	H	3-Cl	4'-Cl	H	O	R/S
VI-23	H	H	4'-Cl	H	O	R/S
VI-24	H	4-OMe	4'-Cl	H	O	R/S
VI-25	H	3-OMe	4'-Cl	H	O	R/S
VI-26	H	4-Br	4'-Cl	H	O	R/S
VI-27	H	3-Ph	4'-Cl	H	O	R/S
VI-28	H	4-Cl	4'-Cl	H	O	R/S
VI-29	H	4-CF_3	4'-Cl	H	O	R/S
VI-30	H	4-F	4'-Cl	H	O	R/S
VI-31	H	4-Et	4'-Cl	H	O	R/S
VI-32	H	3-Cl	4'-Br	H	O	R/S
VI-33	H	3-CF_3	4'-Br	H	O	R/S
VI-34	H	3-OPh	4'-Br	H	O	R/S
VI-35	H	4-OMe	4'-Br	H	O	R/S
VI-36	H	4-Cl	4'-Br	H	O	R/S
VI-37	H	4-CF_3	4'-Br	H	O	R/S
VI-38	H	4-Br	4'-Br	H	O	R/S
VI-39	H	H	4'-Br	H	O	R/S
VI-40	H	4-F	4'-Br	H	O	R/S
VI-41	H	4-Et	4'-Br	H	O	R/S
VI-42	H	3-Cl	4'-F	H	O	R/S
VI-43	H	3-CF_3	4'-F	H	O	R/S
VI-44	H	3-OPh	4'-F	H	O	R/S

VI-45	H	4-OMe	4'-F	H	O	R/S
VI-46	H	4-Cl	4'-F	H	O	R/S
VI-47	H	4-CF_3	4'-F	H	O	R/S
VI-48	H	4-Br	4'-F	H	O	R/S
VI-49	H	H	4'-F	H	O	R/S
VI-50	H	4-F	4'-F	H	O	R/S
VI-51	H	4-Et	4'-F	H	O	R/S
VI-52	H	3-Cl	3',4'-diF	H	O	R/S
VI-53	H	3-CF_3	3',4'-diF	H	O	R/S
VI-54	H	3-OPh	3',4'-diF	H	O	R/S
VI-55	H	4-OMe	3',4'-diF	H	O	R/S
VI-56	H	4-Cl	3',4'-diF	H	O	R/S
VI-57	H	4-CF_3	3',4'-diF	H	O	R/S
VI-58	H	4-Br	3',4'-diF	H	O	R/S
VI-59	H	H	3',4'-diF	H	O	R/S
VI-60	H	4-F	3',4'-diF	H	O	R/S
VI-61	H	4-Et	3',4'-diF	H	O	R/S
VI-62	H	4-CF_3	4'-CF_3	H	O	R/S
VI-63	H	H	4'-CF_3	H	O	R/S
VI-64	H	4-OMe	4'-CF_3	H	O	R/S
VI-65	H	3-CF_3	4'-CF_3	H	O	R/S
VI-66	H	3-Cl	4'-CF_3	H	O	R/S
VI-67	H	4-Me	4'-CF_3	H	O	R/S
VI-68	H	4-Cl	4'-CF_3	H	O	R/S
VI-69	H	4-Br	4'-CF_3	H	O	R/S
VI-70	H	4-iPr	4'-CF_3	H	O	R/S

VI-71	H	4-Cl	H	H	S	R/S
VI-72	H	3-CF_3	H	H	S	R/S
VI-73	H	3-OPh	H	H	S	R/S
VI-74	H	3-Cl	H	H	S	R/S
VI-75	H	4-OMe	H	H	S	R/S
VI-76	H	4-CF_3	H	H	S	R/S
VI-77	H	4-Br	H	H	S	R/S
VI-78	H	H	H	H	S	R/S
VI-79	H	4-F	H	H	S	R/S
VI-80	H	4-Et	H	H	S	R/S
VI-81	H	3-CF_3	4'-Cl	H	S	R/S
VI-82	H	3-Cl	4'-Cl	H	S	R/S
VI-83	H	H	4'-Cl	H	S	R/S
VI-84	H	4-OMe	4'-Cl	H	S	R/S
VI-85	H	3-OMe	4'-Cl	H	S	R/S
VI-86	H	4-Br	4'-Cl	H	S	R/S
VI-87	H	3-Ph	4'-Cl	H	S	R/S
VI-88	H	4-Cl	4'-Cl	H	S	R/S
VI-89	H	4-CF_3	4'-Cl	H	S	R/S
VI-90	H	4-F	4'-Cl	H	S	R/S
VI-91	H	4-Et	4'-Cl	H	S	R/S
VI-92	H	4-CF_3	4'-CF_3	H	S	R/S
VI-93	H	H	4'-CF_3	H	S	R/S
VI-94	H	4-OMe	4'-CF_3	H	S	R/S
VI-95	H	3-CF_3	4'-CF_3	H	S	R/S
VI-96	H	3-Cl	4'-CF_3	H	S	R/S

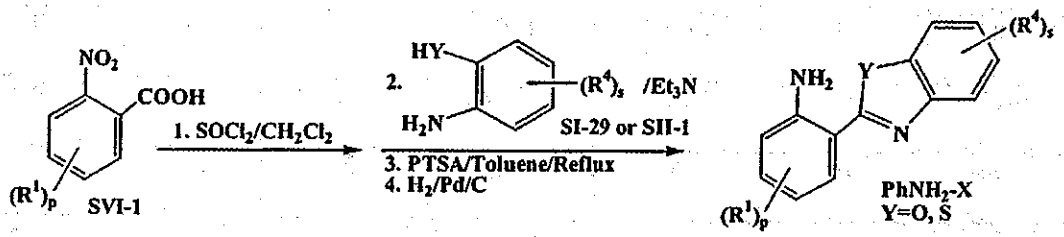
VI-97	H	4-Me	4'-CF_3	H	S	R/S
VI-98	H	4-Cl	4'-CF_3	H	S	R/S
VI-99	H	4-Br	4'-CF_3	H	S	R/S
VI-100	H	4-iPr	4'-CF_3	H	S	R/S
VIa-1	Me	H	4'-CF_3	H	S	R/S
VIa-2	Me	H	4'-CF_3	H	S	R/S

8. Synthesis of 2-benzooxazole and 2-benzothiazole anilines

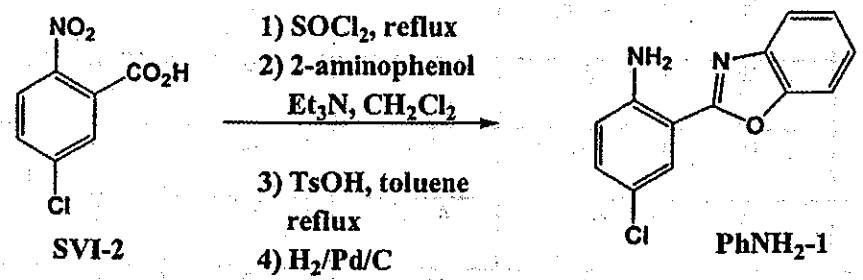
[0277] The 2-benzooxazole and 2-benzothiazole anilines used for the preparation of compounds **VI** and **VIa** were prepared in the same manner as that described for the synthesis of 2-benzooxazol-2-yl-phenols illustrated in **Scheme 2** or by those skilled in the art.

Scheme 5

Synthesis of 2-benzooxazole and 2-benzothiazole anilines

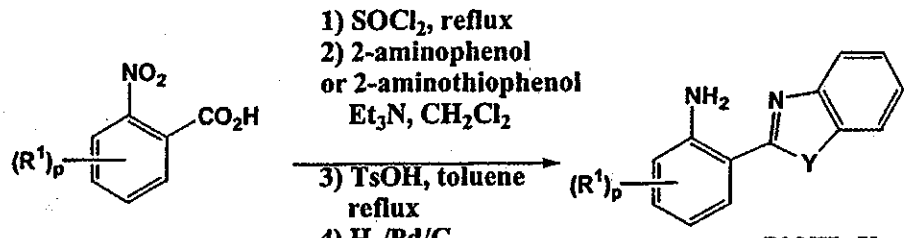


Example 87



[0278] In the similar manner as that described in **Example 18**, **$PhNH_2$-1** can be prepared from **SVI-2.**

Example 88



SVI-3 **$PhNH_2$-X Y=O, S**

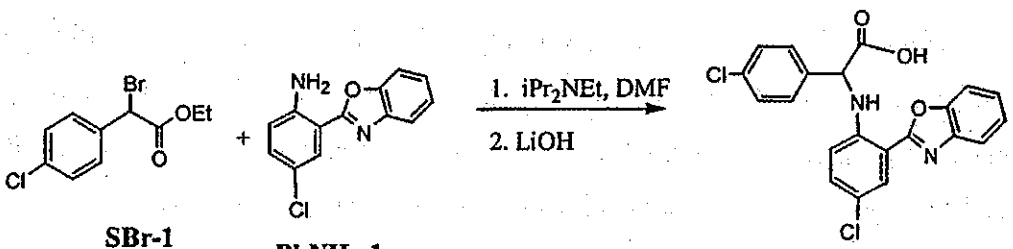
R^1 = H, 5'-CF_3, 5'-Cl, '5-F, 4'-Cl, 4'-Me, 4'-OMe, 4'-Br, 4'-F, 3',4'-diF, '4-CF_3

[0279] In the similar manner as that described in **Example 18**, **$PhNH_2$-X** can be prepared from **SVI-3.**

9. Synthesis of Compounds VI and VIa in Table 6

[0280] Compounds **VI-X** and **VIa-X** were or can be prepared in the same manner as that described for the synthesis of compounds **I-X** and **Ia-X.**

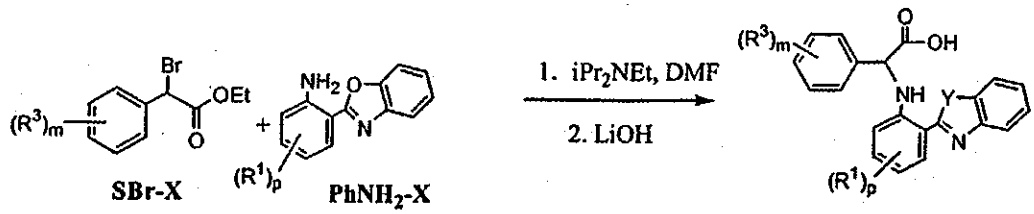
Example 89



SBr-1 **$PhNH_2$-1** **VI-28**

[0281] In the same manner as that described in Example 28 compound VI-28 was prepared from SBr-1 and $PhNH_2$-1.

Example 90

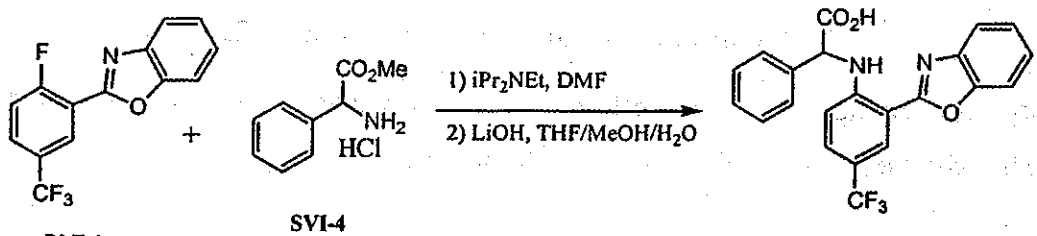


SBr-X $PhNH_2$-X VI-X Y=O, S

R^3 = 3-CF_3, 3-Cl, H, 4-OMe, 3-OMe, 4-Br, 3-Ph, 4-Cl, 4-CF_3, 4-F, 4-Et
R^1 = H, 5'-CF_3, 5'-Cl, '5-F, 4'-Cl, 4'-Me, 4'-OMe, 4'-Br, 4'-F, 3',4'-diF, 3',4'-diOMe, '4-CF_3

[0282] In the same manner as that described in **Example 28** the rest of compounds **VI-X** in **Table 6** can be prepared from **SBr-X** and **$PhNH_2$-X**.

Example 91

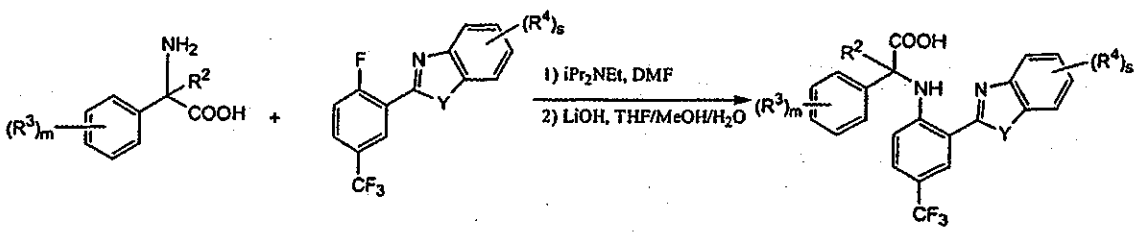


PhF-1 SVI-4 VI-63

[0283] A mixture of **PhF-1** (1.124 g, 4.0 mmol), **SVI-4** (0.914 g, 4.40 mmol) and iPr_2NEt (1.32 mL, 7.6 mmol) in DMF (10 mL) was heated at 100 °C for 24 h. After cooling to room temperature the mixture was poured into a mixture of ice and waterand extracted with EtOAc. The organic layer was washed with brine, dried and concentrated. The residue was recrystallized from MeOH to give a white solid (0.6g).

[0284] To the above product in THF/MeOH (15 mL/30mL) was added 1M LiOH solution (10 mL). The mixture was heated at 70 °C for 0.5 h, cooled to room temperature and quenched by adding 1 N HCl (10 mL). The mixture was concentrated and extracted with EtOAc. The organic layer washed with water, dried and concentrated. Crystallization from MeOH gave **VI-63** as a white solid (0.45 g). ^{1}H NMR (d-DMSO, 400 MHz) δ 9.87 (d, 1H), 8.28 (d, 1H), 7.85 (m, 2H), 7.60 (dd, 1H), 7.50 (m, 7H), 6.83 (d, 1H), 5.61 (d, 1H).

Example 92



SVI-5 PhF-1 Y=O, S VI 70 to VI-80 VI-90 to VI-100

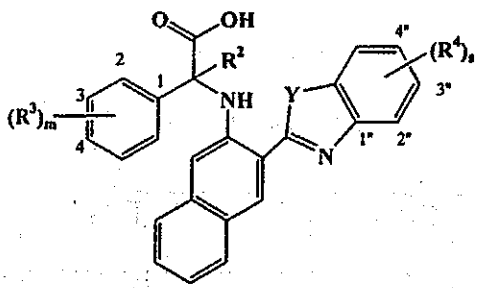
R^2 = H, Me
R^3 = 2'-Cl, 3'-Br, 3-Cl-4-F, 3,5-diCF_3, 4-CF_3, H, 4-OMe, 3-CF_3, 3-Cl, 4-Me, 4-Cl, 4-Br, 4-iPr.
R^4=H, 5'-CF_3, 5'-Cl, '5-F, 4'-Cl, 4'-Me, 4'-OMe, 4'-Br, 4'-F, 3',4'-diF, 3',4'-diOMe, '4-CF_3

[0285] In the same manner as that described in **Example 91** compound **VI-70** to **VI-80** and **VI-90** to **VI-100** in **Table 6** can be prepared from **SVI-5** and **PhF-1**.

10. Enantioselective synthesis and enantiomers separations

[0286] The individual enantiomers of compounds **VI-X** and **VIa-X** listed in **Table 6** can be obtained in the same manner as that described in **Section 4** and **Example 45** to **Example 62**.

Table 7
2-benzooxazole and 2-benzothiazole anilino analogs



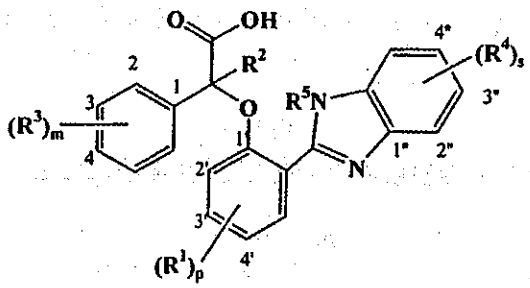
Compounds VII

Compound	R^2	$(R^3)_m$	$(R^4)_s$	Y	Configuration
VII-1	H	4-Cl	H	O	R/S
VII -2	H	3-CF_3	H	O	R/S
VII -3	H	3-OPh	H	O	R/S
VII -4	H	3-Cl	H	O	

VII -5	H	4-OMe	H	O	
VII -6	H	4-CF_3	H	O	
VII -7	H	4-Br	H	O	
VII -8	H	H	H	O	
VII -9	H	4-F	H	O	
VII -10	H	4-Et	H	O	
VII -11	H	4-Cl	H	S	

[0287] All the compounds listed in Table 7 can be prepared with proper starting materials in the same manner as that described for the synthesis of compounds listed in Table 6.

Table 8
2- Benzoimidazole analogs



Compounds VIII

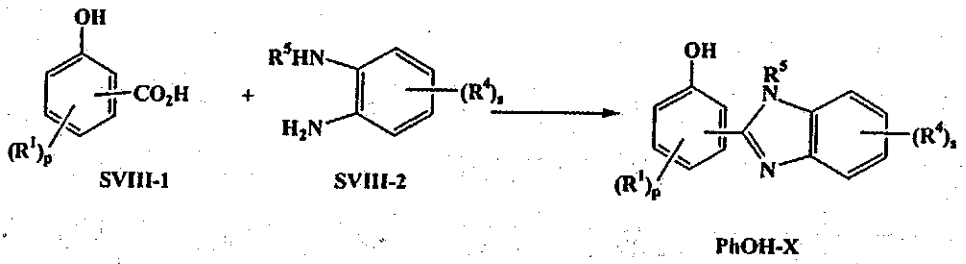
Compound	R^2	$(R^3)_m$	$(R^1)_p$	$(R^4)_s$	R^5	Configuration
VIII-1	H	4-Cl	H	H	Me	R/S
VIII-2	H	3-CF_3	H	H	Me	R/S
VIII-3	H	3-OPh	H	H	Me	R/S
VIII-4	H	3-Cl	H	H	Me	R/S
VIII-5	H	4-OMe	H	H	Me	R/S
VIII-6	H	4-CF_3	H	H	Me	R/S
VIII-7	H	4-Br	H	H	Me	R/S

VIII-9	H	4-F	H	H	Me	R/S
VIII-10	H	4-Et	H	H	Me	R/S
VIII-11	H	4-Cl	4'-Cl	H	Me	R/S
VIII-12	H	3-CF_3	4'-Cl	H	Me	R/S
VIII-13	H	3-OPh	4'-Cl	H	Me	R/S
VIII-14	H	3-Cl	4'-Cl	H	Me	R/S
VIII-15	H	4-OMe	4'-Cl	H	Me	R/S
VIII-16	H	4-CF_3	4'-Cl	H	Me	R/S
VIII-17	H	4-Br	4'-Cl	H	Me	R/S
VIII-18	H	H	4'-Cl	H	Me	R/S
VIII-19	H	4-F	4'-Cl	H	Me	R/S
VIII-20	H	4-Et	4'-Cl	H	Me	R/S
VIII-21	H	4-Cl	4'-Cl	2"-Cl	Me	R/S
VIII-22	H	3-CF_3	4'-Cl	2"-Cl	Me	R/S
VIII-23	H	3-OPh	4'-Cl	2"-Cl	Me	R/S
VIII-24	H	3-Cl	4'-Cl	2"-Cl	Me	R/S
VIII-25	H	4-OMe	4'-Cl	2"-Cl	Me	R/S
VIII-26	H	4-CF_3	4'-Cl	2"-Cl	Me	R/S
VIII-27	H	4-Br	4'-Cl	2"-Cl	Me	R/S
VIII-28	H	H	4'-Cl	2"-Cl	Me	R/S
VIII-29	H	4-F	4'-Cl	2"-Cl	Me	R/S
VIII-30	H	4-Et	4'-Cl	2"-Cl	Me	R/S

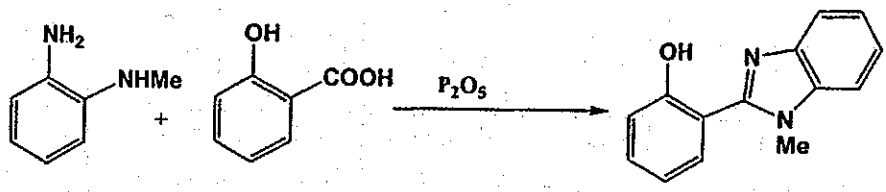
11. Synthesis of 2-Benzoimidazol-2-yl-phenol

[0288] **Scheme 6** illustrates the general route for preparing 2-benzoimidazol-2-yl-phenols. Generally, hydroxyl benzoic acids were treated with o-phenylenediamines under strongly dehydration conditions to afford the corresponding benzoimidazol-2-yl-phenols.

Scheme 6. Synthesis of benzoimidazol-2-yl-phenols

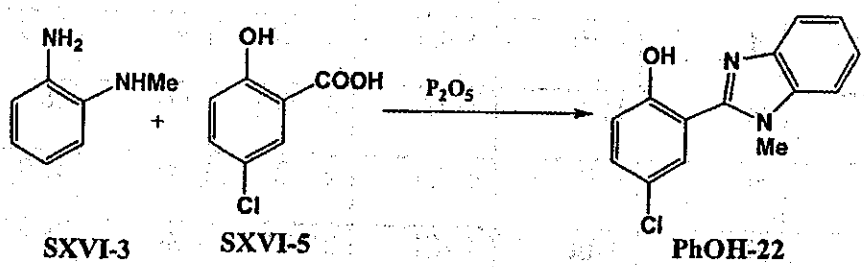


Example 93



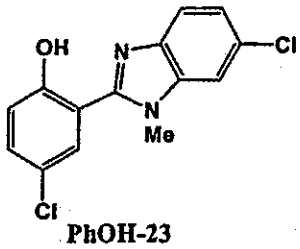
[0289] **PhOH-21** was prepared according to the literature procedure [Youji Huaxue, (1), 32-5; 1986]

Example 94



[0290] PhOH-22 can be prepared in the same manner as that described for the synthesis of PhOH-21 in Example 93.

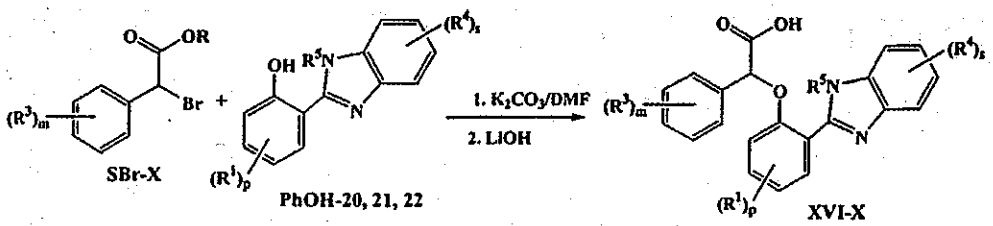
Example 95



PhOH-23

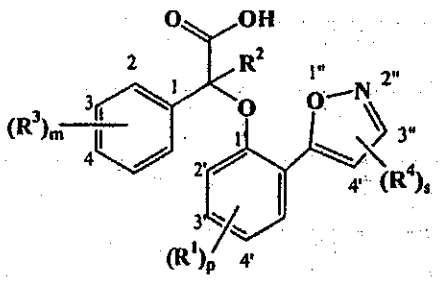
[0291] **PhOH-23** was prepared according to the literature procedure [*Indian J. Chem., Sect. B.* 19B (11), 967-9; 1980]

Example 96



[0292] Compounds **VIII-X** can be prepared with **SBr-X** and **PhOH-21, 22,** and **23** in the same manner as that described in **Example 28.**

Table 9
2-isooxazole analogs



Compounds IX and IXa

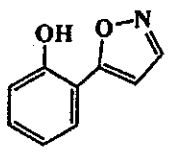
Compound	R^2	$(R^3)_m$	$(R^1)_p$	$(R^4)_s$	Configuration
IX-1	H	3-Cl	4-H	H	R/S
IX-2	H	3-CF_3	4-H	H	R/S

IX-3	H	3-OPh	4-H	H	R/S
IX-4	H	4-OMe	4-H	H	R/S
IX-5	H	4-Cl	4-H	H	R/S
IX-6	H	4-CF_3	4-H	H	R/S
IX-7	H	4-Br	4-H	H	R/S
IX-8	H	H	4-H	H	R/S
IX-9	H	4-Et	4-H	H	R/S
IX-10	H	3-Cl	4-Me	H	R/S
IX-11	H	3-CF_3	4-Me	H	R/S
IX-12	H	3-OPh	4-Me	H	R/S
IX-13	H	4-OMe	4-Me	H	R/S
IX-14	H	4-Cl	4-Me	H	R/S
IX-15	H	4-CF_3	4-Me	H	R/S
IX-16	H	4-Br	4-Me	H	R/S
IX-17	H	H	4-Me	H	R/S
IX-18	H	4-Et	4-Me	H	R/S
IX-19	H	3-Cl	4-Cl	H	R/S
IX-20	H	3-CF_3	4-Cl	H	R/S
IX-21	H	3-OPh	4-Cl	H	R/S
IX-22	H	4-OMe	4-Cl	H	R/S
IX-23	H	4-Cl	4-Cl	H	R/S
IX-24	H	4-CF_3	4-Cl	H	R/S
IX-25	H	4-Br	4-Cl	H	R/S
IX-26	H	H	4-Cl	H	R/S
IX-27	H	4-Et	4-Cl	H	R/S
IX-28	H	3-Cl	4-Br	H	R/S

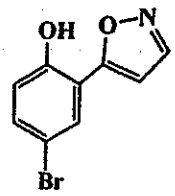
IX-29	H	3-CF_3	4-Br	H	R/S
IX-30	H	3-OPh	4-Br	H	R/S
IX-31	H	4-OMe	4-Br	H	R/S
IX-32	H	4-Cl	4-Br	H	R/S
IX-33	H	4-CF_3	4-Br	H	R/S
IX-34	H	4-Br	4-Br	H	R/S
IX-35	H	H	4-Br	H	R/S
IX-36	H	4-Et	4-Br	H	R/S
IX-37	H	3-Cl	4-Cl, 5-Me	H	R/S
IX-38	H	3-CF_3	4-Cl, 5-Me	H	R/S
IX-39	H	3-OPh	4-Cl, 5-Me	H	R/S
IX-40	H	4-OMe	4-Cl, 5-Me	H	R/S
IX-41	H	4-Cl	4-Cl, 5-Me	H	R/S
IX-42	H	4-CF_3	4-Cl, 5-Me	H	R/S
IX-43	H	4-Br	4-Cl, 5-Me	H	R/S
IX-44	H	H	4-Cl, 5-Me	H	R/S
IX-45	H	4-Et	4-Cl, 5-Me	H	R/S
IX-46	H	3-Cl	4-Cl, 6-Cl	H	R/S
IX-47	H	3-CF_3	4-Cl, 6-Cl	H	R/S
IX-48	H	3-OPh	4-Cl, 6-Cl	H	R/S
IX-49	H	4-OMe	4-Cl, 6-Cl	H	R/S
IX-50	H	4-Cl	4-Cl, 6-Cl	H	R/S
IX-51	H	4-CF_3	4-Cl, 6-Cl	H	R/S
IX-52	H	4-Br	4-Cl, 6-Cl	H	R/S
IX-53	H	H	4-Cl, 6-Cl	H	R/S
IX-54	H	4-Et	4-Cl, 6-Cl	H	R/S

IX-55	H	3-Cl	H	3-(2-benzofuranyl)	R/S
IX-56	H	3-CF_3	H	3-(2-benzofuranyl)	R/S
IX-57	H	3-OPh	H	3-(2-benzofuranyl)	R/S
IX-58	H	4-OMe	H	3-(2-benzofuranyl)	R/S
IX-59	H	4-Cl	H	3-(2-benzofuranyl)	R/S
IX-60	H	4-CF_3	H	3-(2-benzofuranyl)	R/S
IX-61	H	4-Br	H	3-(2-benzofuranyl)	R/S
IX-62	H	H	H	3-(2-benzofuranyl)	R/S
IX-63	H	4-Et	H	3-(2-benzofuranyl)	R/S
IX-64	H	3-CF_3	4-Cl	H	–
IX-65	H	3-CF_3	4-Cl	H	+
IXa-1	Me	3-Cl	4-Cl	H	R/S
IXa-2	Me	3-CF_3	4-Cl	H	R/S
IXa-3	Me	3-OPh	4-Cl	H	R/S
IXa-4	Me	4-OMe	4-Cl	H	R/S
IXa-5	Me	4-Cl	4-Cl	H	R/S
IXa-6	Me	4-CF_3	4-Cl	H	R/S
IXa7	Me	4-Br	4-Cl	H	R/S

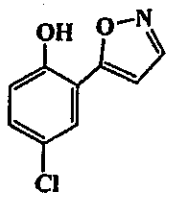
12. 2-isooxazoyl phenols



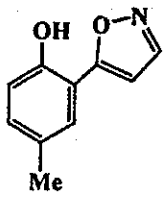
PhOH-24



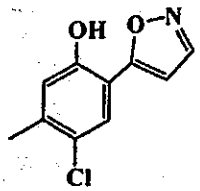
PhOH-25



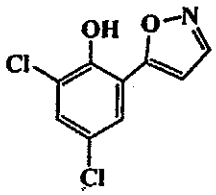
PhOH-26



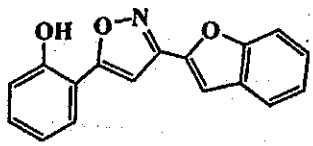
PhOH-27



PhOH-28



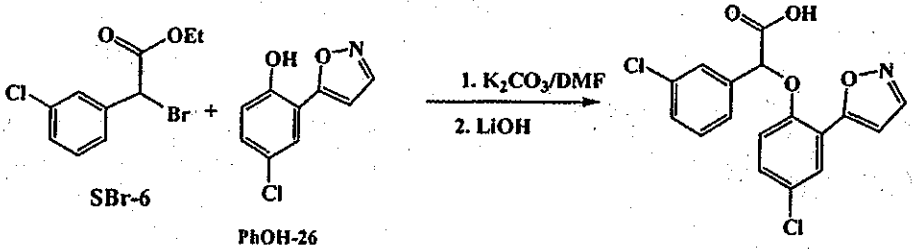
PhOH-29



PhOH-30

[0293] PhOH-24 to PhOH-30 were purchased from different commercial sources.

Example 97



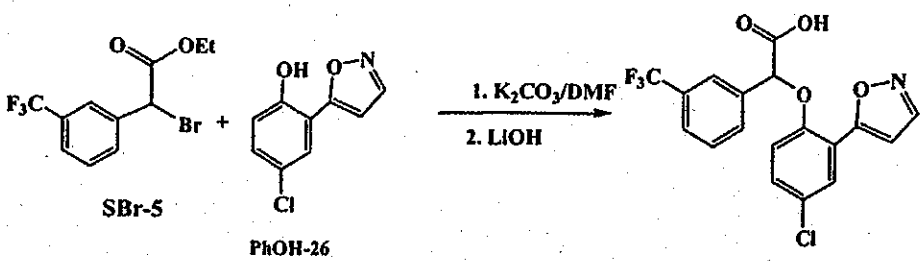
SBr-6

PhOH-26

IX-19

[0294] In the same manner as that described in **Example 28** compound **IX-23** was prepared from **SBr-1** and **PhOH-26.** ^{1}HNMR (400 MHz, d-DMSOd_6): δ 8.76 (d, 1H), 7.87 (d, 1H), 7.59 (s.1H), 7.66 1M, 4H1), 7.36 (s,1H), 7.17 (d.1H), 6.27) (s, 1H).

Example 98



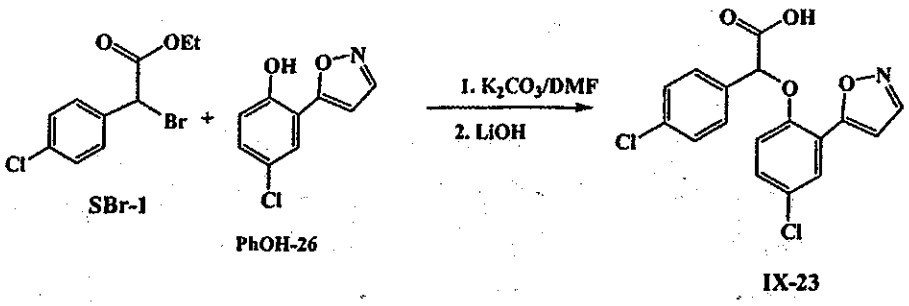
SBr-5

PhOH-26

IX-20

[0295] In the same manner as that described in **Example 28** compound **IX-20** was prepared from **SBr-5** and **PhOH-26. IX-20:** ^{1}H NMR (d-DMSO, 400 MHz) δ 13.69 (br, 1H), 8.76 (d, 1H), 7.87 (d, 1H), 7.59 (s, 1H), 7.48-7.43 (m, 4H), 7.36 (s, 1H), 7.16 (d, 1H), 6.27 (s, 1H).

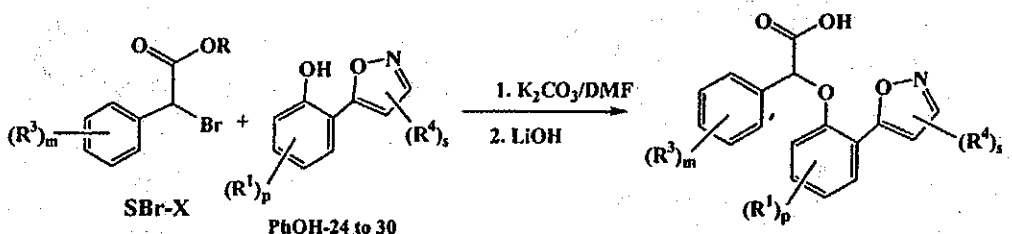
Example 99



SBr-1 PhOH-26 IX-23

[0296] In the same manner as that described in **Example 28** compound **IX-23** was prepared from **SBr-1** and **PhOH-26.** ^{1}H NMR (d-DMSO, 400 MHz) δ (8.74 (d, 1H), 7.87 (d, 1H), 7.52 (m, 2H), 7.45 (m, 3H), 7.33 (d, 1H), 7.14 (d, 1H), 6.27 (s, 1H).

Example 100

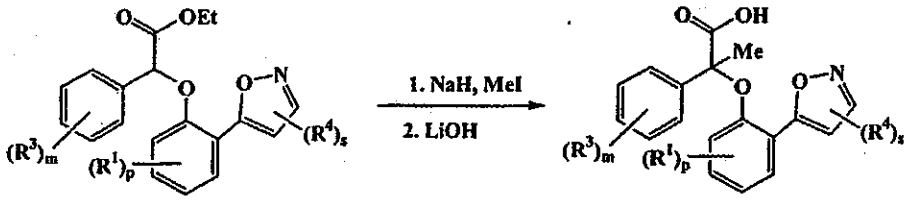


SBr-X PhOH-24 to 30 IX-X

R^3 = 3-CF_3, 3-Cl, 3-OPh, H, 4-OMe, 4-Cl, 4-CF_3, 4-Br, 4-Et
R^1 = H, 4'-Me, 4'-Cl, 4'-Br, 4'-Cl, 5'-Me-, 4'-Cl-6'-Cl
R^4 = H, 3"-(2-benzofuranyl)

[0297] In the same manner as that described in **Example 28**, the rest of compounds **IX-X** can be prepared.

Example 101

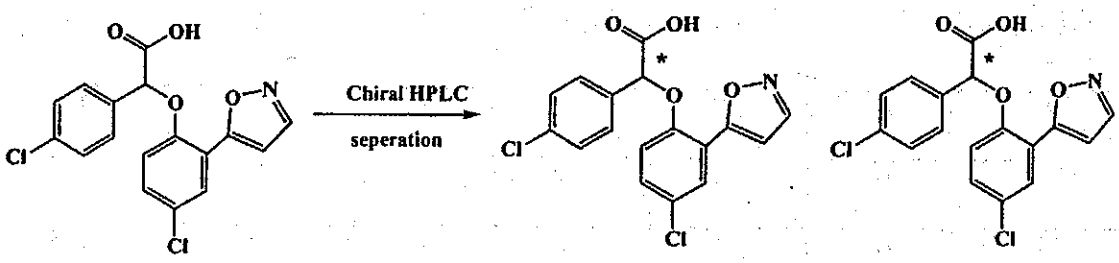


SIX-1 IXa-X

R^3 = 3-CF_3, 3-Cl, 3-OPh, H, 4-OMe, 4-Cl, 4-CF_3, 4-Br, 4-Et
R^1 = H, 4'-Me, 4'-Cl, 4'-Br, 4'-Cl, 5'-Me-, 4'-Cl-6'-Cl
R^4 = H, 3''-(2-benzofuranyl)

[0298] In the same manner as that described in **Example 42** compound **IXa-X** can be prepared from **SIX-1.**

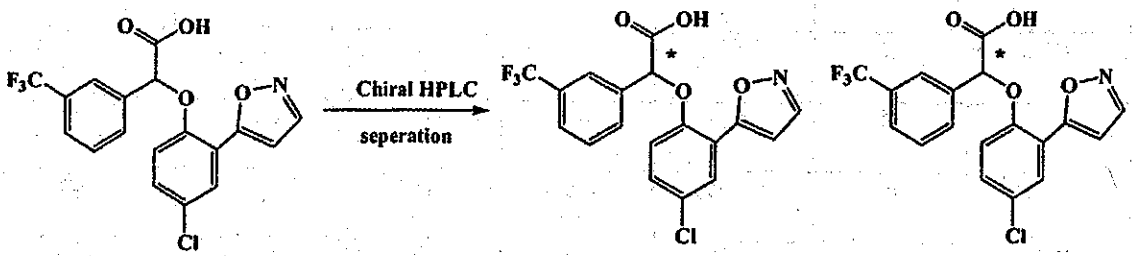
Example 102



(+/-)-IX-23 (+)-IX-23 (-)-IX-23

[0299] Racemic **IX-23** was resolved by chiral HPLC to give (+)-**IX-23** and (-)-**IX-23**. HPLC methods and conditions, including eluents used, solvent flow rate and detection wavelength were: 20% iPrOH-80% Hexanes-0.1% TFA, 30 mL/min., λ=220 nm. For (+)-**IX-23**: RT 6.7 min. For (-)-**IX-23**: RT 7.0 min.

Example 103

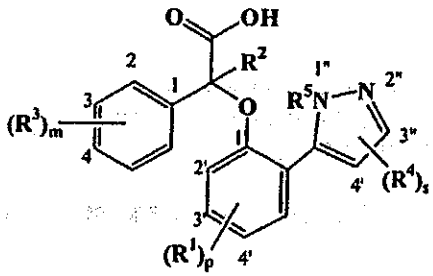


(+/-)-IX-20 (+)-IX-20 (-)-IX-20

[0300] Racemic **IX-20** was resolved by chiral HPLC to give (+)-**IX-20** and (-)-**IX-20**. HPLC methods and conditions, including eluents used, solvent flow rate and detection

wavelength were: 20% iPrOH-80% Hexanes-0.1% TFA, 30 mL/min., λ=220 nm. For (+)-**IX-20**: RT 6.6 min. For (-)-**IX-20**: RT 6.9 min.

Table 10
2-pyrroyl analogs



Compounds X and Xa

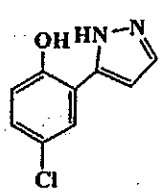
Compound	R^2	$(R^3)_m$	$(R^1)_p$	$(R^4)_s$	R^5	Configuration
X-1	H	4-Cl	4'-Cl	H	H	R/S
X-2	H	3-CF_3	4'-Cl	H	H	R/S
X-3	H	3-OPh	4'-Cl	H	H	R/S
X-4	H	4-OMe	4'-Cl	H	H	R/S
X-5	H	3-Cl	4'-Cl	H	H	R/S
X-6	H	4-CF_3	4'-Cl	H	H	R/S
X-7	H	4-Br	4'-Cl	H	H	R/S
X-8	H	H	4'-Cl	H	H	R/S
X-9	H	3-Cl	4-F	H	Me	R/S
X-10	H	3-CF_3	4-F	H	Me	R/S
X-11	H	3-OPh	4-F	H	Me	R/S
X-12	H	4-OMe	4-F	H	Me	R/S
X-13	H	4-Cl	4-F	H	Me	R/S
X-14	H	4-CF_3	4-F	H	Me	R/S
X-15	H	4-Br	4-F	H	Me	R/S

X-16	H	H	4-F	H	Me	R/S
X-17	H	3-Cl	4-Cl	H	Ph	R/S
X-18	H	3-CF_3	4-Cl	H	Ph	R/S
X-19	H	3-OPh	4-Cl	H	Ph	R/S
X-20	H	4-OMe	4-Cl	H	Ph	R/S
X-21	H	4-Cl	4-Cl	H	Ph	R/S
X-22	H	4-CF_3	4-Cl	H	Ph	R/S
X-23	H	4-Br	4-Cl	H	Ph	R/S
X-24	H	H	4-Cl	H	Ph	R/S
X-25	H	3-Cl	4-Br	H	Ph	R/S
X-26	H	3-CF_3	4-Br	H	Ph	R/S
X-27	H	3-OPh	4-Br	H	Ph	R/S
X-28	H	4-OMe	4-Br	H	Ph	R/S
X-29	H	4-Cl	4-Br	H	Ph	R/S
X-30	H	4-CF_3	4-Br	H	Ph	R/S
X-31	H	4-Br	4-Br	H	Ph	R/S
X-32	H	H	4-Br	H	Ph	R/S
X-33	H	3-Cl	4-Cl, 6-Cl	H	Me	R/S
X-34	H	3-CF_3	4-Cl, 6-Cl	H	Me	R/S
X-35	H	3-OPh	4-Cl, 6-Cl	H	Me	R/S
X-36	H	4-OMe	4-Cl, 6-Cl	H	Me	R/S
X-37	H	4-Cl	4-Cl, 6-Cl	H	Me	R/S
X-38	H	4-CF_3	4-Cl, 6-Cl	H	Me	R/S
X-39	H	4-Br	4-Cl, 6-Cl	H	Me	R/S
X-40	H	H	4-Cl, 6-Cl	H	Me	R/S
X-41	H	3-Cl	4-Me	H	Ph	R/S

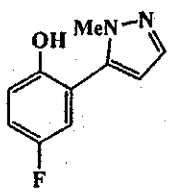
X-42	H	3-CF_3	4-Me	H	Ph	R/S
X-43	H	3-OPh	4-Me	H	Ph	R/S
X-44	H	4-OMe	4-Me	H	Ph	R/S
X-45	H	4-Cl	4-Me	H	Ph	R/S
X-46	H	4-CF_3	4-Me	H	Ph	R/S
X-47	H	4-Br	4-Me	H	Ph	R/S
X-48	H	H	4-Me	H	Ph	R/S
X-49	H	3-Cl	4-Cl, 5-Me	H	Ph	R/S
X-50	H	3-CF_3	4-Cl, 5-Me	H	Ph	R/S
X-51	H	3-OPh	4-Cl, 5-Me	H	Ph	R/S
X-52	H	4-OMe	4-Cl, 5-Me	H	Ph	R/S
X-53	H	4-Cl	4-Cl, 5-Me	H	Ph	R/S
X-54	H	4-CF_3	4-Cl, 5-Me	H	Ph	R/S
X-55	H	4-Br	4-Cl, 5-Me	H	Ph	R/S
X-56	H	H	4-Cl, 5-Me	H	Ph	R/S
X-57	H	3-Cl	H	H	Me	R/S
X-58	H	3-CF_3	H	H	Me	R/S
X-59	H	3-OPh	H	H	Me	R/S
X-60	H	4-OMe	H	H	Me	R/S
X-61	H	4-Cl	H	H	Me	R/S
X-62	H	4-CF_3	H	H	Me	R/S
X-63	H	4-Br	H	H	Me	R/S
X-64	H	H	H	H	Me	R/S
X-65	H	3-Cl	H	H	Ph	R/S
X-66	H	3-CF_3	H	H	Ph	R/S
X-67	H	3-OPh	H	H	Ph	R/S

X-68	H	4-OMe	H	H	Ph	R/S
X-69	H	4-Cl	H	H	Ph	R/S
X-70	H	4-CF_3	H	H	Ph	R/S
X-71	H	4-Br	H	H	Ph	R/S
X-72	H	H	H	H	Ph	R/S
Xa-1	Me	3-Cl	4-Cl	H	Ph	R/S
Xa-2	Me	3-CF_3	4-Cl	H	Ph	R/S
Xa-3	Me	3-OPh	4-Cl	H	Ph	R/S
Xa-4	Me	4-OMe	4-Cl	H	Ph	R/S
Xa-5	Me	4-Cl	4-Cl	H	Ph	R/S
Xa-6	Me	4-CF_3	4-Cl	H	Ph	R/S
Xa-7	Me	4-Br	4-Cl	H	Ph	R/S
Xa-8	Me	H	4-Cl	H	Ph	R/S

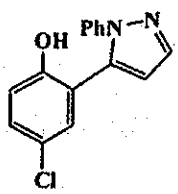
13. 2-pyrazolyl phenols



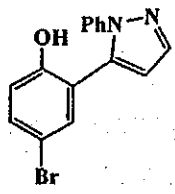
PhOH-31



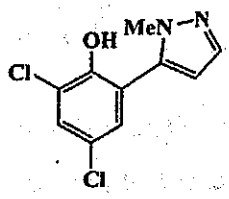
PhOH-32



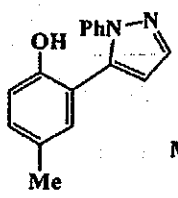
PhOH-33



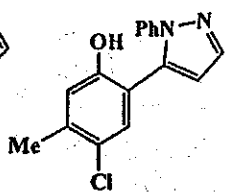
PhOH-34



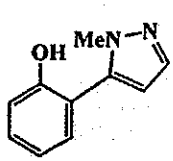
PhOH-35



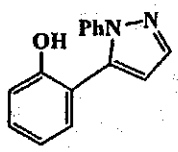
PhOH-36



PhOH-37



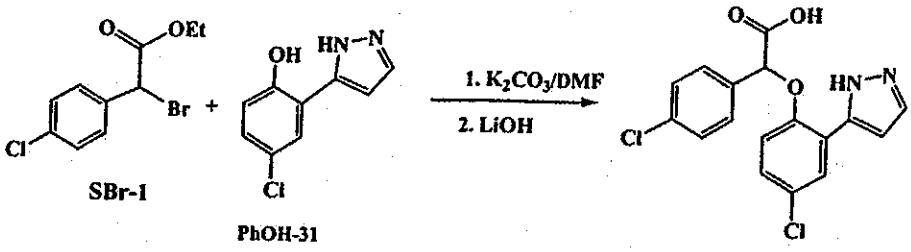
PhOH-38



PhOH-39

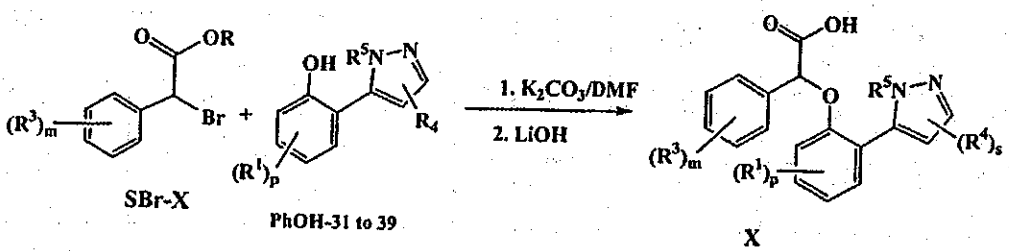
[0301] PhOH-31 to PhOH-39 were purchased from different commercial sources.

Example 104



[0302] In the same manner as that described in **Example 28** compound **X-1**was prepared from **SBr-1** and **PhOH-31.** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50-7.42 (m, 6H), 7.18 (dd, 1H), 6.96 (d, 1H), 6.63 (d, 1H), 6.20 (s, 1H).

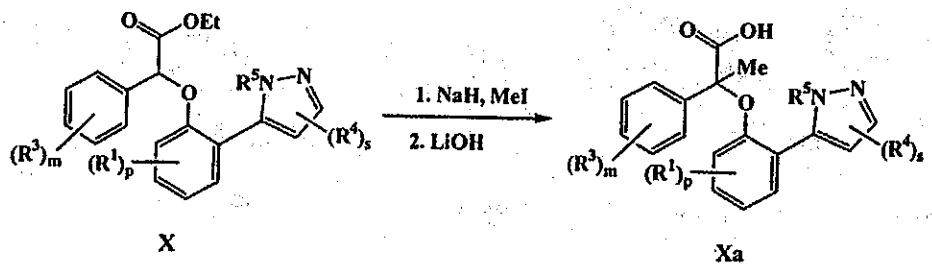
Example 105



R^3 = 3-CF_3, 3-Cl, 3-OPh, H, 4-OMe, 4-Cl, 4-CF_3, 4-Br
R^1 = H, 4'-F, 4'-Me, 4'-Cl, 4'-Br, 4'-Cl-5'-Me-, 4'-Cl-6'-Cl
R^4 = H
R^5 = H, Me, Ph

[0303] The rest of compounds **X** listed in **Table 10** can be prepared in the same manner as that described in **Example 28.**

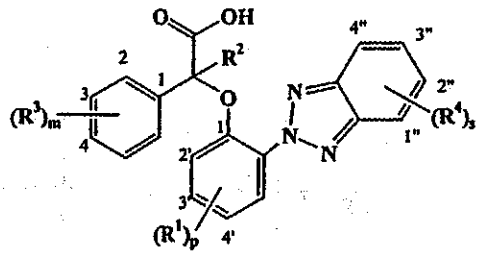
Example 106



R^3 = 3-CF_3, 3-Cl, 3-OPh, H, 4-OMe, 4-Cl, 4-CF_3, 4-Br
R^1 = H, 4'-F, 4'-Me, 4'-Cl, 4'-Br, 4'-Cl-5'-Me-, 4'-Cl-6'-Cl
R^4 = H
R^5 = H, Me, Ph

[0304] Compounds **Xa** listed in **Table 10** can be prepared in the same manner as that described in **Example 42.**

Table 11
2-Benzotriazole analogs



Compound XI and XIa

Compound	R^2	$(R^3)_m$	$(R^1)_p$	$(R^4)_s$	Configuration
XI-1	H	3-Cl	4-Me	H	R/S
XI-2	H	3-CF_3	4-Me	H	R/S
XI-3	H	3-OPh	4-Me	H	R/S
XI-4	H	4-OMe	4-Me	H	R/S
XI-5	H	4-Cl	4-Me	H	R/S
XI-6	H	4-CF_3	4-Me	H	R/S
XI-7	H	4-Br	4-Me	H	R/S
XI-8	H	H	4-Me	H	R/S
XI-9	H	4-Et	4-Me	H	R/S
XI-10	H	3-Cl	4-*t*-octyl	H	R/S
XI-11	H	3-CF_3	4-*t*-octyl	H	R/S
XI-12	H	3-OPh	4-*t*-octyl	H	R/S
XI-13	H	4-OMe	4-*t*-octyl	H	R/S
XI-14	H	4-Cl	4-*t*-octyl	H	R/S
XI-15	H	4-CF_3	4-*t*-octyl	H	R/S
XI-16	H	4-Br	4-*t*-octyl	H	R/S

XI-17	H	H	4-*t*-octyl	H	R/S
XI-18	H	4-Et	4-*t*-octyl	H	R/S
XI-19	H	3-Cl	4-Cl	H	R/S
XI-20	H	3-CF_3	4-Cl	H	R/S
XI-21	H	3-OPh	4-Cl	H	R/S
XI-22	H	4-OMe	4-Cl	H	R/S
XI-23	H	4-Cl	4-Cl	H	R/S
XI-24	H	4-CF_3	4-Cl	H	R/S
XI-25	H	4-Br	4-Cl	H	R/S
XI-26	H	H	4-Cl	H	R/S
XI-27	H	4-Et	4-Cl	H	R/S
XI-28	H	3-Cl	4-Br	H	R/S
XI-29	H	3-CF_3	4-Br	H	R/S
XI-30	H	3-OPh	4-Br	H	R/S
XI-31	H	4-OMe	4-Br	H	R/S
XI-32	H	4-Cl	4-Br	H	R/S
XI-33	H	4-CF_3	4-Br	H	R/S
XI-34	H	4-Br	4-Br	H	R/S
XI-35	H	H	4-Br	H	R/S
XI-36	H	4-Et	4-Br	H	R/S
XI-37	H	3-Cl	4-*t*-Bu	H	R/S
XI-38	H	3-CF_3	4-*t*-Bu	H	R/S
XI-39	H	3-OPh	4-*t*-Bu	H	R/S
XI-40	H	4-OMe	4-*t*-Bu	H	R/S
XI-41	H	4-Cl	4-*t*-Bu	H	R/S
XI-42	H	4-CF_3	4-*t*-Bu	H	R/S

XI-43	H	4-Br	4-*t*-Bu	H	R/S
XI-44	H	H	4-*t*-Bu	H	R/S
XI-45	H	4-Et	4-*t*-Bu	H	R/S
XI-46	H	3-Cl	4'-CF_3	H	R/S
XI-47	H	3-CF_3	4'-CF_3	H	R/S
XI-48	H	3-OPh	4'-CF_3	H	R/S
XI-49	H	4-OMe	4'-CF_3	H	R/S
XI-50	H	4-Cl	4'-CF_3	H	R/S
XI-51	H	4-CF_3	4'-CF_3	H	R/S
XI-52	H	4-Br	4'-CF_3	H	R/S
XI-53	H	H	4'-CF_3	H	R/S
XI-54	H	4-Et	4'-CF_3	H	R/S
XI-55	H	3-Cl	2',4'-di-*t*-Bu	H	R/S
XI-56	H	3-CF_3	2',4'-di-*t*-Bu	H	R/S
XI-57	H	3-OPh	2',4'-di-*t*-Bu	H	R/S
XI-58	H	4-OMe	2',4'-di-*t*-Bu	H	R/S
XI-59	H	4-Cl	2',4'-di-*t*-Bu	H	R/S
XI-60	H	4-CF_3	2',4'-di-*t*-Bu	H	R/S
XI-61	H	4-Br	2',4'-di-*t*-Bu	H	R/S
XI-62	H	H	2',4'-di-*t*-Bu	H	R/S
XI-63	H	4-Et	2',4'-di-*t*-Bu	H	R/S
XI-64	H	3-Cl	2'-*t*-Bu, 4'-Me	2"-Cl	R/S
XI-65	H	3-CF_3	2'-*t*-Bu, 4'-Me	2"-Cl	R/S
XI-66	H	3-OPh	2'-*t*-Bu, 4'-Me	2"-Cl	R/S
XI-67	H	4-OMe	2'-*t*-Bu, 4'-Me	2"-Cl	R/S
XI-68	H	4-Cl	2'-*t*-Bu, 4'-Me	2"-Cl	R/S

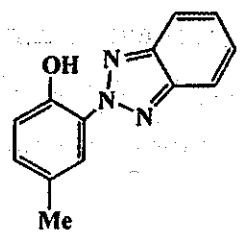
XI-69	H	4-CF_3	2'-*t*-Bu, 4'-Me	2"-Cl	R/S
XI-70	H	4-Br	2'-*t*-Bu, 4'-Me	2"-Cl	R/S
XI-71	H	H	2'-*t*-Bu, 4'-Me	2"-Cl	R/S
XI-72	H	4-Et	2'-*t*-Bu, 4'-Me	2"-Cl	R/S
XI-73	H	4-CF_3	4'-Cl	H	(-)
XI-74	H	4-CF_3	4'-Cl	H	(+)
XI-75	H	4-Cl	4'-Cl	H	(-)
XI-76	H	4-Cl	4'-Cl	H	(+)
XIa-1	Me	3-Cl	4-Me	H	R/S
XIa-2	Me	3-CF_3	4-Me	H	R/S
XIa-3	Me	3-OPh	4-Me	H	R/S
XIa-4	Me	4-OMe	4-Me	H	R/S
XIa-5	Me	4-Cl	4-Me	H	R/S
XIa-6	Me	4-CF_3	4-Me	H	R/S
XIa-7	Me	4-Br	4-Me	H	R/S
XIa-8	Me	H	4-Me	H	R/S
XIa-9	Me	4-Et	4-Me	H	R/S
XIa-10	Me	3-Cl	4-*t*-octyl	H	R/S
XIa-11	Me	3-CF_3	4-*t*-octyl	H	R/S
XIa-12	Me	3-OPh	4-*t*-octyl	H	R/S
XIa-13	Me	4-OMe	4-*t*-octyl	H	R/S
XIa-14	Me	4-Cl	4-*t*-octyl	H	R/S
XIa-15	Me	4-CF_3	4-*t*-octyl	H	R/S
XIa-16	Me	4-Br	4-*t*-octyl	H	R/S
XIa-17	Me	H	4-*t*-octyl	H	R/S
XIa-18	Me	4-Et	4-*t*-octyl	H	R/S

XIa-19	Me	3-Cl	4-Cl	H	R/S
XIa-20	Me	3-CF_3	4-Cl	H	R/S
XIa-21	Me	3-OPh	4-Cl	H	R/S
XIa-22	Me	4-OMe	4-Cl	H	R/S
XIa-23	Me	4-Cl	4-Cl	H	R/S
XIa-24	Me	4-CF_3	4-Cl	H	R/S
XIa-25	Me	4-Br	4-Cl	H	R/S
XIa-26	Me	H	4-Cl	H	R/S
XIa-27	Me	4-Et	4-Cl	H	R/S
XIa-28	Me	3-Cl	4-Br	H	R/S
XIa-29	Me	3-CF_3	4-Br	H	R/S
XIa-30	Me	3-OPh	4-Br	H	R/S
XIa-31	Me	4-OMe	4-Br	H	R/S
XIa-32	Me	4-Cl	4-Br	H	R/S
XIa-33	Me	4-CF_3	4-Br	H	R/S
XIa-34	Me	4-Br	4-Br	H	R/S
XIa-35	Me	H	4-Br	H	R/S
XIa-36	Me	4-Et	4-Br	H	R/S
XIa-37	Me	3-Cl	4-*t*-Bu	H	R/S
XIa-38	Me	3-CF_3	4-*t*-Bu	H	R/S
XIa-39	Me	3-OPh	4-*t*-Bu	H	R/S
XIa-40	Me	4-OMe	4-*t*-Bu	H	R/S
XIa-41	Me	4-Cl	4-*t*-Bu	H	R/S
XIa-42	Me	4-CF_3	4-*t*-Bu	H	R/S
XIa-43	Me	4-Br	4-*t*-Bu	H	R/S
XIa-44	Me	H	4-*t*-Bu	H	R/S

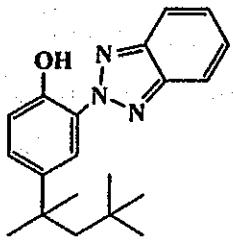
XIa-45	Me	4-Et	4-*t*-Bu	H	R/S
XIa-46	Me	3-Cl	4'-CF_3	H	R/S
XIa-47	Me	3-CF_3	4'-CF_3	H	R/S
XIa-48	Me	3-OPh	4'-CF_3	H	R/S
XIa-49	Me	4-OMe	4'-CF_3	H	R/S
XIa-50	Me	4-Cl	4'-CF_3	H	R/S
XIa-51	Me	4-CF_3	4'-CF_3	H	R/S
XIa-52	Me	4-Br	4'-CF_3	H	R/S
XIa-53	Me	H	4'-CF_3	H	R/S
XIa-54	Me	4-Et	4'-CF_3	H	R/S
XIa-55	Me	3-Cl	2',4'-di-*t*-Bu	H	R/S
XIa-56	Me	3-CF_3	2',4'-di-*t*-Bu	H	R/S
XIa-57	Me	3-OPh	2',4'-di-*t*-Bu	H	R/S
XIa-58	Me	4-OMe	2',4'-di-*t*-Bu	H	R/S
XIa-59	Me	4-Cl	2',4'-di-*t*-Bu	H	R/S
XIa-60	Me	4-CF_3	2',4'-di-*t*-Bu	H	R/S
XIa-61	Me	4-Br	2',4'-di-*t*-Bu	H	R/S
XIa-62	Me	H	2',4'-di-*t*-Bu	H	R/S
XIa-63	Me	4-Et	2',4'-di-*t*-Bu	H	R/S
XIa-64	Me	3-Cl	2'-*t*-Bu, 4'-Me	2"-Cl	R/S
XIa-65	Me	3-CF_3	2'-*t*-Bu, 4'-Me	2"-Cl	R/S
XIa-66	Me	3-OPh	2'-*t*-Bu, 4'-Me	2"-Cl	R/S
XIa-67	Me	4-OMe	2'-*t*-Bu, 4'-Me	2"-Cl	R/S
XIa-68	Me	4-Cl	2'-*t*-Bu, 4'-Me	2"-Cl	R/S
XIa-69	Me	4-CF_3	2'-*t*-Bu, 4'-Me	2"-Cl	R/S
XIa-70	Me	4-Br	2'-*t*-Bu, 4'-Me	2"-Cl	R/S

XIa-71	Me	H	2'-*t*-Bu, 4'-Me	2"-Cl	R/S
XIa-72	Me	4-Et	2'-*t*-Bu, 4'-Me	2"-Cl	R/S
XIa-73	Me	4-CF_3	4'-Cl	H	(-)
XIa-74	Me	4-CF_3	4'-Cl	H	(+)
XIa-75	Me	4-Cl	4'-Cl	H	(-)
XIa-76	Me	4-Cl	4'-Cl	H	(+)

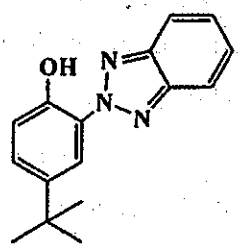
14. 2-Benzotriazol-2-yl-phenols



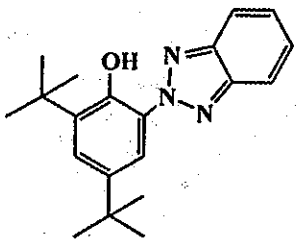
PhOH-40



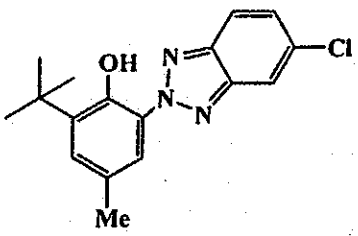
PhOH-41



PhOH-42



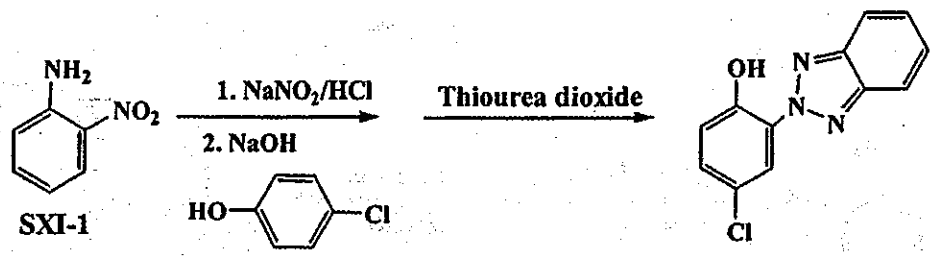
PhOH-43



PhOH-44

[0305] PhOH-40 to PhOH-44 were purchased from different commercial sources.

Example 107



SXI-1

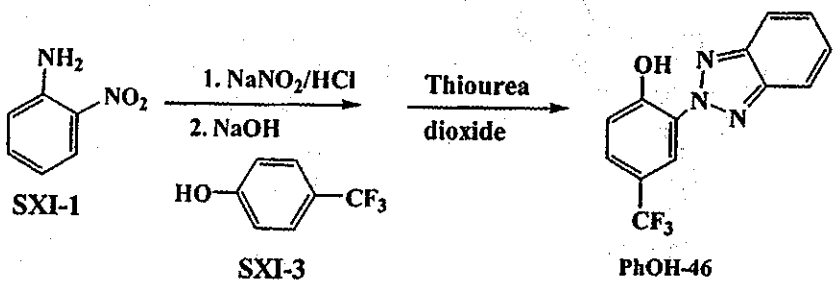
PhOH-45

[0306] Nitro aniline (138.13 g) was mixed with 500 mL of concentrated HCl and stirred for several min. When all the aniline was dissolved, the solution was cooled down to room

temperature and diluted with water (300 mL), and then a solution of $NaNO_2$ (69 g) in 250 mL of water was dropwise added at 0 °C. The solution became a clear and yellowish solution. The diazonium salt solution was added slowly to a solution of phenol (128.5 g) in water (800mL) containing 80 g of NaOH at 0 °C. When the addition was complete, the reaction mixture was stand for several hours, a black precipitate was formed and filtered. The solid was dissolved in ethyl acetate, washed with brine, dried over anhydrous Na_2SO_4. The solution was concentrated to give 133.5 g of nitroazophenol product as light yellow solid. The mother liquor was concentrated again to give another 65 g of the nitroazophenol product. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.98 (s, 1H), 8.20 – 7.05 (m, 7H).

[0307] A mixture of nitroazophenol (40 g), thiourea dioxide (30 g), 500 mL of NaOH solution (4 N) and 500 mL ethanol was stirred for half an hour at 80 °C, and then 15 g of thiourea dioxide was added. The solution was stirred for another one hour, diluted with ice-water, extracted with ethyl acetate, dried over anhydrous Na_2SO_4. The solution was concentrated to give 21 g of **PhOH-45** as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 11.25 (s, 1H), 8.40 – 7.15 (m, 7H).

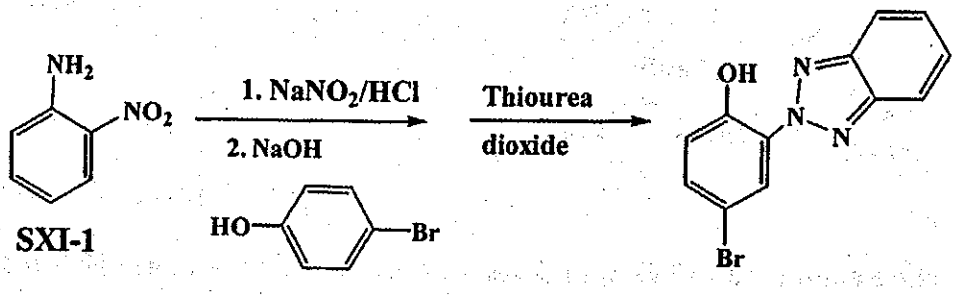
Example 108



SXI-1 SXI-3 PhOH-46

[0308] In the same manner as that described in **Example 107**, **PhOH-46** was prepared from phenol **SXI-3**. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 11.78 (s, 1H), 8.71 – 7.23 (m, 7H).

Example 109



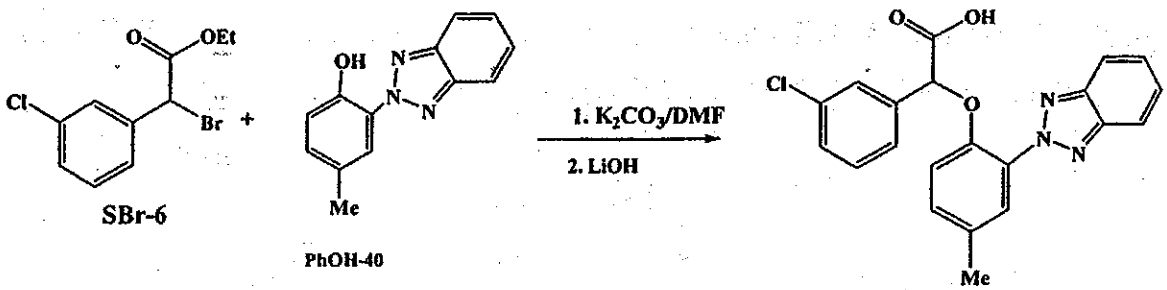
SXI-1 SXI-4 PhOH-47

[0309] PhOH-47 can be prepared from SXI-1 and SXI-4 in the same manner as that described in Example 107.

15. Synthesis of Compounds XI and XIa in Table 11

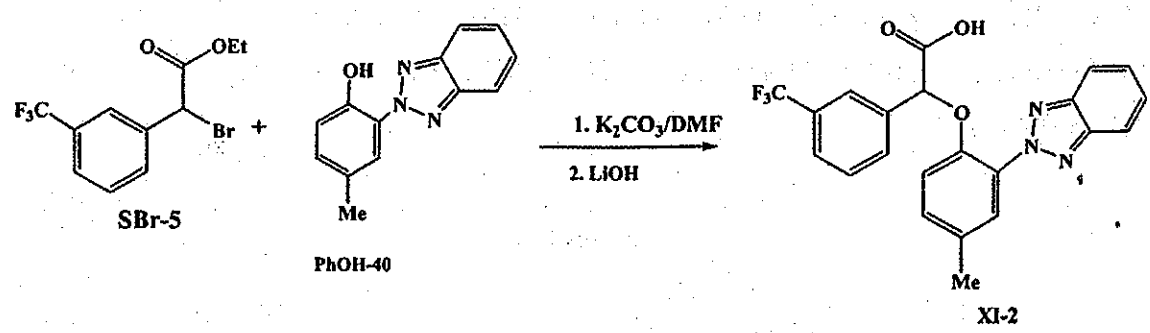
[0310] Compounds **XI** and **XIa** were or can be prepared in the same manner as that described for the synthesis of compounds **I-X** and **Ia-X**.

Example 110



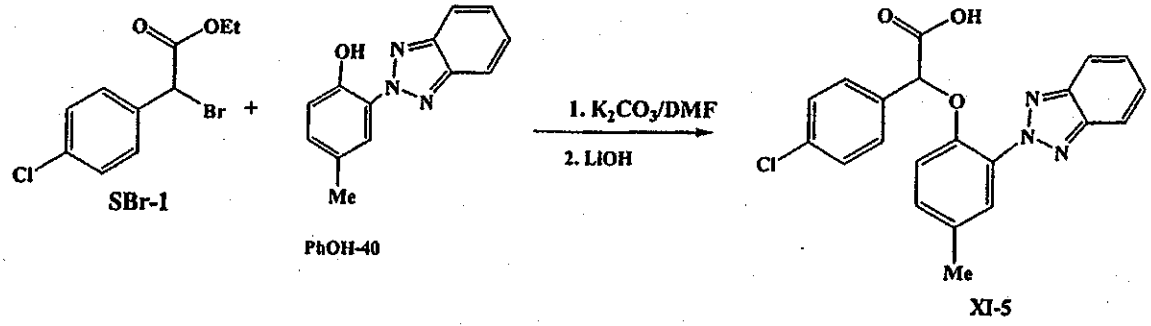
[0311] **XI-1** was prepared from **SBr-6** and **PhOH-40** in the same manner as that described in **Example 28**. ^{1}H-NMR (d-DMSO, 400 MHz) δ 8.15 (m, 2H), 7.63 (d, 1H), 7.57 (m, 3H), 7.40 (m, 4H), 7.20 (d, 1H), 6.15 (s, 1H), 2.38 (s, 3H).

Example 111



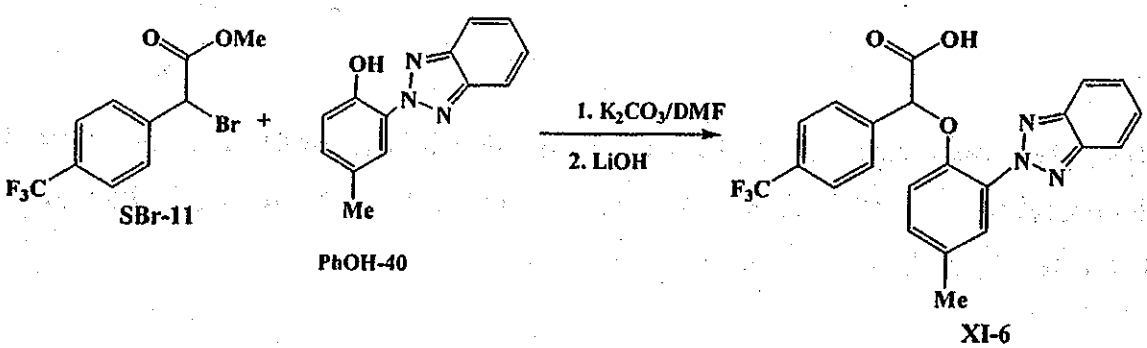
[0312] **XI-2** was prepared from **SBr-5** and **PhOH-40** in the same manner as that described in **Example 28**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.98 (2H, dd, J = 6.6, 3.2 Hz), 7.72 (2H, d, J = 6.0 Hz), 7.66 (1H, d, J = 8.4 Hz), 7.60 (1H, d, J = 2.4 Hz), 7.57 (1H, d, J = 7.6 Hz), 7.51 (2H, dd, J = 6.6, 3.2 Hz), 7.39 (1H, dd, J = 8.8, 2.0 Hz), 7.19 (1H, d, J = 8.8 Hz), 616 (1H, s), 2.40 (3H, s).

Example 112



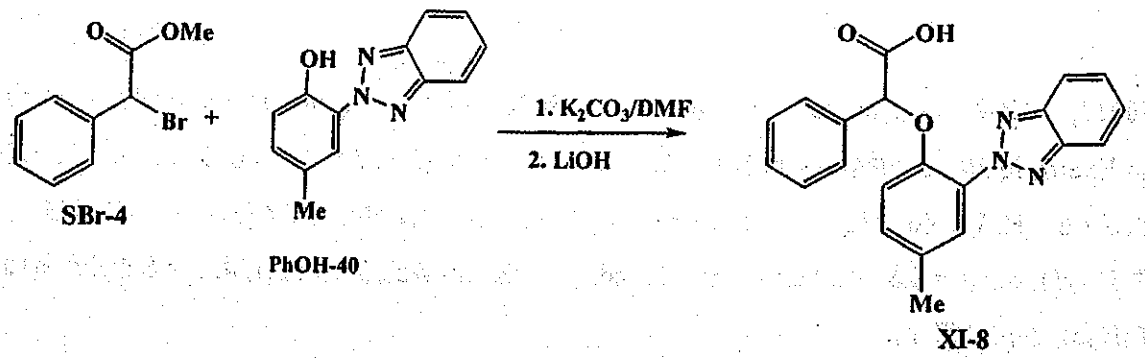
[0313] **XI-5** was prepared from **SBr-1** and **PhOH-40** in the same manner as that described in **Example 28**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.02 (2H, dd, J = 6.8, 3.2 Hz), 7.56 (1H, dd, J = 3.2, 0.8 Hz), 7.50 (2H, dd, J = 6.8, 3.2 Hz), 7.41–7.44 (2H, m), 7.34–7.37 (3H, m), 7.14 (1H, d, J = 8.8 Hz), 5.92 (1H, s), 2.32 (3H, s).

Example 113



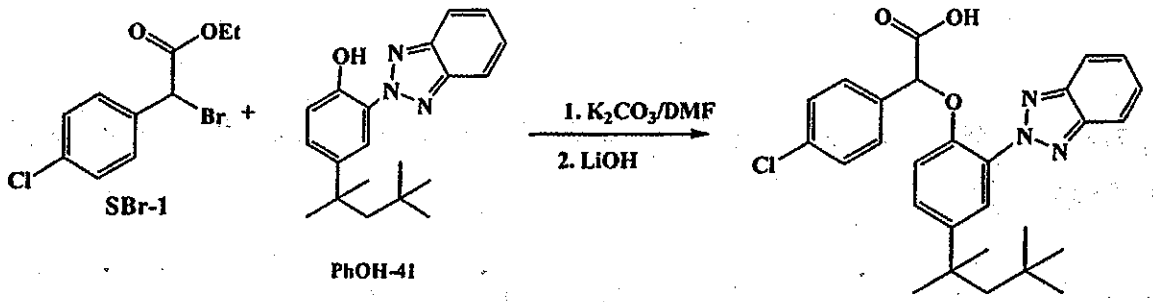
[0314] **XI-6** was prepared from **SBr-11** and **PhOH-40** in the same manner as that described in **Example 28**. ^{1}HNMR (400 MHz, $CDCl_3$): δ 11.25 (br, 1H), 8.0 – 6.90 (m, 11H), 5.90 (s, 1H).

Example 114



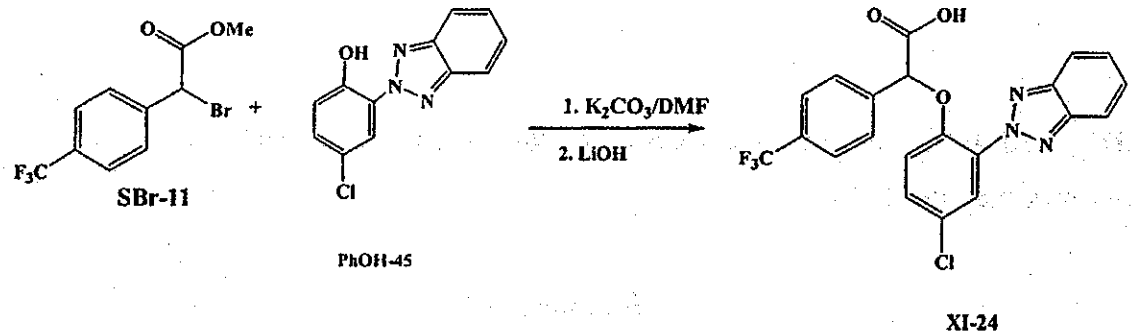
[0315] **XI-8** was prepared from **SBr-4** and **PhOH-40** in the same manner as that described in **Example 28**. ^{1}HNMR (CDCl3, 400 MHz) δ 7.96 (m, 3H), 7.54-7.46 (m, 7H), 7.12 (d, 1H), 6.96 (d, 1H), 5.84 (s, 1H), 2.35 (s, 3H).

Example 115



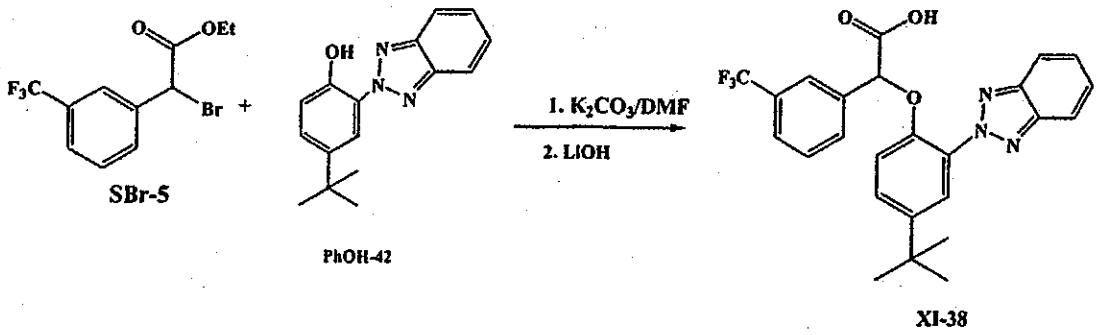
[0316] **XI-14** was prepared from **SBr-1** and **PhOH-41** in the same manner as that described in **Example 28**. ^{1}HNMR (400 MHz, DMSO): δ 8.10 – 7.15 (m, 11H), 6.0 (s, 1H), 1.70 (s, 2H), 1.32 (s, 6H), 0.68 (s, 9H).

Example 116



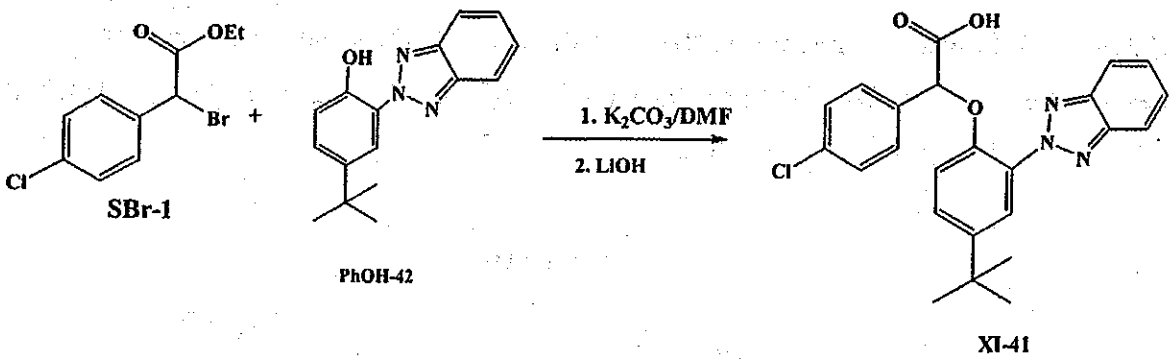
[0317] **XI-24** was prepared from **SBr-11** and **PhOH-45** in the same manner as that described in **Example 28**. ^{1}H-NMR (400 MHz, DMSO): δ 13.58 (s, 1H), 8.06 – 7.33 (m, 11H), 6.25 (s, 1H).

Example 117



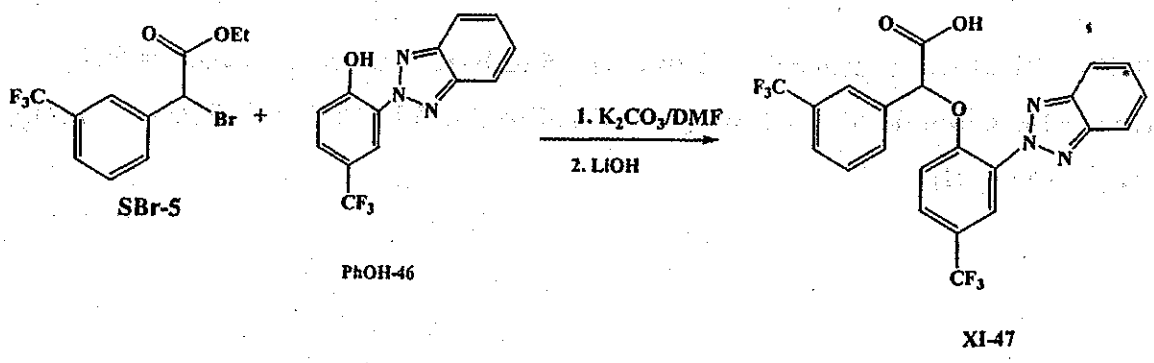
[0318] XI-38 was prepared from SBr-5 and PhOH-42 in the same manner as that described in Example 28.

Example 118



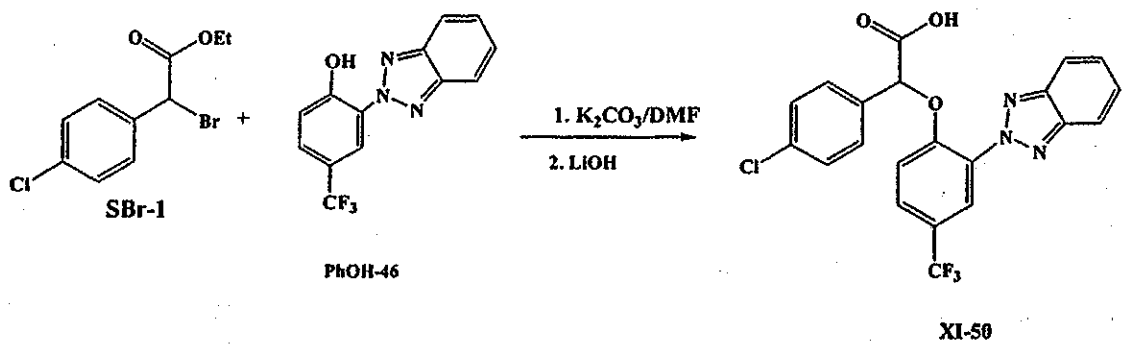
[0319] **XI-41** was prepared from **SBr-1** and **PhOH-42** in the same manner as that described in **Example 28**.

Example 119



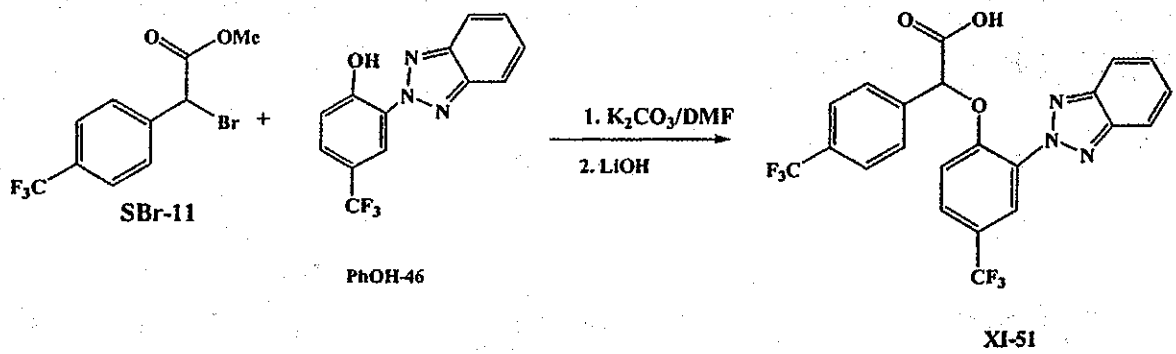
[0320] **XI-47** was prepared from **SBr-5** and **PhOH-46** in the same manner as that described in **Example 28**. ^{1}H-NMR (400 MHz, DMSO): δ 8.22 – 7.45 (m, 11H), 6.42 (s, 1H).

Example 120



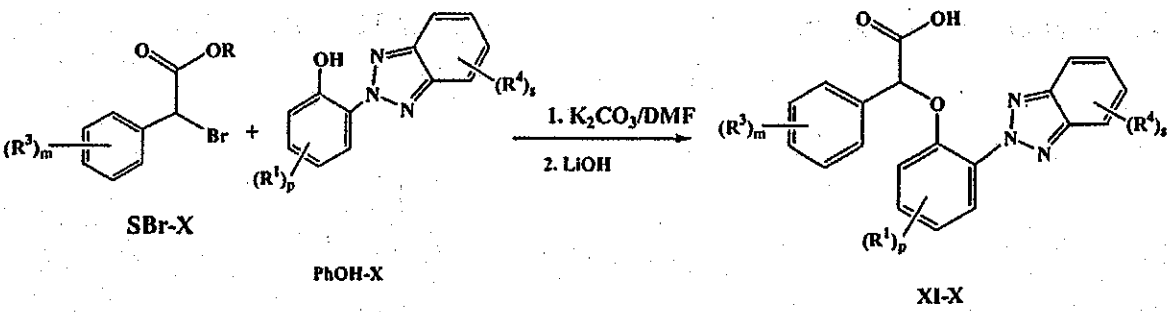
[0321] **XI-50** was prepared from **SBr-1** and **PhOH-46** in the same manner as that described in **Example 28**. ^{1}H-NMR (400 MHz, DMSO): δ 8.20 – 7.40 (m, 11H), 6.22 9s, 1H).

Example 121



[0322] **XI-51** was prepared from **SBr-11** and **PhOH-46** in the same manner as that described in **Example 28**. ^{1}H-NMR (400 MHz, DMSO): δ 8.22 – 7.45 (m, 11H), 6.40 (s, 1H).

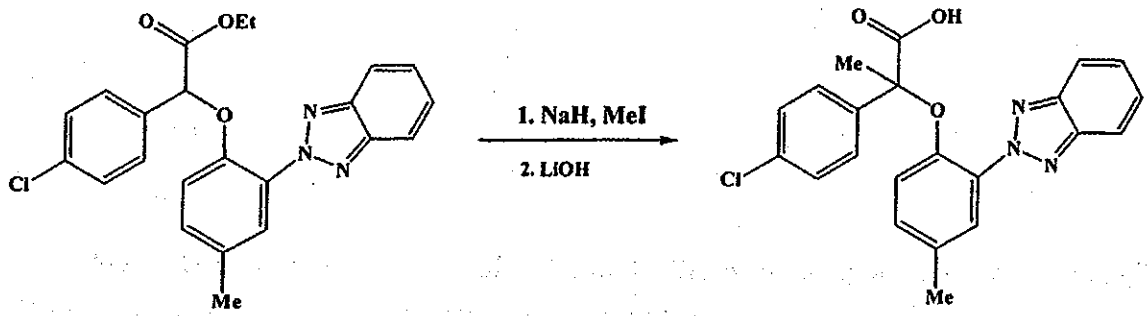
Example 122



R^3 = 3-CF_3, 3-Cl, 3-OPh, H, 4-OMe, 4-Cl, 4-CF_3, 4-Br, 4-Et
R^1 = H, 4'-t-octyl, 4'-tBu, 4'-Me, 4'-Cl, 4'-Br, 2',4'-di-t-Bu, 4'-CF_3
R^4 = H, 2''-Cl

[0323] The rest of **XI** can be prepared from **SBr-X** and **PhOH-X** in the same manner as that described in **Example 28.**

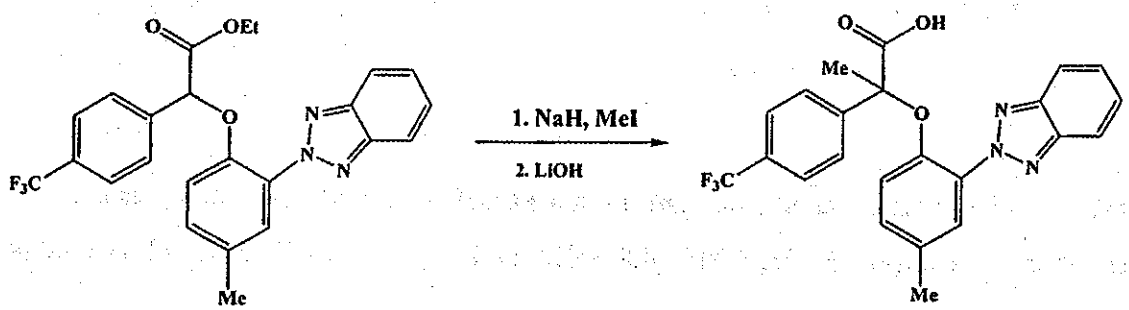
Example 123



SXI-5 **XIa-5**

[0324] **XIa-5** was prepared from **SXI-5** in the same manner as that described in **Example 42.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.02 (2H, dd, J = 6.8, 3.2 Hz), 7.58 (1H, s), 7.51 (2H, dd, J = 6.8, 3.2 Hz), 7.36 (3H, t, J = 8.8 Hz), 7.24 (2H, d, J = 8.4 Hz), 6.94 (1H, d, J = 8.4 Hz), 2.38 (3H, s), 1.78 (3H, s).

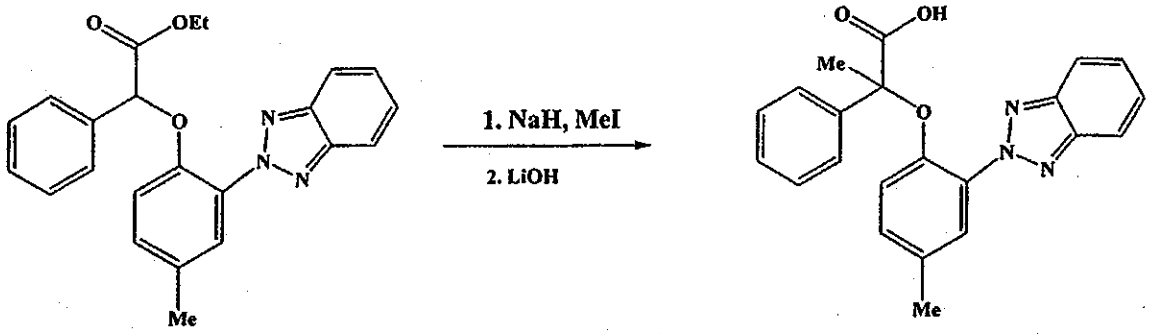
Example 124



SXI-6 **XIa-6**

[0325] **XIa-6** was prepared from **SXI-6** in the same manner as that described in **Example 42.** ^{1}H-NMR (400 MHz, DMSO): δ 8.00 – 6.98 (m, 11H), 2.32 (s, 3H), 1.70 (s, 3H).

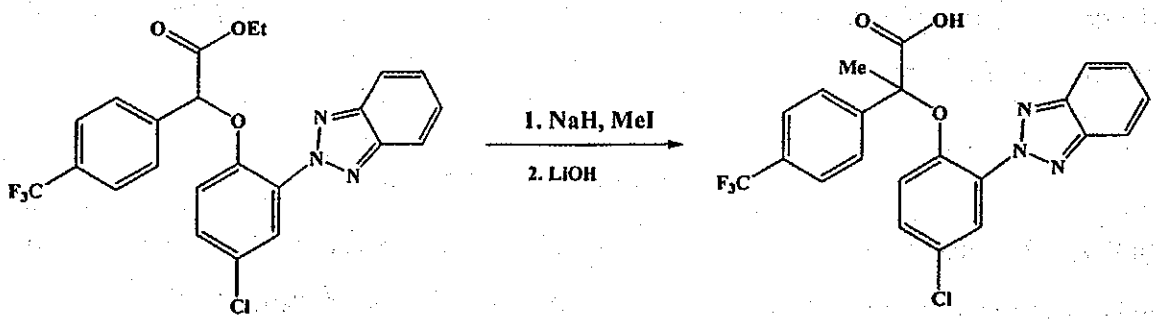
Example 125



SXI-7 XIa-8

[0326] XIa-8 was prepared from SXI-7 in the same manner as that described in Example 42. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 13.41 (br, 1H), 8.03 (m, 2H), 7.58 (d, 1H), 7.53-7.49 (m, 2H), 7.36 (dd, 1H), 7.32 (m, 2H), 7.19 (m, 3H), 6.93 (d, 1H), 2.35 (s, 3H), 1.67 (s, 3H).

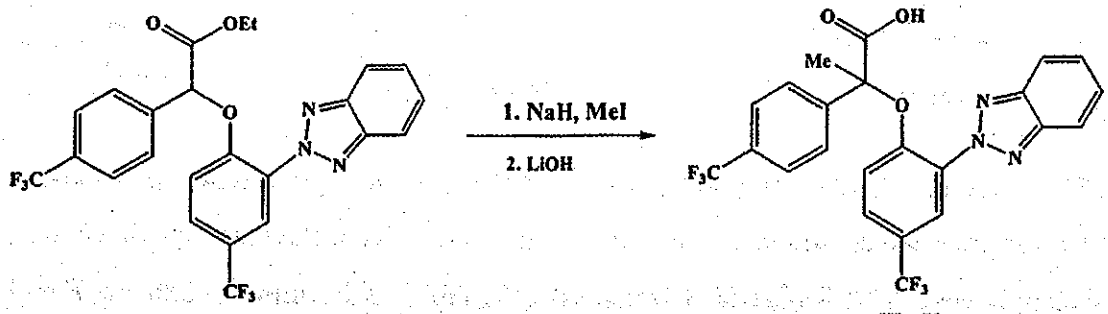
Example 126



SXI-8 XIa-24

[0327] XIa-24 was prepared from SXI-8 in the same manner as that described in Example 42.

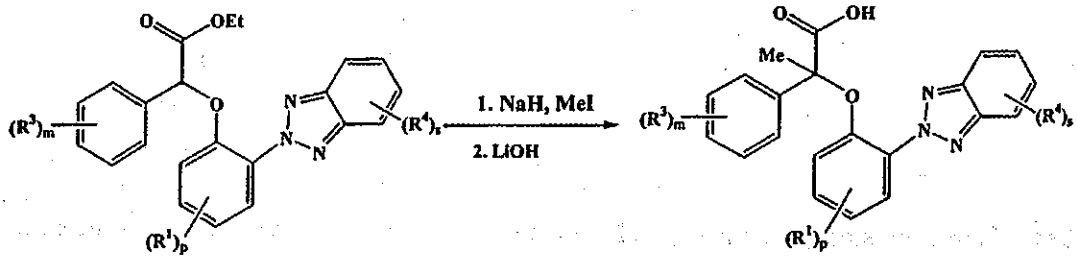
Example 127



SXI-10 XIa-51

[0328] **XIa-51** was prepared from **SXI-10** in the same manner as that described in **Example 42**. . ^{1}H-NMR (400 MHz, DMSO): δ 8.10 – 7.22 (m, 11H), 2.42 (s, 3H), 1.70 (s, 3H).

Example 128



SXI-11 XIa-X

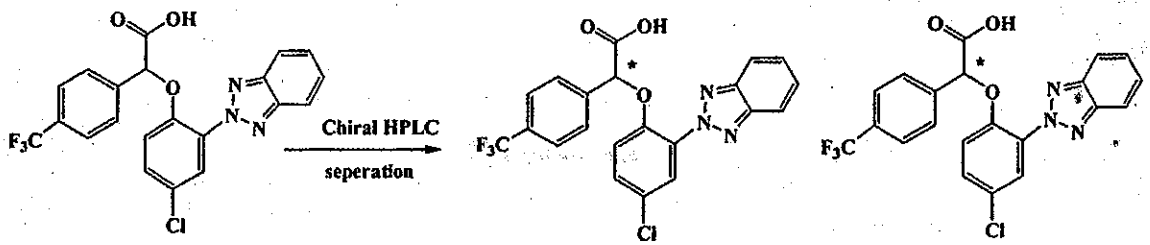
R^3 = 3-CF_3, 3-Cl, 3-OPh, H, 4-OMe, 4-Cl, 4-CF_3, 4-Br, 4-Et
R^1 = H, 4'-t-octyl, 4'-tBu, 4'-Me, 4'-Cl, 4'-Br, 2',4'-di-t-Bu, 4'-CF_3
R^4 = H, 2''-Cl

[0329] The rest of **XIa-X** can be prepared from **SXI-11** in the same manner as that described in **Example 42**.

16. Enantiomer separation

[0330] The enantiomers of compounds **XI** and **XIa** were or can be obtained in the same manner as that decribed in **Section 4** and **Example 49** to **Example 62**.

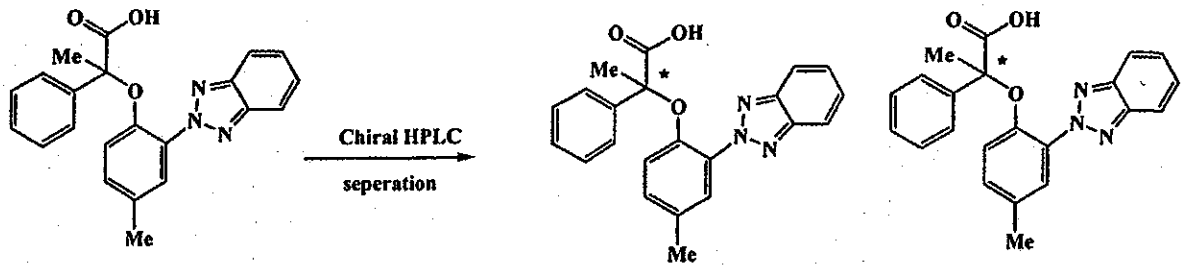
Example 129



(+/-)-XI-24 (+)-XI-24 (-)-XI-24

[0331] Racemic **XI-24** was resolved by chiral HPLC to give **(+)-XI-24** and **(-)-XI-24**. HPLC methods and conditions, including eluents used, solvent flow rate and detection wavelength were: 20% iPrOH-80% Hexanes-0.1% TFA, 30 mL/min., λ=220 nm. For **(+)-XI-24**: RT 4.60 min. For **(-)-XI-24**: RT 5.11 min.

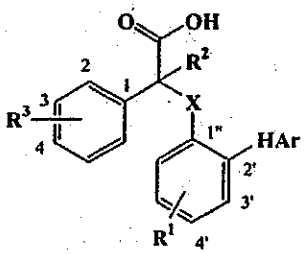
Example 130



(+/-)-XIa-8 (+)-XIa-8 (-)-XIa-8

[0332] Racemic **XIa-8** was resolved by chiral HPLC to give **(+)-XIa-8** and **(-)-XIa-8**. HPLC methods and conditions, including eluents used, solvent flow rate and detection wavelength were: 25% iPrOH-75% Hexanes-0.1% TFA, 30 mL/min., λ=220 nm. For **(+)-XIa-8** : RT 4.75 min. For **(-)-XIa-8**: RT 6.05 min.

Table 12
2-Hetero-aryl analogs



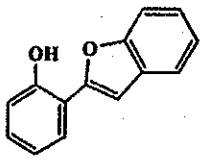
Compound XII and XIIa

Compound	R^1	R^2	R^3	X	HAr	Configuration
XII-1	H	H	3-Cl	O	2-Benzofuran-2-yl	R/S
XII-2	H	H	3-CF_3	O	2-Benzofuran-2-yl	R/S
XII-3	H	H	4-Cl	O	2-Benzofuran-2-yl	R/S
XII-4	H	H	4-CF_3	O	2-Benzofuran-2-yl	R/S
XII-5	H	H	H	O	2-Benzofuran-2-yl	R/S
XII-6	H	H	3-Cl	O	2-(1H-Indol-2-yl)	R/S
XII-7	H	H	3-CF_3	O	2-(1H-Indol-2-yl)	R/S

XII-8	H	H	4-Cl	O	2-(1H-Indol-2-yl)	R/S
XII-9	H	H	4-CF_3	O	2-(1H-Indol-2-yl)	R/S
XII-10	H	H	H	O	2-(1H-Indol-2-yl)	R/S
XII-11	H	H	3-Cl	O	2-(3-Methyl-benzo[b]thiophen-2-yl)	R/S
XII-12	H	H	3-CF_3	O	2-(3-Methyl-benzo[b]thiophen-2-yl)	R/S
XII-13	H	H	4-Cl	O	2-(3-Methyl-benzo[b]thiophen-2-yl)	R/S
XII-14	H	H	4-CF_3	O	2-(3-Methyl-benzo[b]thiophen-2-yl)	R/S
XII-15	H	H	H	O	2-(3-Methyl-benzo[b]thiophen-2-yl)	R/S
XII-16	4-Cl	H	3-Cl	O	2-(5-Chloro-benzofuran-2-yl)	R/S
XII-17	4-Cl	H	3-CF_3	O	2-(5-Chloro-benzofuran-2-yl)	R/S
XII-18	4-Cl	H	4-Cl	O	2-(5-Chloro-benzofuran-2-yl)	R/S
XII-19	4-Cl	H	4-CF_3	O	2-(5-Chloro-benzofuran-2-yl)	R/S
XII-20	4-Cl	H	H	O	2-(5-Chloro-benzofuran-2-yl)	R/S
XII-21	H	H	3-Cl	O	2-Quinolin-2-yl	R/S
XII-22	H	H	3-CF_3	O	2-Quinolin-2-yl	R/S
XII-23	H	H	4-Cl	O	2-Quinolin-2-yl	R/S
XII-24	H	H	4-CF_3	O	2-Quinolin-2-yl	R/S
XII-25	H	H	H	O	2-Quinolin-2-yl	R/S
XII-26	H	H	3-Cl	O	2-Thiophen-2-yl	R/S
XII-27	H	H	3-CF_3	O	2-Thiophen-2-yl	R/S
XII-28	H	H	4-Cl	O	2-Thiophen-2-yl	R/S
XII-29	H	H	4-CF_3	O	2-Thiophen-2-yl	R/S
XII-30	H	H	H	O	2-Thiophen-2-yl	R/S
XII-31	H	H	3-Cl	O	2-(1H-Pyrrol-2-yl)	R/S
XII-32	H	H	3-CF_3	O	2-(1H-Pyrrol-2-yl)	R/S
XII-33	H	H	4-Cl	O	2-(1H-Pyrrol-2-yl)	R/S

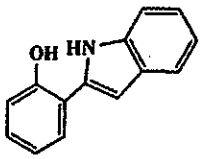
XII-34	H	H	4-CF_3	O	2-(1H-Pyrrol-2-yl)	R/S
XII-35	H	H	H	O	2-(1H-Pyrrol-2-yl)	R/S
XII-36	H	H	3-Cl	NH	2-(5-Methyl-furan-2-yl)	R/S
XII-37	H	H	3-CF_3	NH	2-(5-Methyl-furan-2-yl)	R/S
XII-38	H	H	4-Cl	NH	2-(5-Methyl-furan-2-yl)	R/S
XII-39	H	H	4-CF_3	NH	2-(5-Methyl-furan-2-yl)	R/S
XII-40	H	H	H	NH	2-(5-Methyl-furan-2-yl)	R/S
XII-41	H	H	3-Cl	NH	2-(1H-Indol-2-yl)	R/S
XII-42	H	H	3-CF_3	NH	2-(1H-Indol-2-yl)	R/S
XII-43	H	H	4-Cl	NH	2-(1H-Indol-2-yl)	R/S
XII-44	H	H	4-CF_3	NH	2-(1H-Indol-2-yl)	R/S
XII-45	H	H	H	NH	2-(1H-Indol-2-yl)	R/S
XII-46	H	H	3-Cl	NH	2-Benzo[b]thiophen-2-yl	R/S
XII-47	H	H	3-CF_3	NH	2-Benzo[b]thiophen-2-yl	R/S
XII-48	H	H	4-Cl	NH	2-Benzo[b]thiophen-2-yl	R/S
XII-49	H	H	4-CF_3	NH	2-Benzo[b]thiophen-2-yl	R/S
XII-50	H	H	H	NH	2-Benzo[b]thiophen-2-yl	R/S
XII-51	H	H	3-Cl	NH	2-Quinolin-2-yl	R/S
XII-52	H	H	3-CF_3	NH	2-Quinolin-2-yl	R/S
XII-53	H	H	4-Cl	NH	2-Quinolin-2-yl	R/S
XII-54	H	H	4-CF_3	NH	2-Quinolin-2-yl	R/S
XII-55	H	H	H	NH	2-Quinolin-2-yl	R/S
XII-56	H	H	3-Cl	NH	2-Thiophen-2-yl	R/S
XII-57	H	H	3-CF_3	NH	2-Thiophen-2-yl	R/S
XII-58	H	H	4-Cl	NH	2-Thiophen-2-yl	R/S
XII-59	H	H	4-CF_3	NH	2-Thiophen-2-yl	R/S

XII-60	H	H	H	NH	2-Thiophen-2-yl	R/S
XII-61	H	H	3-Cl	NH	2-Furan-2-yl	R/S
XII-62	H	H	3-CF_3	NH	2-Furan-2-yl	R/S
XII-63	H	H	4-Cl	NH	2-Furan-2-yl	R/S
XII-64	H	H	4-CF_3	NH	2-Furan-2-yl	R/S
XII-65	H	H	H	NH	2-Furan-2-yl	R/S
XIIa-1	H	H	3-Cl	O	2-Benzofuran-2-yl	R/S
XIIa-2	H	H	3-CF_3	O	2-Benzofuran-2-yl	R/S
XIIa-3	H	H	4-Cl	O	2-Benzofuran-2-yl	R/S
XIIa-4	H	H	4-CF_3	O	2-Benzofuran-2-yl	R/S
XIIa-5	H	H	H	O	2-Benzofuran-2-yl	R/S
XIIa-6	H	H	3-Cl	O	2-Thiophen-2-yl	R/S
XIIa-7	H	H	3-CF_3	O	2-Thiophen-2-yl	R/S
XIIa-8	H	H	4-Cl	O	2-Thiophen-2-yl	R/S
XIIa-9	H	H	4-CF_3	O	2-Thiophen-2-yl	R/S
XIIa-10	H	H	H	O	2-Thiophen-2-yl	R/S
XIIa-11	H	H	3-Cl	O	2-(3-Methyl-benzo[b]thiophen-2-yl)	R/S
XIIa-12	H	H	3-CF_3	O	2-(3-Methyl-benzo[b]thiophen-2-yl)	R/S
XIIa-13	H	H	4-Cl	O	2-(3-Methyl-benzo[b]thiophen-2-yl)	R/S
XIIa-14	H	H	4-CF_3	O	2-(3-Methyl-benzo[b]thiophen-2-yl)	R/S
XIIa-15	H	H	H	O	2-(3-Methyl-benzo[b]thiophen-2-yl)	R/S
XIIa-16	4-Cl	H	3-Cl	O	2-(5-Chloro-benzofuran-2-yl)	R/S
XIIa-17	4-Cl	H	3-CF_3	O	2-(5-Chloro-benzofuran-2-yl)	R/S
XIIa-18	4-Cl	H	4-Cl	O	2-(5-Chloro-benzofuran-2-yl)	R/S
XIIa-19	4-Cl	H	4-CF_3	O	2-(5-Chloro-benzofuran-2-yl)	R/S
XIIa-20	4-Cl	H	H	O	2-(5-Chloro-benzofuran-2-yl)	R/S



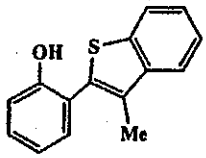
PhOH-48

J. Amer.Chem. Soc.; 55; 1933; 3040, 3047



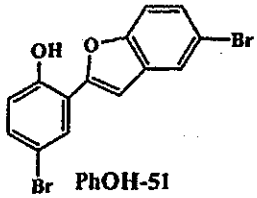
PhOH-49

Can. J. Chem.; 63; 1985; 632-635



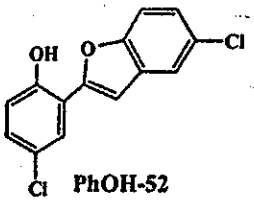
PhOH-50

J. Chem. Res. Miniprint; 8; 1981; 2756-2771



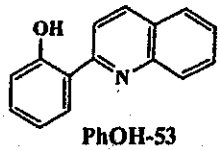
PhOH-51

J. Org. Chem.; 55; 1990; 1240-1248



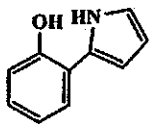
PhOH-52

J. Org. Chem.; 55; 1990; 1240-1248



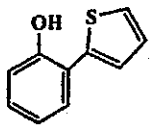
PhOH-53

J. Chem. Soc.; 1959; 1579, 1585



PhOH-54

J. Org. Chem.; 63; 1998; 5031-5041

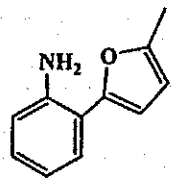


PhOH-55

J. heterocycl. chem.; 22; 1985; 1667-1669

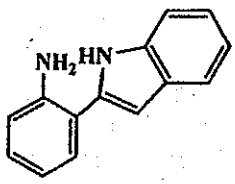
PhOH-48 to **PhOH-55** can be prepared according to the literature procedures cited.

18. 2-Hetero-aryl anilines



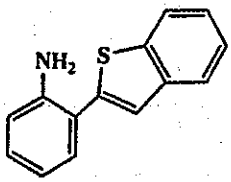
$PhNH_2$-2

Comcercially available



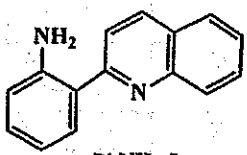
$PhNH_2$-3

Comcercially available



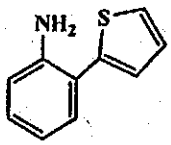
$PhNH_2$-4

J. Chem. Soc. Perkin Trans. 1; 1972; 2023-2030



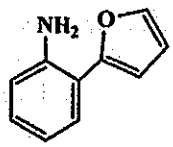
$PhNH_2$-5

Synth. Commum.; 29; 22; 1999; 3959-3970



$PhNH_2$-6

J. Amer. Chem. Soc.; 73; 1951; 2626, 2629



$PhNH_2$-7

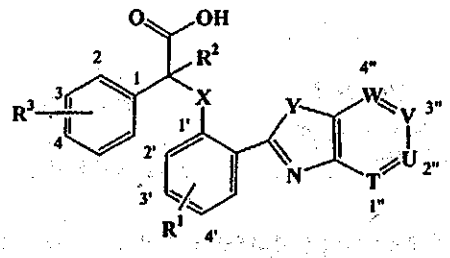
J. Amer. Chem. Soc.; 75; 1953; 6335

[0333] $PhNH_2$-2 to $PhNH_2$-7 can be either purchased from different commercial sources or they can be prepared according the literature procedures cited.

19. Synthesis of Compounds XII and XIIa in Table 12

[0334] Compounds **XII-X** and **XIIa-X** were or can be prepared with **SBr-X** and **PhOH-48** to **PhOH-55** and with **SBr-X** and **$PhNH_2$-2** to **$PhNH_2$-7** in the same manner as that described for the synthesis of compounds **I-X** and **Ia-X.**

Table 13
Aza-benzooxazole and aza-benzothiazole analogs



Compound XIII

Compound	R^1	R^2	R^3	X	Y	T, U, V, W,
XIII-1	H	H	3-Cl	O	O	T=N U=V=W=CH
XIII-2	H	H	3-CF_3	O	O	T=N U=V=W=CH
XIII-3	H	H	4-Cl	O	O	T=N U=V=W=CH
XIII-4	H	H	4-CF_3	O	O	T=N U=V=W=CH
XIII-5	H	H	H	O	O	T=N U=V=W=CH
XIII-6	H	H	3-Cl	O	O	W=N T=U=V=CH
XIII-7	H	H	3-CF_3	O	O	W=N T=U=V=CH
XIII-8	H	H	4-Cl	O	O	W=N T=U=V=CH
XIII-9	H	H	4-CF_3	O	O	W=N T=U=V=CH
XIII-10	H	H	H	O	O	W=N T=U=V=CH
XIII-11	H	H	3-Cl	O	O	U=N T=V=W=CH
XIII-12	H	H	3-CF_3	O	O	U=N T=V=W=CH
XIII-13	H	H	4-Cl	O	O	U=N T=V=W=CH
XIII-14	H	H	4-CF_3	O	O	U=N T=V=W=CH

XIII-15	H	H	H	O	O	U=N T=V=W=CH
XIII-16	4'-Cl	H	3-Cl	O	O	T=N U=V=W=CH
XIII-17	4'-Cl	H	3-CF_3	O	O	T=N U=V=W=CH
XIII-18	4'-Cl	H	4-Cl	O	O	T=N U=V=W=CH
XIII-19	4'-Cl	H	4-CF_3	O	O	T=N U=V=W=CH
XIII-20	4'-Cl	H	H	O	O	T=N U=V=W=CH
XIII-21	4'-Cl	H	3-Cl	O	O	W=N T=U=V=CH
XIII-22	4'-Cl	H	3-CF_3	O	O	W=N T=U=V=CH
XIII-23	4'-Cl	H	4-Cl	O	O	W=N T=U=V=CH
XIII-24	4'-Cl	H	4-CF_3	O	O	W=N T=U=V=CH
XIII-25	4'-Cl	H	H	O	O	W=N T=U=V=CH
XIII-26	4'-Cl	H	3-Cl	O	O	U=N T=V=W=CH
XIII-27	4'-Cl	H	3-CF_3	O	O	U=N T=V=W=CH
XIII-28	4'-Cl	H	4-Cl	O	O	U=N T=V=W=CH
XIII-29	4'-Cl	H	4-CF_3	O	O	U=N T=V=W=CH
XIII-30	4'-Cl	H	H	O	O	U=N T=V=W=CH
XIII-31	4'-CF_3	H	3-Cl	O	O	T=N U=V=W=CH
XIII-32	4'-CF_3	H	3-CF_3	O	O	T=N U=V=W=CH
XIII-33	4'-CF_3	H	4-Cl	O	O	T=N U=V=W=CH
XIII-34	4'-CF_3	H	4-CF_3	O	O	T=N U=V=W=CH
XIII-35	4'-CF_3	H	H	O	O	T=N U=V=W=CH
XIII-36	4'-CF_3	H	3-Cl	O	O	W=N T=U=V=CH
XIII-37	4'-CF_3	H	3-CF_3	O	O	W=N T=U=V=CH
XIII-38	4'-CF_3	H	4-Cl	O	O	W=N T=U=V=CH
XIII-39	4'-CF_3	H	4-CF_3	O	O	W=N T=U=V=CH
XIII-40	4'-CF_3	H	H	O	O	W=N T=U=V=CH

XIII-41	4'-CF_3	H	3-Cl	O	O	U=N T=V=W=CH
XIII-42	4'-CF_3	H	3-CF_3	O	O	U=N T=V=W=CH
XIII-43	4'-CF_3	H	4-Cl	O	O	U=N T=V=W=CH
XIII-44	4'-CF_3	H	4-CF_3	O	O	U=N T=V=W=CH
XIII-45	4'-CF_3	H	H	O	O	U=N T=V=W=CH
XIII-46	4'-Cl	H	3-Cl	O	S	W=N T=U=V=CH
XIII-47	4'-Cl	H	3-CF_3	O	S	W=N T=U=V=CH
XIII-48	4'-Cl	H	4-Cl	O	S	W=N T=U=V=CH
XIII-49	4'-Cl	H	4-CF_3	O	S	W=N T=U=V=CH
XIII-50	4'-Cl	H	H	O	S	W=N T=U=V=CH
XIII-51	4'-CF_3	H	3-Cl	O	S	W=N T=U=V=CH
XIII-52	4'-CF_3	H	3-CF_3	O	S	W=N T=U=V=CH
XIII-53	4'-CF_3	H	4-Cl	O	S	W=N T=U=V=CH
XIII-54	4'-CF_3	H	4-CF_3	O	S	W=N T=U=V=CH
XIII-55	4'-CF_3	H	H	O	S	W=N T=U=V=CH
XIII-56	H	H	3-Cl	NH	O	T=N U=V=W=CH
XIII-57	H	H	3-CF_3	NH	O	T=N U=V=W=CH
XIII-58	H	H	4-Cl	NH	O	T=N U=V=W=CH
XIII-59	H	H	4-CF_3	NH	O	T=N U=V=W=CH
XIII-60	H	H	H	NH	O	T=N U=V=W=CH
XIII-61	H	H	3-Cl	NH	O	W=N T=U=V=CH
XIII-62	H	H	3-CF_3	NH	O	W=N T=U=V=CH
XIII-63	H	H	4-Cl	NH	O	W=N T=U=V=CH
XIII-64	H	H	4-CF_3	NH	O	W=N T=U=V=CH
XIII-65	H	H	H	NH	O	W=N T=U=V=CH
XIII-66	H	H	3-Cl	NH	O	U=N T=V=W=CH

XIII-67	H	H	3-CF_3	NH	O	U=N T=V=W=CH
XIII-68	H	H	4-Cl	NH	O	U=N T=V=W=CH
XIII-69	H	H	4-CF_3	NH	O	U=N T=V=W=CH
XIII-70	H	H	H	NH	O	U=N T=V=W=CH
XIII-71	4'-Cl	H	3-Cl	NH	O	T=N U=V=W=CH
XIII-72	4'-Cl	H	3-CF_3	NH	O	T=N U=V=W=CH
XIII-73	4'-Cl	H	4-Cl	NH	O	T=N U=V=W=CH
XIII-74	4'-Cl	H	4-CF_3	NH	O	T=N U=V=W=CH
XIII-75	4'-Cl	H	H	NH	O	T=N U=V=W=CH
XIII-76	4'-Cl	H	3-Cl	NH	O	W=N T=U=V=CH
XIII-77	4'-Cl	H	3-CF_3	NH	O	W=N T=U=V=CH
XIII-78	4'-Cl	H	4-Cl	NH	O	W=N T=U=V=CH
XIII-79	4'-Cl	H	4-CF_3	NH	O	W=N T=U=V=CH
XIII-80	4'-Cl	H	H	NH	O	W=N T=U=V=CH
XIII-81	4'-Cl	H	3-Cl	NH	O	U=N T=V=W=CH
XIII-82	4'-Cl	H	3-CF_3	NH	O	U=N T=V=W=CH
XIII-83	4'-Cl	H	4-Cl	NH	O	U=N T=V=W=CH
XIII-84	4'-Cl	H	4-CF_3	NH	O	U=N T=V=W=CH
XIII-85	4'-Cl	H	H	NH	O	U=N T=V=W=CH
XIII-86	4'-CF_3	H	3-Cl	NH	O	T=N U=V=W=CH
XIII-87	4'-CF_3	H	3-CF_3	NH	O	T=N U=V=W=CH
XIII-88	4'-CF_3	H	4-Cl	NH	O	T=N U=V=W=CH
XIII-89	4'-CF_3	H	4-CF_3	NH	O	T=N U=V=W=CH
XIII-90	4'-CF_3	H	H	NH	O	T=N U=V=W=CH
XIII-91	4'-CF_3	H	3-Cl	NH	O	W=N T=U=V=CH
XIII-92	4'-CF_3	H	3-CF_3	NH	O	W=N T=U=V=CH

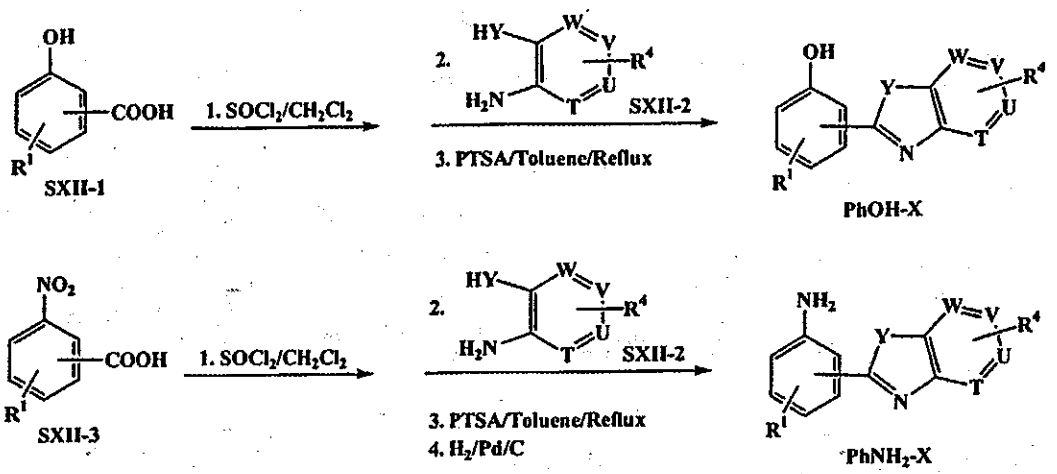
XIII-93	4'-CF_3	H	4-Cl	NH	O	W=N T=U=V=CH
XIII-94	4'-CF_3	H	4-CF_3	NH	O	W=N T=U=V=CH
XIII-95	4'-CF_3	H	H	NH	O	W=N T=U=V=CH
XIII-96	4'-CF_3	H	3-Cl	NH	O	U=N T=V=W=CH
XIII-97	4'-CF_3	H	3-CF_3	NH	O	U=N T=V=W=CH
XIII-98	4'-CF_3	H	4-Cl	NH	O	U=N T=V=W=CH
XIII-99	4'-CF_3	H	4-CF_3	NH	O	U=N T=V=W=CH
XIII-100	4'-CF_3	H	H	NH	O	U=N T=V=W=CH
XIII-101	4'-Cl	H	3-Cl	NH	S	W=N T=U=V=CH
XIII-102	4'-Cl	H	3-CF_3	NH	S	W=N T=U=V=CH
XIII-103	4'-Cl	H	4-Cl	NH	S	W=N T=U=V=CH
XIII-104	4'-Cl	H	4-CF_3	NH	S	W=N T=U=V=CH
XIII-105	4'-Cl	H	H	NH	S	W=N T=U=V=CH
XIII-106	4'-CF_3	H	3-Cl	NH	S	W=N T=U=V=CH
XIII-107	4'-CF_3	H	3-CF_3	NH	S	W=N T=U=V=CH
XIII-108	4'-CF_3	H	4-Cl	NH	S	W=N T=U=V=CH
XIII-109	4'-CF_3	H	4-CF_3	NH	S	W=N T=U=V=CH
XIII-110	4'-CF_3	H	H	NH	S	W=N T=U=V=CH

20. Synthesis of aza-benzooxazole and aza-benzothiazole phenols and anilines

[0335] The aza-benzooxazole and aza-benzothiazole phenols and anilines used for the preparation of compounds **XIII** can be prepared in the same manner as that described for the synthesis of 2-benzooxazol-2-yl-phenols illustrated in **Scheme II** or by those skilled in the arts.

Scheme 7

. Synthesis of aza-benzooxazole and aza-benzothiazole phenols and anilines

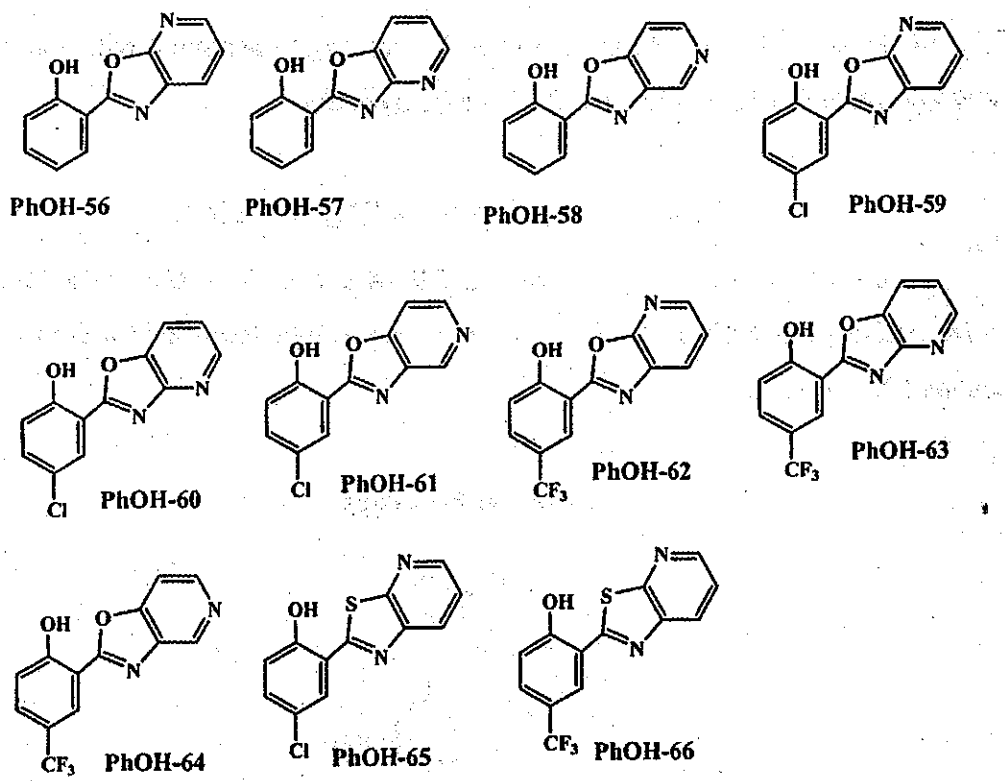


Y=O, S

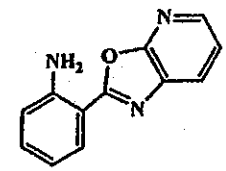
T=CR^4, CH, N; U=CR^4, CH, N; V=CR^4, CH, N; W=CR^4, CH, N;

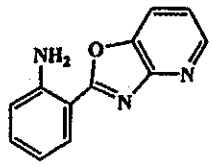
R^1=H, 4'-Cl, 4'-Me, 4'-OMe, 4'-Br, 4'-F, 3',4'-diF, 3',4'-diOMe, '4-CF_3

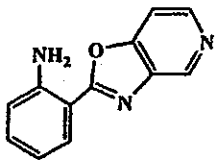
R^4=H, halo, haloalkyl, alkyl, Oalkyl etc.

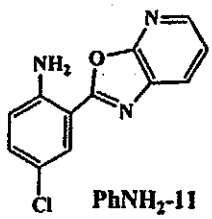


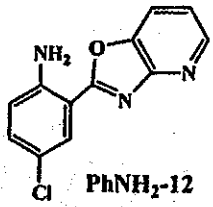
[0336] **PhOH-56** to **PhOH-66** can be prepared according to **Scheme7** with readily available aza-2-amino-phenols and aza-2-amino-benzenethiol.

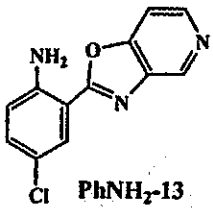

$PhNH_2$-8

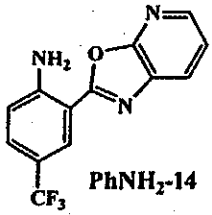

$PhNH_2$-9

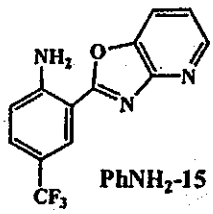

$PhNH_2$-10

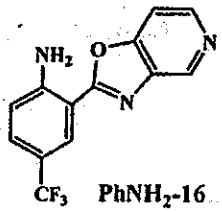

$PhNH_2$-11

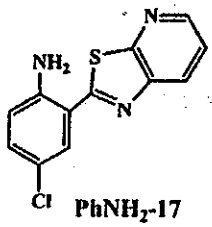

$PhNH_2$-12

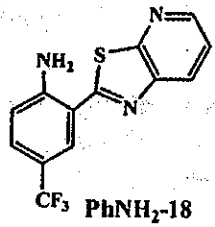

$PhNH_2$-13


$PhNH_2$-14


$PhNH_2$-15


$PhNH_2$-16


$PhNH_2$-17

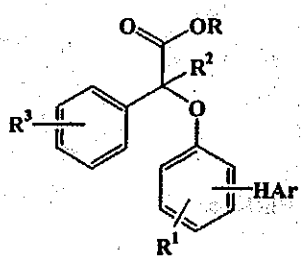

$PhNH_2$-18

[0337] **$PhNH_2$-8** to **$PhNH_2$-18** can be prepared according to **Scheme7** with readily available aza-2-amino-phenols and aza-2-amino-benzenethiol.

21. Synthesis of Compounds XIII in Table 13

[0338] Compounds **XIII** can be prepared with **SBr-X** and **PhOH-56** to **PhOH-66** and with **SBr-X** and **$PhNH_2$-8** to **$PhNH_2$-18** in the same manner as that described for the synthesis of compounds **I-X** and **Ia-X.**

Table 14: Prodrugs



Compounds XIV

Compound	R^1	R^2	R^3	HAr	Racemic or enantiomer	R
XIV-1	4'-CF_3	H	4-Cl	2-benzooxazole	+/-	CH_2CH_2NHAc
XIV-2	4'-CF_3	H	3-CF_3	2-benzooxazole	+/-	CH_2CH_2NHAc
XIV-3	4'-CF_3	H	3-CF_3	2-benzooxazole	+	CH_2CH_2NHAc
XIV-4	4'-CF_3	H	3-CF_3	2-benzooxazole	-	CH_2CH_2NHAc
XIV-5	4'-CF_3	H	3-Cl	2-benzooxazole	+/-	CH_2CH_2NHAc
XIV-6	4'-CF_3	H	4-CF_3	2-benzooxazole	+/-	CH_2CH_2NHAc
XIV-7	4'-CF_3	H	H	2-benzooxazole	+/-	CH_2CH_2NHAc
XIV-8	4'-CF_3	H	H	2-benzooxazole	+	CH_2CH_2NHAc
XIV-9	4'-CF_3	H	H	2-benzooxazole	-	CH_2CH_2NHAc
XIV-10	4'-Cl	H	4-Cl	2-benzooxazole	+/-	CH_2CH_2NHAc
XIV-11	4'-Cl	H	3-CF_3	2-benzooxazole	+/-	CH_2CH_2NHAc
XIV-12	4'-Cl	H	3-CF_3	2-benzooxazole	+	CH_2CH_2NHAc
XIV-13	4'-Cl	H	3-CF_3	2-benzooxazole	-	CH_2CH_2NHAc
XIV-14	4'-Cl	H	3-Cl	2-benzooxazole	+/-	CH_2CH_2NHAc
XIV-15	4'-Cl	H	4-CF_3	2-benzooxazole	+/-	CH_2CH_2NHAc
XIV-16	4'-Cl	H	H	2-benzooxazole	+/-	CH_2CH_2NHAc
XIV-17	4'-CF_3	Me	4-Cl	2-benzooxazole	+/-	CH_2CH_2NHAc
XIV-18	4'-CF_3	Me	3-CF_3	2-benzooxazole	+/-	CH_2CH_2NHAc
XIV-19	4'-CF_3	Me	3-Cl	2-benzooxazole	+/-	CH_2CH_2NHAc
XIV-20	4'-CF_3	Me	4-CF_3	2-benzooxazole	+/-	CH_2CH_2NHAc
XIV-21	4'-CF_3	Me	H	2-benzooxazole	+/-	CH_2CH_2NHAc
XIV-22	4'-Cl	Me	4-Cl	2-benzooxazole	+/-	CH_2CH_2NHAc
XIV-23	4'-Cl	Me	3-CF_3	2-benzooxazole	+/-	CH_2CH_2NHAc
XIV-24	4'-Cl	Me	3-Cl	2-benzooxazole	+/-	CH_2CH_2NHAc
XIV-25	4'-Cl	Me	4-CF_3	2-benzooxazole	+/-	CH_2CH_2NHAc

XIV-26	4'-Cl	Me	H	2-benzooxazole	+/-	CH_2CH_2NHAc
XIV-27	4'-CF_3	H	3-CF_3	2-benzothiazole	+/-	CH_2CH_2NHAc
XIV-28	4'-Cl	H	3-CF_3	2-benzothiazole	+/-	CH_2CH_2NHAc
XIV-29	4'-CF_3	H	4-Cl	2-benzothiazole	+/-	CH_2CH_2NHAc
XIV-30	4'-Cl	H	4-Cl	2-benzothiazole	+/-	CH_2CH_2NHAc
XIV-31	4'-CF_3	Me	3-CF_3	2-benzothiazole	+/-	CH_2CH_2NHAc
XIV-32	4'-Cl	Me	3-CF_3	2-benzothiazole	+/-	CH_2CH_2NHAc
XIV-33	4'-CF_3	Me	4-Cl	2-benzothiazole	+/-	CH_2CH_2NHAc
XIV-34	4'-Cl	Me	4-Cl	2-benzothiazole	+/-	CH_2CH_2NHAc
XIV-35	4'-CF_3	H	4-Cl	2-benzotriazole	+/-	CH_2CH_2NHAc
XIV-36	4'-CF_3	H	3-CF_3	2-benzotriazole	+/-	CH_2CH_2NHAc
XIV-37	4'-CF_3	H	3-Cl	2-benzotriazole	+/-	CH_2CH_2NHAc
XIV-38	4'-CF_3	H	4-CF_3	2-benzotriazole	+/-	CH_2CH_2NHAc
XIV-39	4'-CF_3	H	H	2-benzotriazole	+/-	CH_2CH_2NHAc
XIV-40	4'-Cl	H	4-Cl	2-benzotriazole	+/-	CH_2CH_2NHAc
XIV-41	4'-Cl	H	3-CF_3	2-benzotriazole	+/-	CH_2CH_2NHAc
XIV-42	4'-Cl	H	3-Cl	2-benzotriazole	+/-	CH_2CH_2NHAc
XIV-43	4'-Cl	H	4-CF_3	2-benzotriazole	+/-	CH_2CH_2NHAc
XIV-44	4'-Cl	H	H	2-benzotriazole	+/-	CH_2CH_2NHAc
XIV-45	4'-CF_3	Me	4-Cl	2-benzotriazole	+/-	CH_2CH_2NHAc
XIV-46	4'-CF_3	Me	3-CF_3	2-benzotriazole	+/-	CH_2CH_2NHAc
XIV-47	4'-CF_3	Me	3-Cl	2-benzotriazole	+/-	CH_2CH_2NHAc
XIV-48	4'-CF_3	Me	4-CF_3	2-benzotriazole	+/-	CH_2CH_2NHAc
XIV-49	4'-CF_3	Me	H	2-benzotriazole	+/-	CH_2CH_2NHAc
XIV-50	4'-Cl	Me	4-Cl	2-benzotriazole	+/-	CH_2CH_2NHAc
XIV-51	4'-Cl	Me	3-CF_3	2-benzotriazole	+/-	CH_2CH_2NHAc

XIV-53	4'-Cl	Me	4-CF_3	2-benzotriazole	+/-	CH_2CH_2NHAc
XIV-54	4'-Cl	Me	H	2-benzotriazole	+/-	CH_2CH_2NHAc
XIV-55	4'-CF_3	H	4-Cl	2-benzooxazole	+/-	CH_2COOEt
XIV-56	4'-CF_3	H	3-CF_3	2-benzooxazole	+/-	CH_2COOEt
XIV-57	4'-CF_3	H	3-CF_3	2-benzooxazole	+	CH_2COOEt
XIV-58	4'-CF_3	H	3-CF_3	2-benzooxazole	-	CH_2COOEt
XIV-59	4'-CF_3	H	3-Cl	2-benzooxazole	+/-	CH_2COOEt
XIV-60	4'-CF_3	H	4-CF_3	2-benzooxazole	+/-	CH_2COOEt
XIV-61	4'-CF_3	H	H	2-benzooxazole	+/-	CH_2COOEt
XIV-62	4'-CF_3	H	H	2-benzooxazole	+	CH_2COOEt
XIV-63	4'-CF_3	H	H	2-benzooxazole	-	CH_2COOEt
XIV-64	4'-Cl	H	4-Cl	2-benzooxazole	+/-	CH_2COOEt
XIV-65	4'-Cl	H	3-CF_3	2-benzooxazole	+/-	CH_2COOEt
XIV-66	4'-Cl	H	3-CF_3	2-benzooxazole	+	CH_2COOEt
XIV-67	4'-Cl	H	3-CF_3	2-benzooxazole	-	CH_2COOEt
XIV-68	4'-Cl	H	3-Cl	2-benzooxazole	+/-	CH_2COOEt
XIV-69	4'-Cl	H	4-CF_3	2-benzooxazole	+/-	CH_2COOEt
XIV-70	4'-Cl	H	H	2-benzooxazole	+/-	CH_2COOEt
XIV-71	4'-CF_3	Me	4-Cl	2-benzooxazole	+/-	CH_2COOEt
XIV-72	4'-CF_3	Me	3-CF_3	2-benzooxazole	+/-	CH_2COOEt
XIV-73	4'-CF_3	Me	3-Cl	2-benzooxazole	+/-	CH_2COOEt
XIV-74	4'-CF_3	Me	4-CF_3	2-benzooxazole	+/-	CH_2COOEt
XIV-75	4'-CF_3	Me	H	2-benzooxazole	+/-	CH_2COOEt
XIV-76	4'-Cl	Me	4-Cl	2-benzooxazole	+/-	CH_2COOEt
XIV-77	4'-Cl	Me	3-CF_3	2-benzooxazole	+/-	CH_2COOEt

XIV-79	4'-Cl	Me	4-CF_3	2-benzooxazole	+/-	CH_2COOEt
XIV-80	4'-Cl	Me	H	2-benzooxazole	+/-	CH_2COOEt
XIV-81	4'-CF_3	H	3-CF_3	2-benzothiazole	+/-	CH_2COOEt
XIV-82	4'-Cl	H	3-CF_3	2-benzothiazole	+/-	CH_2COOEt
XIV-83	4'-CF_3	H	4-Cl	2-benzothiazole	+/-	CH_2COOEt
XIV-84	4'-Cl	H	4-Cl	2-benzothiazole	+/-	CH_2COOEt
XIV-85	4'-CF_3	Me	3-CF_3	2-benzothiazole	+/-	CH_2COOEt
XIV-86	4'-Cl	Me	3-CF_3	2-benzothiazole	+/-	CH_2COOEt
XIV-87	4'-CF_3	Me	4-Cl	2-benzothiazole	+/-	CH_2COOEt
XIV-88	4'-Cl	Me	4-Cl	2-benzothiazole	+/-	CH_2COOEt
XIV-89	4'-CF_3	H	4-Cl	2-benzotriazole	+/-	CH_2COOEt
XIV-90	4'-CF_3	H	3-CF_3	2-benzotriazole	+/-	CH_2COOEt
XIV-91	4'-CF_3	H	3-Cl	2-benzotriazole	+/-	CH_2COOEt
XIV-92	4'-CF_3	H	4-CF_3	2-benzotriazole	+/-	CH_2COOEt
XIV-93	4'-CF_3	H	H	2-benzotriazole	+/-	CH_2COOEt
XIV-94	4'-Cl	H	4-Cl	2-benzotriazole	+/-	CH_2COOEt
XIV-95	4'-Cl	H	3-CF_3	2-benzotriazole	+/-	CH_2COOEt
XIV-96	4'-Cl	H	3-Cl	2-benzotriazole	+/-	CH_2COOEt
XIV-97	4'-Cl	H	4-CF_3	2-benzotriazole	+/-	CH_2COOEt
XIV-98	4'-Cl	H	H	2-benzotriazole	+/-	CH_2COOEt
XIV-99	4'-CF_3	Me	4-Cl	2-benzotriazole	+/-	CH_2COOEt
XIV-100	4'-CF_3	Me	3-CF_3	2-benzotriazole	+/-	CH_2COOEt
XIV-101	4'-CF_3	Me	3-Cl	2-benzotriazole	+/-	CH_2COOEt
XIV-102	4'-CF_3	Me	4-CF_3	2-benzotriazole	+/-	CH_2COOEt
XIV-103	4'-CF_3	Me	H	2-benzotriazole	+/-	CH_2COOEt

XIV-104	4'-Cl	Me	4-Cl	2-benzotriazole	+/-	CH_2COOEt
XIV-105	4'-Cl	Me	3-CF_3	2-benzotriazole	+/-	CH_2COOEt
XIV-106	4'-Cl	Me	3-Cl	2-benzotriazole	+/-	CH_2COOEt
XIV-107	4'-Cl	Me	4-CF_3	2-benzotriazole	+/-	CH_2COOEt
XIV-108	4'-Cl	Me	H	2-benzotriazole	+/-	CH_2COOEt
XIV-109	4'-CF_3	H	4-Cl	2-benzooxazole	+/-	Et
XIV-110	4'-CF_3	H	3-CF_3	2-benzooxazole	+/-	Et
XIV-111	4'-CF_3	H	3-CF_3	2-benzooxazole	+	Et
XIV-112	4'-CF_3	H	3-CF_3	2-benzooxazole	-	Et
XIV-113	4'-CF_3	H	3-Cl	2-benzooxazole	+/-	Et
XIV-114	4'-CF_3	H	4-CF_3	2-benzooxazole	+/-	Et
XIV-115	4'-CF_3	H	H	2-benzooxazole	+/-	Et
XIV-116	4'-CF_3	H	H	2-benzooxazole	+	Et
XIV-117	4'-CF_3	H	H	2-benzooxazole	-	Et
XIV-118	4'-Cl	H	4-Cl	2-benzooxazole	+/-	Et
XIV-119	4'-Cl	H	3-CF_3	2-benzooxazole	+/-	Et
XIV-120	4'-Cl	H	3-CF_3	2-benzooxazole	+	Et
XIV-121	4'-Cl	H	3-CF_3	2-benzooxazole	-	Et
XIV-122	4'-Cl	H	3-Cl	2-benzooxazole	+/-	Et
XIV-123	4'-Cl	H	4-CF_3	2-benzooxazole	+/-	Et
XIV-124	4'-Cl	H	H	2-benzooxazole	+/-	Et
XIV-125	4'-CF_3	Me	4-Cl	2-benzooxazole	+/-	Et
XIV-126	4'-CF_3	Me	3-CF_3	2-benzooxazole	+/-	Et
XIV-127	4'-CF_3	Me	3-Cl	2-benzooxazole	+/-	Et
XIV-128	4'-CF_3	Me	4-CF_3	2-benzooxazole	+/-	Et
XIV-129	4'-CF_3	Me	H	2-benzooxazole	+/-	Et

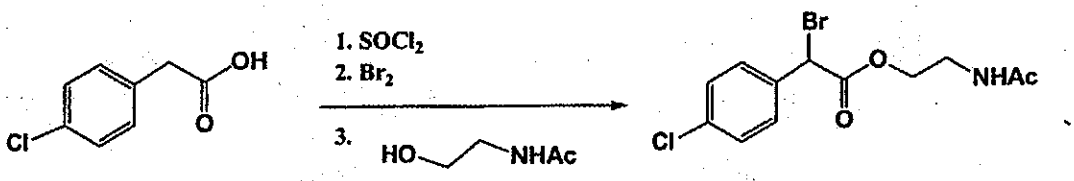
XIV-130	4'-Cl	Me	4-Cl	2-benzooxazole	+/-	Et
XIV-131	4'-Cl	Me	3-CF_3	2-benzooxazole	+/-	Et
XIV-132	4'-Cl	Me	3-Cl	2-benzooxazole	+/-	Et
XIV-133	4'-Cl	Me	4-CF_3	2-benzooxazole	+/-	Et
XIV-134	4'-Cl	Me	H	2-benzooxazole	+/-	Et
XIV-135	4'-CF_3	H	3-CF_3	2-benzothiazole	+/-	Et
XIV-136	4'-Cl	H	3-CF_3	2-benzothiazole	+/-	Et
XIV-137	4'-CF_3	H	4-Cl	2-benzothiazole	+/-	Et
XIV-138	4'-Cl	H	4-Cl	2-benzothiazole	+/-	Et
XIV-139	4'-CF_3	Me	3-CF_3	2-benzothiazole	+/-	Et
XIV-140	4'-Cl	Me	3-CF_3	2-benzothiazole	+/-	Et
XIV-141	4'-CF_3	Me	4-Cl	2-benzothiazole	+/-	Et
XIV-142	4'-Cl	Me	4-Cl	2-benzothiazole	+/-	Et
XIV-143	4'-CF_3	H	4-Cl	2-benzotriazole	+/-	Et
XIV-144	4'-CF_3	H	3-CF_3	2-benzotriazole	+/-	Et
XIV-145	4'-CF_3	H	3-Cl	2-benzotriazole	+/-	Et
XIV-146	4'-CF_3	H	4-CF_3	2-benzotriazole	+/-	Et
XIV-147	4'-CF_3	H	H	2-benzotriazole	+/-	Et
XIV-148	4'-Cl	H	4-Cl	2-benzotriazole	+/-	Et
XIV-149	4'-Cl	H	3-CF_3	2-benzotriazole	+/-	Et
XIV-150	4'-Cl	H	3-Cl	2-benzotriazole	+/-	Et
XIV-151	4'-Cl	H	4-CF_3	2-benzotriazole	+/-	Et
XIV-152	4'-Cl	H	H	2-benzotriazole	+/-	Et
XIV-153	4'-CF_3	Me	4-Cl	2-benzotriazole	+/-	Et
XIV-154	4'-CF_3	Me	3-CF_3	2-benzotriazole	+/-	Et
XIV-155	4'-CF_3	Me	3-Cl	2-benzotriazole	+/-	Et

XIV-156	4'-CF_3	Me	4-CF_3	2-benzotriazole	+/-	Et
XIV-157	4'-CF_3	Me	H	2-benzotriazole	+/-	Et
XIV-158	4'-Cl	Me	4-Cl	2-benzotriazole	+/-	Et
XIV-159	4'-Cl	Me	3-CF_3	2-benzotriazole	+/-	Et
XIV-160	4'-Cl	Me	3-Cl	2-benzotriazole	+/-	Et
XIV-161	4'-Cl	Me	4-CF_3	2-benzotriazole	+/-	Et
XIV-162	4'-Cl	Me	H	2-benzotriazole	+/-	Et

22. Synthesis of compound XIV-X listed in Table 14.

[0339] Compounds **XIV-X** listed in **Table 14** were or can be prepared with **SBr-14, 15, 16, 17** and **18** and **PhOH-X** in the same manner as described in **Example 28 Step A**. Alternatively, they were or can be prepared from esterification of the corresponding acids in the same manner as that described in **Examples 136** to **138**.

Example 131

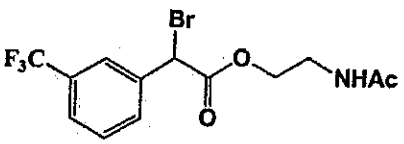


SI-5 SBr-14

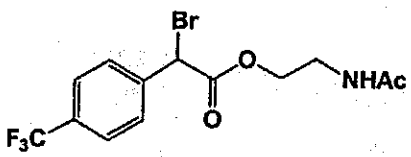
[0340] A 500 mL three neck roundbottom flask was equipped with an efficient condenser attached to an acid scrubber, a magnetic stir bar, and placed under argon. 4-Chlorophenylacetic acid **SI-5** (99.9 g, 0.50 mole) was charged, followed by thionyl chloride (50.0 mL (81.6 g), 0.68 mole). The condenser was cooled with 4°C water. The mixture was heated to an internal temperature of 55-60°C. Gas evolution was observed and the solids dissolved as the internal temperature rose to 55-60°C over 45 min.. The mixture was then stirred at 55-60°C for 45 min.. Bromine (33.0 mL (102.4 g), 0.65 mole) was charged and the mixture maintained at 55-60°C for 18 h. The internal temperature was then raised to 80-85°C over 1.5 h and heating continued for 18h (based on other runs, the reaction is complete after 6-7h). The mixture was cooled to 20-25°C and anhydrous dichloromethane (500 mL) added. In a separate flask was place 2-acetylethanolamine (190 mL (213 g), 2.07 mole) and anhydrous dichloromethane (500 mL) under argon and the mixture cooled to 2.8°C. To this

was added the acyl halide solution at such a rate as to keep the internal temperature below 21 °C (caution: exothermic). After the addition was complete (approx. 20 min.), the mixture was stirred in the cold bath for 0.5h, at which time the internal temperature was 4.8 °C. This mixture was carefully added to 1.5 L water containing sodium bicarbonate (148 g , 1.8 mole) at such a rate that frothing was moderate. The pH at the end of the addition (15 min.) was 7, by pH paper. Sodium thiosulfate (18.7 g, 0.12 mole) was added in portions and gas evolution was observed. Bromine was found to be absent at this time by testing with a Peroxid 100 (quantifix) strip. The layers were then partitioned in a separatory funnel (100 mL dichloromethane used in transfer), and the organic phase extracted with 250 mL water, dried over magnesium sulfate (17 g), and filtered. The filter cake was washed with dichloromethane (150 mL). Rotary evaporation and pumping at high vacuum afforded an oil, which was slurried in 100 mL hexane: ethyl acetate (70:30). Additional hexane (300 mL) was added until a white color formed in the top layer of the biphasic mixture. Vigorous agitation afforded a solid, which was filtered away from the supernatant to yield crude (2-acetamidoethyl)-4-chlorophenylbromoacetate **SBr-14** (147g) as a light tan solid.

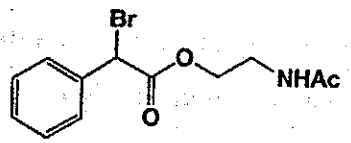
Example 132



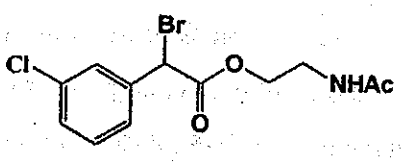
SBr-15



SBr-16



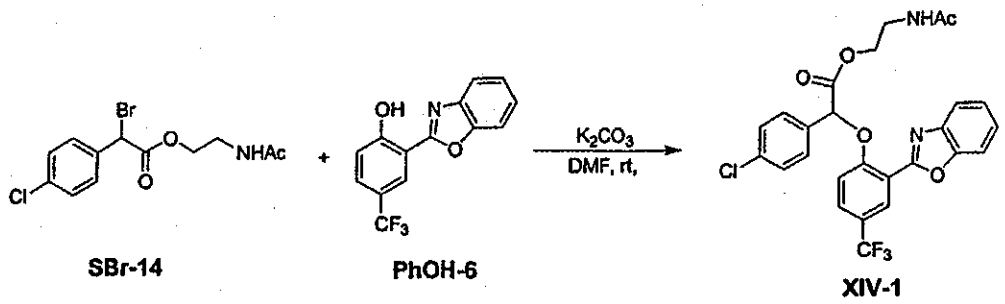
SBr-17



SBr-18

[0341] SBr-15, 16, 17, and 18 were prepared in the same manner as that described in Example 131.

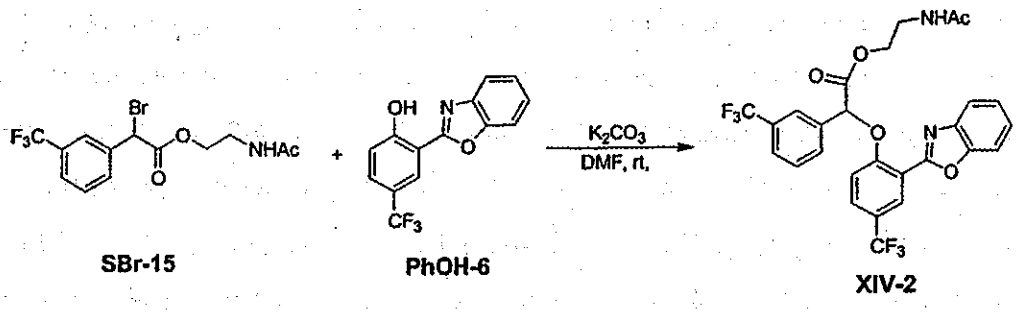
Example 133



SBr-14 PhOH-6 XIV-1

[0342] In the same manner as that described in **Example 28 Step A**, compound **XIV-1** was prepared from **SBr-14** and **PhOH-6**.

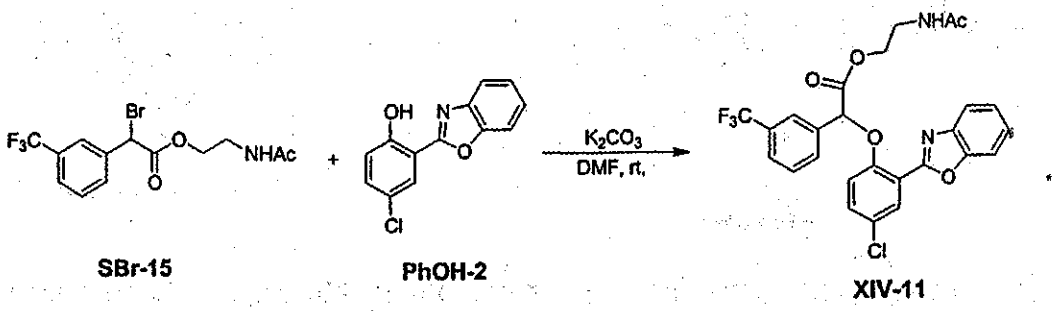
Example 134



SBr-15 PhOH-6 XIV-2

[0343] In the same manner as that described in **Example 28 Step A**, compound **XIV-2** was prepared from **SBr-15** and **PhOH-6**.

Example 135



SBr-15 PhOH-2 XIV-11

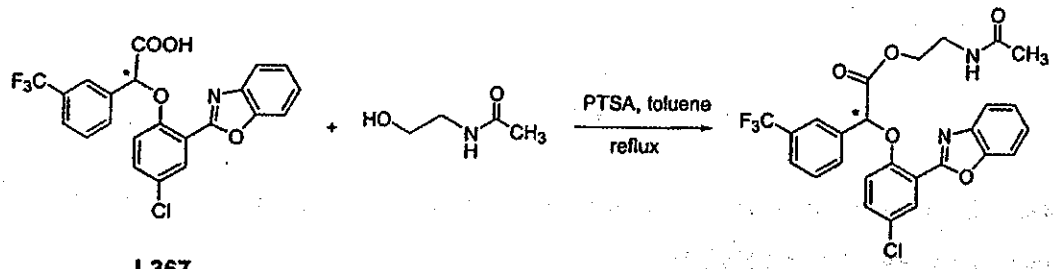
[0344] In the same manner as that described in **Example 28 Step A**, compound **XIV-11** was prepared from **SBr-15** and **PhOH-2**.

23. Enantiomers Preparation

[0345] The enantiomers of compounds **XIV-X** can be obtained from the corresponding enantiomerically pure acids with esterfication as that described in **Example 136, Example**

137 and **Example 138.** Alternatively, it can be obtained from the (+/-) racemic mixture with a chiral HPLC separation as that described in **Section 4.**

Example 136

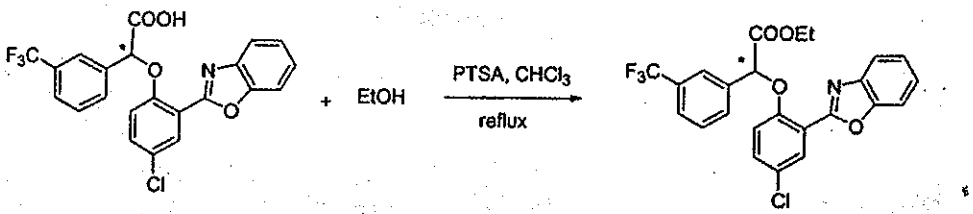


I-367
(+)-isomer

enantiomer 1

[0346] A mixture of **I-367** (11.74 g, ee >99.9%), N-acetylethanolamine (13.51 g) and TsOH monohydrate (0.25 g) in toluene (200 mL) was refluxed overnight using a Dean-Stark apparatus. The reaction mixture was concentrated to dryness, water was added, and the resultant mixture was stirred at room temperature for 0.5 h. Filtration and washing with water gave a off-white solid, which was recrystallized from iPrOH-hexanes to give **enantiomer 1** as an white solid. ^{1}HNMR (d-DMSO, 400 MHz) δ 8.33 (s, 1H), 8.13 (d, 1H), 8.01 (d, 1H), 7.82-7.65 (m, 6H), 7.48 (m, 2H), 7.30 (d, 1H), 6.48 (s, 1H), 4.16 (m, 1H), 4.02 (m, 1H), 3.27 (m, 1H), 3.18 (m, 1H), 1.69 (s, 3H).

Example 137

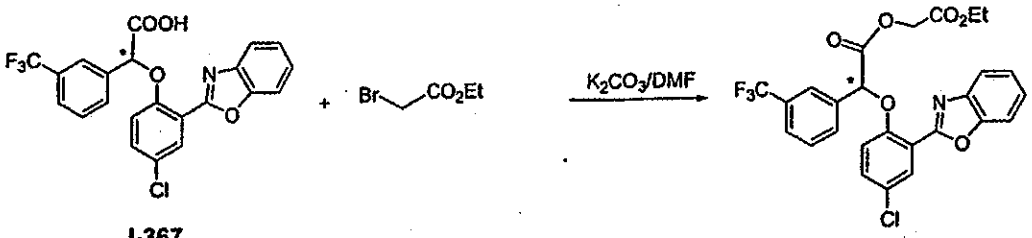


I-367
(+)-isomer

enantiomer 2

[0347] A mixture of **I-367** (5.87 g, ee >99.9%), EtOH (150 mL) and TsOH monohydrate (0.125 g) was refluxed overnight. The reaction mixture was concentrated to afford **enantiomer 2** as a white solid. ^{1}HNMR (d-DMSO, 400 MHz) δ 8.32 (s, 1H), 8.11 (s, 1H), 8.01 (d, 1H), 7.82-7.65 (m, 5H), 7.48 (m, 2H), 7.30 (d, 1H), 6.48 (s, 1H), 4.08 (m, 2H), 1.02 (m, 3H).

Example 138

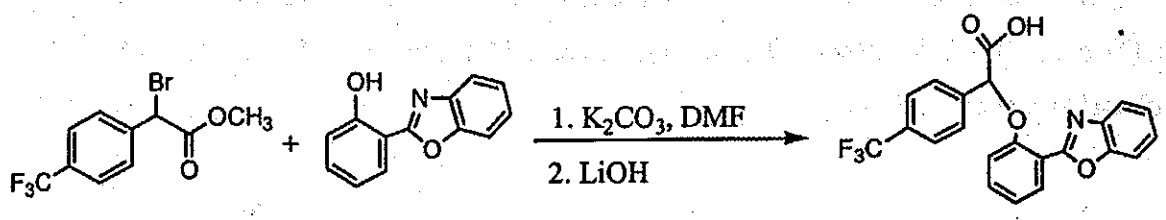


I-367
(+)-isomer

enantiomer 3

[0348] To a solution of **(+)-I-367** (1.1546 g, 2.58 mmol) in DMF (10 mL) at 0 °C was added K_2CO_3 (0.3597 g, 2.60 mmol), and then followed by ethyl bromoacetate (0.30 mL, 2.70 mmol). After stirring for 40 min at 0 °C, the reaction mixture was diluted with EtOAc and aq. NH_4Cl/H_2O. The organic layer was washed with aq. NH_4Cl/H_2O, and then brine/water, dried over Na_2SO_4, concentrated *in vacuo*. Purification *via* chromatography with EtOAc/hexanes (10% to 30%) to afford **enantiomer 3** (1.0211 g, 74%) as a white solid. Chiral HPLC analysis of enantiomer was carried out at $\lambda = 220$ nm by injecting 10 µL of an approximately a 0.5 mg/mL solution of the sample dissolved in mobile phase onto a 25 cm × 4.6 mm Regis Technologies (R,R) Whelk-O 1 5 µm column with a 1.5 mL/min flow of (3/97/0.1) *i*PrOH/hexanes/TFA. Under these conditions, **enantiomer 3** eluted at 12.3 min, and the corresponding pro-drug ester of **I-368 (- isomer)** elutes at 13.1 min (approximate retention times). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (1H, s), 8.26 (1H, d, J = 2.0 Hz), 7.98 (1H, d, J = 7.6 Hz), 7.81 (1H, m), 7.69 (1H, d, J = 7.2 Hz), 7.56 (2H, m), 7.46 (1H, m), 7.39 (2H, m), 7.12 (1H, d, J = 8.4 Hz), 5.98 (1H, s), 4.93 (1H, d, J = 15.6 Hz), 4.58 (1H, d, J = 15.6 Hz), 4.14 (2H, m), 1.67 (3H, t, J = 7.2 Hz) ppm.

Example 139

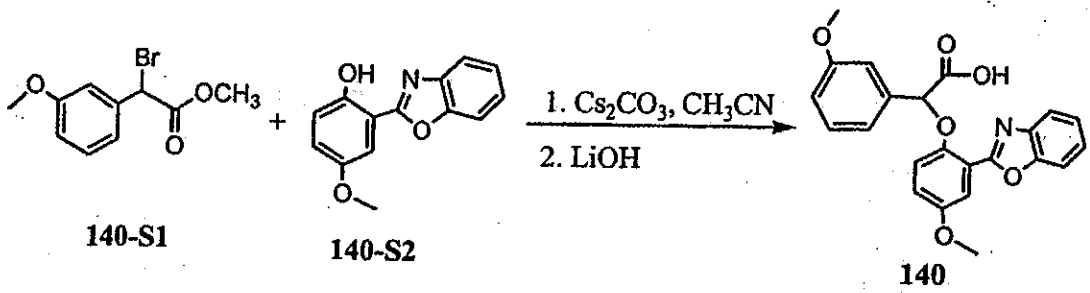


139-S1 **139-S2**

139 (I-6)

[0349] In the same manner as that described in **Example 28** compound **139** was prepared from **139-S1** and **139-S2.** ^{1}HNMR (400 MHz, DMSO-d_6): δ 8.20 – 7.22 (m, 12H), 6.50 (s, 1H).

Example 140

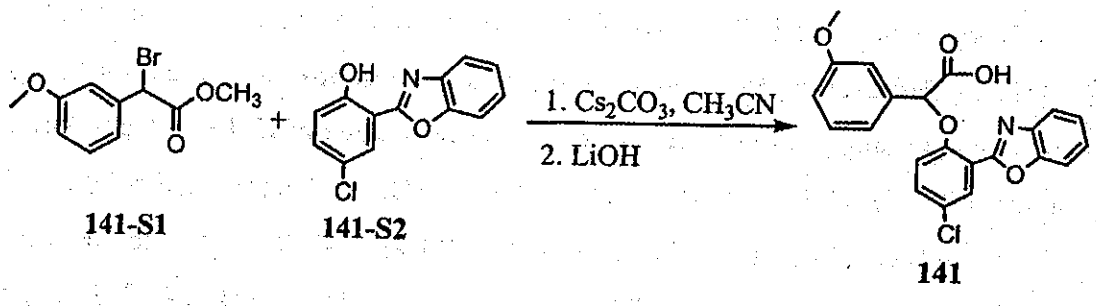


140-S1 **140-S2** **140**

[0350] In the same manner as that described in **Example 28** compound **140** was prepared from **140-S1** and **140-S2.** ^{1}HNMR (400 MHz, DMSO-d_6): δ 7.81 – 6.92 (m, 11H), 5.95 (s, 1H), 3.79 (s, 3H), 3.74 (s, 3H).

[0351] The two enantiomers of **140** were separated by HPLC. Column: PIRKLE COVALENT, (R, R) Whelk-O 2 10/100, 25 cm x 21.1 mm. Flow: 30 ml/min, 50% iPrOH/Hexanes-0.1% TFA.

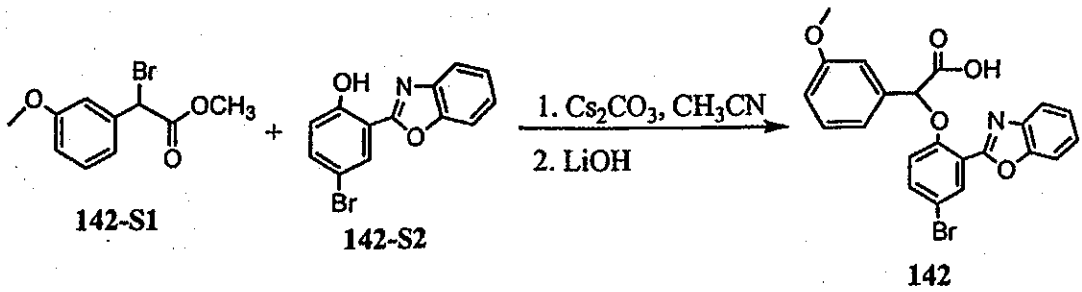
Example 141



141-S1 **141-S2** **141**

[0352] In the same manner as that described in **Example 28** compound **141** was prepared from **141-S1** and **141-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.40 (br, 1H), 8.08 – 6.93 (m, 11H), 6.11 (s, 1H), 3.75 (s, 3H).

[0353] The two enantiomers of **141** were separated by HPLC. Column: PIRKLE COVALENT, (R, R) Whelk-O 2 10/100, 25 cm x 21.1 mm. Flow: 30 ml/min, 50% iPrOH/Hexanes-0.1% TFA.

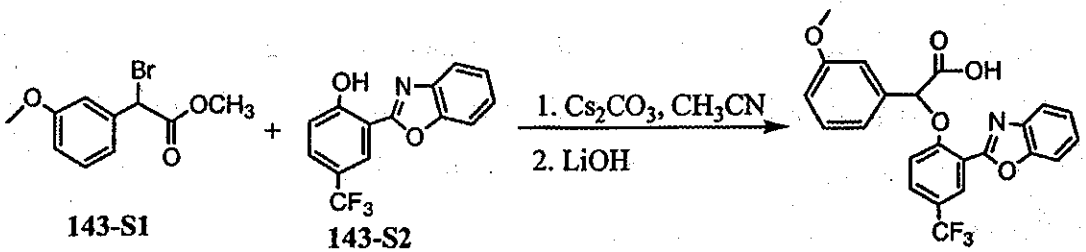


142-S1 142-S2 142

[0354] In the same manner as that described in **Example 28** compound **142** was prepared from **142-S1** and **142-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.20 – 6.93 (m, 11H), 6.11 (s, 1H), 3.75 (s, 3H).

[0355] The two enantiomers were separated by HPLC. Column: PIRKLE COVALENT, (R, R) Whelk-O 2 10/100, 25 cm x 21.1 mm. Flow: 30 ml/min, 50% iPrOH/Hexanes-0.1% TFA.

Example 143

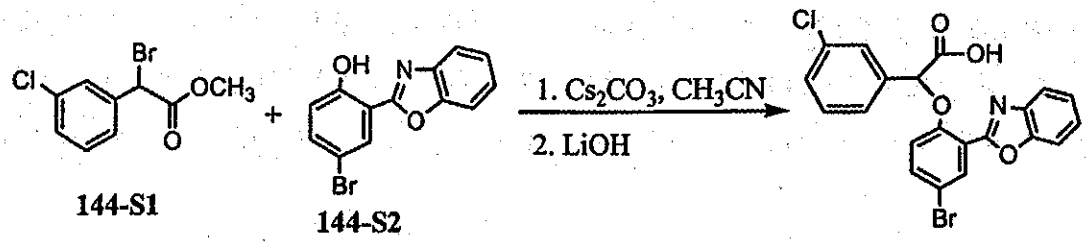


143-S1 143-S2 143 (I-96)

[0356] In the same manner as that described in **Example 28** compound **143** was prepared from **143-S1** and **143-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.38 – 6.95 (m, 11H), 6.26 (s, 1H), 3.75 (s, 3H).

[0357] The two enantiomers were separated by HPLC. Column: PIRKLE COVALENT, (R, R) Whelk-O 2 10/100, 25 cm x 21.1 mm. Flow: 30 ml/min, 50% iPrOH/Hexanes-0.1% TFA.

Example 144

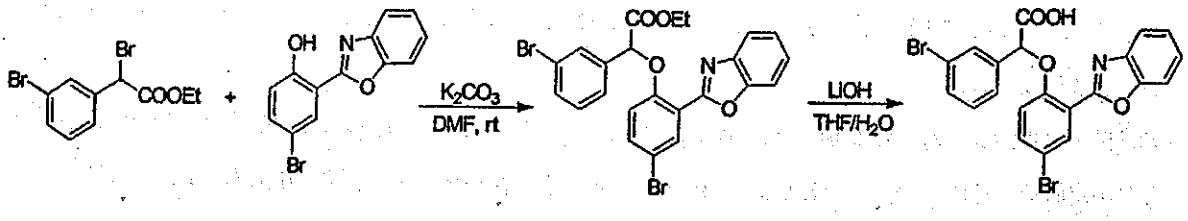


144-S1 144-S2 144 (I-318)

[0358] In the same manner as that described in **Example 28** compound **144** was prepared from **144-S1** and **144-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.25 – 7.16 (m, 11H), 6.23 (s, 1H).

[0359] The two enantiomers were separated by HPLC. Column: PIRKLE COVALENT, (R, R) Whelk-O 2 10/100, 25 cm x 21.1 mm. Flow: 30 ml/min, 50% iPrOH/Hexanes-0.1% TFA.

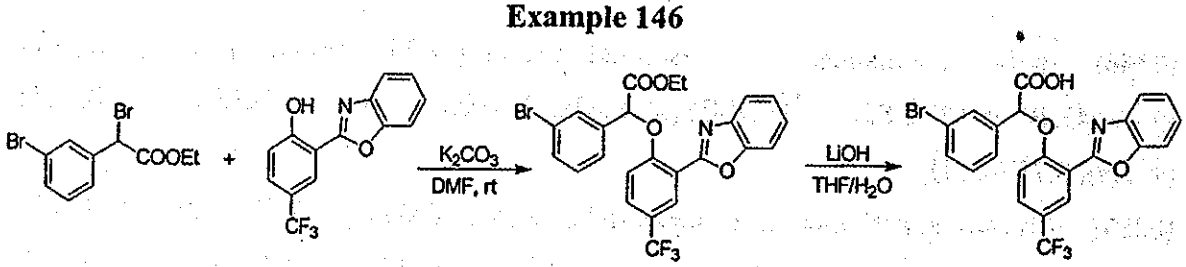
Example 145



145-S1 **145-S2** **145-S3** **145**

[0360] In the same manner as that described in **Example 28** compound **145** was prepared from **145-S1** and **145-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.6 (1H, br, COO*H*), 8.25 (1H, d, J = 2.8 Hz), 8.21 (1H, t, J = 2.0 Hz), 7.88–7.90 (1H, m), 7.79–7.83 (2H, m), 7.69 (1H, d, J = 7.6 Hz), 7.60–7.62 (1H, m), 7.41–7.50 (3H, m), 7.18 (1H, d, J = 9.2 Hz), 6.24 (1H, s) ppm.

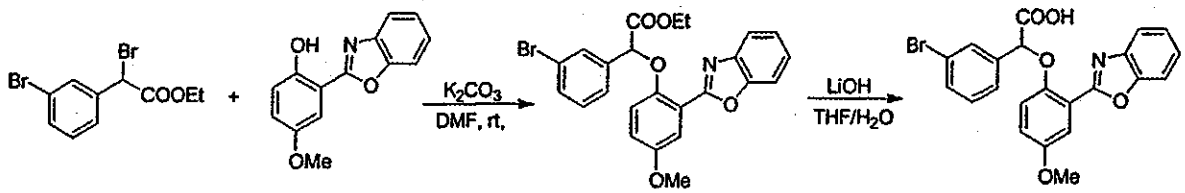
Example 146



146-S1 **146-S2** **146-S3** **146 (I-115)**

[0361] In the same manner as that described in **Example 28** compound **146** was prepared from **146-S1** and **146-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.7 (1H, br, COO*H*), 8.42 (1H, s), 8.25 (1H, s), 8.02 (1H, d, J = 9.2 Hz), 7.91 (1H, d, J = 8.0 Hz), 7.84 (1H, d, J = 7.2 Hz), 7.73 (1H, d, J = 7.2 Hz), 7.62 (1H, d, J = 8.4 Hz), 7.39–7.51 (4H, m), 6.38 (1H, s) ppm.

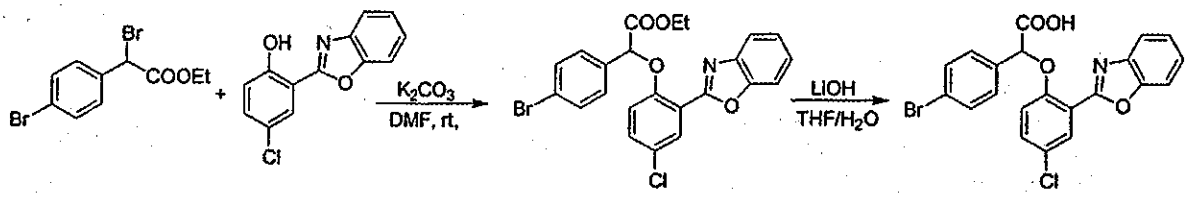
Example 147



147-S1 147-S2 147-S3 147

[0362] In the same manner as that described in **Example 28** compound **147** was prepared from **147-S1** and **147-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.5 (1H, br, COO*H*), 8.16 (1H, s), 7.85–7.87 (1H, m), 7.77–7.80 (1H, m), 7.67 (1H, d, J = 8.0 Hz), 7.64 (1H, d, J = 3.2 Hz), 7.59 (1H, dd, J = 7.2, 1.2 Hz), 7.39–7.49 (3H, m), 7.13–7.21 (2H, m), 6.08 (1H, s), 3.80 (3H, s) ppm.

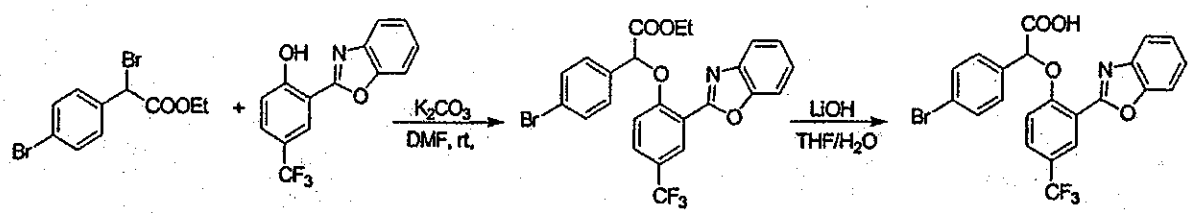
Example 148



148-S1 148-S2 148-S3 148 (I-195)

[0363] In the same manner as that described in **Example 28** compound **148** was prepared from **148-S1** and **148-S2.** NMR (400 MHz, DMSO-d_6): δ 13.5 (1H, br, COO*H*), 8.11 (1H, d, J = 2.8 Hz), 7.86–7.88 (1H, m), 7.81–7.83 (1H, m), 7.65–7.75 (5H, m), 7.41–7.49 (2H, m), 7.23 (1H, d, J = 9.6 Hz), 6.18 (1H, s) ppm.

Example 149

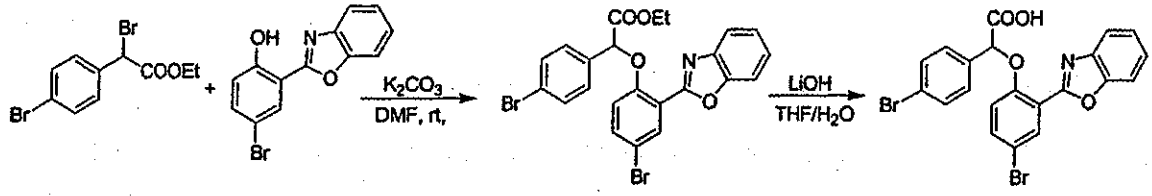


149-S1 149-S2 149-S3 149 (I-99)

[0364] In the same manner as that described in **Example 28** compound **149** was prepared from **149-S1** and **149-S2.** . ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.7 (1H, br, COO*H*), 8.41

(1H, s), 8.00 (1H, d, J = 8.0 Hz), 7.90 (1H, d, J = 8.0 Hz), 7.85 (1H, d, J = 7.2 Hz), 7.78 (2H, d, J = 8.6 Hz), 7.73 (2H, d, J = 8.6 Hz), 7.39–7.51 (3H, m), 6.33 (1H, s) ppm.

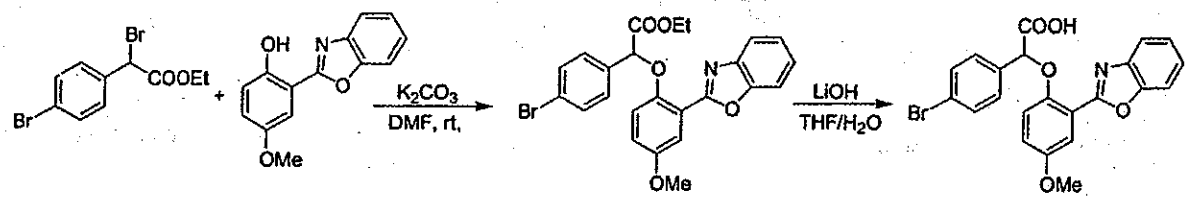
Example 150



150-S1 **150-S2** **150-S3** **150 (I-324)**

[0365] In the same manner as that described in **Example 28** compound **150** was prepared from **150-S1** and **150-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.5 (1H, br, COO*H*), 8.23 (1H, d, J = 2.8 Hz), 7.69–7.88 (7H, m), 7.41–7.49 (2H, m), 7.17 (1H, d, J = 9.2 Hz), 6.17 (1H, s) ppm.

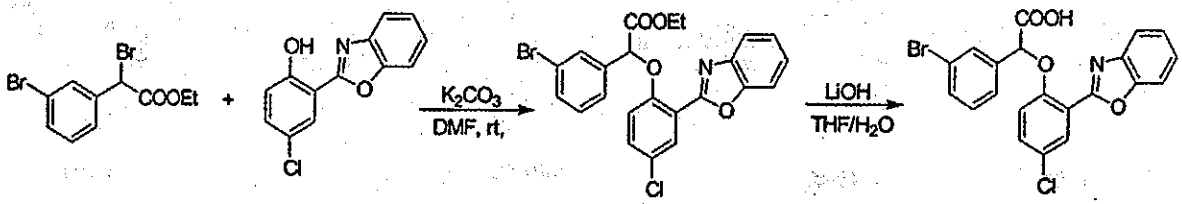
Example 151



151-S1 **151-S2** **151-S3** **151**

[0366] In the same manner as that described in **Example 28** compound **151** was prepared from **151-S1** and **151-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.4 (1H, br, COO*H*), 7.83–7.85 (1H, m), 7.77–7.80 (1H, m), 7.66–7.72 (4H, m), 7.62 (1H, d, J = 3.2 Hz), 7.40–7.47 (2H, m), 7.11–7.19 (2H, m), 6.01 (1H, s), 3.81 (3H, s) ppm.

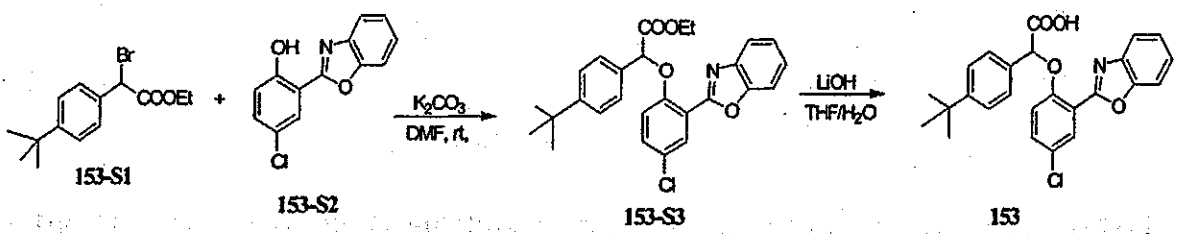
Example 152



152-S1 **152-S2** **152-S3** **152**

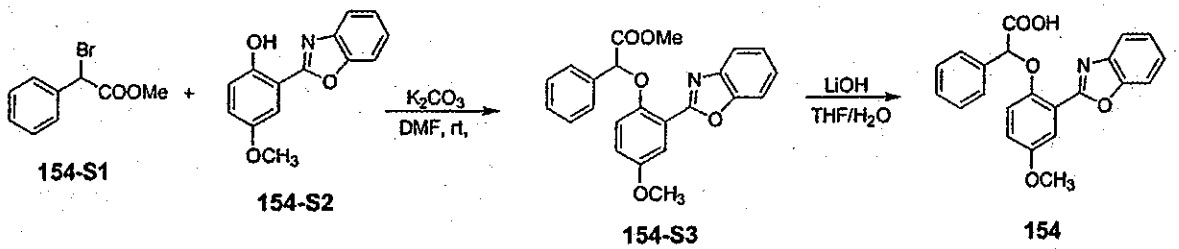
[0367] In the same manner as that described in **Example 28** compound **152** was prepared from **152-S1** and **152-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.6 (1H, br, COO*H*), 8.22 (1H, s), 8.13 (1H, d, J = 2.8 Hz), 7.88–7.90 (1H, m), 7.81–7.83 (1H, m), 7.67–7.71 (2H, m), 7.60–7.62 (1H, m), 7.41–7.49 (3H, m), 7.23 (1H, d, J = 9.2 Hz), 6.24 (1H, s) ppm.

Example 153



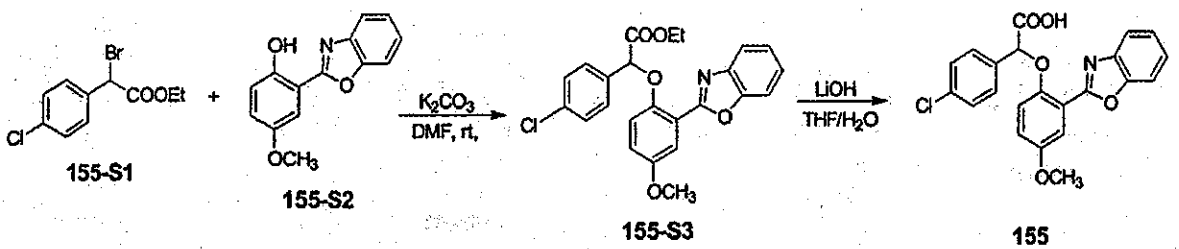
[0368] In the same manner as that described in **Example 28** compound **153** was prepared from **153-S1** and **153-S2.** ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 8.09 (d, J=2.4Hz,1H), 7.86 (m,1H), 7.78 (m,1H), 7.67 (m, 3H), 7.45-7.42 (m,4H), 7.23 (d, J=9.2 Hz,1H), 6.09 (s,1H), 1.28 (s, 9H).

Example 154



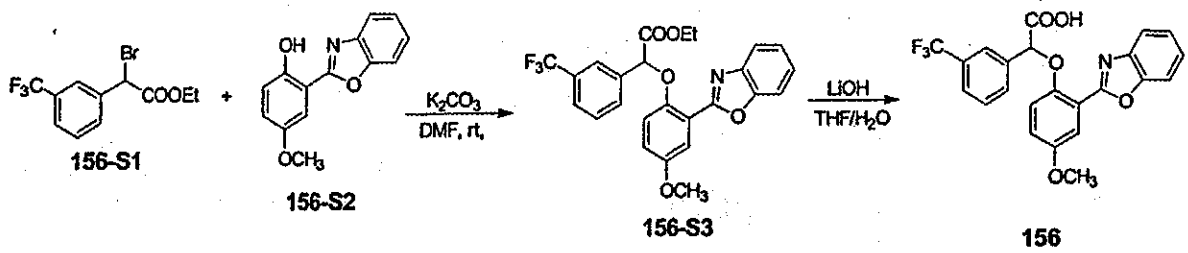
[0369] In the same manner as that described in **Example 28** compound **154** was prepared from **154-S1** and **154-S2.** ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 7.83 (m,1H), 7.73 (m, 3H), 7.62 (d, J=2.4 Hz,1H), 7.44 (m,4H), 7.38 (m, 1H), 7.15 (m, 2H), 5.96 (s, 1H).

Example 155



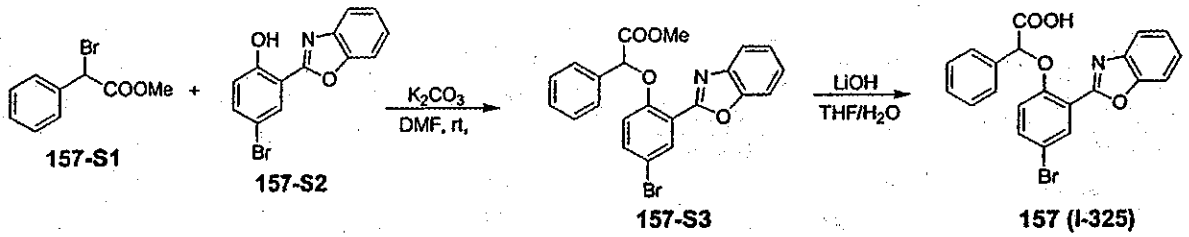
[0370] In the same manner as that described in **Example 28** compound **155** was prepared from **155-S1** and **155-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.85 (m, 1H), 7.76 (m, 3H), 7.63 (m, 1H), 7.55 (m, 2H), 7.44 (m, 2H), 7.17 (m, 2H), 6.03 (s,1H).

Example 156



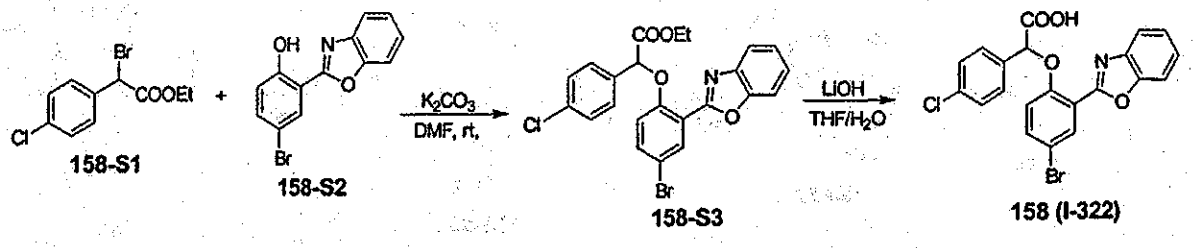
[0371] In the same manner as that described in **Example 28** compound **156** was prepared from **156-S1** and **156-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.27 (s,1H), 7.99 (d, *J*=2.8 Hz,1H), 7.81-7.75 (m, 2H), 7.71 (m, 2H), 7.63 (d, *J*=2.4 Hz,1H), 7.47 (m, 2H), 7.20 (m, 2H), 6.26 (s, 1H).

Example 157



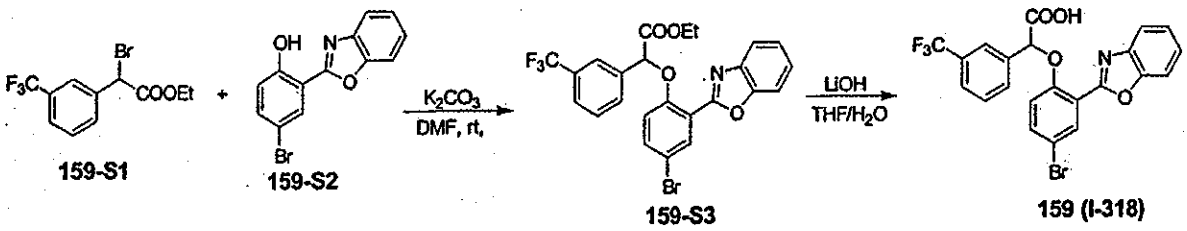
[0372] In the same manner as that described in **Example 28** compound **157** was prepared from **157-S1** and **157-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.40 (s,1H), 8.22 (d, *J*=2.8 Hz,1H), 7.85 (m,1H), 7.79-7.74 (m, 4H), 7.48-7.38 (m, 5H), 7.19 (d, *J*=9.2 Hz, 1H), 6.14 (s, 1H).

Example 158



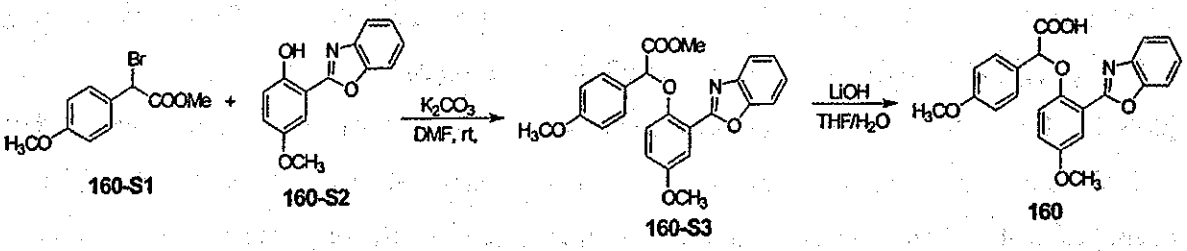
[0373] In the same manner as that described in **Example 28** compound **158** was prepared from **158-S1** and **158-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.23 (d,*J*=2.4 Hz,1H), 7.87 (m, 1H), 7.79 (m, 4H), 7.58 (m,2H), 7.47-7.42 (m,2H), 7.18 (d, *J*=9.2 Hz,1H), 6.20 (s,1H).

Example 159



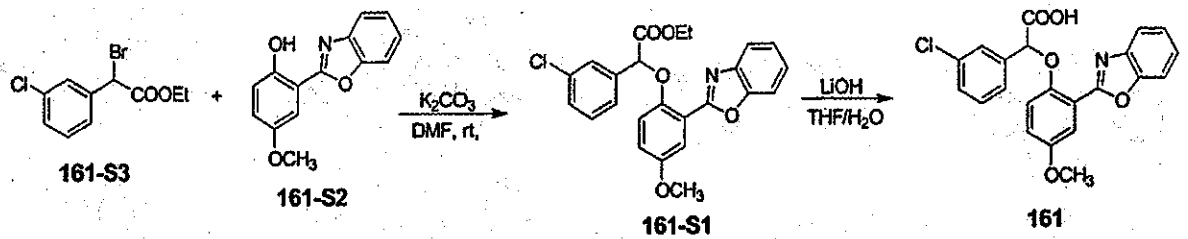
[0374] In the same manner as that described in **Example 28** compound **159** was prepared from **159-S1** and **159-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 (s,1H), 8.25 (d, *J*=2.4 Hz,1H), 8.03 (d, *J*=8Hz,1H), 7.83-7.71 (m, 5H), 7.48 (m, 2H), 7.26 (d, *J*=9.6 Hz,1H), 6.38 (s, 1H).

Example 160



[0375] In the same manner as that described in **Example 28** compound **160** was prepared from **160-S1** and **160-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.20 (s,1H), 7.84 (m, 1H), 7.76 (m,1H), 7.63 (m, 3H), 7.47-7.40 (m, 2H), 7.17-7.11 (m, 2H), 7.01 (m, 2H), 5.89 (s,1H), 3.79 (s, 3H), 3.75 (s, 3H).

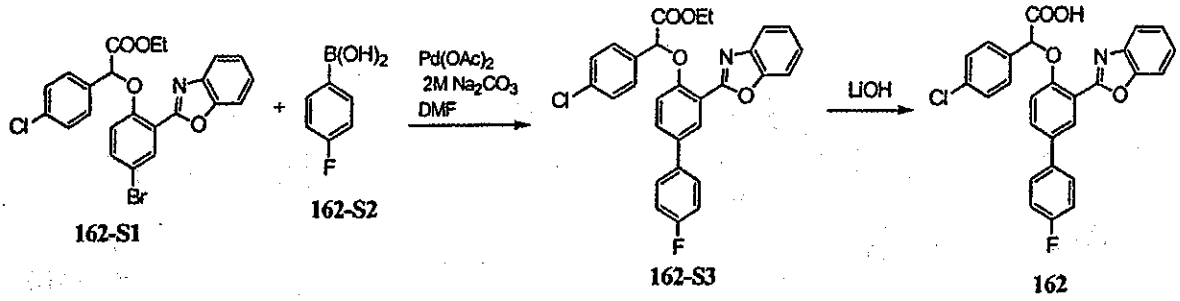
Example 161



[0376] In the same manner as that described in **Example 28** compound **161** was prepared from **161-S1** and **161-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.01 (m,1H), 7.85 (m1H), 7.77

(m,1H), 7.65 (m, 2H), 7.50-7.41 (m,4H), 7.21 (dd, *J*=2.8 and 8.8 Hz,1H), 7.13 (d, *J*=9.6 Hz,1H), 6.08 (s,1H), 3.80 (s, 3H).

Example 162



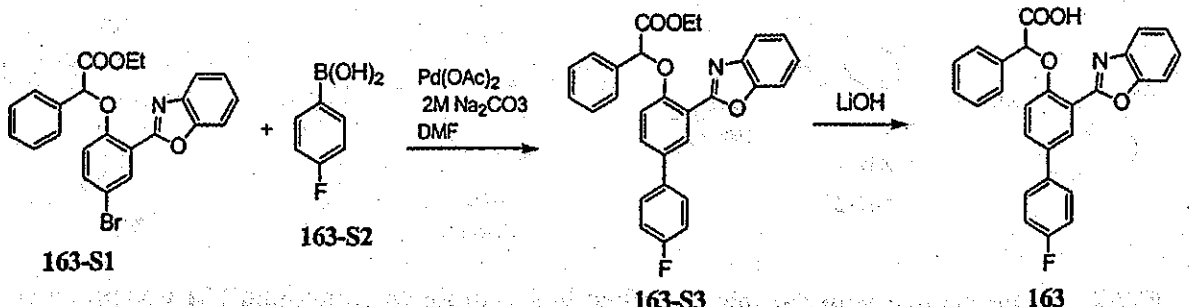
162-S1 **162-S2** **162-S3** **162**

[0377] A mixture of ester **162-S1** (205 mg, 0.42 mmol), 4-fluorophenyl boronic acid (71 mg, 0.51 mmol), $Pd(OAc)_2$ (19 mg, 0.084 mmol), 2M Na_2CO_3 (0.42 mL) in DMF (9 mL) was stirred overnight at room temperature under nitrogen. The mixture was diluted with EtOAc, filtered, washed with brine, dried, and concentrated. Purification *via* flash column (hexane/EtOAc 5:1) gave ester **162-S3** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.35 (d, *J*=2.8Hz,1H), 7.89 (m, 2H), 7.83 (m,3H), 7.74 (m, 2H), 7.59 (m, 2H), 7.45 (m, 2H), 7.28 (m, 3H), 6.38 (s,1H), 4.13 (m, 2H), 1.08 (t, *J*=7.2Hz, 3H).

[0378] To a solution of the above ester (90 mg) in THF /MeOH (3 mL / 3 mL) was added 1 M LiOH solution (1 mL). The resulting mixture was stirred at room temperature for 0.5 h, quenched with 1N aqueous HCl and concentrated to remove the organic solvents. To the residue was added water. The formed solid was filtered, washed with water, and dried to afford acid **162** (82 mg) as a white solid.

[0379] ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.35 (d,J=2.4Hz,1H), 7.90-7.78 (m,5H), 7.74 (m,2H), 7.57 (m,2H), 7.48-7.41 (m,2H), 7.32-7.26 (m,3H), 6.23 (s,1H).

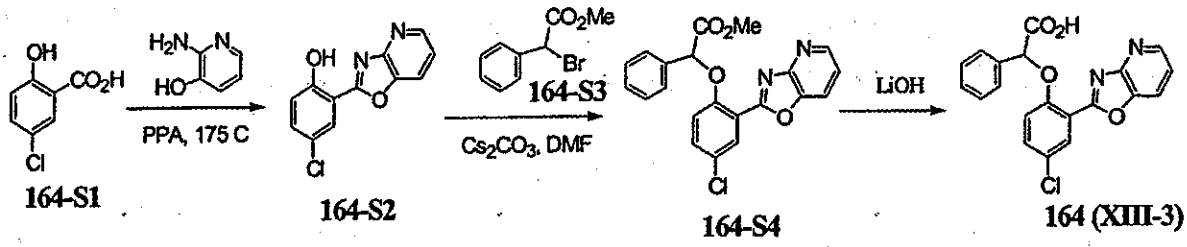
Example 163



163-S1 **163-S2** **163-S3** **163**

[0380] In the same manner as that described in Example 162 compound 163 was prepared from 163-S1 and 163-S2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.33 (d, *J*=2.4 Hz,1H), 7.90 (dd, *J*=2.4 and 8.4 Hz,1H), 7.84 (m,1H), 7.79-7.74 (m, 5H), 7.49-7.36 (m, 5H), 7.29 (m, 3H), 6.16 (s,1H).

Example 164

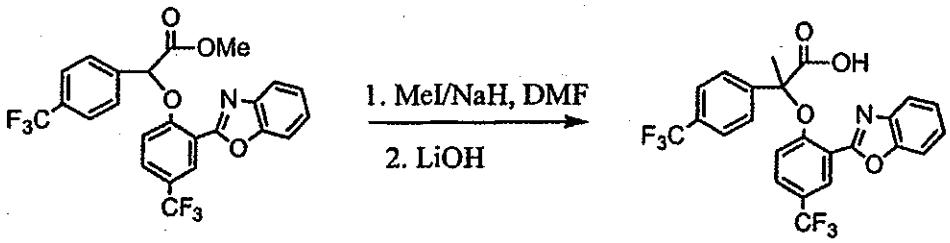


[0381] A mixture of **164-S1** (0.7 g), 2-amino-3-hydroxy-pyridine (0.45 g) and PPA (9.0 g) was heated for 1h at 175 °C under nitrogen. The mixture was then poured into water, basified by adding saturated aqueous $NaHCO_3$ solution. The resulting mixture was extracted with EtOAc, washed with brine, dried and concentrated to give phenol **164-S2** as a pale yellow solid (265 mg). Pure product was obtained by recrystallization from MeOH. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.30 (s,1H), 8.58 (m,1H), 8.29 (m,1H), 8.01 ((d, *J*=2.8Hz,1H), 7.55 (m, 2H), 7.19 (d, *J*=8.4Hz, 1H).

[0382] A mixture of the above phenol **164-S2** (109 mg), bromide **164-S3** (121 mg), Cs_2CO_3 (172 mg) in DMF was stirred at room temperature for 3 h. The mixture was quenched with saturated aqueous NH_4Cl solution, extracted with Et_2O. The organic layer was dried and concentrated. Purification *via* flash column (hexane/EtOAc 5:1) gave ester **164-S4** as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (m,1H), 8.34 (d, *J*=2.4Hz,1H), 7.86 (m,1H), 7.76 (m, 2H), 7.47-7.42 (m, 4H), 7.38 (m,1H), 6.93 (d, *J*=9.2Hz,1H), 5.78 (s,1H), 3.72 (s, 3H).

[0383] To a solution of the above ester (40 mg) in THF /MeOH (3 mL / 3 mL) was added 0.08 M LiOH solution (1.5 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 4 h, quenched with 0.5 N aqueous HCl and concentrated. The residue was extracted with EtOAc and the organic layer was dried and concentrated. Purification *via* flash column (5% to 20% iPrOH in hexanes containing 0.1% TFA) gave acid **164** as a white solid (22 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (m,1H), 8.24 (d, *J*=2.8Hz,1H), 7.98 (m,1H), 7.57 (m, 2H), 7.45-7.38 (m, 5H), 6.85 (d, *J*=8.4Hz,1H), 5.75 (s,1H).

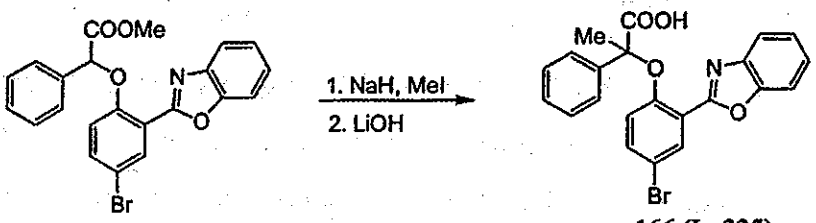
Example 165



165-S1 **165 (Ia-91)**

[0384] In the same manner as that described in **Example 42** compound **165** was prepared from **165-S1**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 – 7.22 (m, 11H), 1.80 (s, 3H).

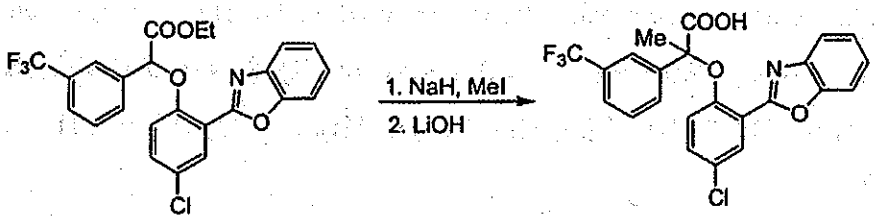
Example 166



166-S1 **166 (Ia-325)**

[0385] In the same manner as that described in **Example 42** compound **166** was prepared from **166-S1**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.22 (d,J=2.4 Hz,1H), 7.85 (m,1H), 7.79 (m,1H), 7.74 (m,2H), 7.69 (dd, *J*=2.4 and 8.8 Hz,1H), 7.51-7.32 (m, 5H), 6.85 (d, *J*=8.8 Hz,1H), 1.95 (s, 3H).

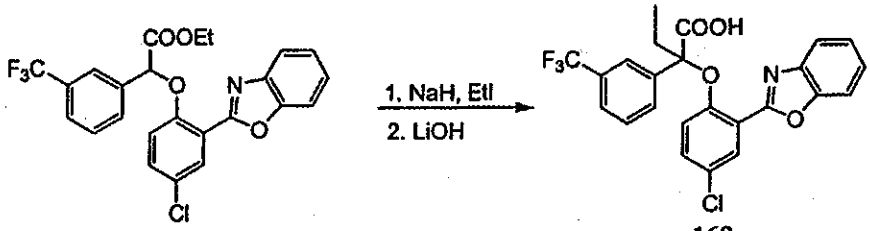
Example 167



167-S1 **167 (Ia-191)**

[0386] In the same manner as that described in **Example 42** compound **167** was prepared from **167-S1**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.34 (s,1H), 8.12 (m, H), 7.99 (m, 1H), 7.81 (m,1H), 7.73-7.63 (m, 4H), 7.46 (m, 2H), 7.01 (d, *J*=8.8 Hz, 1H), 1.92 (s, 3H).

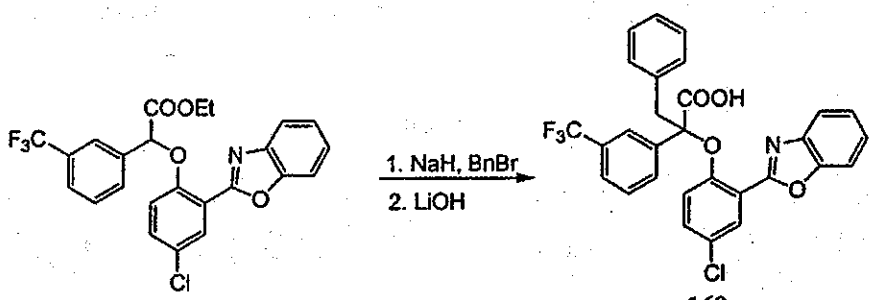
Example 168



168-S1 168

[0387] In the same manner as that described in **Example 42** compound **168** was prepared from **168-S1**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 (s,1H), 8.12 (d, *J*=2.4 Hz,1H), 7.95 (m,1H), 7.85 (m,1H), 7.79 (m,1H), 7.74 (m,1H), 7.67 (m,1H), 7.59 (m,1H), 7.48 (m, 2H), 6.89 (d, *J*=8.8 Hz,1H), 2.62 (m,1H), 2.40 (m,1H), 0.59 (t, *J*=6.8 Hz, 3H).

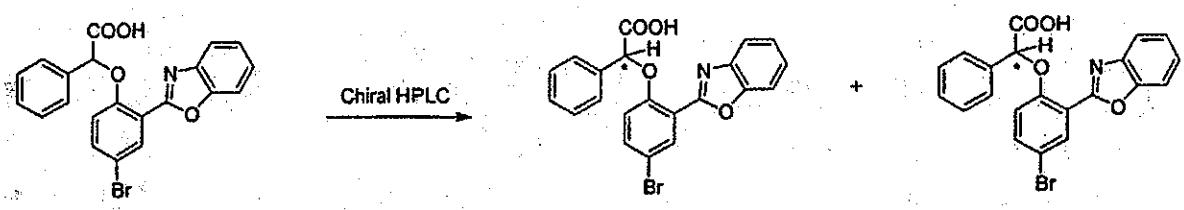
Example 169



169-S1 169

[0388] In the same manner as that described in **Example 42** compound **169** was prepared from **169-S1**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.14 (s,1H), 7.97 (d, *J*=2.8 Hz,1H), 7.91 (d, *J*=8Hz,1H), 7.79 (m,1H), 7.65 (m,1H), 7.49 (dd, *J*=2.8 and 9.2 Hz,1H), 7.48-7.37 (m, 4H), 7.17 (d, *J*=9.6 Hz,1H), 6.79 (m,1H), 6.72 (m, 2H), 6.54 (m, 2H), 3.75 (d, *J*=15.2Hz,1H), 3.54 (d, *J*=14.4 Hz,1H).

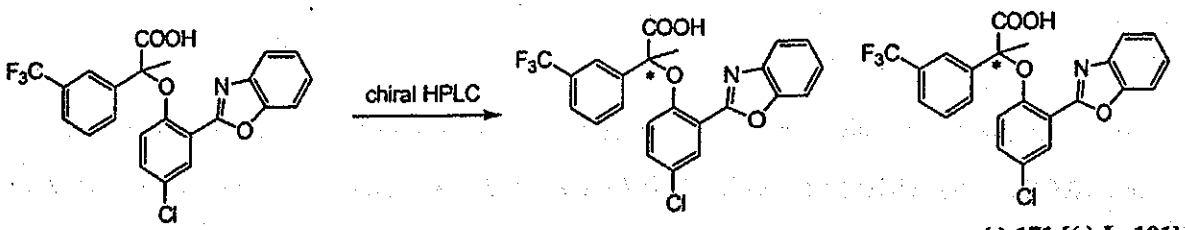
Example 170



171 (+)-170 [(+)-I-325] (-)-170 [(-)-I-325]

[0389] The two enantiomers were isolated by chiral HPLC using a 25 cm × 21.1 mm Regis Technologies (R,R) WHELK-O 2 10/100 column at ambient temperature. The column was eluted with (50/50/0.1) *i*PrOH/hexanes/0.1%TFA at a flow of 30 mL/min.

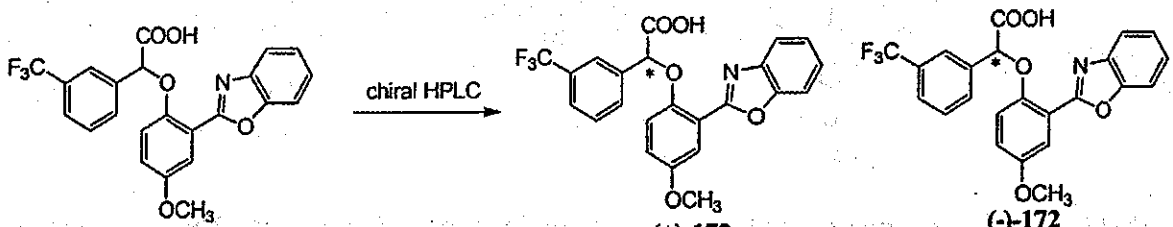
Example 171



171 (+)-171 [(+)-Ia-191] (-)-171 [(-)-Ia-191]

[0390] The two enantiomers were separated by chiral HPLC using a 25 cm × 21.1 mm Regis Technologies (R,R) WHELK-O 2 10/100 column at ambient temperature. HPLC methods and condition: 25% iPrOH-75% Hexanes-0.1% TFA, 30 mL/min., λ=220 nm.

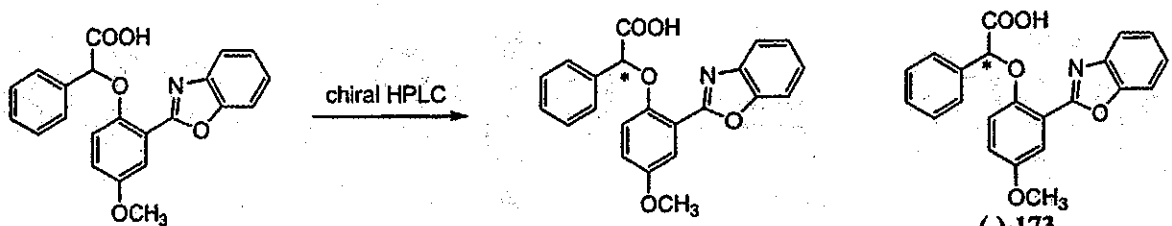
Example 172



172 (+)-172 (-)-172

[0391] The two enantiomers were separated by chiral HPLC using a 25 cm × 21.1 mm Regis Technologies (R,R) WHELK-O 2 10/100 column at ambient temperature. HPLC methods and conditions: 25% iPrOH-75% Hexanes-0.1% TFA, 30 mL/min., λ=220 nm.

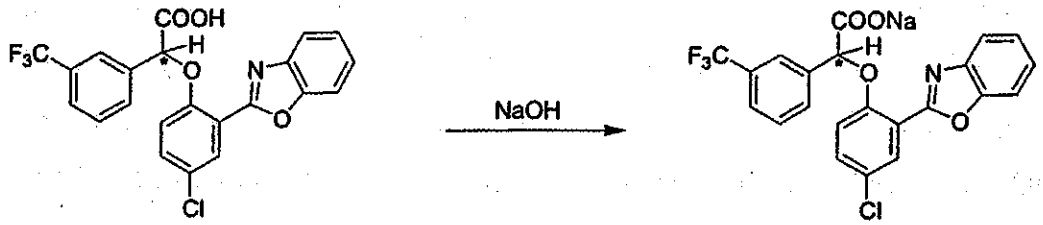
Example 173



173 (+)-173 (-)-173

[0392] The two enantiomers were separated by chiral HPLC using a 25 cm × 21.1 mm Regis Technologies (R,R) WHELK-O 2 10/100 column at ambient temperature. HPLC methods and conditions: 50% iPrOH-50% Hexanes-0.1% TFA, 30 mL/min., λ=220 nm.

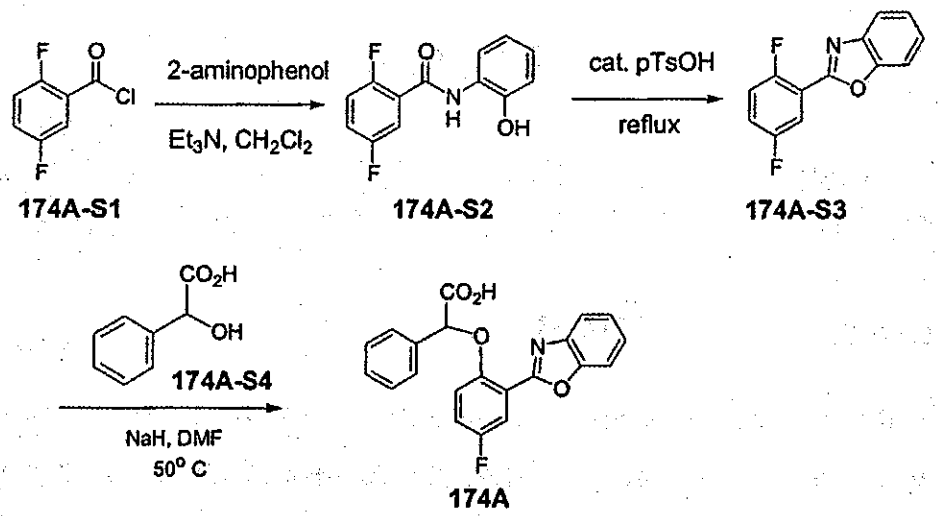
Example 174



(+)-174 **(+)-174 Na salt**

[0393] A suspension of **(+)-174** (1.80 g, 4.02 mol) in ca. 100 mL of CH_3CN was heated until it was a clear solution, then cooled to rt. A solution of aq. NaOH (2N, 2.01 mL, 4.02 mmol) was added, and stripped off solvents *in vacuo*. The residue was dissolved in water and lyophilized to afford desired sodium salt (1.87 g) as a white solid. ^1H NMR (400 MHz, DMSO-d_6): δ 8.33 (1H, s), 8.04–8.07 (2H, m), 7.81 (1H, m), 7.72 (1H, m), 7.59 (3H, m), 7.45 (2H, m), 7.12 (1H, d, J = 9.2 Hz), 5.51 (1H, s) ppm.

Example 174A



174A-S1 **174A-S2** **174A-S3** **174A**

[0394] To a solution of 2-aminophenol (10.64 g, 0.0975 mol) and Et_3N (14.24 mL, 0.102 mol) in CH_2Cl_2 (200 mL) at 0 °C was added drop wise 2,5-difluoro-benzoyl chloride **174A-S1** (16.39g, 0.093 mol). The resulting mixture was stirred at 0 °C to rt overnight, diluted with EtOAc and washed with 1N HCl and water. The organic layer was dried over Na_2SO_4 and

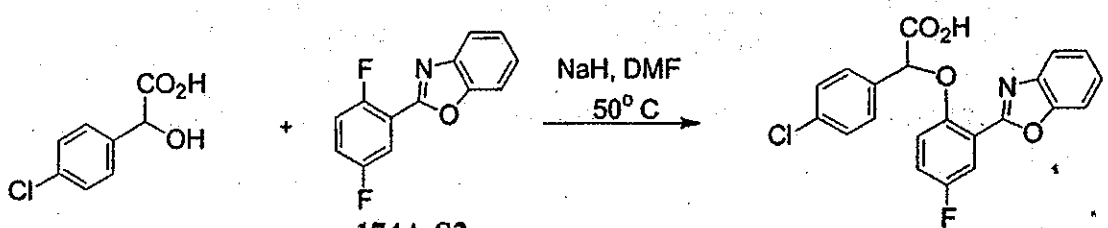
concentrated *in vacuo* to afford crude **174A-S2** as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.06 (s,1H), 9.52 (d, J=8.0 Hz), 8.0-6.79 (m, 7H).

[0395] To a suspension of the above crude product **174A-S2** in toluene (300 mL) was added pTsOH monohydrate (5.0 g). The resulting suspension was refluxed at 120 °C with a Dean-Stark condenser for 16 h. The reaction was cooled to rt, concentrated *in vacuo*, diluted with EtOAc, washed with sat. $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated *in vacuo* to afford **174A-S3** (18.73g, 87% for two steps) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.96 (m,1H), 7.85–7.79 (m,2H), 7.56 (m,2H), 7.48–7.40 (m,2H).

[0396] To a solution of **174A-S4** (1.88 g, 12.32 mmol) in DMF (30 mL) at 0 °C was added NaH (0.96 g, 24.03 mmol). The resulting mixture was warmed up to rt, and stirred at rt for 1 h. To this reaction mixture was added a solution of **174A-S3** (2.85 g, 12.32 mmol) in DMF (20 mL), and the resulting mixture was heated at 50 °C for 12 hrs. After cooling to r.t., the reaction mixture was quenched with cold 2 N HCl solutions, extracted EtOAc. The organic layer was washed with H_2O, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was recrystallized from Et_2O to afford **174A** as a greenish solid (1.2 g). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.38 (br,1H), 7.89-7.83 (m,2H), 7.77–7.72 (m,3H), 7.48-7.37 (m,6H), 7.24 (m,1H), 6.19 (s,1H).

[0397] The two enantiomers were separated by HPLC. Column: PIRKLE COVALENT, (R, R) Whelk-O 2 10/100, 25 cm x 21.1 mm. Flow: 30 ml/min, iPrOH/Hexanes-0.1% TFA.

Example 174B

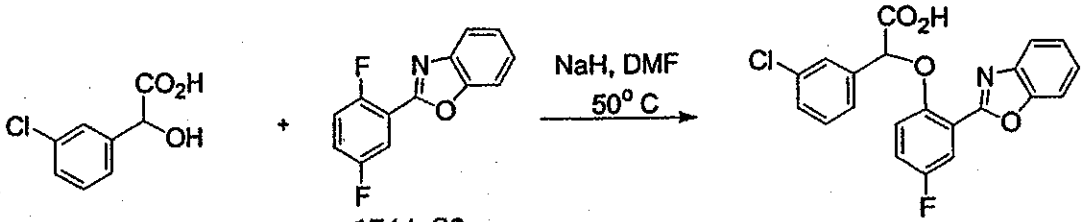


174B-S1 **174A-S3** **174B**

[0398] In the same manner as that described in **Example 174A** compound **174B** was prepared from **174A-S3** and **174B-S1.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.38 (br,1H), 7.91-7.83 (m,2H), 7.81–7.78 (m,3H), 7.48-7.41 (m,5H), 7.24 (m,1H), 6.15 (s,1H).

[0399] The two enantiomers were separated by HPLC. Column: PIRKLE COVALENT, (R, R) Whelk-O 2 10/100, 25 cm x 21.1 mm. Flow: 30 ml/min, iPrOH/Hexanes-0.1% TFA.

Example 174C

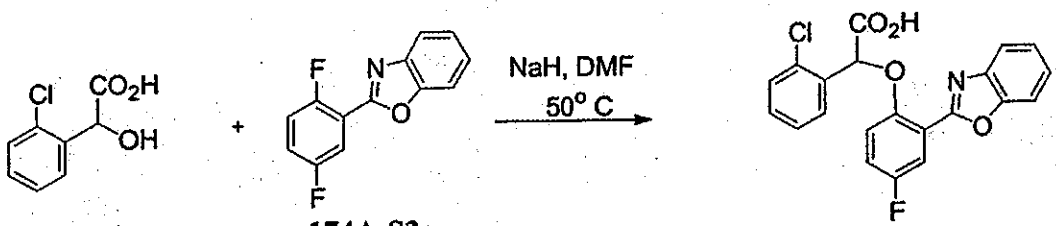


174C-S1 **174A-S3** **174C**

[0400] In the same manner as that described in **Example 174A** compound **174C** was prepared from **174A-S3** and **174C-S1.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (m,1H), 7.86 (m,1H), 7.67 (m,1H), 7.58 (m,1H), 7.48 (m,3H), 7.38 (m,2H), 7.13 (m,1H), 6.81 (m,1H), 5.62 (s,1H).

[0401] The two enantiomers were separated by HPLC. Column: PIRKLE COVALENT, (R, R) Whelk-O 2 10/100, 25 cm x 21.1 mm. Flow: 30 ml/min, iPrOH/Hexanes-0.1% TFA.

Example 174D

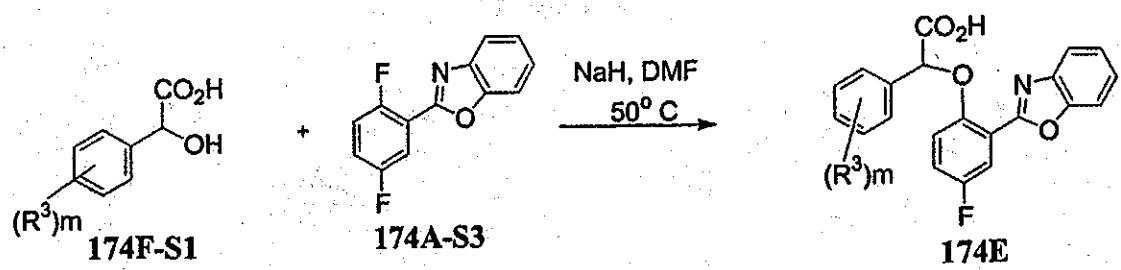


174D-S1 **174A-S3** **174D**

[0402] In the same manner as that described in **Example 174A** compound **174D** was prepared from **174A-S3** and **174D-S1.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93-7.86 (m,2H), 7.66 (m,1H), 7.55-7.46 (m,4H), 7.37-7.33 (m,2H), 7.15 (m,1H), 6.82 (m,1H), 6.18 (s,1H).

[0403] The two enantiomers were separated by HPLC. Column: PIRKLE COVALENT, (R, R) Whelk-O 2 10/100, 25 cm x 21.1 mm. Flow: 30 ml/min, iPrOH/Hexanes-0.1% TFA.

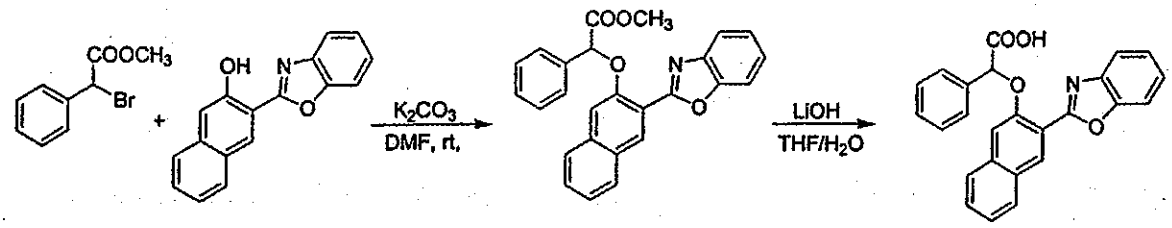
Example 174E



174F-S1 **174A-S3** **174E**

[0404] In the same manner as that described in **Example 174A** compound **174F** was prepared from **174A-S3** and **174F-S1.**

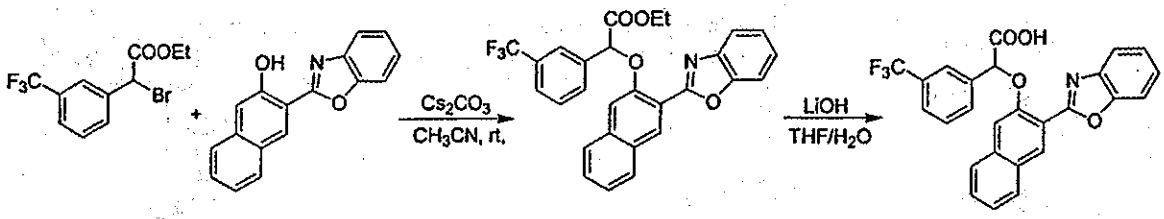
Example 175



175-S1 **175-S2** **175-S3** **175 (III-8)**

[0405] In the same manner as that described in **Example 28** compound **175** was prepared from **175-S1** and **175-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.4 (1H, br, COO*H*), 8.80 (1H, s), 8.07 (1H, d, J = 8.0 Hz), 7.86–7.88 (2H, m), 7.78–7.82 (3H, m), 7.60 (1H, td, J = 7.8, 1.2 Hz), 7.55 (1H, s), 7.43–7.75 (5H, m), 7.39 (1H, tt, J = 7.2, 1.2 Hz), 6.21 (1H, s) ppm.

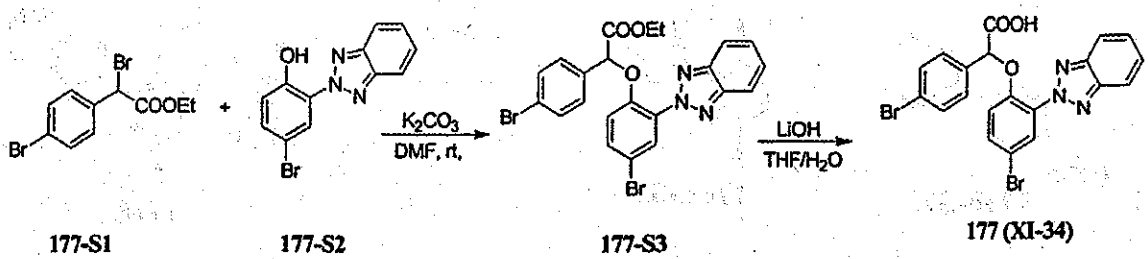
Example 176



176-S1 **176-S2** **176-S3** **176 (III-2)**

[0406] In the same manner as that described in **Example 28** compound **176** was prepared from **176-S1** and **176-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.82 (1H, s), 8.41 (1H, s), 8.09 (2H, t, J = 8.2 Hz), 7.88 (1H, d, J = 8.0 Hz), 7.83–7.86 (1H, m), 7.77–7.80 (2H, m), 7.73 (1H, t, J = 7.6 Hz), 7.61 (1H, td, J = 6.8, 1.2 Hz), 7.58 (1H, s), 7.45–7.52 (3H, m), 6.43 (1H, s) ppm.

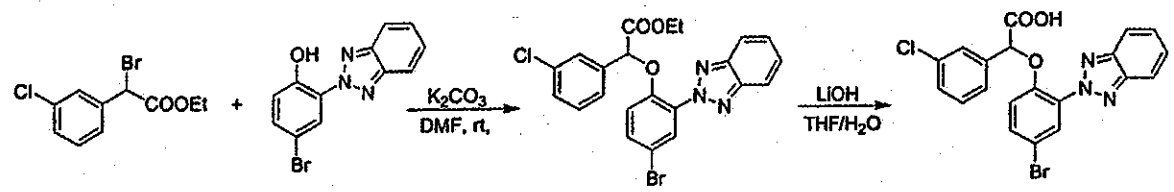
Example 177



177-S1 **177-S2** **177-S3** **177 (XI-34)**

[0407] In the same manner as that described in **Example 28** compound **177** was prepared from **177-S1** and **177-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.5 (1H, br, COO*H*), 8.00–8.06 (3H, m), 7.78 (1H, dd, J = 9.2, 2.4 Hz), 7.51–7.54 (4H, m), 7.36 (2H, d, J = 8.4 Hz), 7.24 (1H, d, J = 8.8 Hz), 6.07 (1H, s) ppm.

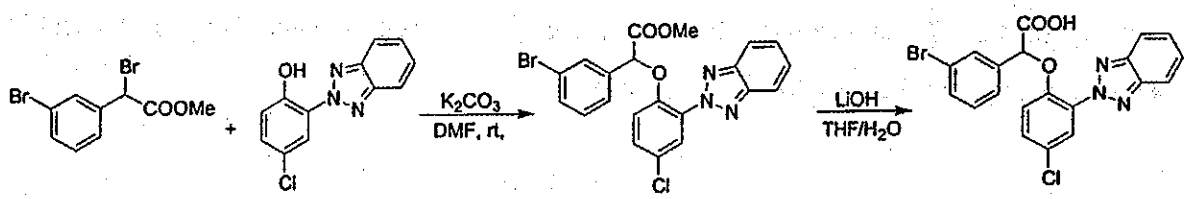
Example 178



178-S1 **178-S2** **178-S3** **178 (XI-28)**

[0408] In the same manner as that described in **Example 28** compound **178** was prepared from **178-S1** and **178-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.01–8.06 (3H, m), 7.79 (1H, dd, J = 8.8, 2.8 Hz), 7.51–7.56 (2H, m), 7.47 (1H, m), 7.35–7.37 (3H, m), 7.25 (1H, d, J = 8.8 Hz), 6.13 (1H, s) ppm.

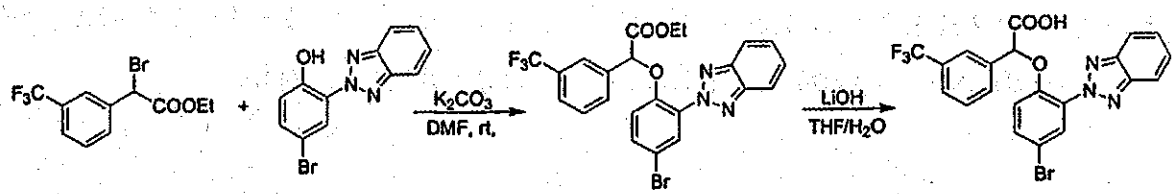
Example 179



179-S1 **179-S2** **179-S3** **179**

[0409] In the same manner as that described in **Example 28** compound **179** was prepared from **179-S1** and **179-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.03–8.06 (2H, m), 7.94 (1H, d, J = 2.4 Hz), 7.68 (1H, dd, J = 8.8, 2.8 Hz), 7.62 (1H, m), 7.48–7.54 (3H, m), 7.41 (1H, d, J = 7.6 Hz), 7.26–7.32 (2H, m), 6.13 (1H, s) ppm.

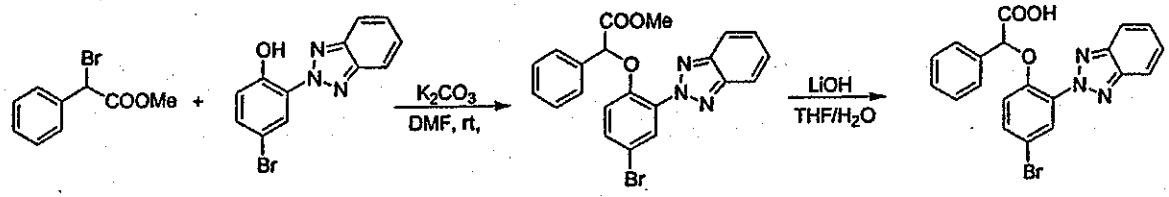
Example 180



180-S1 **180-S2** **180-S3** **180 (XI-29)**

[0410] In the same manner as that described in **Example 28** compound **180** was prepared from **180-S1** and **180-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04 (1H, d, J = 2.8 Hz), 7.97–8.02 (2H, m), 7.81 (1H, dd, J = 8.8, 2.8 Hz), 7.71–7.73 (2H, m), 7.67 (1H, d, J = 8.2 Hz), 7.58 (1H, d, J = 8.2 Hz), 7.51–7.55 (2H, m), 7.29 (1H, d, J = 8.8 Hz), 6.28 (1H, s) ppm.

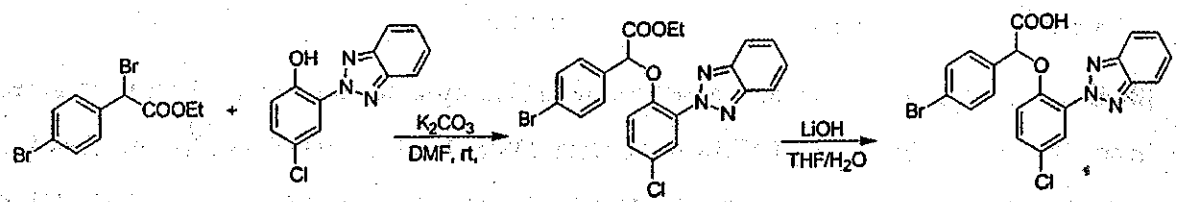
Example 181



181-S1 **181-S2** **181-S3** **181 (XI-35)**

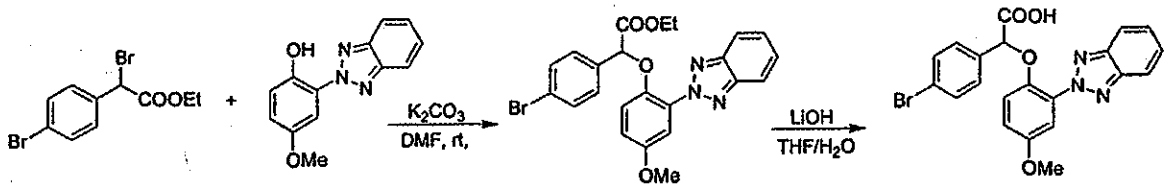
[0411] In the same manner as that described in **Example 28** compound **181** was prepared from **181-S1** and **181-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.98–8.06 (2H, m), 7.98 (1H, d, J = 2.4 Hz), 7.77 (1H, dd, J = 9.2, 2.4 Hz), 7.50–7.55 (2H, m), 7.34–7.39 (2H, m), 7.27–7.31 (3H, m), 7.24 (1H, d, J = 8.8 Hz), 6.03 (1H, s) ppm. The two enantiomers were isolated by chiral HPLC using a 25 cm × 21.1 mm Regis Technologies (R,R) WHELK-O 2 10/100 column at ambient temperature. The column was eluted with (15/85/0.1) *i*PrOH/hexanes/TFA at a flow of 30 mL/min. Detection was at 220 nm. The **(+)-181** eluted at 4.0 to 5.3 min, and the **(–)-181** at 5.8 to 7.1 min.

Example 182



182-S1 **181-S2** **182-S3** **182 (XI-25)**

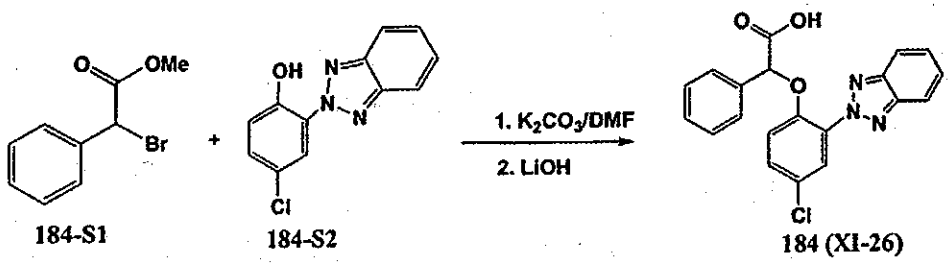
[0412] In the same manner as that described in **Example 28** compound **182** was prepared from **182-S1** and **182-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.5 (1H, br, COO*H*), 8.04 (2H, q, J = 3.2 Hz), 7.91 (1H, d, J = 2.8 Hz), 7.66 (1H, dd, J = 9.2, 2.8 Hz), 7.52–7.54 (4H, m), 7.36 (2H, d, J = 8.4 Hz), 7.29 (1H, d, J = 9.6 Hz), 6.09 (1H, s) ppm.



183-S1 183-S2 183-S3 183

[0413] In the same manner as that described in **Example 28** compound **183** was prepared from **183-S1** and **183-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.3 (1H, br, COO*H*), 8.02 (2H, q, *J* = 3.2 Hz), 7.48–7.52 (4H, m), 7.32–7.35 (3H, m), 7.21 (1H, d, *J* = 8.8 Hz), 7.14 (1H, dd, *J* = 9.6, 3.2 Hz), 5.86 (1H, s), 3.77 (3H, s) ppm.

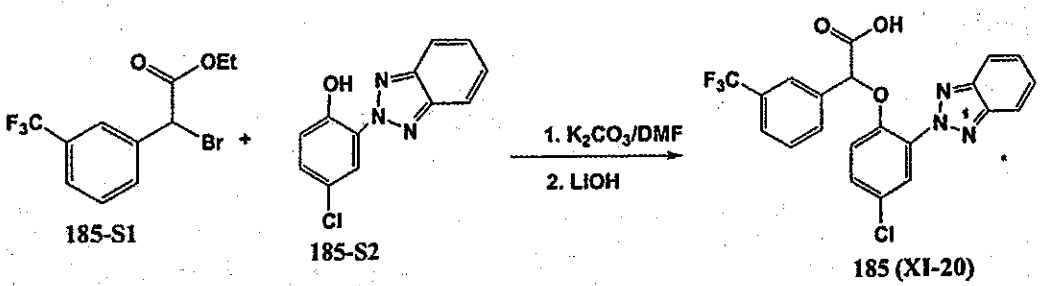
Example 184



184-S1 184-S2 184 (XI-26)

[0414] In the same manner as that described in **Example 28** compound **184** was prepared from **184-S1** and **184-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04 (m, 2H), 7.88 (d, *J*=2.4 Hz, 1H), 7.67 (dd, *J*=2.8 and 9.2 Hz,1H), 7.53 (m, 2H), 7.38 (m,2H), 7.29 (m,4H), 6.04 (s,1H).

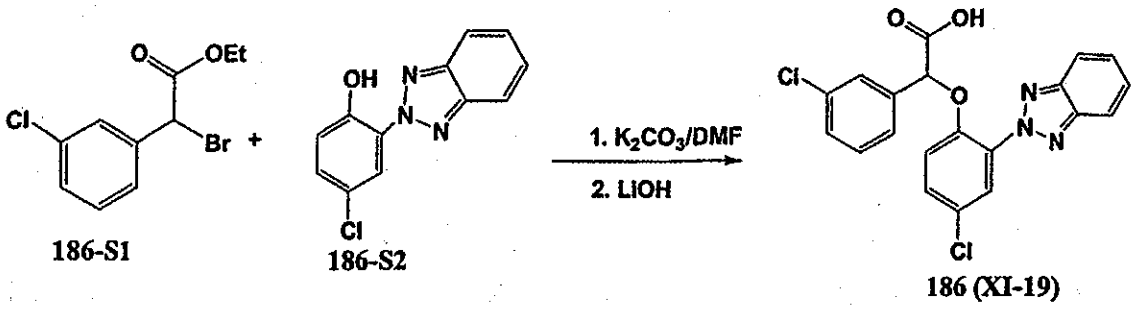
Example 185



185-S1 185-S2 185 (XI-20)

[0415] In the same manner as that described in **Example 28** compound **185** was prepared from **185-S1** and **185-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.02 (m, 2H), 7.96 (d, *J*=2.8 Hz, 1H), 7.74-7.66 (m, 4H), 7.60-7.51 (m, 3H), 7.37 (d, *J*=8.8 Hz,1H), 6.29 (s,1H).

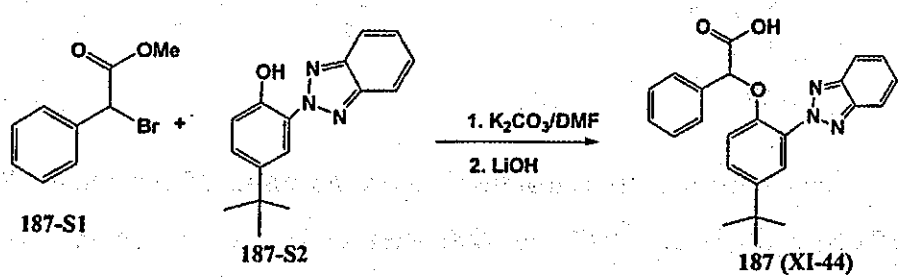
Example 186



186-S1 186-S2 186 (XI-19)

[0416] In the same manner as that described in **Example 28** compound **186** was prepared from **186-S1** and **186-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.05 (m, 2H), 7.94 (d, *J*=2.8 Hz,1H), 7.69 (dd, *J*=2.8 and 8.8 Hz,1H), 7.56-7.52 (m,2H), 7.48 (s,1H), 7.39-7.30 (m, 4H), 6.15 (s,1H).

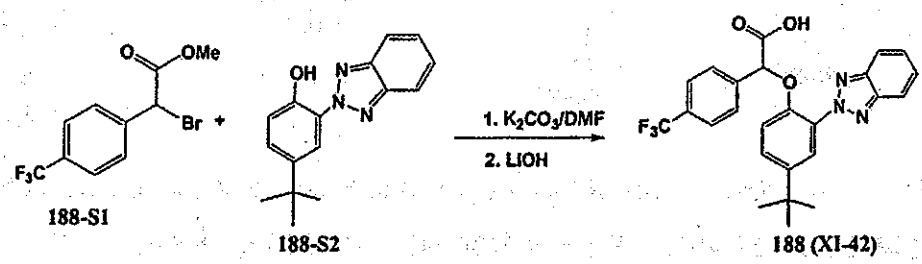
Example 187



187-S1 187-S2 187 (XI-44)

[0417] In the same manner as that described in **Example 28** compound **187** was prepared from **187-S1** and **187-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04 (m, 2H), 7.67 (m,1H), 7.57 (m,1H), 7.50 (m, 2H), 7.40 (m, 2H), 7.28 (m, 3H), 7.17 (m,1H), 5.94 (s,1H), 1.30 (s,9H).

Example 188

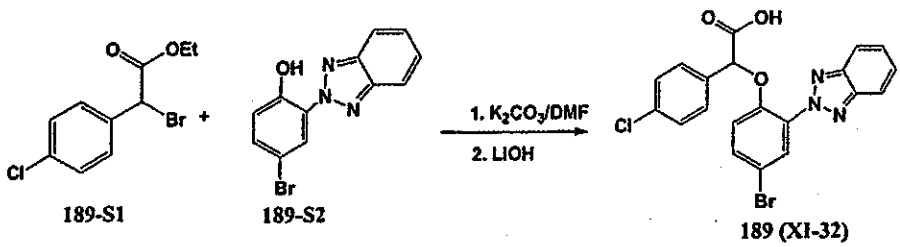


188-S1 188-S2 188 (XI-42)

[0418] In the same manner as that described in **Example 28** compound **188** was prepared from **188-S1** and **188-S2.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, *J*=2.4 Hz, 1H), 8.01 (m,

2H), 7.69 (m, 4H), 7.54 (m, 2H), 7.44 (dd, *J*=2.4 and 8.8Hz,1H), 6.97 (d, *J*=8Hz,1H), 5.91 (s,1H), 1.39 (s, 9H).

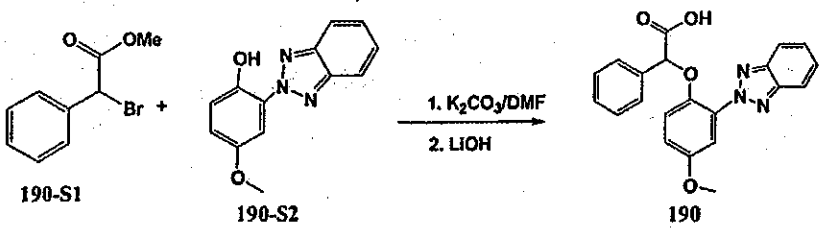
Example 189



189-S1 189-S2 189 (XI-32)

[0419] In the same manner as that described in **Example 28** compound **189** was prepared from **189-S1** and **189-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.0 (m,2H), 7.94 (d, *J*=2.8Hz,1H), 7.74 (dd, *J*=2.4 and 8.8Hz,1H), 7.52 (m,2H), 7.34 (m,4H), 7.19 (d, *J*=8.8Hz,1H), 5.97 (s,1H).

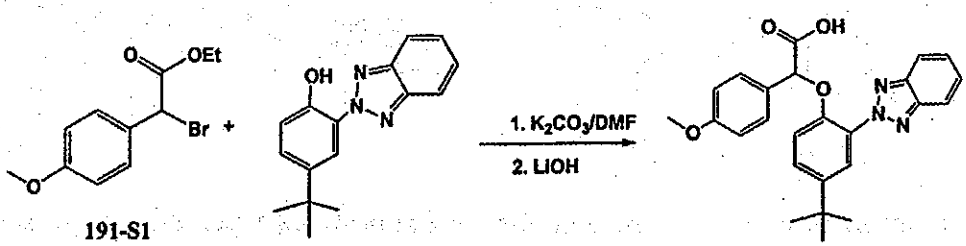
Example 190



190-S1 190-S2 190

[0420] In the same manner as that described in **Example 28** compound **190** was prepared from **190-S1** and **190-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04 (m, 2H), 7.52 (m, 2H), 7.36(m, 2H), 7.33 (d, *J*=3.2 Hz,1H), 7.27 (m,3H), 7.21 (d, *J*=8.8 Hz,1H), 7.13 (dd, *J*=3.2 and 9.2Hz,1H), 5.82 (s,1H), 3.79 (s, 3H).

Example 191

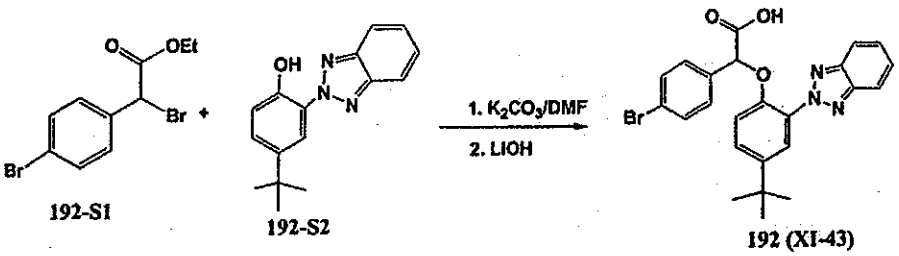


191-S1 191-S2 191 (XI-40)

[0421] In the same manner as that described in **Example 28** compound **191** was prepared from **191-S1** and **191-S2.** ^{1}H NMR (400 MHz,$CDCl_3$): δ 8.12 (d, *J*=2.4 Hz,1H), 8.01

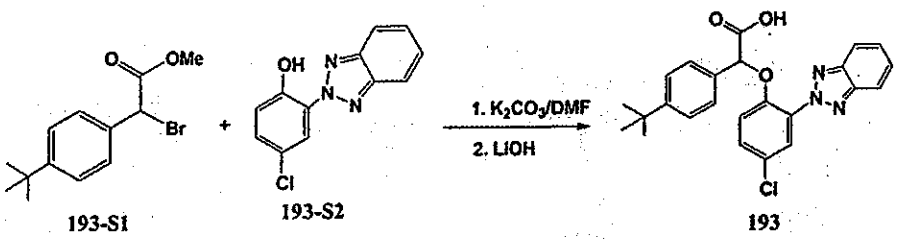
(m,2H), 7.54 (m, 2H), 7.42 (m, 3H), 7.06 (d, *J*=8.8Hz,1H), 6.90 (d, *J*=8.8Hz, 2H), 5.82 (s,1H), 3.79 (s, 3H), 1.38 (s, 9H).

Example 192



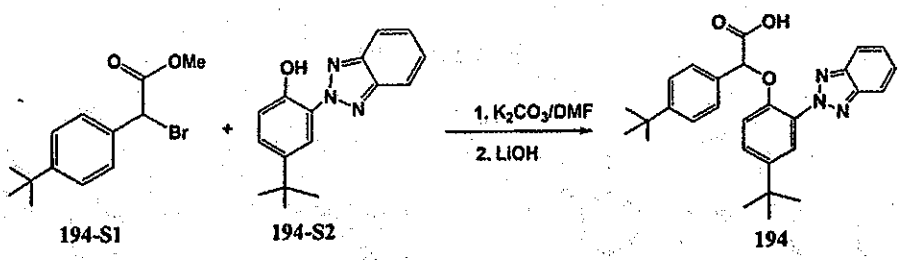
[0422] In the same manner as that described in **Example 28** compound **192** was prepared from **192-S1** and **192-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04 (m, 2H), 7.69 (d, *J*=2.8 Hz,1H), 7.58 (dd, *J*=2.4 and 8.8Hz,1H), 7.51 (m, 4H), 7.36 (m, 2H), 7.15 (d, *J*=8.8Hz,1H), 5.97 (s,1H), 1.30 (s, 9H).

Example 193



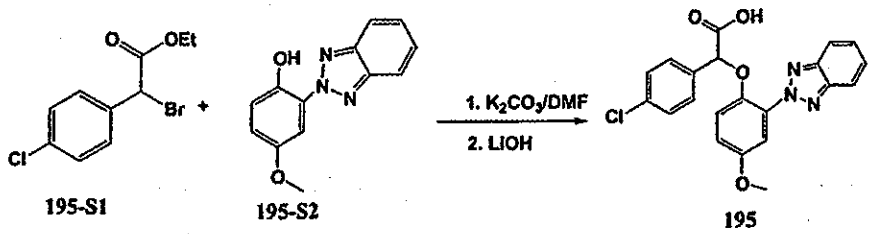
[0423] In the same manner as that described in **Example 28** compound **193** was prepared from **193-S1** and **193-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.05 (m,2H), 7.87 (d, J=2.8 Hz,1H), 7.67 (dd, J=2.8 and 8.8Hz,1H), 7.52 (m,2H), 7.31 (m,5H), 5.99 (s,1H), 1.21 (s,9H).

Example 194



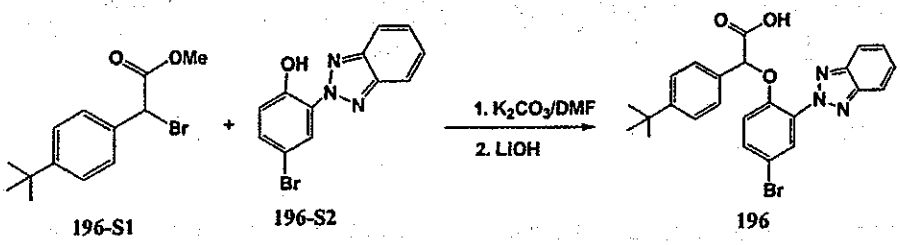
[0424] In the same manner as that described in **Example 28** compound **194** was prepared from **194-S1** and **142-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04 (m,2H), 7.65 (d, *J*=2.8 Hz,1H), 7.48 (dd, *J*=2.8 and 8.8Hz,1H), 7.51 (m, 2H), 7.30 (m, 4H), 7.18 (d, *J*=8.8Hz,1H), 5.89 (s, 1H), 1.30 (s, 9H), 1.23 (s, 9H).

Example 195



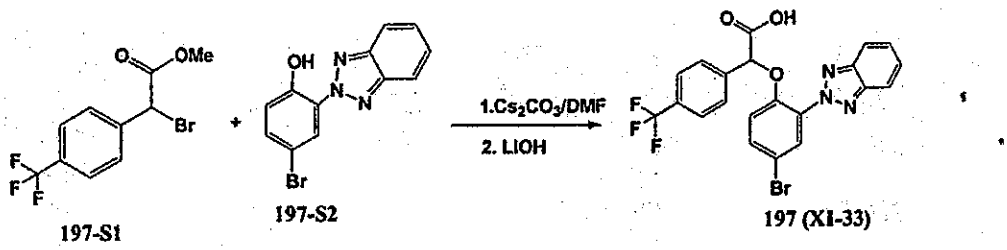
[0425] In the same manner as that described in **Example 28** compound **195** was prepared from **195-S1** and **195-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.03 (m, 2H), 7.52 (m, 2H), 7.38 (m, 5H), 7.21 (d, *J*=8.8 Hz,1H), 7.14 (dd, *J*=2.8 and 9.6Hz,1H), 5.87 (s,1H), 3.77(s,3H).

Example 196

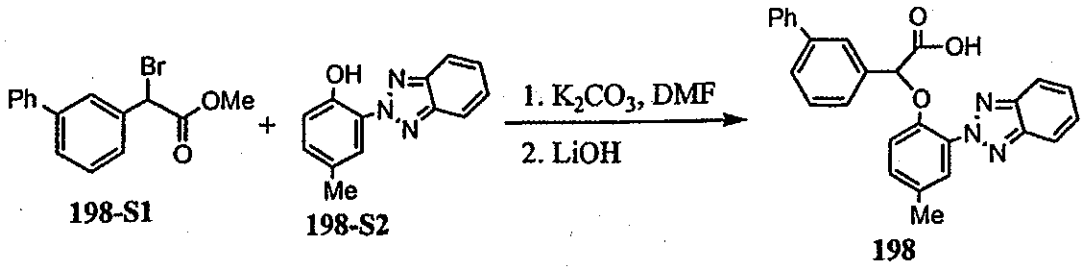


[0426] In the same manner as that described in **Example 28** compound **196** was prepared from **196-S1** and **196-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.05 (m,2H), 7.97 (d, *J*=2.8 Hz,1H), 7.76 (dd, *J*=2.4 and 9.2Hz,1H), 7.54 (m, 2H), 7.36 (m, 2H), 7.31 (m, 4H), 7.24 (d, *J*=3.2Hz,1H), 5.99 (s,1H), 1.22 (s, 9H).

Example 197



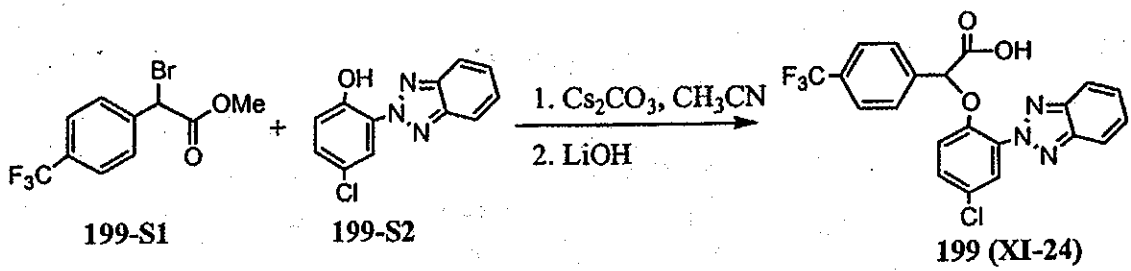
[0427] In the same manner as that described in **Example 28** compound **197** was prepared from **197-S1** and **197-S2.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (m,1H), 7.98 (m, 2H), 7.67 (m, 4H), 7.55 (m, 2H), 7.48 (m,1H), 6.88 (d, *J*=8.8 Hz,1H), 5.87 (s,1H).



198-S1 198-S2 198

[0428] In the same manner as that described in **Example 28** compound **198** was prepared from **198-S1** and **198-S2**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.0-7.0 (m, 16H), 6.0 (s, 1H), 2.26 (s, 3H).

Example 199

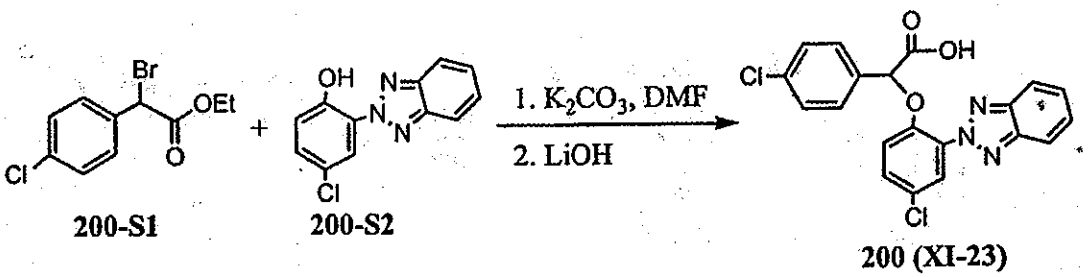


199-S1 199-S2 199 (XI-24)

[0429] In the same manner as that described in **Example 28** compound **199** was prepared from **199-S1** and **199-S2**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.06-7.33 (m, 11H), 6.24 (s, 1H).

[0430] The two enantiomers were separated by HPLC. Column: PIRKLE COVALENT, (R, R) Whelk-O 2 10/100, 25 cm x 21.1 mm. Flow: 30 ml/min, 8% iPrOH/Hexanes-0.1% TFA.

Example 200

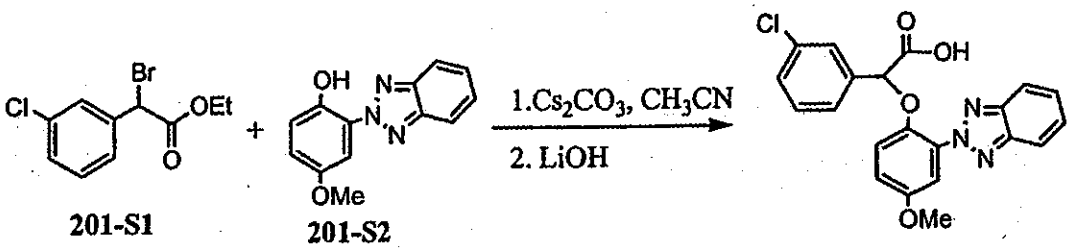


200-S1 200-S2 200 (XI-23)

[0431] In the same manner as that described in **Example 28** compound **200** was prepared from **200-S1** and **200-S2**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.05-7.28 (m, 16H), 6.09 (s, 1H).

[0432] The two enantiomers were separated by HPLC. Column: PIRKLE COVALENT, (R,R) Whelk-O 2 10/100, 25 cm x 21.1 mm. Flow: 30 ml/min, 15% iPrOH/Hexanes-0.1% TFA.

Example 201

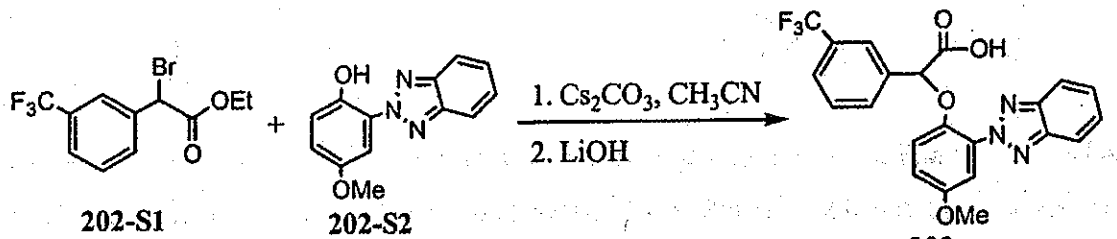


201-S1 201-S2 201

[0433] In the same manner as that described in **Example 28** compound **201** was prepared from **201-S1** and **201-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.03-7.16 (m, 11H), 5.94 (s, 1H), 3.78 (s, 3H).

[0434] The two enantiomers were separated by HPLC. Column: PIRKLE COVALENT, (R, R) Whelk-O 2 10/100, 25 cm x 21.1 mm. Flow: 30 ml/min, 15% iPrOH/Hexanes-0.1% TFA.

Example 202

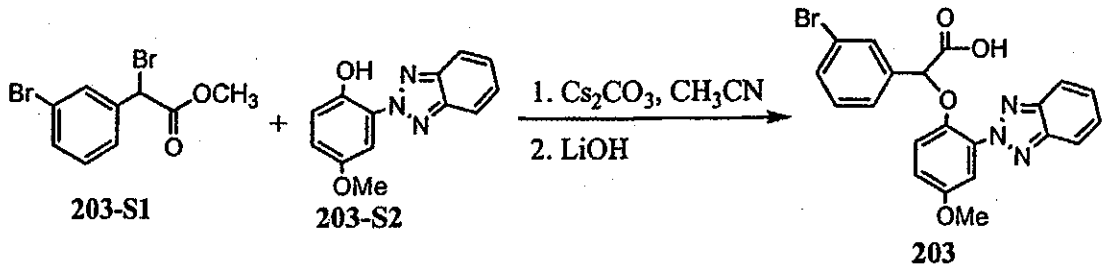


202-S1 202-S2 202

[0435] In the same manner as that described in **Example 28** compound **202** was prepared from **202-S1** and **202-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.99 -7.16 (m, 11H), 6.08 (s, 1H), 3.78 (s, 3H).

[0436] The two enantiomers were separated by chiral HPLC. Column: PIRKLE COVALENT, (R, R) Whelk-O 2 10/100, 25 cm x 21.1 mm. Flow: 30 ml/min, 8% iPrOH/Hexanes-0.1% TFA.

Example 203

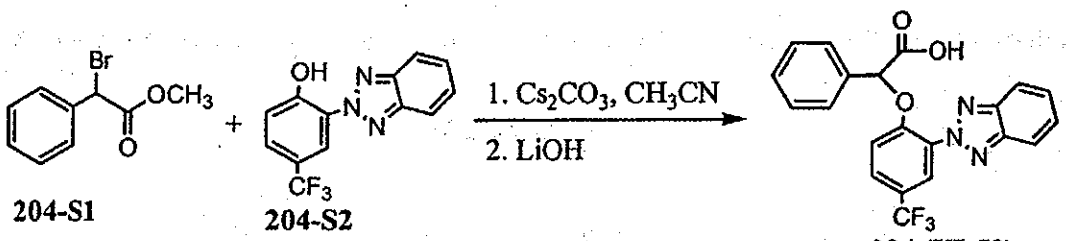


203-S1 203-S2 203

[0437] In the same manner as that described in **Example 28** compound **203** was prepared from **203-S1** and **203-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04 -7.16 (m, 11H), 5.94 (s, 1H), 3.78 (s, 3H).

[0438] The two enantiomers were separated by chiral HPLC. Column: PIRKLE COVALENT, (R, R) Whelk-O 2 10/100, 25 cm x 21.1 mm. Flow: 30 ml/min, 15% iPrOH/Hexanes-0.1% TFA.

Example 204

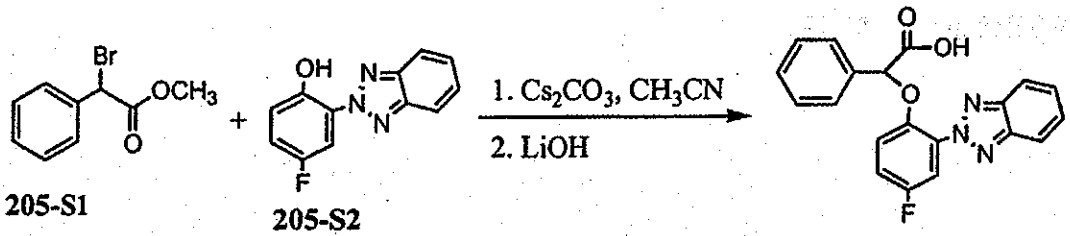


204-S1 204-S2 204 (XI-53)

[0439] In the same manner as that described in **Example 28** compound **204** was prepared from **204-S1** and **204-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.17 -7.29 (m, 12H), 6.20 (s, 1H).

[0440] The two enantiomers were separated by chiral HPLC. Column: PIRKLE COVALENT, (R, R) Whelk-O 2 10/100, 25 cm x 21.1 mm. Flow: 30 ml/min, 10% iPrOH/Hexanes-0.1% TFA.

Example 205

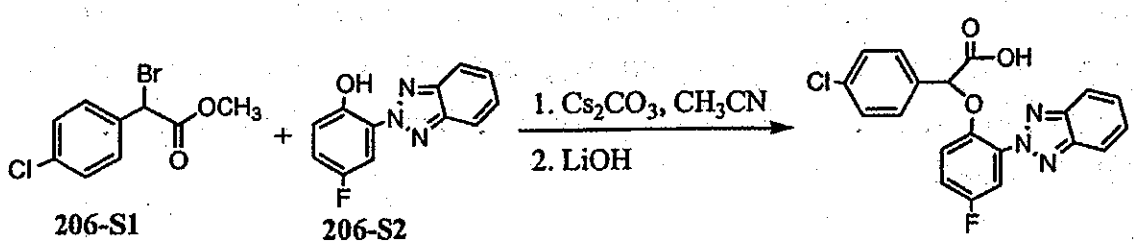


205-S1 205-S2 205

[0441] In the same manner as that described in **Example 28** compound **205** was prepared from **205-S1** and **205-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04 -7.27 (m, 12H), 5.96 (s, 1H).

[0442] The two enantiomers were separated by chiral HPLC. Column: PIRKLE COVALENT, (R, R) Whelk-O 2 10/100, 25 cm x 21.1 mm. Flow: 30 ml/min, 15% iPrOH/Hexanes-0.1 %TFA.

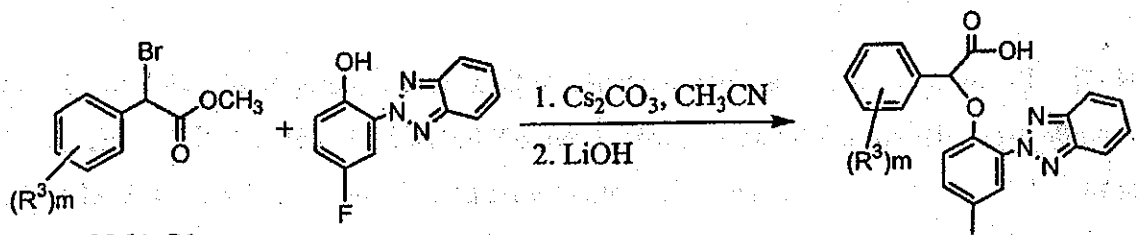
Example 206



206-S1 **206-S2** **206**

[0443] In the same manner as that described in **Example 28** compound **206** was prepared from **206-S1** and **206-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.03 -7.29 (m, 11H), 6.01(s, 1H).

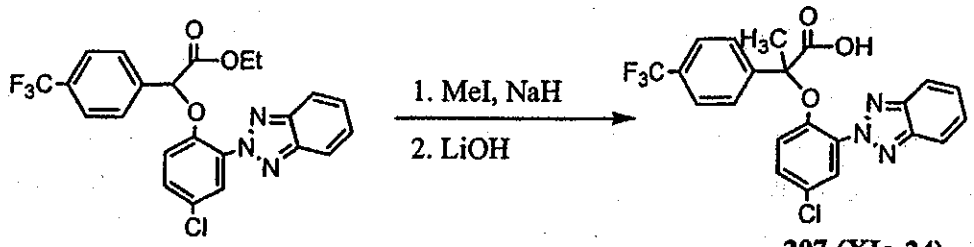
Example 206A



206A-S1 **206A-S2** **206A**

[0444] In the same manner as that described in **Example 28** compound **206A** was prepared from **20A6-S1** and **206A-S2.**

Example 207

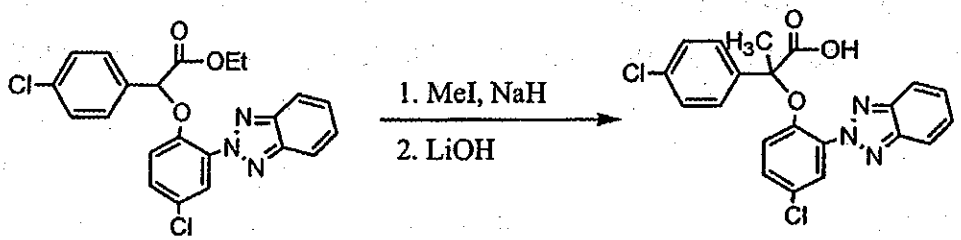


207-S1 **207 (XIa-24)**

[0445] In the same manner as that described in **Example 42** compound **207** was prepared from **207-S1.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.05-7.08 (m, 11H), 1.76 (s, 3H).

[0446] The two enantiomers of **207** were separated by HPLC. Column: PIRKLE COVALENT, (R, R) Whelk-O 2 10/100, 25 cm x 21.1 mm. Flow: 8 ml/min, 15% iPrOH/Hexanes-0.1% TFA.

Example 208

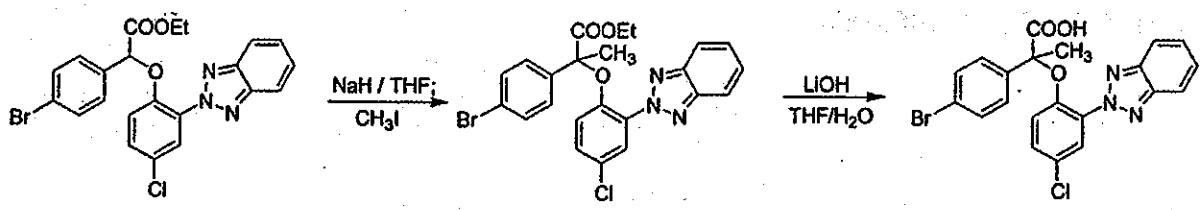


208-S1 **208 (XIa-23)**

[0447] In the same manner as that described in **Example 42** compound **208** was prepared from **208-S1.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.06-7.03 (m, 16H), 1.72 (s, 3H).

[0448] The two enantiomers were separated by HPLC. Column: PIRKLE COVALENT, (R, R) Whelk-O 2 10/100, 25 cm x 21.1 mm. Flow: 30 ml/min, 8% iPrOH/Hexanes-0.1% TFA.

Example 209

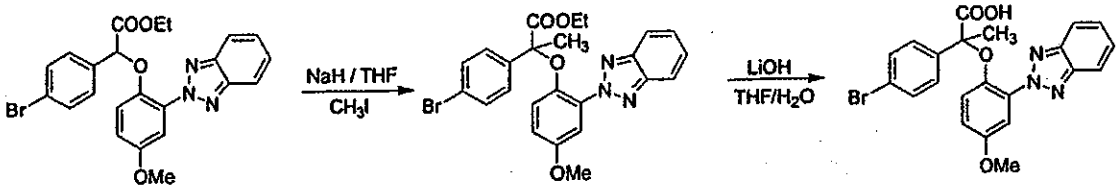


209-S1 **209-S2** **209 (XIa-25)**

[0449] In the same manner as that described in **Example 42** compound **209** was prepared from **209-S1.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.7 (1H, br, COO*H*), 8.05 (2H, q, J = 2.8

Hz), 7.94 (1H, d, J = 2.4 Hz), 7.63 (1H, dd, J = 8.8, 2.8 Hz), 7.52–7.55 (2H, m), 7.40–7.42 (2H, m), 7.32–7.35 (2H, m), 7.04 (1H, d, J = 8.8 Hz), 1.72 (3H, s) ppm.

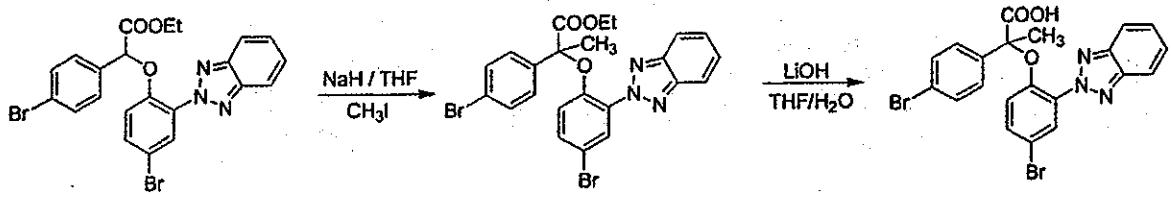
Example 210



210-S1 210-S2 210

[0450] In the same manner as that described in **Example 42** compound **210** was prepared from **210-S1**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.4 (1H, br, COO*H*), 8.01 (2H, q, J = 2.8 Hz), 7.49–7.52 (2H, m), 7.35–7.37 (3H, m), 7.26–7.28 (2H, m), 7.15 (1H, dd, J = 8.8, 3.0 Hz), 7.04 (1H, d, J = 8.8 Hz), 3.79 (3H, s), 1.56 (3H, s) ppm.

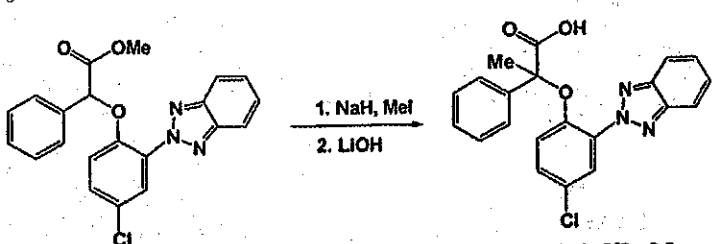
Example 211



211-S1 211-S2 211 (XIa-34)

[0451] In the same manner as that described in **Example 42** compound **211** was prepared from **211-S1**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.7 (1H, br, COO*H*), 8.03–8.06 (3H, m), 7.75 (1H, dd, J = 9.2, 2.8 Hz), 7.52–7.55 (2H, m), 7.40–7.42 (2H, m), 7.32–7.35 (2H, m), 6.98 (1H, d, J = 9.2 Hz), 1.72 (3H, s) ppm.

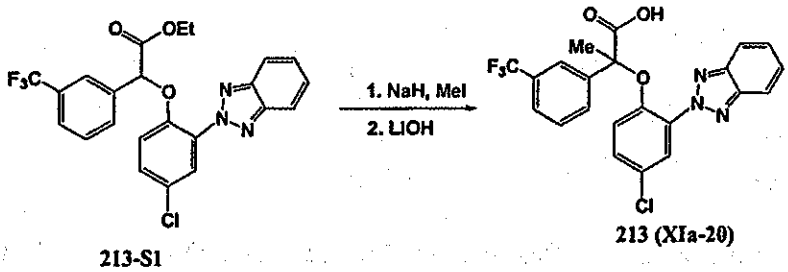
Example 212



212-S1 212 (XIa-26)

[0452] In the same manner as that described in **Example 42** compound **212** was prepared from **212-S1.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.0 (m, 2H), 7.81 (m,1H), 7.54 (m,3H), 7.34 (m,2H), 7.15 (d, *J*=9.2 Hz,1H), 7.08 (m,3H), 1.62 (s,3H).

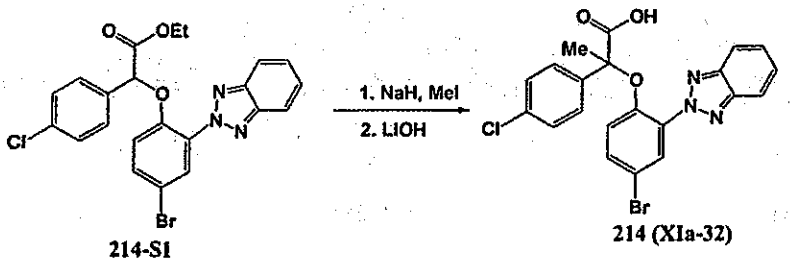
Example 213



213-S1 213 (XIa-20)

[0453] In the same manner as that described in **Example 42** compound **213** was prepared from **213-S1.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.0 (m, 2H), 7.95 (m,1H), 7.69-7.61 (m, 5H), 7.53 (m, 3H), 1.82 (s, 3H).

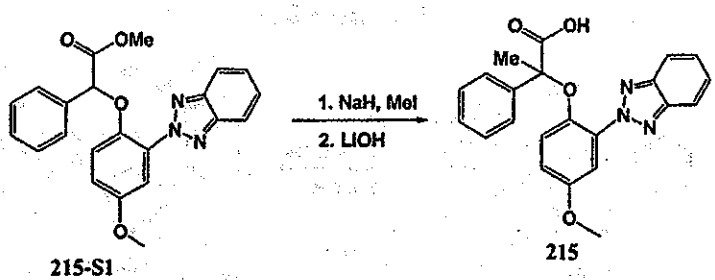
Example 214



214-S1 214 (XIa-32)

[0454] In the same manner as that described in **Example 42** compound **214** was prepared from **214-S1.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.06 (m,2H), 7.76 (dd, *J*=2.8 and 9.2 Hz,1H), 7.54 (m, 2H), 7.41 (m, 2H), 7.26 (m, 2H), 6.99 (d, *J*=9.2Hz,1H), 1.72 (s, 3H),

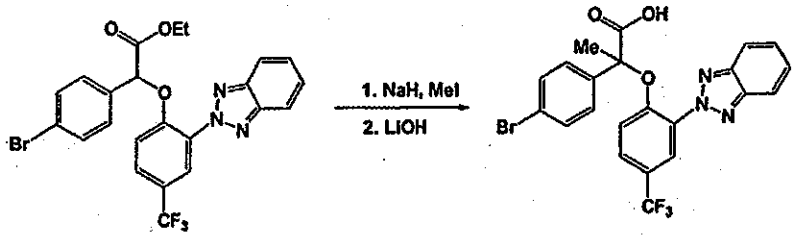
Example 215



215-S1 215

[0455] In the same manner as that described in **Example 42** compound **215** was prepared from **215-S1.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.02 (m, 2H), 7.51 (m,1H), 7.32 (d, *J*=2.8 Hz, 1H), 7.28 (m, 2H), 7.14 (m, 4H), 7.04 (d, *J*=8.8 Hz,1H), 7.38 (s, 3H), 1.57 (s, 3H).

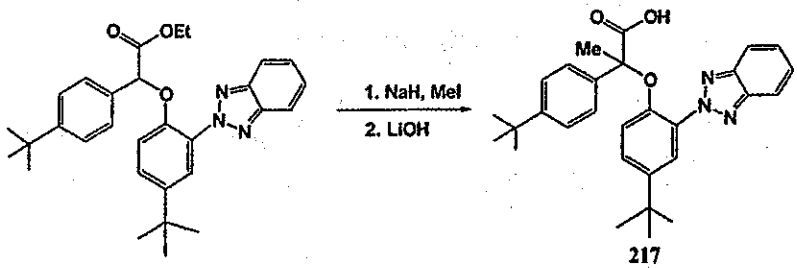
Example 216



216-S1 **216 (XIa-52)**

[0456] In the same manner as that described in **Example 42** compound **216** was prepared from **216-S1.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.21 (m,1H), 8.09 (m, 2H), 7.95 (m,1H), 7.56 (m, 2H), 7.45(m, 4H), 7.19 (d, *J*=9.2 Hz,1H), 1.82 (s, 3H).

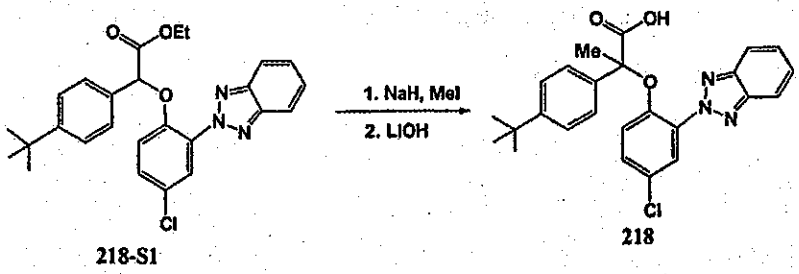
Example 217



217-S1 **217**

[0457] In the same manner as that described in **Example 42** compound **217** was prepared from **217-S1.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.05 (m, 2H), 7.68 (d, *J*=2.8 Hz,1H), 7.15 (dd, *J*=2.8 and 8.8 Hz,1H), 7.52 (m, 2H), 7.22 (m, 2H), 7.17 (m, 2H), 6.97 (d, *J*=8.8 Hz,1H), 1.68 (s, 3H), 1.30 (s, 9H), 1.19 (s, 9H).

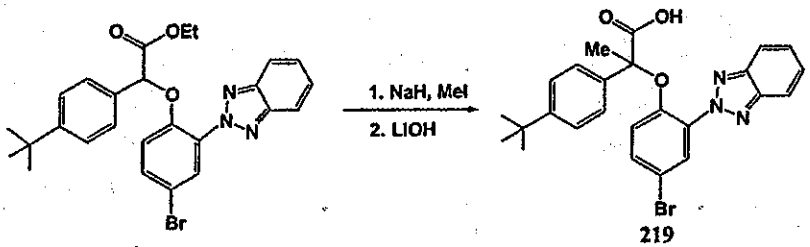
Example 218



218-S1 **218**

[0458] In the same manner as that described in **Example 42** compound **218** was prepared from **218-S1**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.05 (m, 2H), 7.72 (d, *J*=2.4 Hz,1H), 7.54 (m, 2H), 7.48 (dd, *J*=2.4 and 8.8 Hz,1H), 7.28 (m, 2H), 7.21 (d, *J*=8.8 Hz,1H), 7.03 (m, 2H), 1.60 (s,3 H), 1.21 (s, 9H).

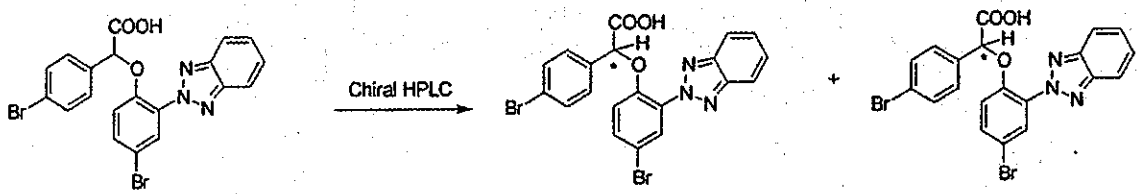
Example 219



219-S1 219

[0459] In the same manner as that described in **Example 42** compound **219** was prepared from **219-S1**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.02 (m, 2H), 7.83 (d, *J*=2.8 Hz,1H), 7.67 (dd, *J*=2.4 and 9.2Hz,1H), 7.53 (m, 2H), 7.18 (m, 2H), 7.04 (m, 3H), 1.58 (s, 3H), 1.12 (s, 9H).

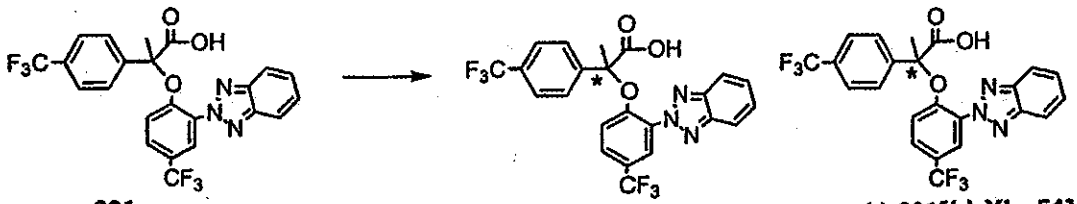
Example 220



220 (+)-220 [(+)-XI-34] (-)-220 [(-)-XI-34]

[0460] The two enantiomers of **220** were isolated by chiral HPLC using a 25 cm × 21.1 mm Regis Technologies (R,R) WHELK-O 2 10/100 column at ambient temperature. The column was eluted with (15/85/0.1) *i*PrOH/hexanes/TFA at a flow of 30 mL/min. Detection was at 220 nm. Chiral HPLC analysis of enantiomer was carried out at λ = 220 nm by injecting 10 μL of an approximately a 0.5 mg/mL solution of the sample dissolved in mobile phase onto a 25 cm × 4.6 mm Regis Technologies (R,R) Whelk-O 1 5 μm column with a 1.5 mL/min flow of (15/85/0.1) *i*PrOH/hexanes/TFA.

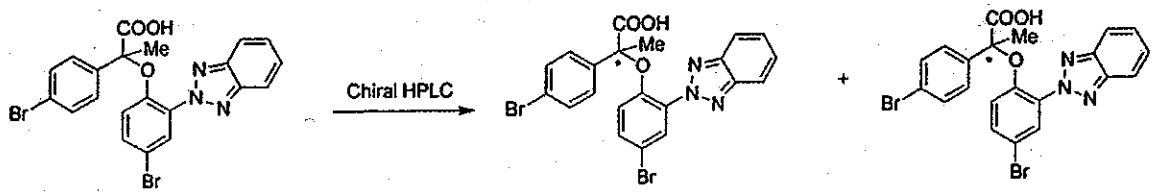
Example 221



221 (+)-221[(+)-XIa-51] (-)-221[(-)-XIa-51]

[0461] In the same manner as that described in **Example 220** compounds **(+)-221 and (-)-221** were prepared from **221.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.18-7.25 (m, 11H), 1.72 (s, 3H).

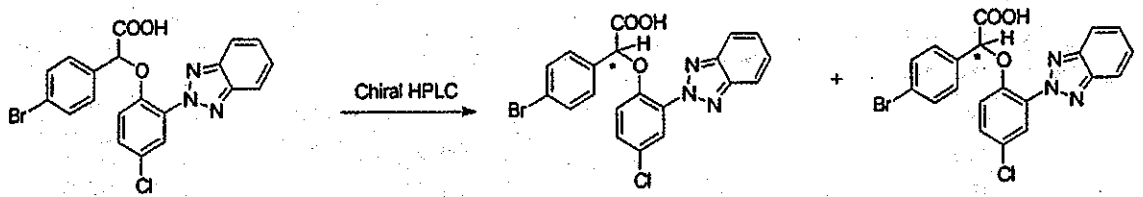
Example 222



222 (+)-222 [(+)-XIa-34] (-)-222 [(-)-XIa-34]

[0462] The two enantiomers were isolated by chiral HPLC using a 25 cm × 21.1 mm Regis Technologies (R,R) WHELK-O 2 10/100 column at ambient temperature. The column was eluted with (15/85/0.1) *i*PrOH/hexanes/TFA at a flow of 30 mL/min. Detection was at 220 nm. One enantiomer eluted at 3.8 to 4.7 min, and the other enantiomer at 5.1 to 6.1 min. Chiral HPLC analysis of enantiomer was carried out at λ = 220 nm by injecting 10 μL of an approximately a 0.5 mg/mL solution of the sample dissolved in mobile phase onto a 25 cm × 4.6 mm Regis Technologies (R,R) Whelk-O 1 5 μm column with a 1.5 mL/min flow of (15/85/0.1) *i*PrOH/hexanes/TFA. Under these conditions, one enantiomer eluted at 4.7 min, the other enantiomer at 6.6 min.

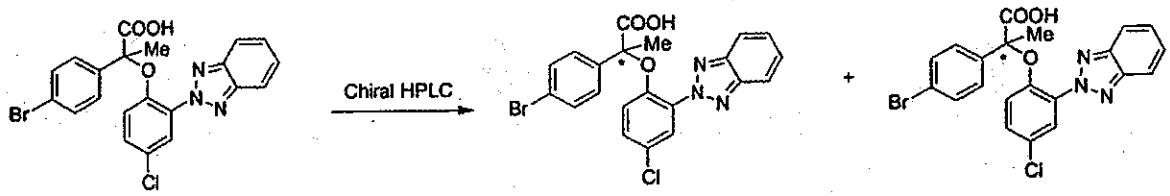
Example 223



223 (+)-223 [(+)-XI-25] (-)-223 [(-)-XI-25]

[0463] The two enantiomers were isolated by chiral HPLC using a 25 cm × 21.1 mm Regis Technologies (R,R) WHELK-O 2 10/100 column at ambient temperature. The column was eluted with (15/85/0.1) *i*PrOH/hexanes/TFA at a flow of 30 mL/min. Detection was at 220 nm. One enantiomer eluted at 3.6 to 4.8 min, and the other enantiomer at 5.5 to 6.9 min. Chiral HPLC analysis of enantiomer was carried out at λ = 220 nm by injecting 10 μL of an approximately a 0.5 mg/mL solution of the sample dissolved in mobile phase onto a 25 cm × 4.6 mm Regis Technologies (R,R) Whelk-O 1 5 μm column with a 1.5 mL/min flow of (15/85/0.1) *i*PrOH/hexanes/TFA. Under these conditions, one enantiomer eluted at 5.0 min, and the other enantiomer at 7.1 min.

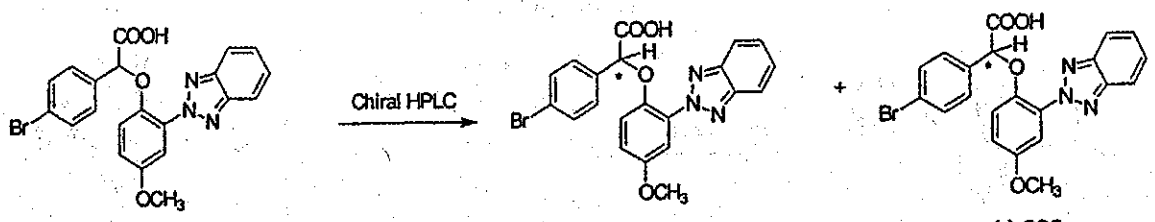
Example 224



224 (+)-224 [(+)-XIa-25] (-)-224 [(-)-XIa-25]

[0464] The two enantiomers were isolated by chiral HPLC using a 25 cm × 21.1 mm Regis Technologies (R,R) WHELK-O 2 10/100 column at ambient temperature. The column was eluted with (15/85/0.1) *i*PrOH/hexanes/TFA at a flow of 30 mL/min. Detection was at 220 nm. One enantiomer eluted at 3.6 to 4.6 min, and the other enantiomer at 5.1 to 6.0 min. Chiral HPLC analysis of enantiomer was carried out at λ = 220 nm by injecting 10 μL of an approximately a 0.5 mg/mL solution of the sample dissolved in mobile phase onto a 25 cm × 4.6 mm Regis Technologies (R,R) Whelk-O 1 5 μm column with a 1.5 mL/min flow of (15/85/0.1) *i*PrOH/hexanes/TFA. Under these conditions, one enantiomer eluted at 4.6 min, and the other enantiomer at 6.4 min.

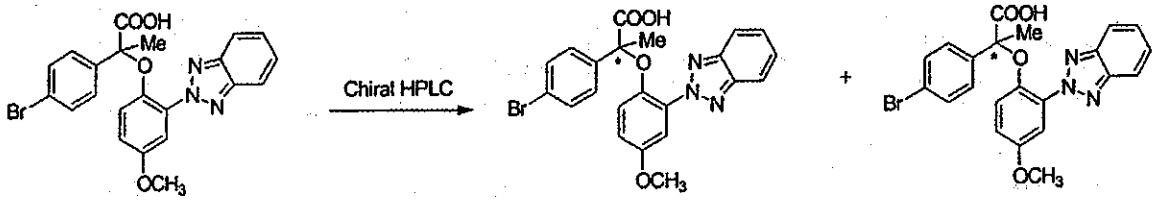
Example 225



225 (+)-225 (-)-225

[0465] The two enantiomers were isolated by chiral HPLC using a 25 cm × 21.1 mm Regis Technologies (R,R) WHELK-O 2 10/100 column at ambient temperature. The column was eluted with (25/75/0.1) *i*PrOH/hexanes/TFA at a flow of 30 mL/min. Detection was at 220 nm. One enantiomer eluted at 4.8 to 6.2 min, and the other enantiomer at 7.3 to 9.2 min. Chiral HPLC analysis of enantiomer was carried out at $\lambda = 220$ nm by injecting 10 μL of an approximately a 0.5 mg/mL solution of the sample dissolved in mobile phase onto a 25 cm × 4.6 mm Regis Technologies (R,R) Whelk-O 1 5 μm column with a 1.5 mL/min flow of (25/75/0.1) *i*PrOH/hexanes/TFA. Under these conditions, one enantiomer eluted at 6.0 min, and the other enantiomer at 9.5 min.

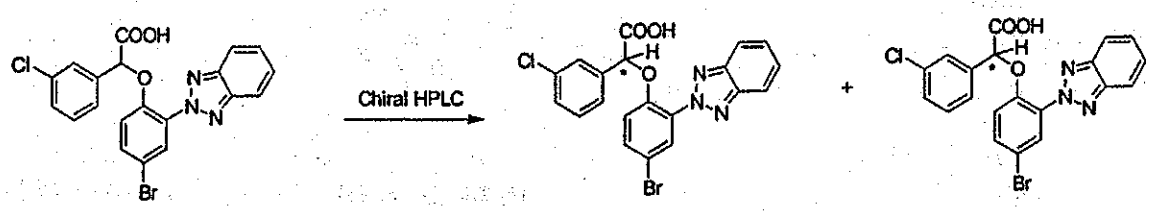
Example 226



226 (+)-226 (-)-226

[0466] The two enantiomers were isolated by chiral HPLC using a 25 cm × 21.1 mm Regis Technologies (R,R) WHELK-O 2 10/100 column at ambient temperature. The column was eluted with (25/75/0.1) *i*PrOH/hexanes/TFA at a flow of 30 mL/min. Detection was at 220 nm. One enantiomer eluted at 4.5 to 5.5 min, and the other enantiomer at 6.6 to 7.3 min. Chiral HPLC analysis of enantiomer was carried out at $\lambda = 220$ nm by injecting 10 μL of an approximately a 0.5 mg/mL solution of the sample dissolved in mobile phase onto a 25 cm × 4.6 mm Regis Technologies (R,R) Whelk-O 1 5 μm column with a 1.5 mL/min flow of (25/75/0.1) *i*PrOH/hexanes/TFA. Under these conditions, one enantiomer eluted at 5.7 min, and the other enantiomer at 8.6 min.

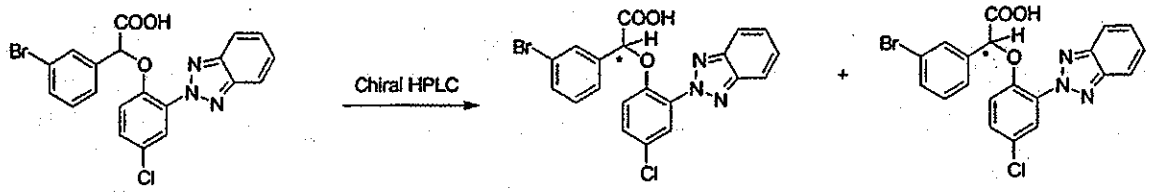
Example 227



227 (+)-227 [(+)-XI-28] (-)-227 [(-)-XI-28]

[0467] The two enantiomers were isolated by chiral HPLC using a 25 cm × 21.1 mm Regis Technologies (R,R) WHELK-O 2 10/100 column at ambient temperature. The column was eluted with (10/90/0.1) *i*PrOH/hexanes/TFA at a flow of 30 mL/min. Detection was at 220 nm. One enantiomer eluted at 4.8 to 5.5 min, and the other enantiomer at 6.1 to 6.9 min. Chiral HPLC analysis of enantiomer was carried out at $\lambda = 220$ nm by injecting 10 μL of an approximately a 0.5 mg/mL solution of the sample dissolved in mobile phase onto a 25 cm × 4.6 mm Regis Technologies (R,R) Whelk-O 1 5 μm column with a 1.5 mL/min flow of (15/85/0.1) *i*PrOH/hexanes/TFA. Under these conditions, one enantiomer eluted at 4.9 min, and the other enantiomer at 6.5 min.

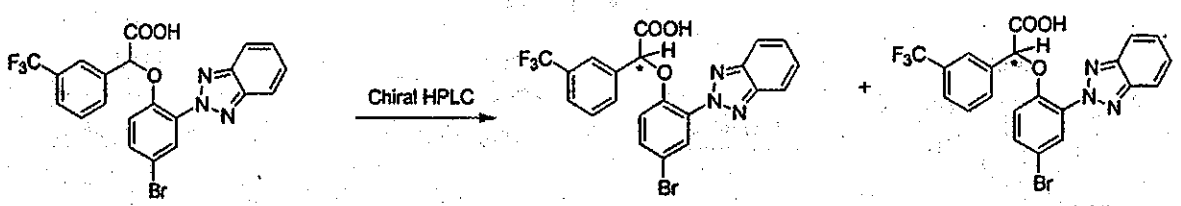
Example 228



228 (+)-228 (-)-228

[0468] The two enantiomers were isolated by chiral HPLC using a 25 cm × 21.1 mm Regis Technologies (R,R) WHELK-O 2 10/100 column at ambient temperature. The column was eluted with (10/90/0.1) *i*PrOH/hexanes/TFA at a flow of 30 mL/min. Detection was at 220 nm. One enantiomer eluted at 4.7 to 5.3 min, and the other enantiomer at 6.2 to 6.9 min. Chiral HPLC analysis of enantiomer was carried out at $\lambda = 220$ nm by injecting 10 μL of an approximately a 0.5 mg/mL solution of the sample dissolved in mobile phase onto a 25 cm × 4.6 mm Regis Technologies (R,R) Whelk-O 1 5 μm column with a 1.5 mL/min flow of (15/85/0.1) *i*PrOH/hexanes/TFA. Under these conditions, one enantiomer eluted at 4.9 min, and the other enantiomer at 6.8 min.

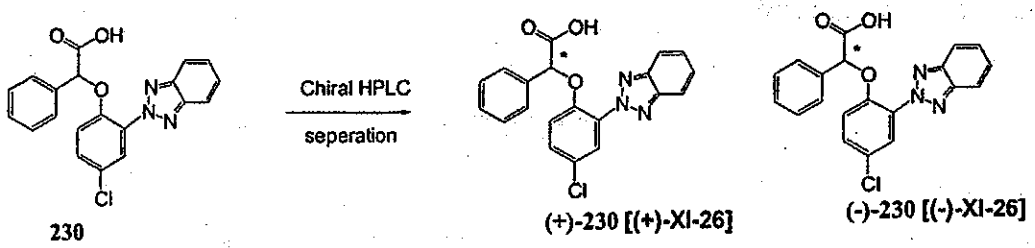
Example 229



229 (+)-229 [(+)-XI-33] (-)-229 [(-)-XI-33]

[0469] The two enantiomers were isolated by chiral HPLC using a 25 cm × 21.1 mm Regis Technologies (R,R) WHELK-O 2 10/100 column at ambient temperature. The column was eluted with (5/95/0.1) *i*PrOH/hexanes/TFA at a flow of 30 mL/min. Detection was at 220 nm. One enantiomer eluted at 6.2 to 7.2 min, and the other enantiomer at 7.6 to 8.6 min. Chiral HPLC analysis of enantiomer was carried out at λ = 220 nm by injecting 10 μL of an approximately a 0.5 mg/mL solution of the sample dissolved in mobile phase onto a 25 cm × 4.6 mm Regis Technologies (R,R) Whelk-O 1 5 μm column with a 1.5 mL/min flow of (15/85/0.1) *i*PrOH/hexanes/TFA. Under these conditions, one enantiomer eluted at 4.1 min, and the other enantiomer at 5.0 min.

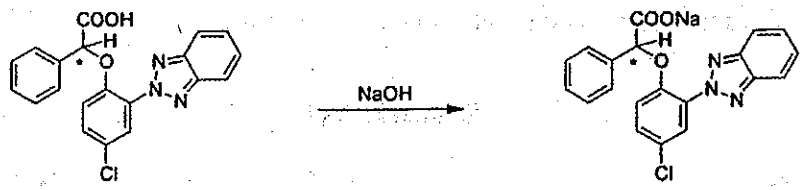
Example 230



230 (+)-230 [(+)-XI-26] (-)-230 [(-)-XI-26]

[0470] The two enantiomers were separated by chiral HPLC using a 25 cm × 21.1 mm Regis Technologies (R,R) WHELK-O 2 10/100 column at ambient temperature. HPLC methods and conditions: 20% iPrOH-80% Hexanes-0.1% TFA, 30 mL/min., λ=220 nm. For (+)-enantiomer: RT 3.92 min. $[\alpha]_d$= +7.9 in acetone. For (–)-enantiomer: RT 5.0 min.

Example 231

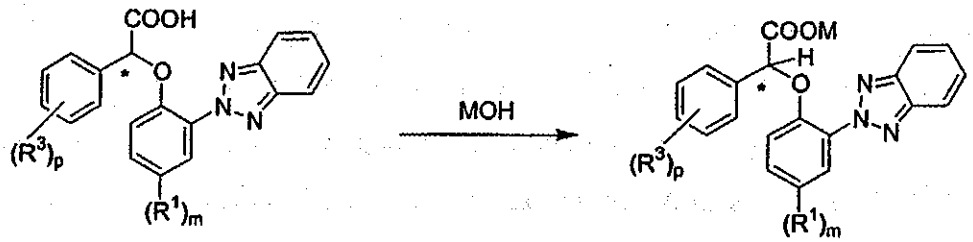


231 231 Na salt

[0471] To a solution of **231** (1.05 g, 2.77 mol, 98% ee) in ca. 10 mL of THF was added 2N aq. NaOH (1.384 mL, 2.77 mmol) with stirring, and then diluted with heptane (50 mL), After removal of solvents *in vacuo,* the residue was dissolved in 5 mL of THF and then diluted with 30 mL of heptanes. After stripping off THF and most of heptanes *in vacuo*, the resulting white precipitate was filtered and rinsed with heptane twice to afford desired sodium salt (1.06 g, 96%, 98+% ee) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.02 (2H, dd, *J* =

6.8, 3.2 Hz), 7.79 (1H, d, J = 2.8 Hz), 7.58 (1H, dd, J = 9.2, 2.8 Hz), 7.51 (2H, dd, J = 6.8, 3.2 Hz), 7.34–7.37 (2H, m), 7.17 (1H, d, J = 9.2 Hz), 7.11 (3H, m), 5.26 (1H, s) ppm.

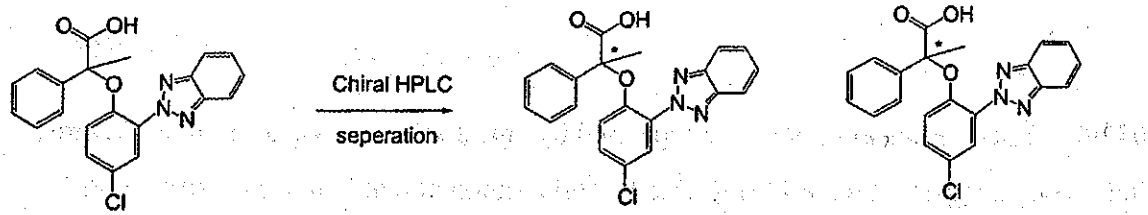
Example 232



232 **232 M salt**

[0472] In the same manner as that described in **Example 231** different salts of compound **232 M salts** were prepared.

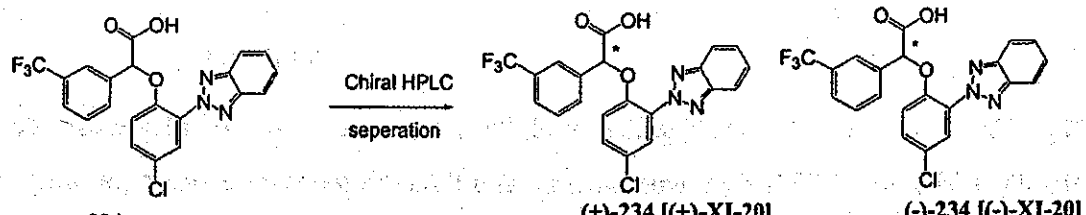
Example 233



233 **(+)-233 [(+)-XIa-26]** **(-)-233 [(-)-XIa-26]**

[0473] The two enantiomers were separated by chiral HPLC using a 25 cm × 21.1 mm Regis Technologies (R,R) WHELK-O 2 10/100 column at ambient temperature. HPLC methods and conditions: 15% iPrOH-85% Hexanes-0.1% TFA, 30 mL/min., λ=220 nm. One enantiomer: RT 4.0 min. The other enantiomer: RT 4.8 min.

Example 234

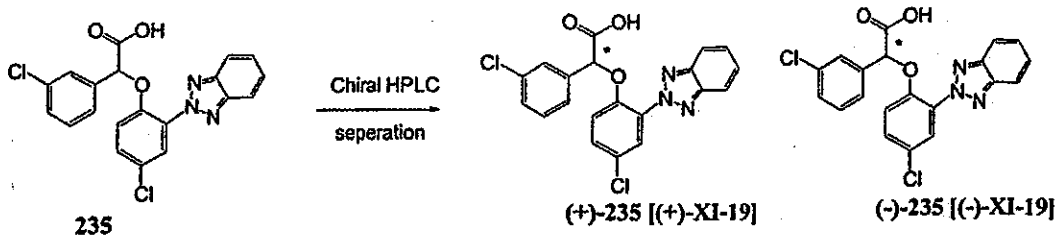


234 **(+)-234 [(+)-XI-20]** **(-)-234 [(-)-XI-20]**

[0474] The two enantiomers were separated by chiral HPLC using a 25 cm × 21.1 mm Regis Technologies (R,R) WHELK-O 2 10/100 column at ambient temperature. HPLC

methods and conditions: 8% iPrOH-92% Hexanes-0.1% TFA, 30 mL/min., λ=220 nm. One enantiomer: RT 5.8 min. The other enantiomer : RT 6.4 min.

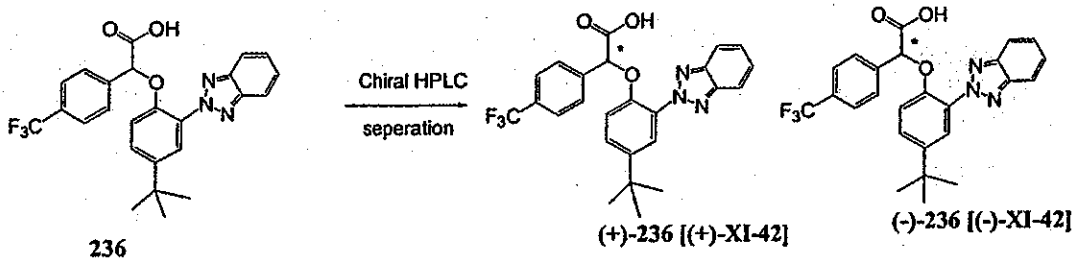
Example 235



235 (+)-235 [(+)-XI-19] (-)-235 [(-)-XI-19]

[0475] The two enantiomers were separated by chiral HPLC using a 25 cm × 21.1 mm Regis Technologies (R,R) WHELK-O 2 10/100 column at ambient temperature. HPLC methods and conditions: 15% iPrOH-85% Hexanes-0.1% TFA, 30 mL/min., λ=220 nm. One enantiomer: RT 4.5 min. The other enantiomer: RT 5.3 min.

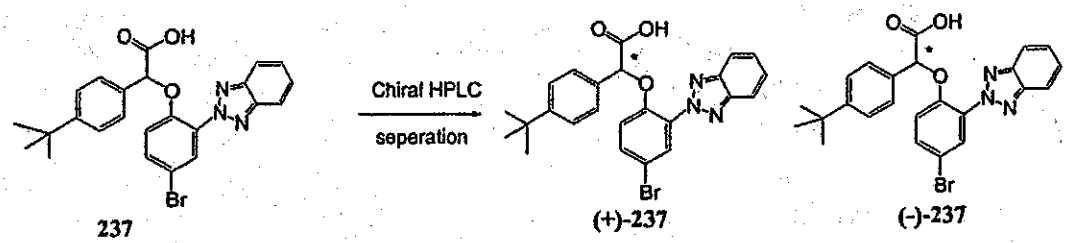
Example 236



236 (+)-236 [(+)-XI-42] (-)-236 [(-)-XI-42]

[0476] The two enantiomers were separated by chiral HPLC using a 25 cm × 21.1 mm Regis Technologies (R,R) WHELK-O 2 10/100 column at ambient temperature. HPLC methods and conditions: 15% iPrOH-85% Hexanes-0.1% TFA, 30 mL/min., λ=220 nm. One enantiomer: RT 4.0 min. The other enantiomer: RT 5.0 min.

Example 237

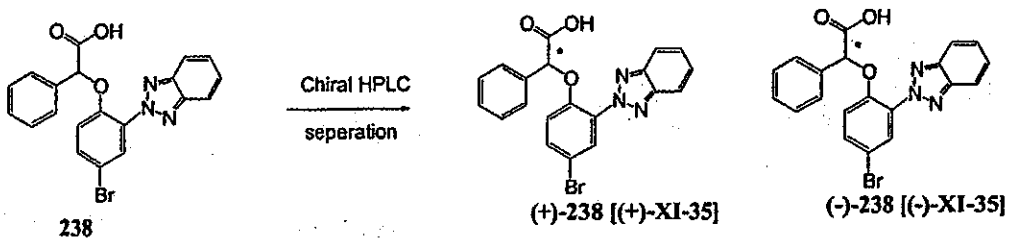


237 (+)-237 (-)-237

[0477] The two enantiomers were separated by chiral HPLC using a 25 cm × 21.1 mm Regis Technologies (R,R) WHELK-O 2 10/100 column at ambient temperature. HPLC

methods and conditions: 25% iPrOH-75% Hexanes-0.1% TFA, 30 mL/min., λ=220 nm. One enantiomer: RT 3.5 min. The other enantiomer : RT 4.2 min.

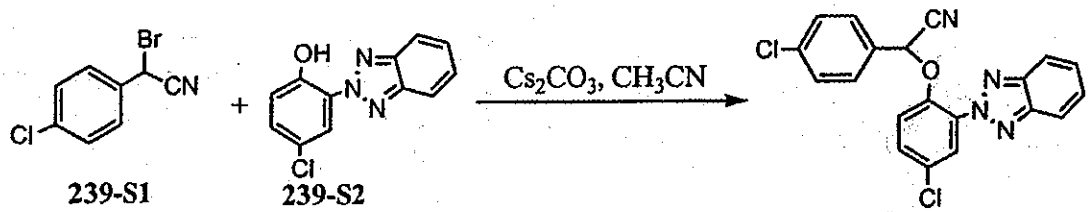
Example 238



238 (+)-238 [(+)-XI-35] (-)-238 [(-)-XI-35]

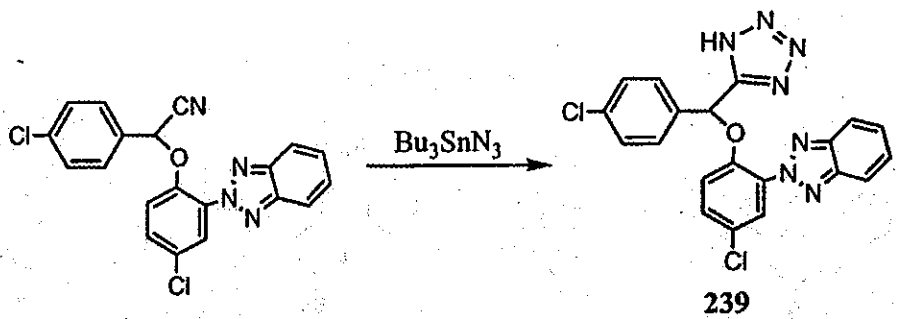
[0478] The two enantiomers were separated by chiral HPLC using a 25 cm × 21.1 mm Regis Technologies (R,R) WHELK-O 2 10/100 column at ambient temperature. HPLC methods and conditions: 20% iPrOH-80% Hexanes-0.1% TFA, 30 mL/min., λ=220 nm. One enantiomer: RT 4.2 min. The other enantiomer: RT 5.3 min.

Example 239



239-S1 239-S2 239-S3

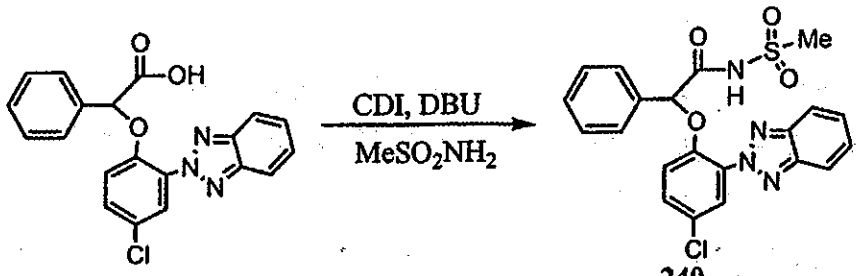
[0479] A mixture of **239-S1** (6.6 g), **239-S2** (5.06 g) with Cs_2CO_3 (12 g) in CH_3CN was stirred for 12 hours. The salt was filtered off. The filtrate was concentrated, and purified with chromatography (hexane/ethyl acetate 10:1) gave **239-S3** (3.2 g) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 8.01 -7.26 (m, 11H), 6.11(s, 1H), 3.49 (d, 2H).



239-S3 239

[0480] A solution of **239-S3** (2.0 g), Bu_3SnN_3 (1.7 mL) in THF was refluxed overnight, then concentrated, and treated with 1N HCl. The solution was extracted with ethyl acetate, dried and concentrated. Purification with chromatography (ethyl acetate) gave **239** (0.64 g) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 -7.15 (m, 11H), 6.86(s, 1H).

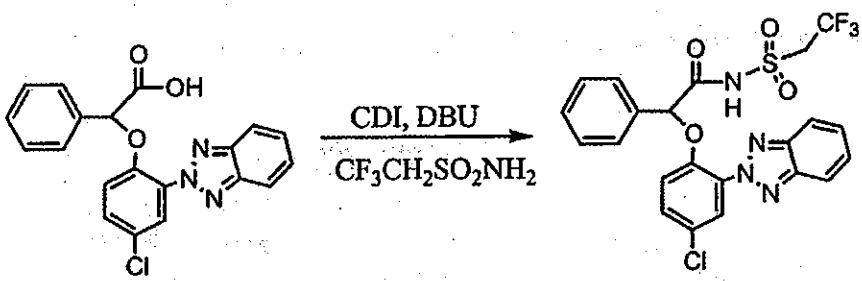
Example 240



240-S1 **240**

[0481] A solution of **240-S1** (1.1 g), CDI (0.56 g) in THF was stirred for half an hour at 60 °C. After cooling down, sulfonyl amide (0.33 g) and DBU (0.65 mL) was added. The reaction mixture was stirred overnight, concentrated, diluted with ethyl acetate, washed with HCl (0.5 N), and dried. The solvent was removed, and the residue was purified by chromatography (ethyl acetate) to give **240** (1.16 g) as a white solid.^{1}H NMR (400 MHz, $CDCl_3$): δ 11.92 (s, 1H), 8.23 – 6.88 (m, 12H), 5.85 (s, 1H), 3.32 (s, 3H).

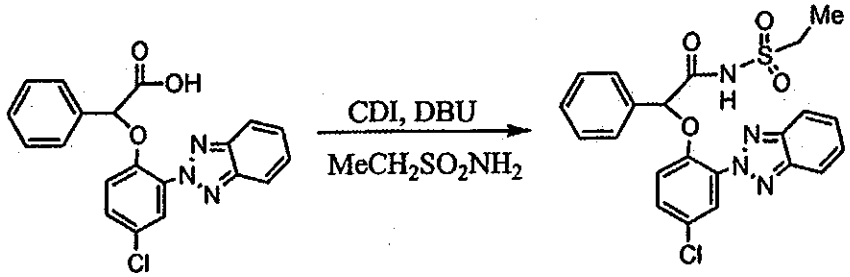
Example 241



241-S1 **241**

[0482] In the same manner as that described in **Example 240** compound **241** was prepared from **241-S1**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.57 (s, 1H), 8.24 – 6.93 (m, 12H), 5.89 (s, 1H), 4.22 (m, 2H).

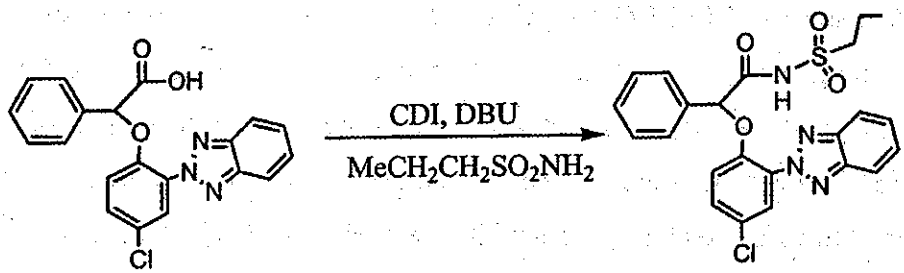
Example 242



242-S1 **242**

[0483] In the same manner as that described in **Example 240** compound **242** was prepared from **242-S1.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.77 (s, 1H), 8.23 – 6.90 (m, 12H), 5.89 (s, 1H), 3.46 (m, 2H), 1.32 (t, 3H).

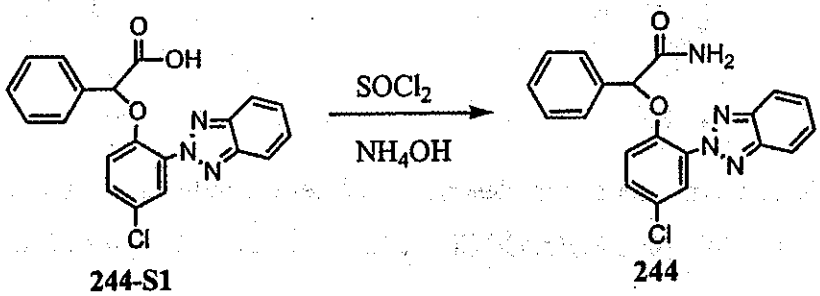
Example 243



243-S1 **243**

[0484] In the same manner as that described in **Example 240** compound **243** was prepared from **243-S1.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.77 (s, 1H), 8.23 – 6.90 (m, 12H), 5.85 (s, 1H), 3.42 (m, 2H), 1.80 (m, 2H), 0.98 (t, 3H).

Example 244

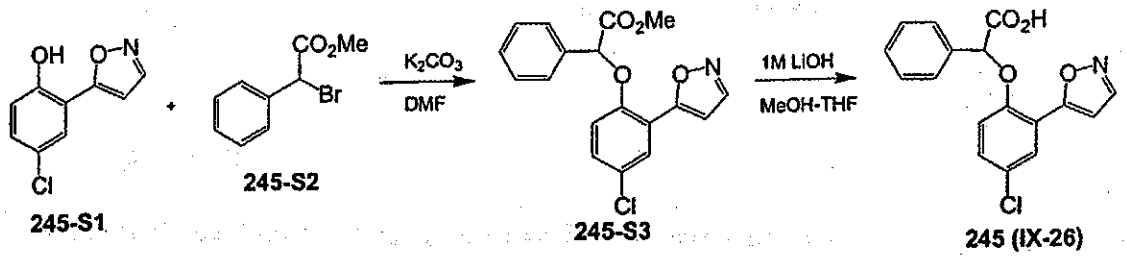


244-S1 **244**

[0485] A mixture of acid **244-S1** (3.0 g), $SOCl_2$ in toluene was refluxed for two hours, and concentrated. The residue was diluted with THF, and the solution was drop to ammonium solution (28 N, 60 mL) at 0 °C. The white precipitate was collected by filtration as the desired

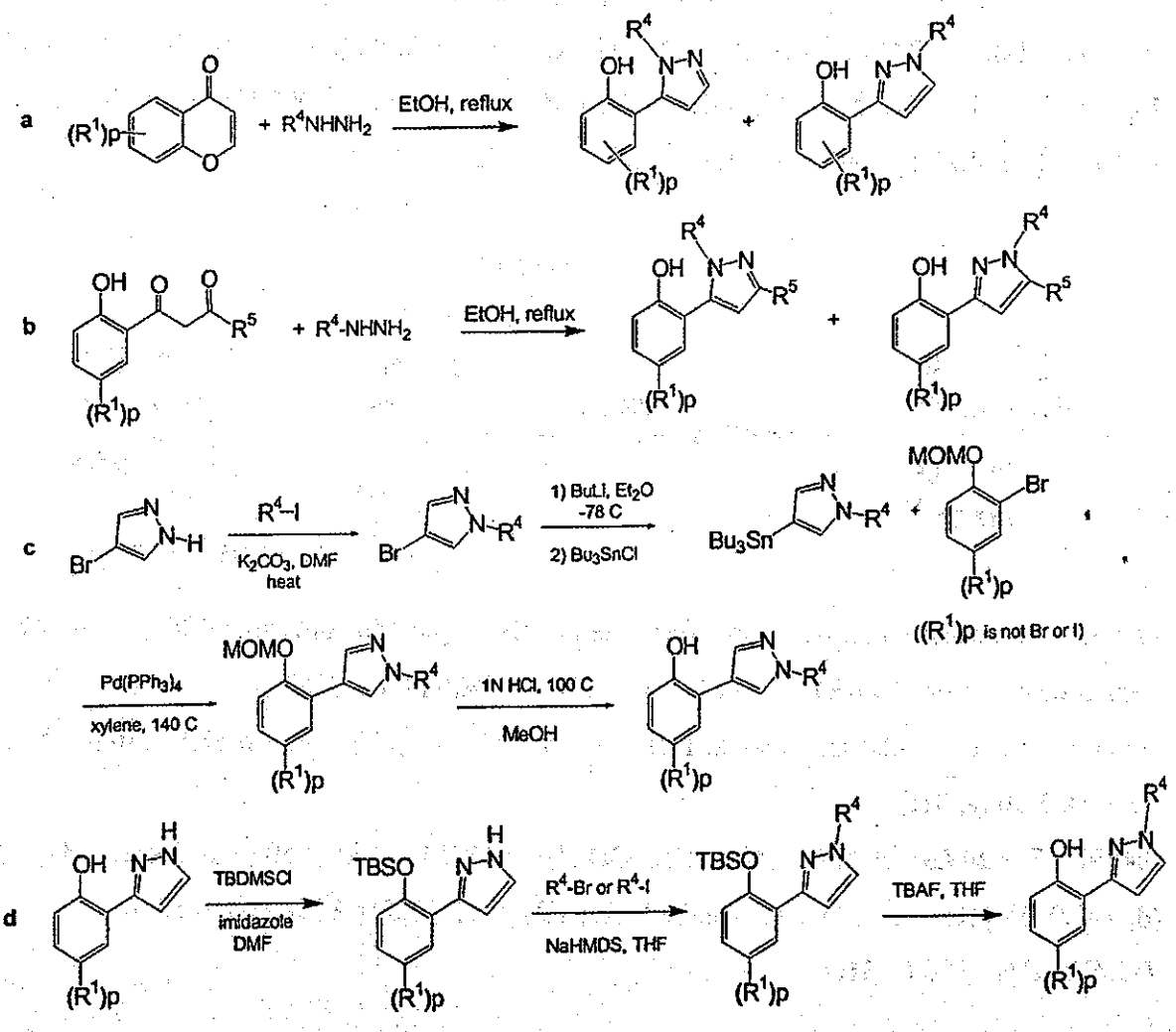
product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (br, 1H), 8.05 – 6.96 (m, 12H), 5.71 (s, 1H), 5.63 (br, 1H).

Example 245

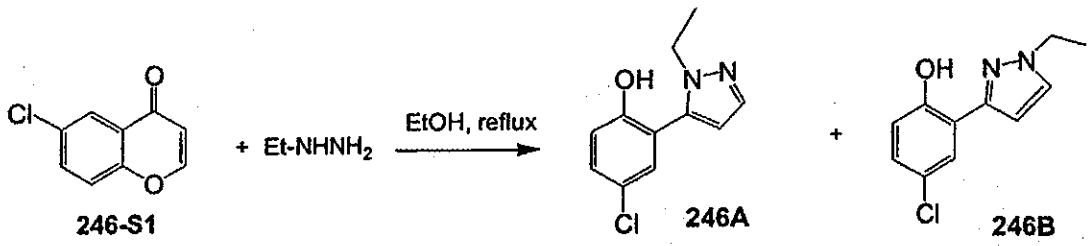


[0486] In the same manner as that described in **Example 28** compound **245** was prepared from **245-S1** and **245-S2**. ^{1}HNMR (400 MHz, DMSO-d_6) δ 8.74 (d, *J*=1.6 Hz, 1H), 7.86 (d, *J*=2.4Hz, 1H), 7.52-7.35 (m, 7H), 7.14 (d, *J*=8.8Hz,1H), 6.21 (s, 1H).

Scheme 8. Synthesis of 2-Pyrazole phenols



Example1 246

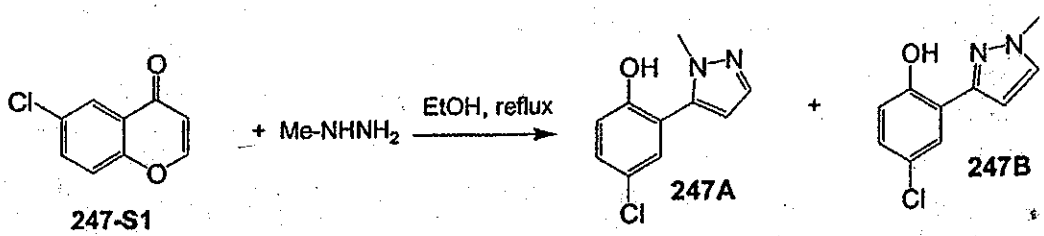


246-S1 246A 246B

(246A : 246b = 1 : 4)

[0487] A solution of 6-chlorochromone **246-S1** (5.57 g, 29.91 mmol), ethylhydrazine oxalate (4.58 g, 29.91 mmol) and Et_3N (10.40 mL, 74.77 mmol) in EtOH (60 mL) was refluxed overnight. The mixture was concentrated, dissolved in EtOAc, washed with 1 N HCl and brine, dried and concentrated. Purification *via* flash column (hexane/EtOAc 10:1 to 3:1) gave **246A** (1.3 g) and **246B** (5.13 g) as white solids, respectively. For **246A**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, *J*=1.6 Hz,1H), 7.31 (dd, *J*=2.4 and 8.8 Hz, 1H), 7.18 (d, *J*=2.8 Hz,1H), 6.97 (m,1H), 6.33 (d, *J*=2.0 Hz, 1H), 6.27 (s, 1H), 4.07 (q, *J*=7.2 Hz, 2H), 1.36 (t, *J*=7.2 Hz,3H). For **246B**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.90 (s,1H), 7.51 (d, *J*=2.4Hz,1H), 7.45 (d, *J*=2.0 Hz,1H), 7.15 (dd, *J*=2.4 and 8.8 Hz, 1H), 6.95 (d, *J*=8.8 Hz,1H), 6.58 (d, *J*=2.8Hz,1H), 4.22 (q, *J*=7.2 Hz,2H), 1.54 (t, *J*=7.2 Hz,3H).

Example 247



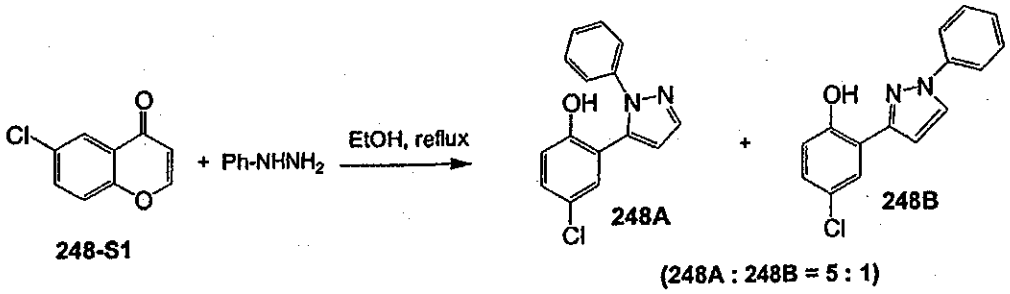
247-S1 247A 247B

(247A : 247B = 1 : 6)

[0488] In the same manner as that described in **Example 246** compounds **247A** and **247B** were prepared from **247-S1.** For **247A**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, *J*=1.6 Hz,1H), 7.31 (dd, J=2.4 and 8.8 Hz, 1H), 7.19 (d, *J*=2.8 Hz,1H), 6.95 (m,1H), 6.36 (d, *J*=2.0 Hz,1H), 3.80 (s, 3H).

[0489] For **247B**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.80 (s,1H), 7.50 (d, *J*=2.4Hz,1H), 7.41 (d, *J*=2.0 Hz,1H), 7.13 (dd, *J*=2.4 and 8.8 Hz, 1H), 6.95 (d, *J*=8.8 Hz,1H), 6.58 (d, *J*=2.4Hz,1H), 3.98 (s, 3H).

Example 248

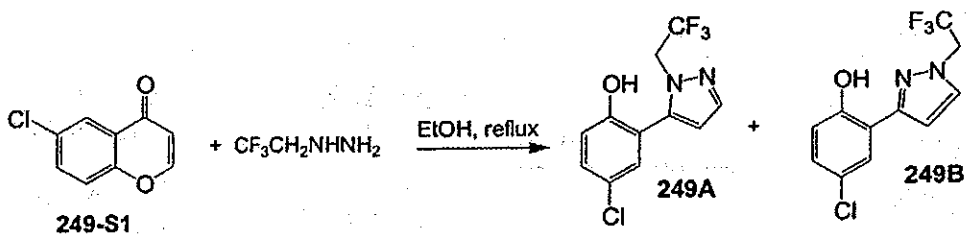


248-S1

(248A : 248B = 5 : 1)

[0490] In the same manner as that described in **Example 246** compounds **246A** and **246B** were prepared from **248-S1.** For **248A**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J*=2.0 Hz,1H), 7.35-7.26 (m, 5H), 7.20 (dd, *J*=2.4 and 8.8 Hz, 1H), 7.02 (d, *J*=2.8 Hz,1H), 6.80 (d, *J*=8.8 Hz,1H), 6.55 (d, *J*=2.0Hz,1H), 5.90 (s,1H). For **248B**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.90 (s,1H), 8.01 (d, *J*=2.4Hz,1H), 7.70 (m, 2H), 7.58 (d, *J*=2.4 Hz,1H), 7.54 (m, 2H), 7.38 (m,1H), 7.21 (dd, *J*=2.8 and 8.8 Hz, 1H), 7.02 (d, *J*=8.4 Hz,1H), 6.85 (d, *J*=2.8Hz,1H).

Example 249

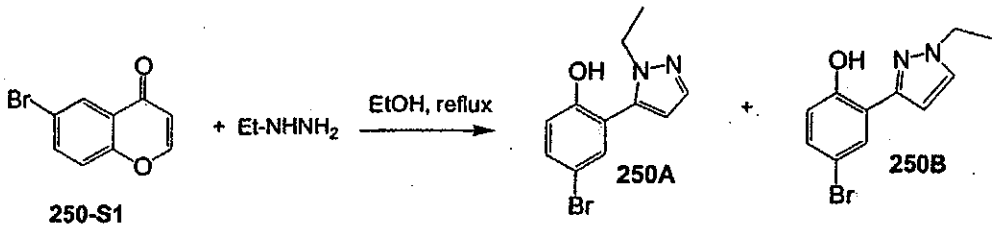


249-S1

(249A : 249B= 13 : 1)

[0491] In the same manner as that described in **Example 246** compounds **249A** and **249B** were prepared from **249-S1.** For **249A**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J*=1.6 Hz,1H), 7.33 (dd, *J*=2.8 and 8.8 Hz, 1H), 7.21 (d, *J*=2.8 Hz,1H), 6.95 (d, *J*=8.4 Hz,1H), 6.43 (d, *J*=2.0Hz,1H), 5.64 (s,1H), 4.70 (m, 2H). For **249B**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.38 (s,1H), 7.59 (d, *J*=2.8Hz, 1H), 7.52 (d, *J*=2.8 Hz,1H), 7.17 (dd, *J*=2.8 and 8.8 Hz, 1H), 6.98 (d, *J*=8.4 Hz,1H), 6.73 (d, *J*=2.4Hz,1H), 4.78 (m, 2H).

Example 250

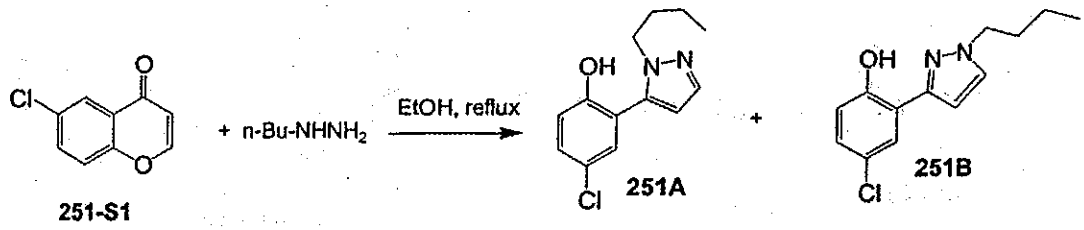


250-S1

(250A : 250B = 1 : 4)

[0492] In the same manner as that described in **Example 246** compounds **250A** and **250B** were prepared from **250-S1.** For **250A**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J*=1.6 Hz,1H), 7.46 (dd, *J*=2.8 and 8.8 Hz, 1H), 7.37 (d, *J*=2.8 Hz,1H), 6.94 (d, *J*=8.8 Hz,1H), 6.32 (d, *J*=1.6 Hz,1H), 4.09 (q, *J*=7.2 Hz, 2H), 1.39 (t, *J*=7.2 Hz,3H). For **250B**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.95 (s,1H), 7.65 (d, *J*=2.0Hz,1H), 7.44 (d, *J*=2.4 Hz,1H), 7.27 (dd, *J*=2.8 and 9.2 Hz, 1H), 6.91 (d, *J*=9.2 Hz,1H), 6.58 (d, *J*=2.4Hz,1H), 4.22 (q, *J*=7.2 Hz,2H), 1.54 (t, *J*=7.2 Hz,3H).

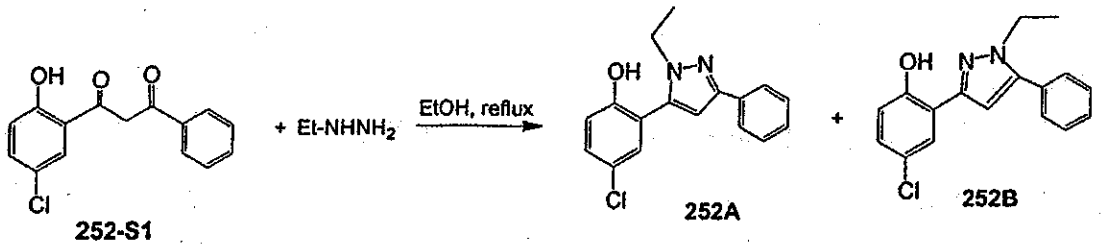
Example 251



251-S1

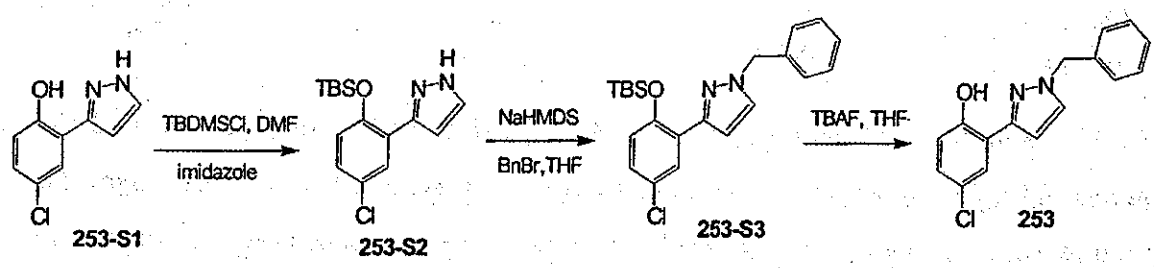
[0493] In the same manner as that described in **Example 246** compounds **251A** and **251B** were prepared from **251-S1.** For **251A**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J*=2.0 Hz,1H), 7.32 (dd, *J*=2.8 and 8.8 Hz, 1H), 7.17 (d, *J*=2.8 Hz,1H), 6.98 (d, *J*=8.8Hz,1H), 6.33 (d, *J*=2.0 Hz,1H), 4.05 (m, 2H), 1.75 (m, 2H), 1.22 (m, 2H), 0.85 (t, *J*=7.2 Hz,3H). For **251B**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.92 (s,1H), 7.51 (d, *J*=2.8Hz,1H), 7.42 (d, *J*=2.8 Hz,1H), 7.13 (dd, *J*=2.8 and 8.8 Hz, 1H), 6.95 (d, *J*=8.8 Hz,1H), 6.58 (d, *J*=2.8Hz,1H), 4.17 (m, 2H), 1.88 (m, 2H), 1.39 (m, 2H), 0.98 (t, *J*=7.2 Hz, 3H).

Example 252



[0494] A solution of **252-S1** (0.76 g, 2.76 mmol), ethylhydrazine oxalate (0.414 g, 2.76 mmol) and Et_3N (0.96 mL, 6.9 mmol) in EtOH (10 mL) was refluxed overnight. The mixture was concentrated, dissolved in EtOAc, washed with 1 N HCl and brine, dried and concentrated. Purification *via* flash column (hexane/EtOAc 10:1) gave **252A** (0.28 g) and **252B** (0.23 g) as white solids, respectively. For **252A**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (m, 2H), 7.35-7.22 (m, 5H), 7.02 (d, J=2.8 Hz,1H), 6.57 (s,1H), 5.90 (s,1H), 4.10 (q, J=7.2 Hz,2H), 1.41 (t, J=7.2 Hz,3H). For **252B**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.05 (s,1H), 7.55 (m,6H), 7.20 (d, J=2.8 Hz,1H), 6.97 (d, J=2.8Hz, 1H), 6.64 (s,1H), 4.22 (q, J=7.2 Hz,2H), 1.50 (t, J=7.2 Hz,3H).

Example. 253



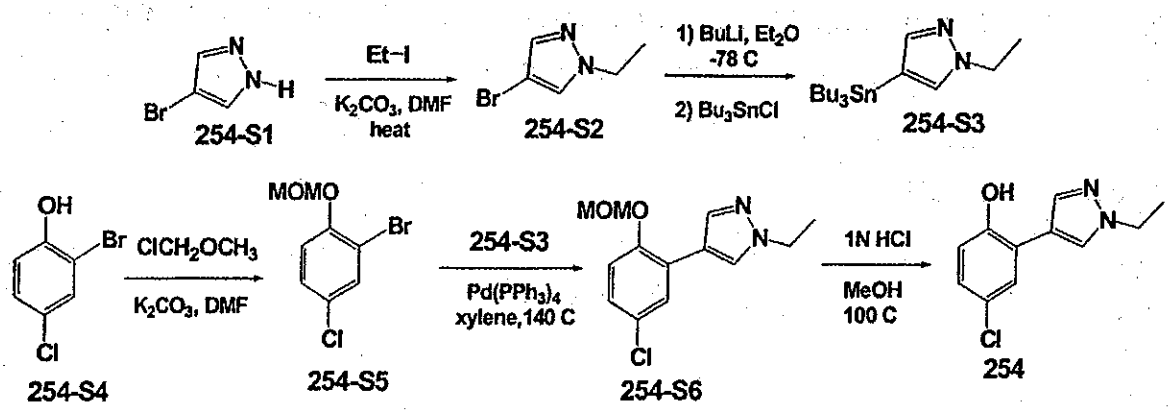
[0495] A mixture of **253-S1**(5.116 g, 26.29 mmol), TBSCl (4.36 g, 28.92 mmol) and imidazole (2.68 g, 39.44 mmol) in DMF (100 mL) was stirred at room temperature overnight. The mixture was diluted with EtOAc, washed with brine, dried and concentrated. Purification *via* flash column (hexane/EtOAc 10:1) gave **253-S2** as colorless oil (7.8 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (m,2H), 7.15 (m,1H), 6.88 (d, J=9.2Hz,1H), 6.60 (m,1H), 0.98 (s,9H), 0.22 (s,3H), 0.21(s,3H).

[0496] To a solution of **253-S2** (0.6 g, 1.94 mmol) in THF (10 mL) was added NaHMDS (1.0 M in THF, 2.14 mL, 2.14 mmol) at 0 °C. After 5 min. at 0 °C, BnBr (242 μL, 2.04 mmol) was added. The mixture was warmed to room temperature, and kept at this temperature for 2 h. The reaction was quenched with brine, extracted with EtOAc, washed with brine, dried and concentrated. Purification *via* flash column (hexane/EtOAc 30:1) gave

253-S3 as colorless oil (0.4 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (m,1H), 7.36-7.22 (m,6H), 7.14 (m,1H), 6.81 (m,1H), 6.71 (m,1H), 5.37 (s,2H), 0.92 (s,9H), 0.13 (s,3H), 0.01(s,3H).

[0497] To a solution of **253-S3** (0.4 g, 1.0 mmol) in THF (5 mL) was added TBAF (1.0 M in THF, 1.5 mL, 1.5 mmol) at 0 °C. The mixture was warmed to room temperature, and kept at this temperature for 0.5 h. The reaction was quenched with brine, extracted with EtOAc, washed with brine, dried and concentrated to give **253** as a white solid (0.28 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (m,1H), 7.44 (m,1H), 7.40-7.33 (m,3H), 7.24 (m,2H), 7.15 (m,1H), 6.93 (m,1H), 6.62 (m,1H), 5.34 (s,2H).

Example 254



[0498] A mixture of 4-bromopyrazole **254-S1** (0.47 g, 3.20 mmol), iodoethane (2.5 g, 16.0 mmol) and K_2CO_3 (0.88 g,6.4 mmol) in DMF (5 mL) was heated at 80 °C overnight. The mixture was diluted with ether, washed with brine, dried and concentrated. Purification *via* flash column (hexane/EtOAc 10:1) gave **254-S2** as colorless oil (0.45 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (s,1H), 7.41 (s,1H), 4.18 (q,2H), 1.45 (t,3H).

[0499] To a solution of **254-S2** (0.45 g, 2.57mmol) in Et_2O (5 mL) was added n-BuLi (2.5 M in hexanes, 1.13 ml, 2.83 mmol) at - 78°C. After 20 min at - 78□C, Bu_3SnCl (852 µL, 2.83 mmol) was added drop wise. The reaction mixture was slowly warmed to room temperature over 5 h, then, quenched with saturated aqueous NH_4Cl solution, extracted with Et_2O. The organic layer was washed with brine, dried and concentrated to give **254-S3** as a crude product, which was used for next reaction without further purification.

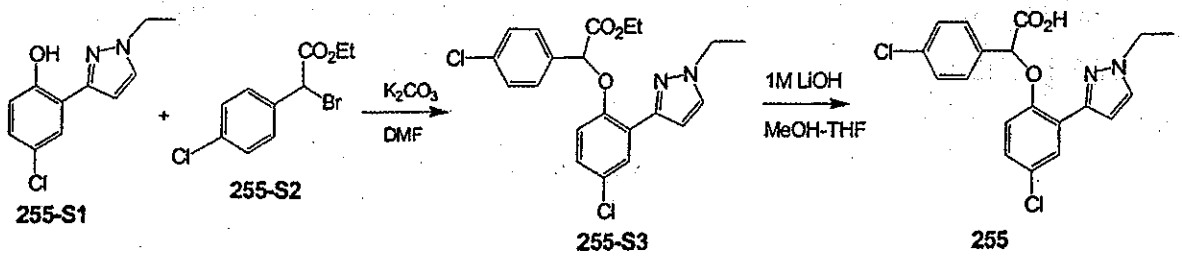
[0500] A mixture of 2-bromo-4-Cl-phenol **254-S4** (8.57 g, 41.31 mmol), MOMCl (3.99 g, 49.57 mmol) and K_2CO_3 (11.4 g, 82.62 mmol) in DMF (60 mL) was stirred overnight. The mixture was quenched with saturated aqueous $NaHCO_3$ solution, extracted with ethyl ether.

The organic layer was washed with brine, dried and concentrated. Purification *via* flash column (hexane/EtOAc 20:1) gave **254-S5** as colorless oil (10.0 g).

[0501] A mixture of **254-S3** (ca.1.8 mmol), **254-S5** (407 mg, 1.62 mmol) and $Pd(PPh_3)_4$ (104 mg, 0.09 mmol) in xylene (4 mL) was heated at 140 °C under nitrogen for 3 h. The mixture was concentrated, and the residue was purified by flash column (hexane/EtOAc 8:1) to give **254-S6** as colorless oil (249 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (s,1H), 7.84 (s,1H), 7.47 (m,1H), 7.11 (m,2H), 5.24 (s,2H), 4.22 (q,2H), 3.50 (s,3H), 1.53 (t,3H).

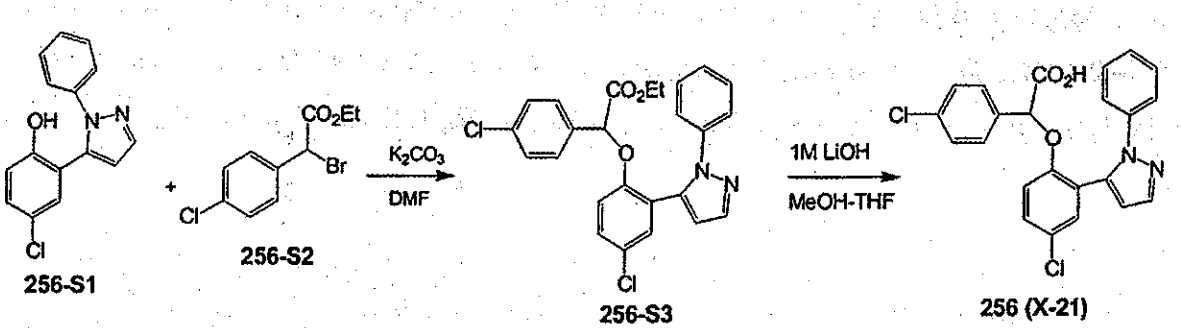
[0502] A mixture of **254-S6**(249 mg), 1N HCl aqueous solution (5 mL), THF (5 mL) and MeOH (3 mL) was heated at 100 °C for 3 h. The mixture was concentrated, extracted with ether, washed with brine, dried, and concentrated to give **254** as a pale yellow solid (208 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (s,1H), 7.80 (s,1H), 7.36 (d, 1H), 7.18 (dd, 1H), 6.84 (d,1H),4.23 (q,2H), 1.56 (t,3H).

Example 255



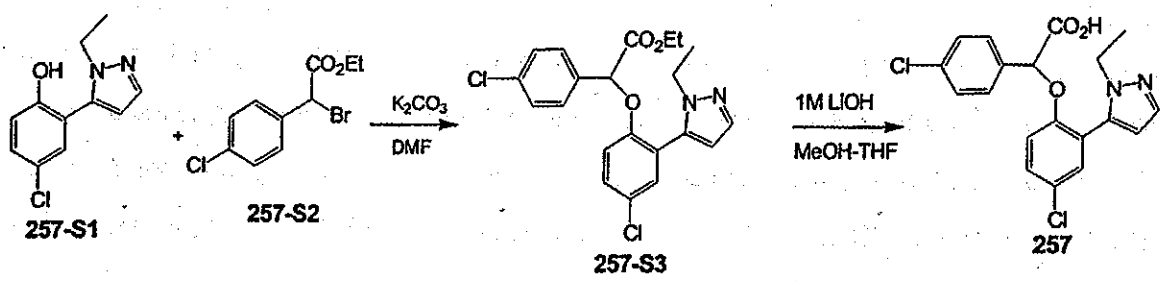
[0503] In the same manner as that described in **Example 28** compound **255** was prepared from **255-S1** and **255-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.91 (d, J=2.8 Hz, 1H), 7.78 (d, J=2.0 Hz, 1H), 7.54 (m, 2H), 7.47 (m,2H), 7.21 (dd, J=2.4 and 8.8 Hz, 1H), 7.09 (d,J=2.0Hz,1H), 6.98 (d, J=8.8Hz,1H), 6.09 (s,1H), 4.18 (m,2H), 1.42 (t, J=7.6Hz, 3H).

Example 256



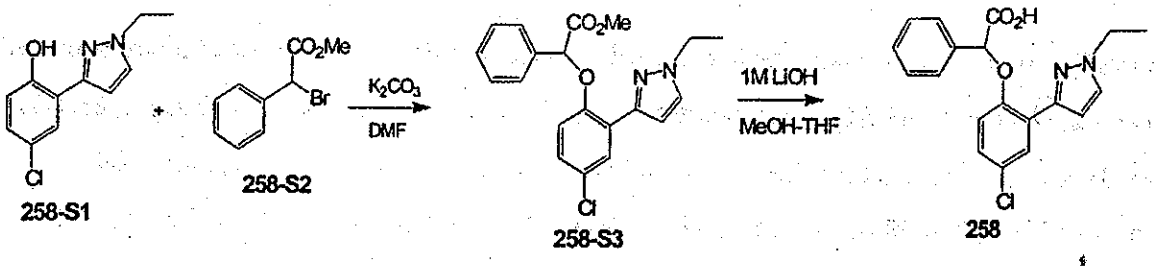
[0504] In the same manner as that described in **Example 28** compound **256** was prepared from **256-S1** and **256-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.77 (d, J=1.6Hz,1H), 7.38 (m,3H), 7.26 (m,3H), 7.21 (d, J=2.4 Hz, 1H), 7.16 (m, 5H), 6.95 (d, J=9.6 Hz, 1H), 6.62 (d, J=2.0 Hz, 1H), 5.75 (s, 1H).

Example 257



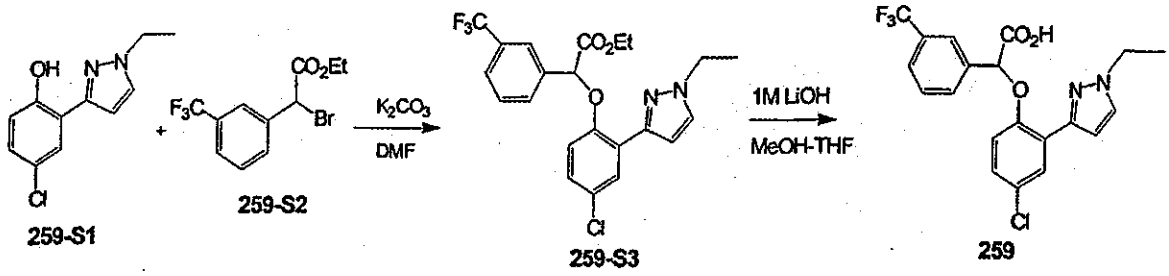
[0505] In the same manner as that described in **Example 28** compound **257** was prepared from **257-S1** and **257-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.48 (m,2H), 7.43 (m,2H), 7.33 (m,3H), 7.08 (d, J=9.6 Hz, 1H), 6.27 (d, J=2.0 Hz, 1H), 5.96 (s, 1H), 4.02 (m,2H), 1.15 (t, J=7.2Hz,3H).

Example 258



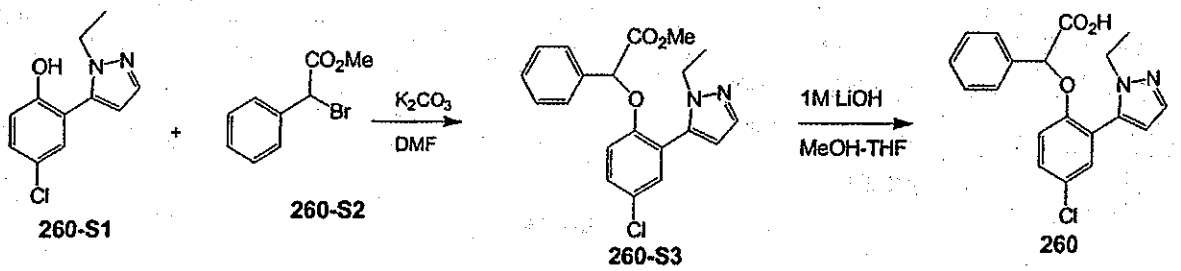
[0506] In the same manner as that described in **Example 28** compound **258** was prepared from **258-S1** and **258-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.91 (d, J=2.8Hz,1H), 7.78 (d,J=2.4 Hz,1H), 7.53 (m,2H), 7.36 (m,3H), 7.22 (dd, J=2.8 and 9.2 Hz,1H), 7.11 (d, J=2.4 Hz, 1H), 7.0 (d, J=9.2 Hz, 1H), 6.04(s, 1H), 4.18 (m,2H), 1.40 (t, J=7.6 Hz, 3H).

Example 259



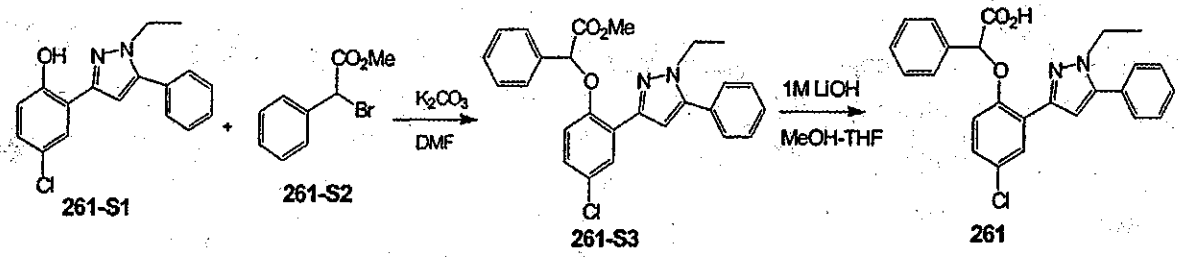
[0507] In the same manner as that described in **Example 28** compound **259** was prepared from **259-S1** and **259-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.89 (m,2H), 7.80 (m,2H), 7.74 (m,1H), 7.65 (m,1H), 7.25 (dd, J=2.8 and 9.2 Hz,1H), 7.05 (m, 2H), 6.25 (s, 1H), 4.19 (m,2H), 1.40 (t, J=7.6 Hz, 3H).

Example 260



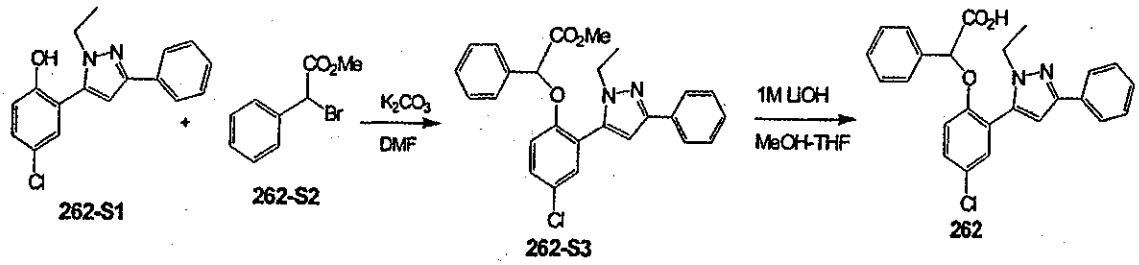
[0508] In the same manner as that described in **Example 28** compound **260** was prepared from **260-S1** and **260-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.48 (m,2H), 7.33 (m,7H), 7.09 (d,J=9.6 Hz,1H), 6.27 (d, J=2.0 Hz, 1H), 5.91(s, 1H), 4.05 (m,2H), 1.16 (t, J=7.6 Hz, 3H).

Example 261



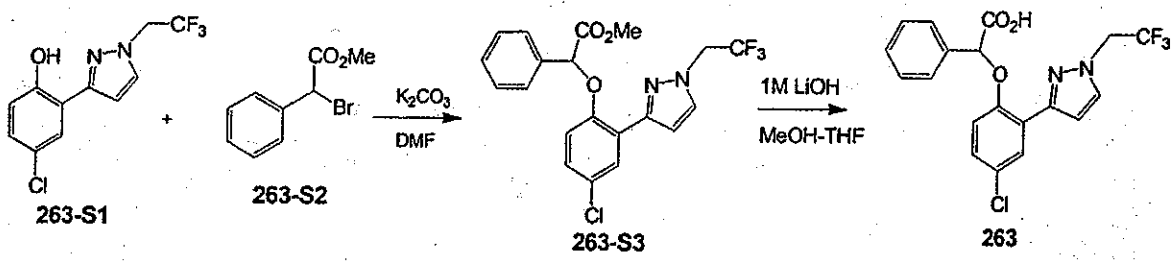
[0509] In the same manner as that described in **Example 28** compound **261** was prepared from **261-S1** and **261-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.91 (d,J=2.8 Hz, 1H), 7.59-7.20 (m,12H), 6.98 (d,J=9.2Hz,1H), 5.96 (s,1H), 4.20 (m,2H), 1.32 (t, J=7.2 Hz, 3H).

Example 262



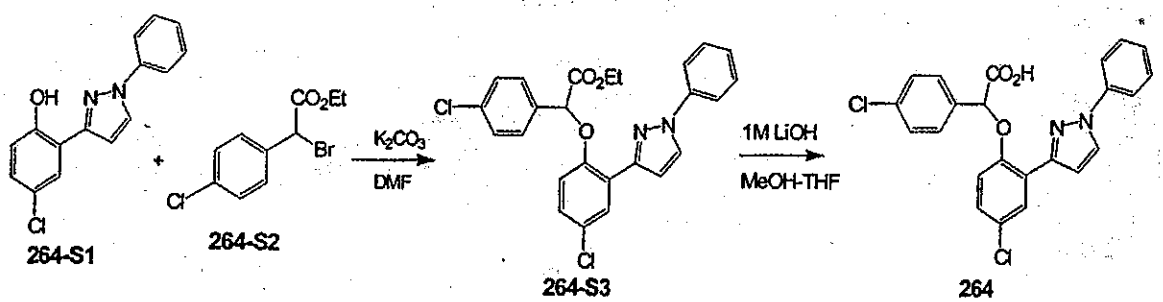
[0510] In the same manner as that described in **Example 28** compound **262** was prepared from **262-S1** and **262-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.83 (m, 2H), 7.54 (dd, J=2.8 and 8.8 Hz,1H), 7.44-7.29 (m,9H), 7.13 (d, J=9.2 Hz, 1H), 6.77(s, 1H), 5.96 (s,1H), 4.08 (m,2H), 1.24 (t, J=7.2 Hz, 3H).

Example 263



[0511] In the same manner as that described in **Example 28** compound **263** was prepared from **263-S1** and **263-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.69 (m,2H), 7.56 (m,2H), 7.42 (m,3H), 7.18 (m,1H), 6.84 (d, J=2.8 Hz, 1H), 6.76 (d, J=8.8 Hz, 1H), 5.68 (s, 1H), 4.86 (m,2H).

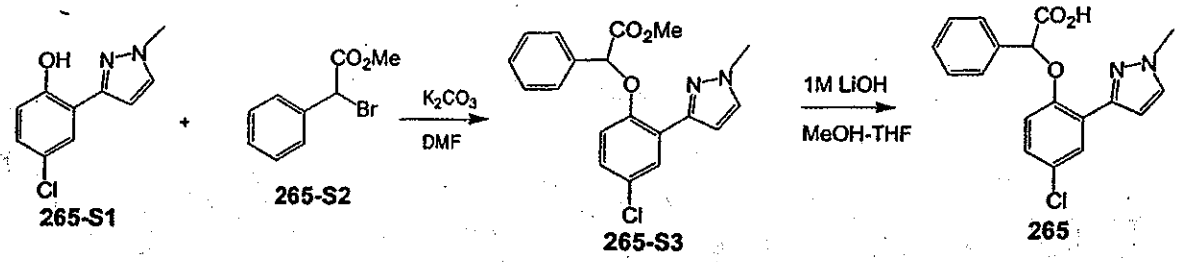
Example 264



[0512] In the same manner as that described in **Example 28** compound **264** was prepared from **264-S1** and **264-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.58 (d, J=2.8Hz,1H), 8.06

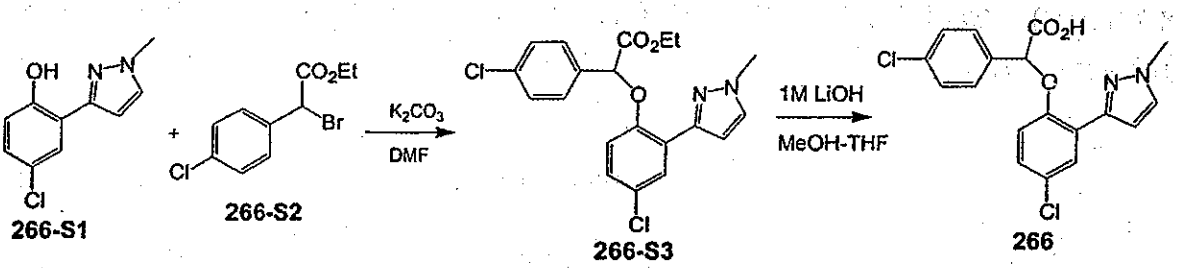
(d, J=3.2 Hz,1H), 7.92 (m,2H), 7.56-7.45 (m,5H), 7.40 (d, J=2.8Hz,1H), 7.33 (m,2H), 7.06 (d, J=8.8 Hz, 1H), 6.14 (s, 1H).

Example 265



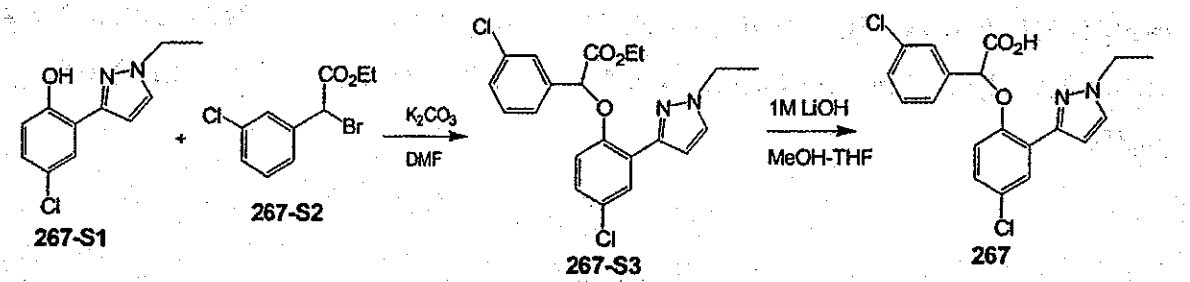
[0513] In the same manner as that described in **Example 28** compound **265** was prepared from **265-S1** and **265-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.92 (d, J=2.8Hz,1H), 7.76 (d,J=2.0 Hz,1H), 7.54 (m,2H), 7.42-7.33 (m,3H), 7.23 (dd, J=2.8 and 9.2 Hz,1H), 7.15 (d, J=2.0 Hz, 1H), 7.01 (d, J=9.2 Hz, 1H), 6.07(s, 1H), 3.90 (s,2H).

Example 266



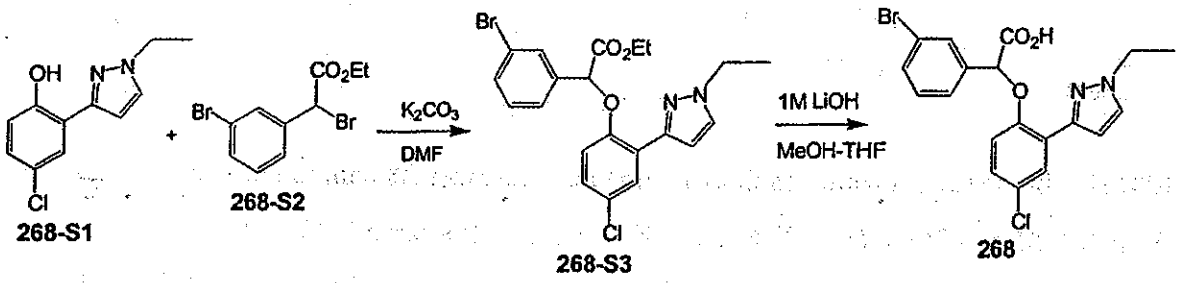
[0514] In the same manner as that described in **Example 28** compound **266** was prepared from **266-S1** and **266-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.89 (d, J=2.4Hz,1H), 7.74 (d,J=2.0 Hz,1H), 7.53 (m,2H), 7.45 (m,2H), 7.22 (dd, J=2.8 and 8.8 Hz,1H), 7.11 (d, J=2.0 Hz, 1H), 7.0 (d, J=9.2 Hz, 1H), 6.09(s, 1H), 3.95 (s,3H).

Example 267



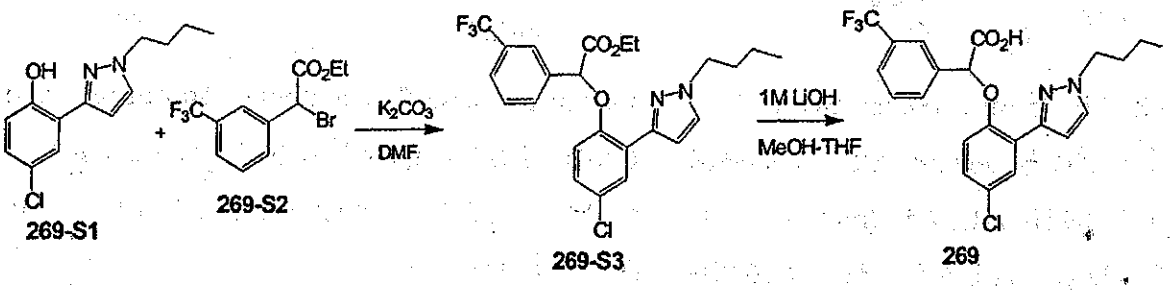
[0515] In the same manner as that described in **Example 28** compound **267** was prepared from **267-S1** and **267-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.90 (d, J=2.8Hz,1H), 7.81 (d,J=2.0 Hz,1H), 7.58 (m,1H), 7.46-7.41 (m,3H), 7.24 (dd, J=2.8 and 9.2 Hz,1H), 7.10 (d, J=2.4 Hz, 1H), 6.99 (d, J=8.8 Hz, 1H), 6.11(s, 1H), 4.21 (m,2H), 1.40 (t, J=7.6 Hz, 3H).

Example 268



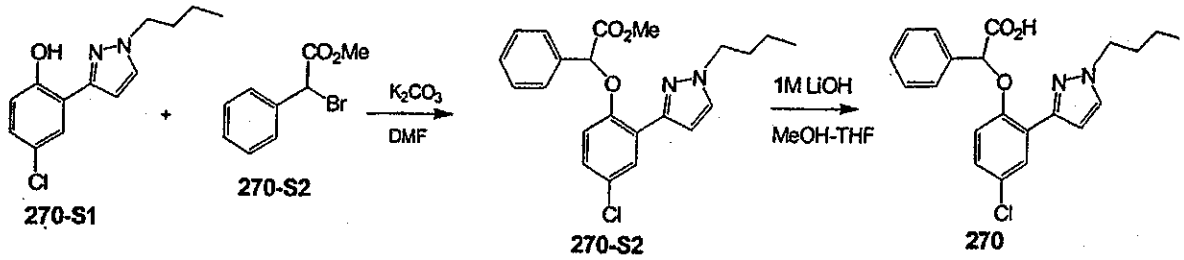
[0516] In the same manner as that described in **Example 28** compound **268** was prepared from **268-S1** and **268-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.90 (d, J=2.8Hz,1H), 7.81 (d,J=2.0 Hz,1H), 7.73 (m,1H), 7.56 (m,1H), 7.49 (m,1H), 7.37 (m,1H), 7.24 (dd, J=2.4 and 8.8 Hz,1H), 7.09 (d, J=2.4 Hz, 1H), 7.02 (d, J=8.8 Hz, 1H), 6.10(s, 1H), 4.19 (m,2H), 1.40 (t, J=7.6 Hz, 3H).

Example 269



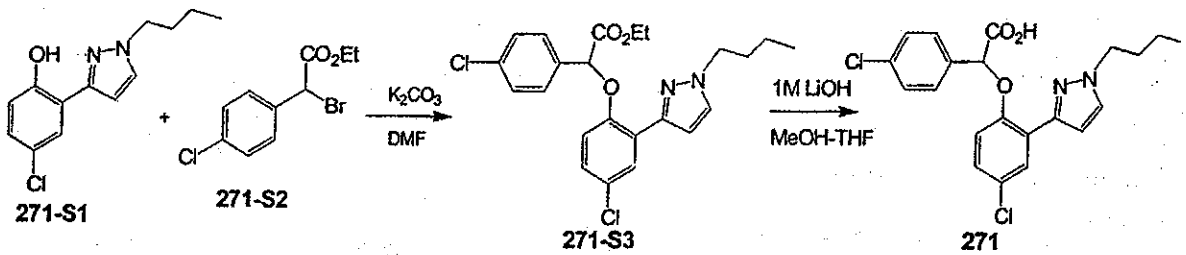
[0517] In the same manner as that described in **Example 28** compound **269** was prepared from **269-S1** and **269-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.90 (s,1H), 7.88 (d, J=2.8Hz,1H), 7.82 (s,1H), 7.79 (d,J=2.4 Hz,1H), 7.74 (m,1H), 7.65 (m,1H), 7.24 (dd, J=2.8 and 8.8 Hz,1H), 7.05 (m,2H), 6.25 (s, 1H), 4.14 (m,2H), 1.78 (m,2H), 1.25 (m,2H), 0.88 (m,3H).

Example 270



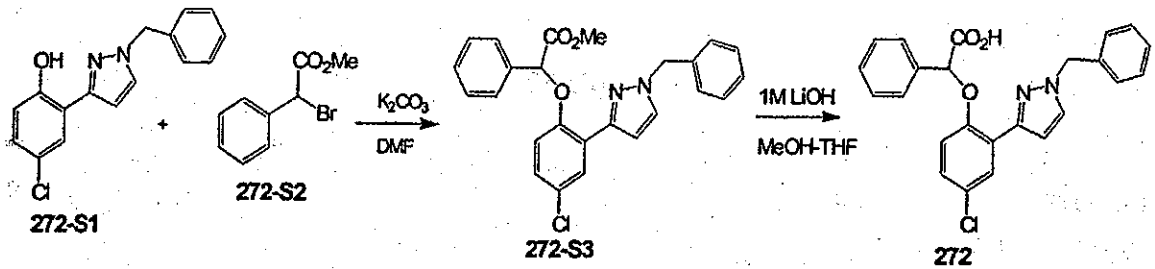
[0518] In the same manner as that described in **Example 28** compound **270** was prepared from **270-S1** and **270-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.91 (d, J=2.8Hz,1H), 7.78 (d,J=2.4 Hz,1H), 7.53 (m,2H), 7.39 (m,3H), 7.22 (dd, J=2.4 and 8.8 Hz,1H), 7.12 (d, J=2.4 Hz, 1H), 7.01 (d, J=8.8 Hz, 1H), 6.03 (s, 1H), 4.15 (t, J=7.2Hz,2H), 1.78 (m,2H), 1.27 (m,2H), 0.90 (t, J=7.6 Hz, 3H).

Example 271



[0519] In the same manner as that described in **Example 28** compound **271** was prepared from **271-S1** and **271-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.91 (d, J=2.4Hz,1H), 7.78 (d,J=1.6 Hz,1H), 7.54 (m,4H), 7.23 (dd, J=2.8 and 9.2 Hz,1H), 7.o9 (d, J=2.0 Hz, 1H), 7.0 (d, J=9.2Hz,1H), 6.09 (s,1H), 4.14 (m,2H), 1.78 (m,2H), 1.27 (m,2H), 0.90 (t, J=6.8 Hz, 3H).

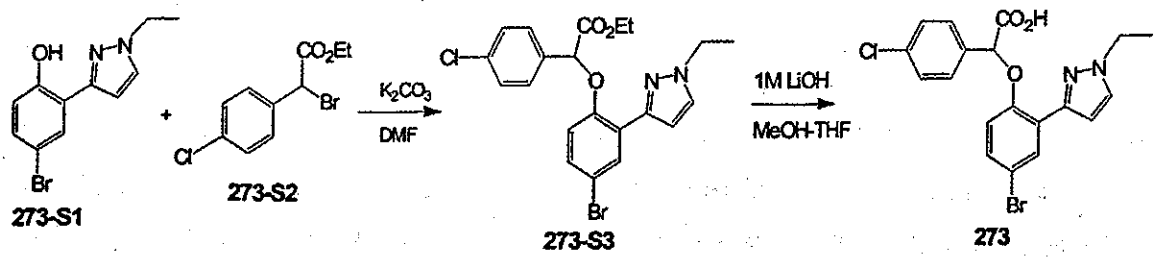
Example 272



[0520] In the same manner as that described in **Example 28** compound **272** was prepared from **272-S1** and **272-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.90 (m,2H), 7.53 (m,2H),

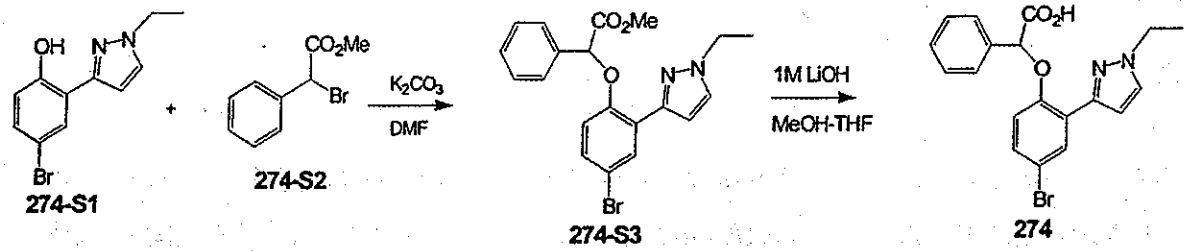
7.39-7.33 (m,5H), 7.30 (m,3H), 7.22 (dd, J=2.8 and 9.2 Hz,1H), 7.18 (d, J=2.4 Hz, 1H), 7.02 (d, J=8.8 Hz, 1H), 6.04(s, 1H), 5.38 (s,2H).

Example 273



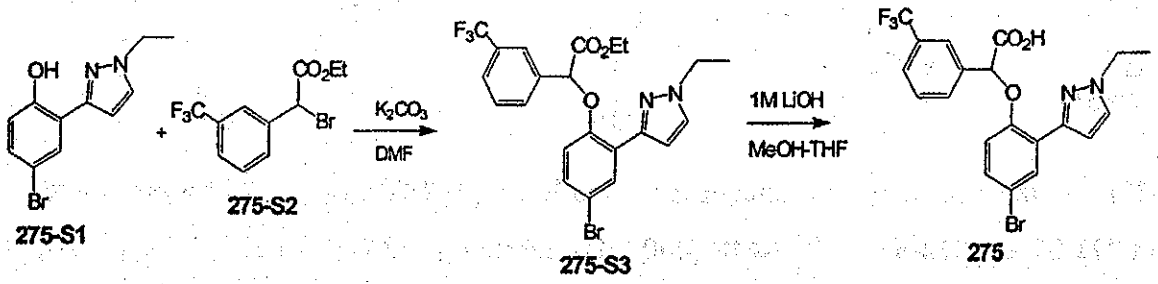
[0521] In the same manner as that described in **Example 28** compound **273** was prepared from **273-S1** and **273-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04 (d, J=2.8Hz,1H), 7.78 (d,J=2.4 Hz,1H), 7.53 (m,2H), 7.47 (m,2H), 7.33 (dd, J=2.8 and 8.8 Hz,1H), 7.09 (d, J=2.0 Hz, 1H), 6.95 (d, J=8.8 Hz, 1H), 6.09 (s, 1H), 4.19 (t, J=7.6Hz,2H), 1.40 (t, J=7.6 Hz, 3H).

Example 274



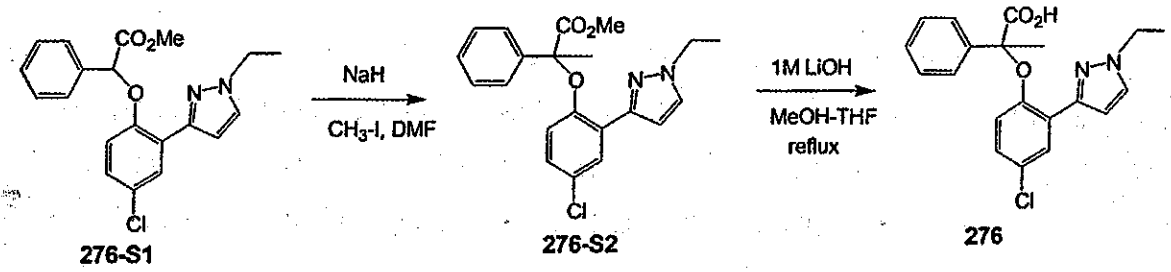
[0522] In the same manner as that described in **Example 28** compound **274** was prepared from **274-S1** and **274-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04 (d, J=2.4Hz,1H), 7.79 (d,J=2.4 Hz,1H), 7.53 (m,2H), 7.41-7.32 (m,4H), 7.11 (d,J=2.0Hz,1H), 6.97 (d, J=8.8 Hz, 1H), 6.04(s, 1H), 4.19 (m,2H), 1.42 (t, J=7.6 Hz, 3H).

Example 275



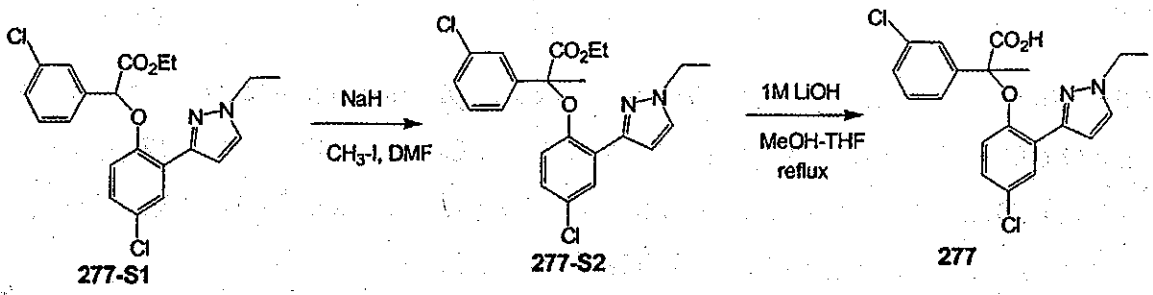
[0523] In the same manner as that described in **Example 28** compound **275** was prepared from **275-S1** and **275-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.02 (d, J=2.4Hz,1H), 7.89 (s,1H), 7.80 (m,2H), 7.73 (m,1H), 7.64 (m,1H), 7.37 (dd, J=2.8 and 8.8 Hz,1H), 7.04 (d, J=2.4 Hz, 1H), 6.98 (d, J=8.8 Hz, 1H), 6.24(s, 1H), 4.19 (m,2H), 1.40 (t, J=7.6 Hz, 3H).

Example 276



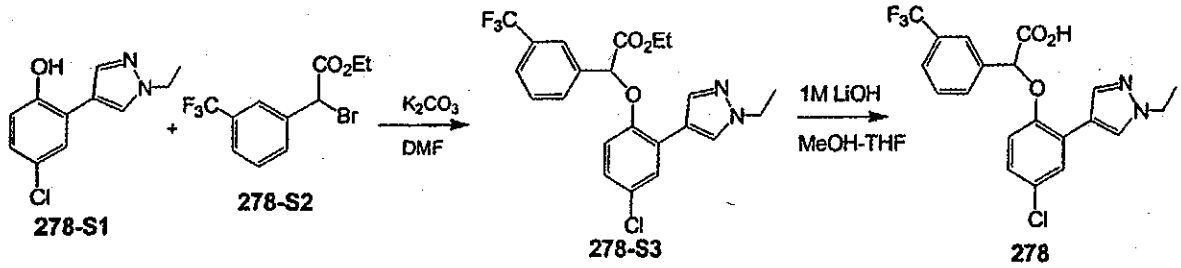
[0524] In the same manner as that described in **Example 42** compound **276** was prepared from **276-S1** and **276-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.88 (d, J=2.4Hz,1H), 7.80 (d,J=2.4 Hz,1H), 7.56 (m,2H), 7.41-7.32 (m,3H), 7.10 (dd, J=2.8 and 9.2 Hz,1H), 7.00 (d, J=2.0 Hz, 1H), 6.53 (d, J=8.8 Hz, 1H), 4.20 (m,2H), 1.88 (s,3H), 1.41 (t, J=6.8 Hz, 3H).

Example 277



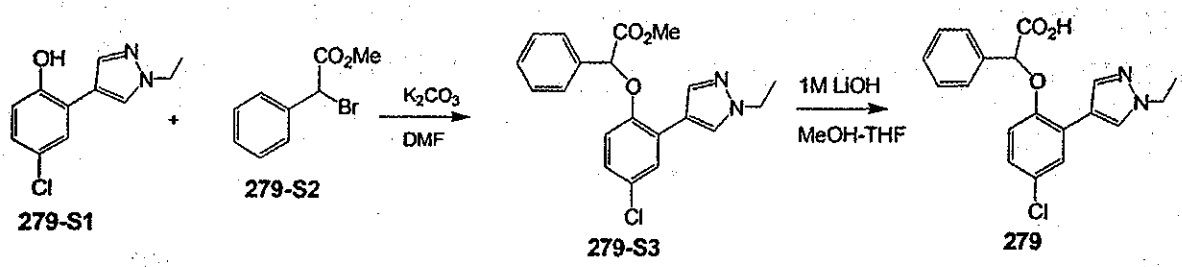
[0525] In the same manner as that described in **Example 42** compound **277** was prepared from **277-S1** and **277-S2.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, J=2.8Hz,1H), 7.70 (d,J=2.4 Hz,1H), 7.52 (m,1H), 7.41-7.39 (m,1H), 7.37-7.34 (m,2H), 7.08 (dd, J=2.4 and 9.2 Hz,1H), 6.84 (d, J=2.8 Hz, 1H), 6.41 (d, J=9.2 Hz, 1H), 4.46 (q, J=7.2 Hz,2H), 2.04 (s,3H), 1.61 (t, J=7.6 Hz, 3H).

Example 278



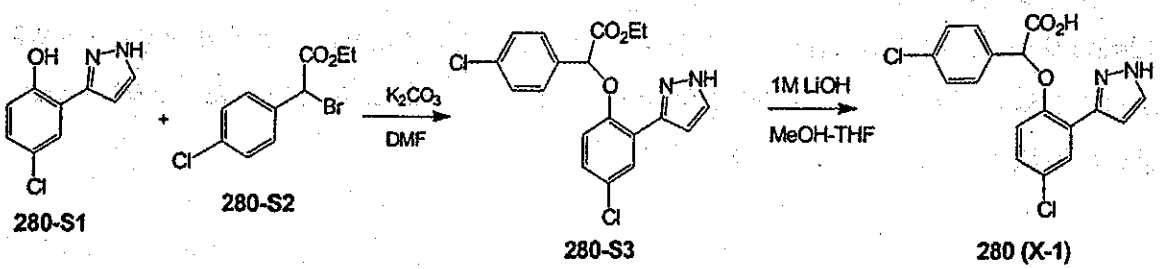
[0526] In the same manner as that described in **Example 28** compound **278** was prepared from **278-S1** and **278-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.44 (s,1H), 8.11 (s,1H), 7.88 (s,1H), 7.80 (d, J=8Hz,1H), 7.73 (d,J=7.6Hz,1H), 7.68 (d,J=2.8Hz,1H), 7.66 (m,1H), 7.14 (dd, J=2.8 and 8.8 Hz,1H), 6.98 (d, J=9.2 Hz, 1H), 6.24 (s,1H), 4.14 (q, J=7.6Hz,2H), 1.37 (t, J=7.6 Hz, 3H).

Example 279



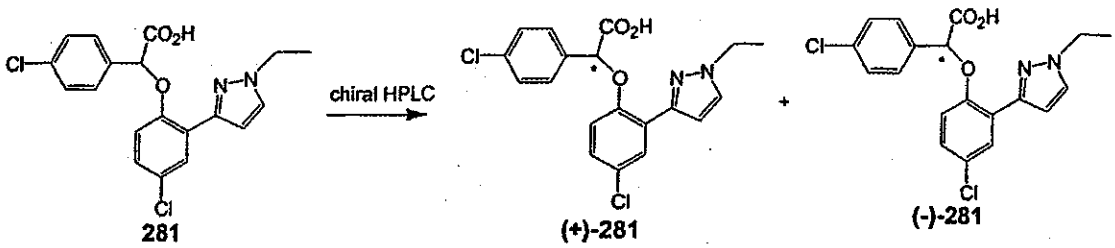
[0527] In the same manner as that described in **Example 28** compound **279** was prepared from **279-S1** and **279-S2.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.49 (s,1H), 8.12 (s,1H), 7.67 (d,J=2.4 Hz,1H), 7.51 (m,2H), 7.40-7.34 (m,3H), 7.09(dd, J=2.4 and 8.4 Hz,1H), 6.93 (d, J=8.8 Hz, 1H), 6.01 (s,1H), 4.14 (q, J=7.6Hz,2H), 1.39 (t, J=7.6 Hz, 3H).

Example 280



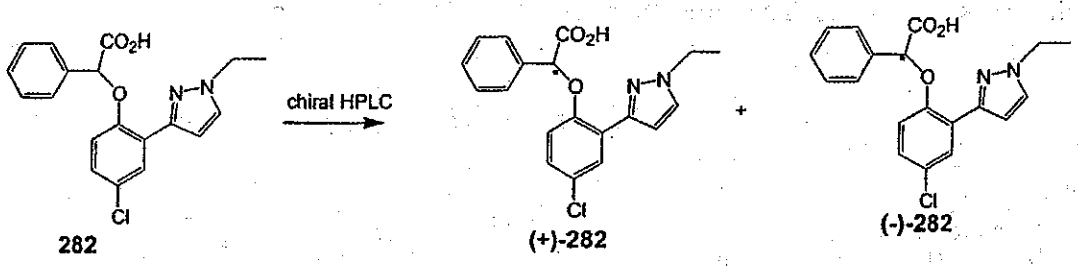
[0528] In the same manner as that described in **Example 28** compound **280** was prepared from **280-S1** and **280-S2.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.42 (m,6H), 7.19 (dd, J=2.8 and 8.8 Hz,1H), 6.97 (d, J=8.8 Hz, 1H), 6.65 (d, J=2.0Hz, 1H), 6.21 (s,1H).

Example 281



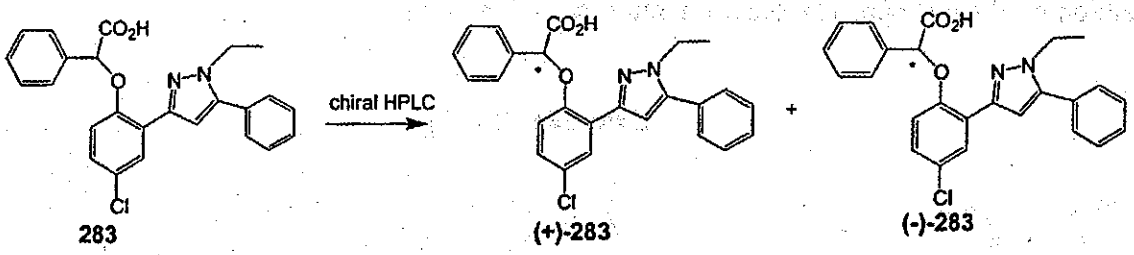
[0529] The two enantiomers were separated by chiral HPLC using a 25 cm × 21.1 mm Regis Technologies (R,R) WHELK-O 2 10/100 column at ambient temperature. HPLC methods and conditions: 50% iPrOH-50% Hexanes-0.1% TFA, 30 mL/min., λ=220 nm. One enantiomer: RT 6.85 min. The other enantiomer: RT 9.6 min.

Example 282



[0530] The two enantiomers were separated by chiral HPLC using a 25 cm × 21.1 mm Regis Technologies (R,R) WHELK-O 2 10/100 column at ambient temperature. HPLC methods and conditions: 50% iPrOH-50% Hexanes-0.1% TFA, 50 mL/min., λ=220 nm. One enantiomer: RT 6.70 min. The other enantiomer: RT 8.5 min.

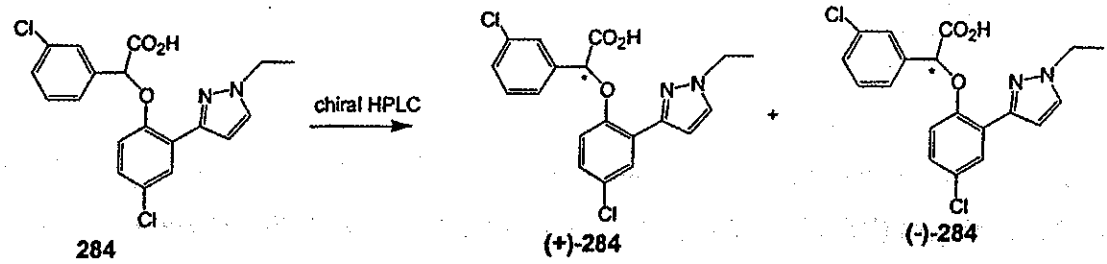
Example 283



[0531] The two enantiomers were separated by chiral HPLC using a 25 cm × 21.1 mm Regis Technologies (R,R) WHELK-O 2 10/100 column at ambient temperature. HPLC

methods and conditions: 50% iPrOH-50% Hexanes-0.1% TFA, 30 mL/min., λ=220 nm. One enantiomer: RT 6.19 min. The other enantiomer: RT 8.20 min.

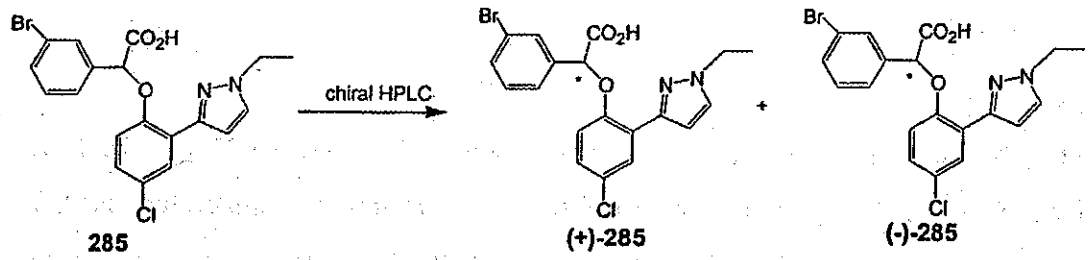
Example 284



284 (+)-284 (-)-284

[0532] The two enantiomers were separated by chiral HPLC using a 25 cm × 21.1 mm Regis Technologies (R,R) WHELK-O 2 10/100 column at ambient temperature. HPLC methods and conditions: 40% iPrOH-60% Hexanes-0.1% TFA, 30 mL/min., λ=220 nm. One enantiomer: RT 7.15 min. The other enantiomer: RT 10.0 min.

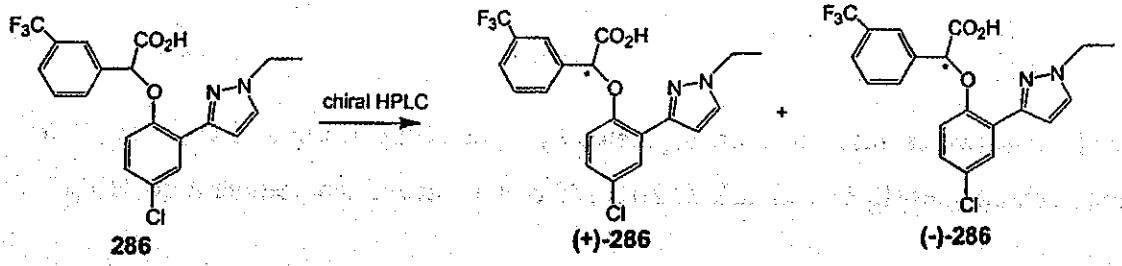
Example 285



285 (+)-285 (-)-285

[0533] The two enantiomers were separated by chiral HPLC using a 25 cm × 21.1 mm Regis Technologies (R,R) WHELK-O 2 10/100 column at ambient temperature. HPLC methods and condition: 40% iPrOH-60% Hexanes-0.1% TFA, 50 mL/min., λ=220 nm. One enantiomer: RT 6.0 min. The other enantiomer : RT 8.70 min.

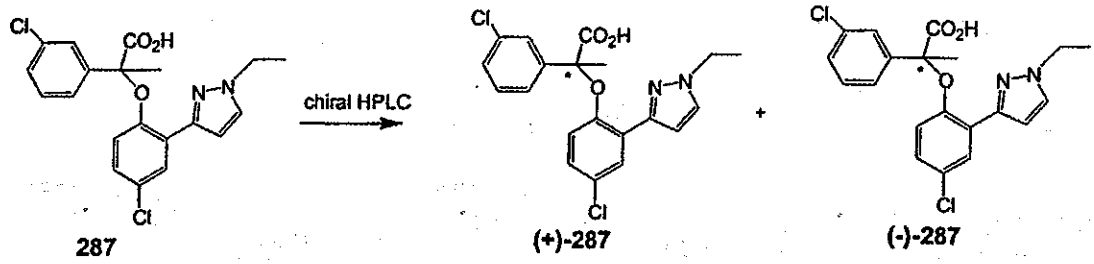
Example 286



286 (+)-286 (-)-286

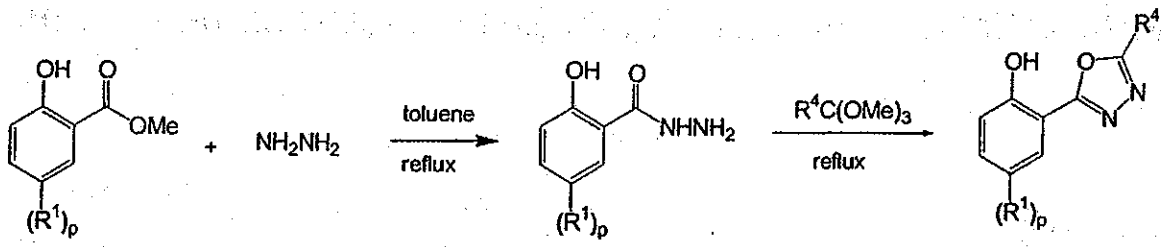
[0534] The two enantiomers were separated by chiral HPLC using a 25 cm × 21.1 mm Regis Technologies (R,R) WHELK-O 2 10/100 column at ambient temperature. HPLC methods and conditions: 40% iPrOH-60% Hexanes-0.1% TFA, 30 mL/min., λ=220 nm. One enantiomer: RT 6.7 min. The other enantiomer: RT 8.30 min.

Example 287

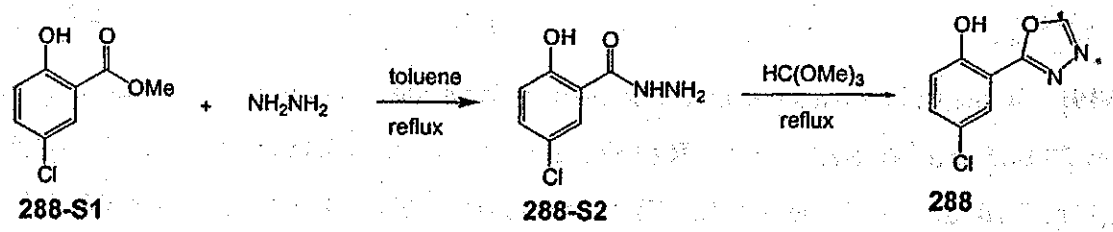


287 (+)-287 (-)-287

[0535] The two enantiomers were separated by chiral HPLC using a 25 cm × 21.1 mm Regis Technologies (R,R) WHELK-O 2 10/100 column at ambient temperature. HPLC methods and conditions: 40% iPrOH-60% Hexanes-0.1% TFA, 40 mL/min., λ=220 nm. One enantiomer: RT 11.2 min. The other enantiomer: RT 14.0 min.



Example 288

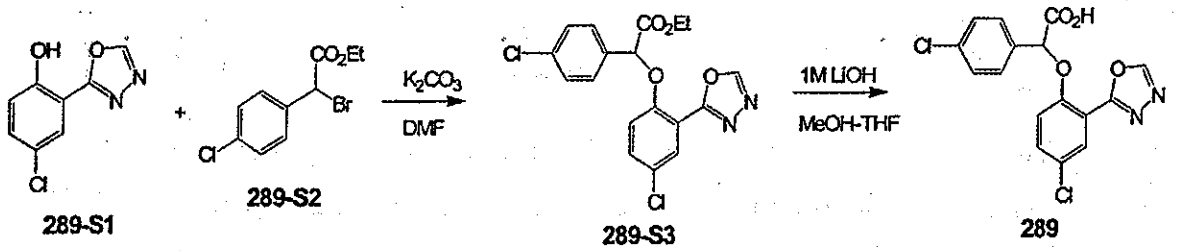


288-S1 288-S2 288

[0536] A mixture of methyl-5-chloro-2-hydroxybenzoate **288** (24.9 g, 0.133 mol) and hydrazine hydrate (11.33 mL,0.20 mol) in toluene was heated overnight at 120 °C in a sealed tube. After cooling to room temperature, the solids were collected by filtration, washed with MeOH and air dried to give a white solid (21.38 g). ^{1}HNMR (400 MHz, DMSO-d_6) δ 7.88 (d,J=2.8 Hz,1H), 7.38 (dd, J=2.8 and 8.8Hz,1H), 6.92 (d,J=8.8Hz,1H).

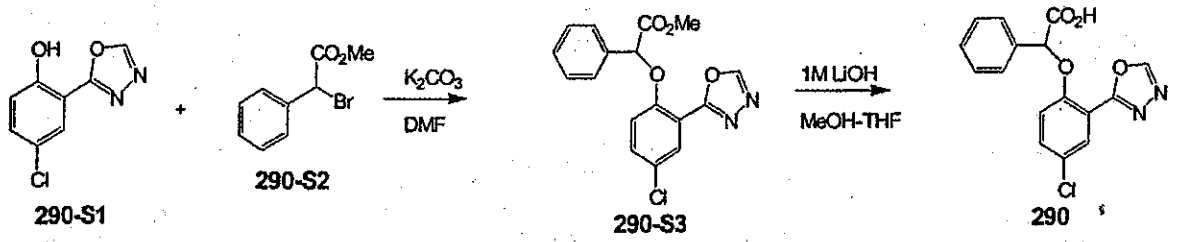
[0537] A mixture of the above product (21.38 g) and trimethyl othoformate (150 mL) was heated overnight at 110 °C. The reaction mixture was concentrated to remove about 100 mL of trimethyl othoformate. Then, 300 mL of toluene was added, and the mixture was refluxed overnight. The mixture was filtered, and the filtrate was concentrated. The residue was recrystallized from MeOH to give **288** as a pale yellow solid (9.0 g). ^{1}HNMR (400 MHz, DMSO-d_6) δ 9.34 (s,1H), 7.76 (d,J=2.8 Hz,1H), 7.47 (dd, J=2.8 and 8.8Hz,1H), 7.08 (d,J=8.4Hz,1H).

Example 289



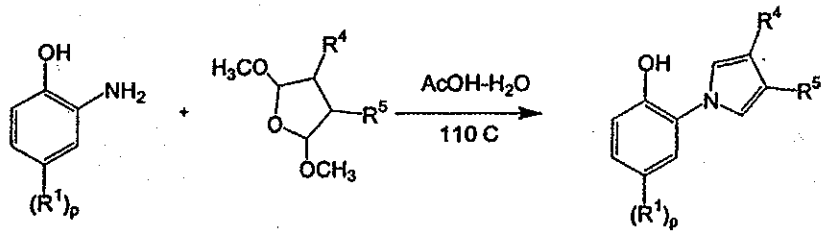
[0538] In the same manner as that described in **Example 28** compound **289** was prepared from **289-S1** and **289-S2.** ^{1}HNMR (400 MHz, DMSO-d_6) δ 9.43 (s,1H), 7.94 (d, J=2.8 Hz,1H), 7.71 (d,J=2.8Hz,1H), 7.68 (m,2H), 7.52 (m,2H), 7.25 (d,J=9.2Hz,1H), 6.21 (s,1H).

Example 290

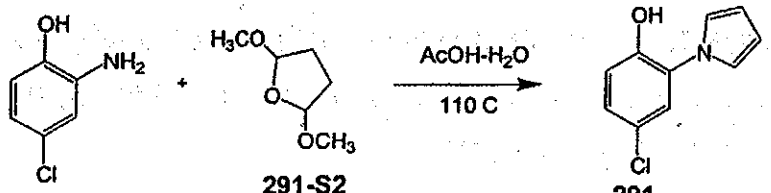


[0539] In the same manner as that described in **Example 28** compound **290** was prepared from **290-S1** and **290-S2.** ^{1}HNMR (400 MHz, DMSO-d_6) δ 9.45 (s,1H), 7.92 (d,J=2.4 Hz,1H), 7.70 (dd, J=2.8 and 9.2 Hz,1H), 7.65 (m,2H), 7.39 (m,3H), 7.26 (d,J=8.8Hz,1H), 6.15 (s,1H).

Scheme10. Synthesis of 2-Pyrrole Phenols



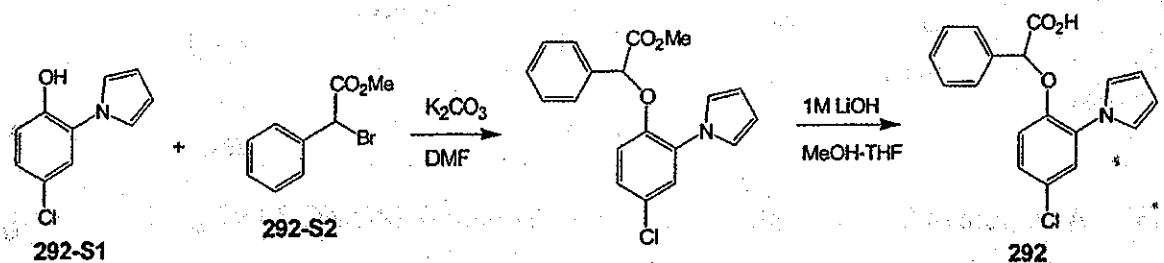
Example 291



291-S1 **291-S2** **291**

[0540] A mixture of 2-amino-4-chlorophenol (5.69 g, 39.63 mmol) and 2,5-dimethoxy-tetrafuran (5.24 g, 39.63 mmol) in $AcOH/H_2O$ (9:1, 200 mL) was heated for 30 min. at 110 °C under nitrogen. The mixture was concentrated, extracted with EtOAc, washed with saturated aqueous $NaHCO_3$, dried and concentrated. Purification via flash column (0-5% EtOAc in hexanes) gave **291** as a red oil (6.37 g, 83%). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.25 (m, 2H), 6.97 (d, J=8.8 Hz,1H), 6.85 (m,2H), 6.41 (m,2H), 5.26 (s,1H).

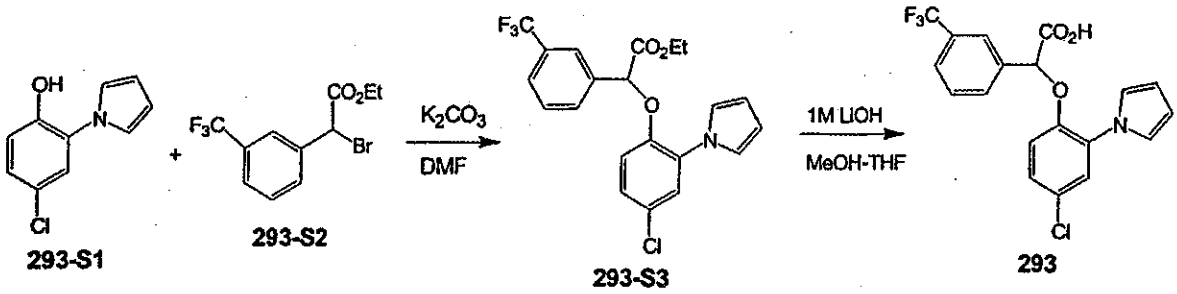
Example 292



292-S1 **292-S2** **292-S3** **292**

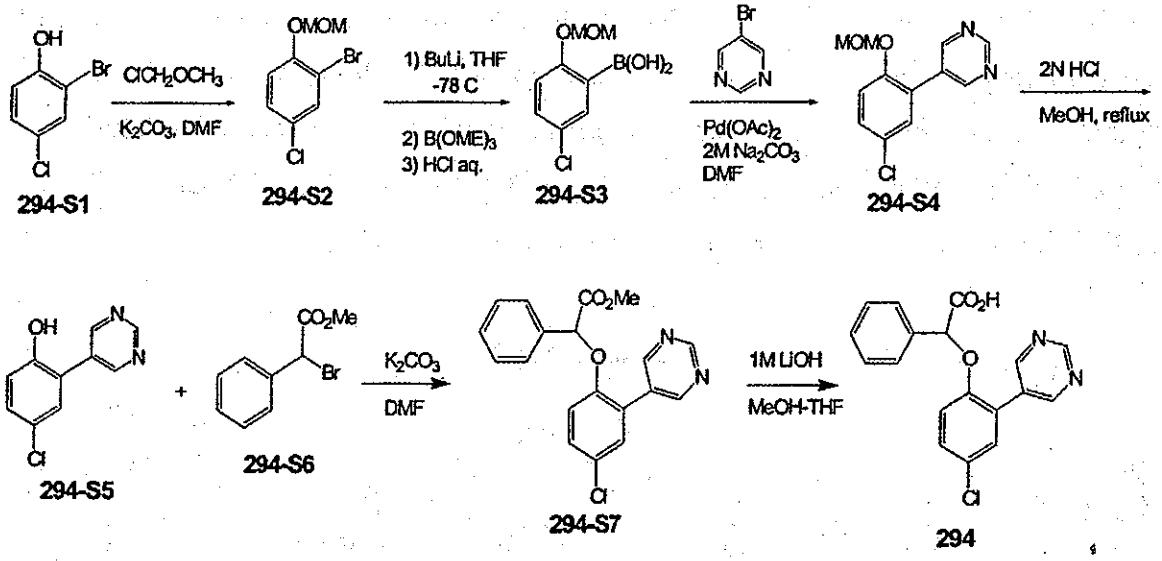
[0541] In the same manner as that described in **Example 28** compound **292** was prepared from **292-S1** and **292-S2**. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.42 (m,2H), 7.36 (m,3H), 7.33 (d, J=2.4 Hz,1H), 7.15 (dd, J=2.8 and 8.8 Hz,1H), 7.06 (m, 2H), 6.90 (d,J=8.4Hz,1H), 6.35 (m, 2H), 5.44 (s, 1H).

Example 293



[0542] In the same manner as that described in **Example 28** compound **293** was prepared from **293-S1** and **293-S2.** ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.69 (s,1H), 7.62 (m,2H), 7.48 (m,1H), 7.35 (d, J=2.4 Hz,1H), 7.18 (dd, J=2.8 and 8.8 Hz,1H), 7.01 (m, 2H), 6.92 (d,J=8.4Hz,1H), 6.34 (m, 2H), 5.46 (s, 1H).

Example 294



[0543] A mixture of 2-Br-4-Cl-phenol (8.57 g, 41.31 mmol), MOMCl (3.99 g, 49.57 mmol) and K_2CO_3 (11.4 g, 82.62 mmol) in DMF (60 mL) was stirred overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ solution, extracted with ethyl ether. The organic layer was washed with brine, dried and concentrated. Purification *via* flash column (hexane/EtOAc 20:1) gave **294-S2** as colorless oil (10.0 g).

[0544] To a solution of **294-S2** (1.683 g, 6.69 mmol) in THF (20 mL) was added n-BuLi (2.5 M in hexanes, 2.94 mL, 7.36 mmol) at –78 °C. After 20 min. at – 78 °C, trimethyl boronate (1.15 mL, 10.04 mmol) was added drop wise. The mixture was slowly warmed to room temperature over 2 h. After 0.5 h at room temperature, the reaction mixture was

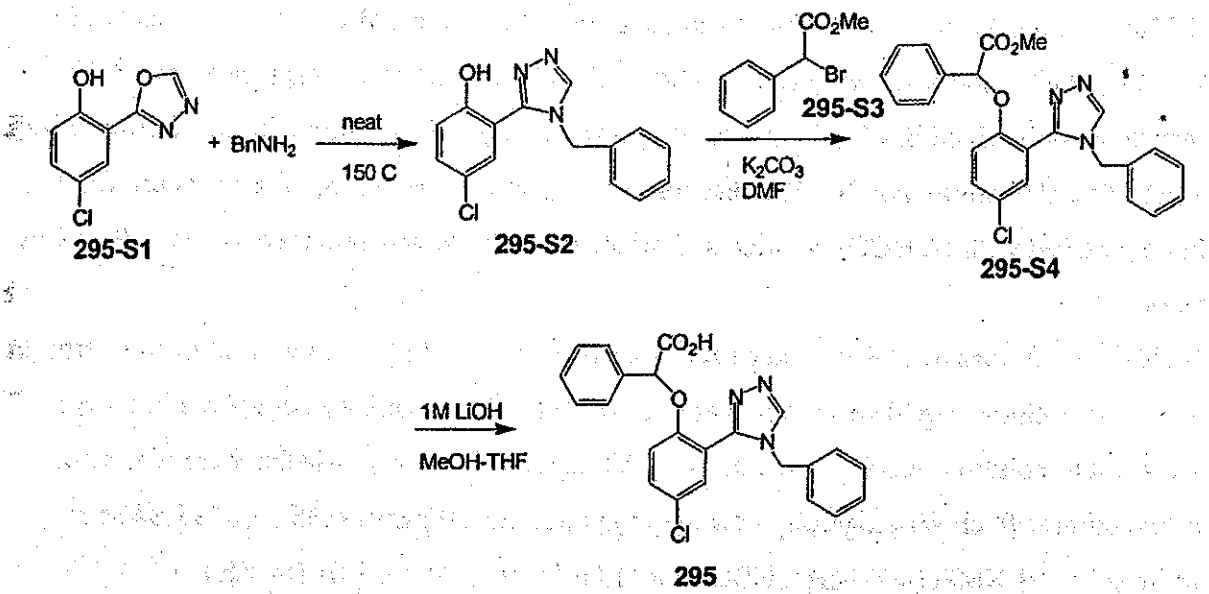
quenched with 1 N HCl aqueous solution, and stirred for 10 min. The mixture was extracted with Et_2O, washed with brine, dried and concentrated to give pale yellow oil. Crystallization from Et_2O/hexane gave **294-S3** as a white solid (1.0 g). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.80 (d,J=2.0 Hz,1H), 7.36 (dd, J=2.4 and 8.8 Hz, 1H), 7.09 (d,J=8.8Hz,1H), 6.0 (br, 2H), 5.27 (s,2H), 3.50 (s,3H).

[0545] A mixture of **294-S3** (171 mg, 0.97 mmol), 5-bromopyrimidine (138 mg,0.87 mmol), $Pd(OAc)_2$ and 2M Na_2CO_3 (0.97 mL,1.58 mmol) in DMF (5mL) was stirred overnight at room temperature under nitrogen. The reaction mixture was quenched with brine, extracted with Et_2O, washed with brine, dried and concentrated. Purification via flash column (Hexane/EtOAc 10:1 to 5:1) gave **294-S4** as a white solid (31 mg). ^{1}HNMR (400 MHz, $CDCl_3$) δ 9.19 (s,1H), 8.90 (s,2H), 7.36 (dd, J=2.4 and 8.8 Hz, 1H), 7.32 (d,J=2.4Hz,1H), 7.22 (d,J=8.8 Hz,1H), 5.19 (s,2H), 3.42 (s,3H).

[0546] A mixture of **294-S4** (31 mg), MeOH (5 mL) and 1 N HCl (5 mL) was heated at 100 °C for 2 h. The mixture was concentrated, dissolved in EtOAc, washed with brine, dried and concentrated to give **294-S5** as a white solid (18 mg). ^{1}HNMR (400 MHz, $CDCl_3$) δ 9.21 (s,1H), 8.97 (s,2H), 7.32-7.25 (m,2H), 6.88 (d,J=8.8 Hz,1H).

[0547] **294** was prepared from **294-S5** and **294-S6** in the same manner as that described in **Example 28.** ^{1}HNMR (400 MHz, DMSO-d_6) δ 9.16 (s,1H), 9.07 (s, 2H), 7.61 (d,J=2.8Hz,1H), 7.49 (dd, J=2.8 and 8.4 Hz,1H), 7.48-7.39 (m, 5H), 7.18 (d,J=8.8Hz,1H), 6.10 (s, 1H).

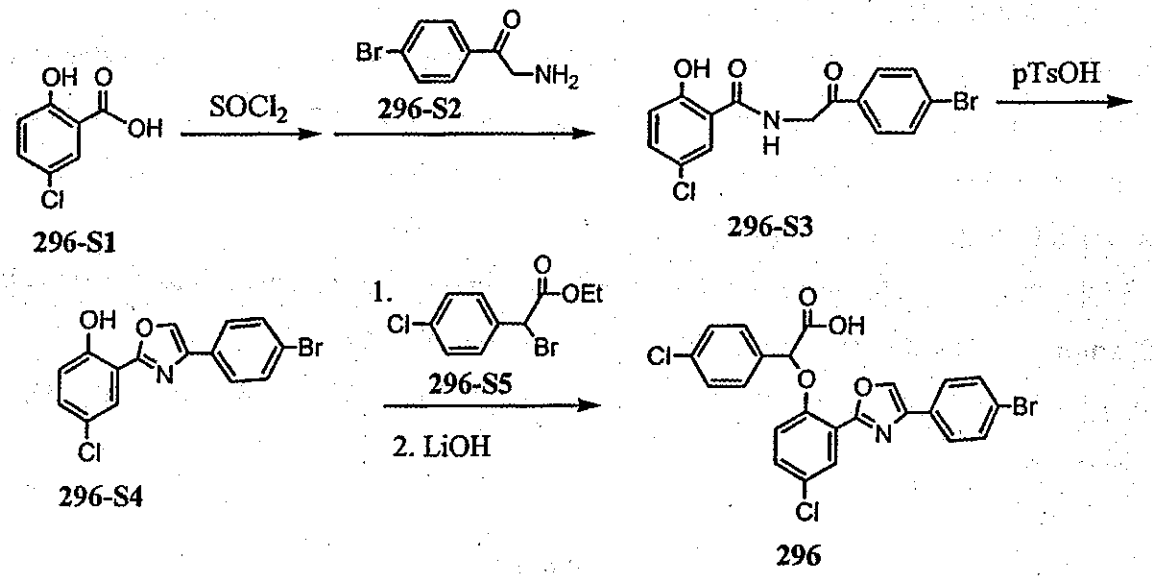
Example 295



[0548] A mixture of **295-S1** (500 mg) and benzylamine (3 mL) was heated overnight at 150 °C in a sealed tube under nitrogen. The mixture was diluted with EtOAc, washed with 2 N HCl and brine, dried and concentrated. Purification via flash column (hexane/EtOAc 10:1 to 5:1) gave **295-S2** as a white solid (0.25 g). ^{1}HNMR (400 MHz, DMSO-d_6) δ 12.50 (s,1H), 9.37 (m,1H), 7.96(d,J=2.4Hz,1H), 7.44 (dd, J=2.4 and 8.8 Hz,1H), 7.30 (m,4H), 7.22 (m,1H), 6.92 (d,J=9.2Hz,1H), 4.49 (d,J=6 Hz,2H).

[0549] **295** was prepared from **295-S2** and **295-S3** in the same manner as that described in **Example 28.** ^{1}HNMR (400 MHz, DMSO-d_6) δ 7.77 (d,J=2.8Hz,1H), 7.48-7.41 (m, 3H), 7.34-7.23 (m,9H), 7.12 (d,J=8.8Hz,1H), 6.16 (s, 1H), 4.55 (m,2H).

Example 296

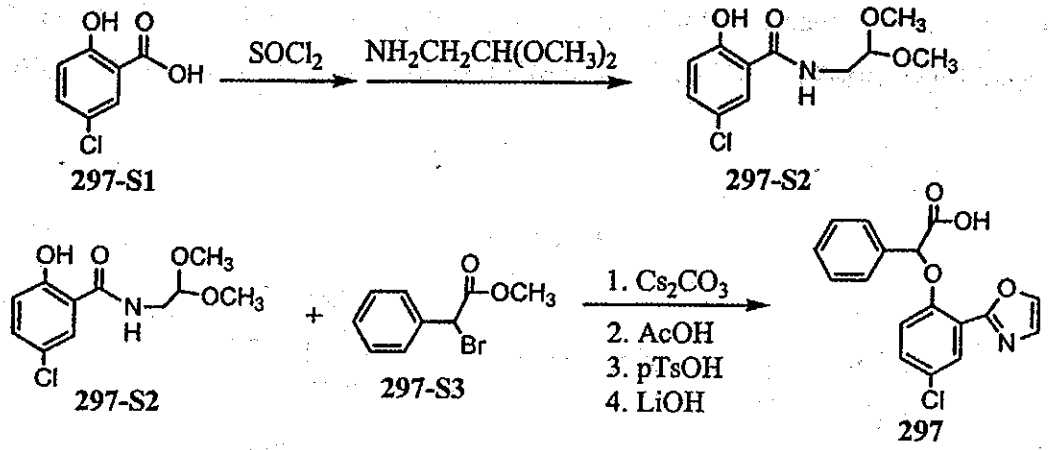


[0550] To a suspension of 5-chlorosalicyclic acid (2.07 g) in CH_2Cl_2 (50 mL) was added 2.63 mL $SOCl_2$, and refluxed for half an hour. The reaction mixture was concentrated. The residue was dissolved in CH_2Cl_2 (60 mL), and was charged 3 g of amino ketone followed by 5 mL of triethyl amine at 0 °C. The reaction solution was stirred at room temperature for 2 hours, washed with $NaHCO_3$ solution and dried. The solvent was removed to give **296-S3** as amber oil.

[0551] A mixture of **296-S3** and pTsOH (0.5 g) in toluene (200 mL) was refluxed overnight with a Dean-Stark trap. The solvent was removed, and the residue was dissolved in ethyl acetate. The solution was washed with $NaHCO_3$ aqueous solution, dried and concentrated. Purification with chromatography (hexanes/ethyl acetate 5/1) gave 0.35 g of **296-S4** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.06 (s, 1H), 7.87 – 7.01 (m, 8H).

[0552] The phenol **296-S4** was reacted with 0.5 g **296-S5** and 800 mg Cs_2CO_3 in CH_3CN (60 mL) overnight. The salt was filtered off, and the filtrate was removed. Purification with chromatography (hexanes/ethyl acetate 5/1) gave the ester product, which was hydrolyzed with LiOH (1N, 30 mL) to give **296** (0.21 g) as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 8.01 – 7.13 (m, 12H), 6.14 (s, 1H).

Example 297

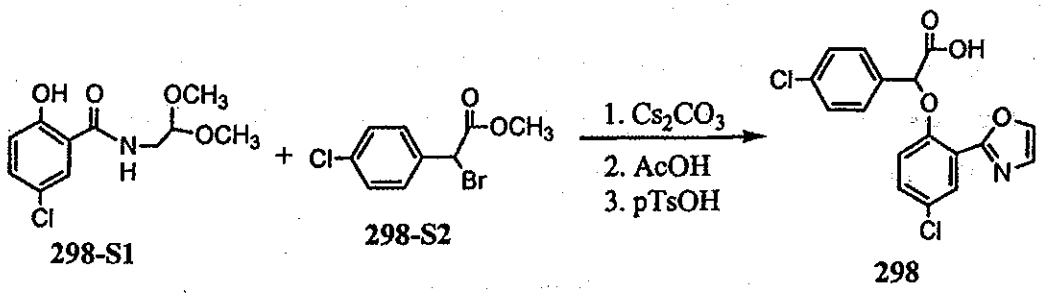


[0553] In the same manner as that described in **Example 296** compound **297-S3** was prepared from **297-S1**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.17 (s, 1H), 7.34 – 6.91 (m, 3H), 6.51 (br, 1H), 4.49 (m, 1H), 3.57 (m, 2H), 3.44 (ss, 6H).

[0554] A mixture of **297-S2** (1.5 g), **297-S3**(1.32 g) and Cs_2CO_3 (1.88 g) was stirred for several hours. The salt was filtered out. The solution was concentrated, diluted with ethyl acetate, washed with brine and dried. The solvent was removed, and the residue was treated with 80% AcOH for several hours, concentrated and extracted with ethyl acetate. Purification with chromatography (hexanes/ethyl acetate 5/1) gave the aldehyde compound (2.2 g) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.73 (s, 1H), 9.29 (br. 1H), 8.19 – 6.66 (m, 8H), 5.75 (s, 1H), 4.36 (d, 2H), 3.76 (s, 3H).

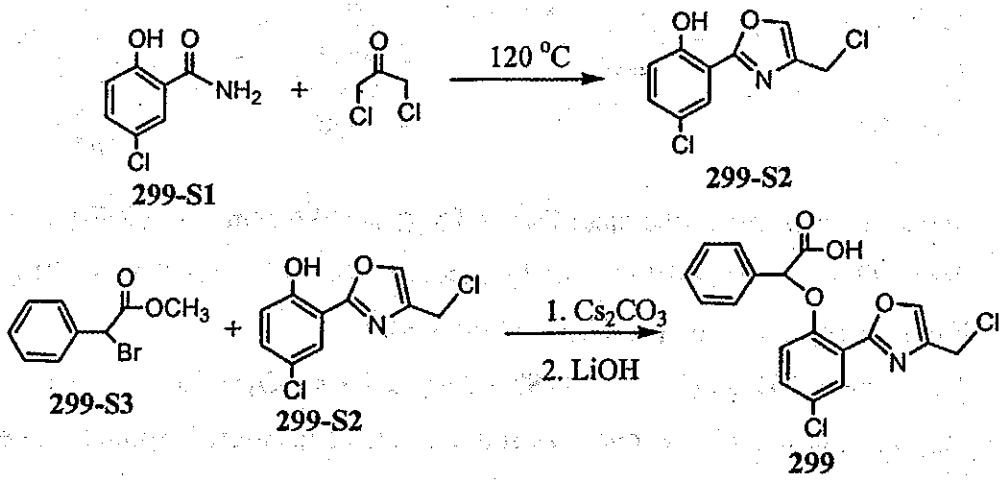
[0555] The solution of aldehyde in toluene with 5 mL AcOH was refluxed overnight, concentrated. Purification with chromatography (hexanes/ethyl acetate 5/1) gave the ester product. The hydrolysis with LiOH (1N, 20 mL) gave **297** (0.13 g) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 8.35 – 7.15 (m, 10H), 6.26 (s, 1H).

Example 298



[0556] In the same manner as that described in **Example 297** compound **298** was prepared from **298-S1 and 298-S2.** ^{1}H NMR (400 MHz, DMSO): δ 7.86 – 6.86 (m, 9H), 5.95 (s, 1H).

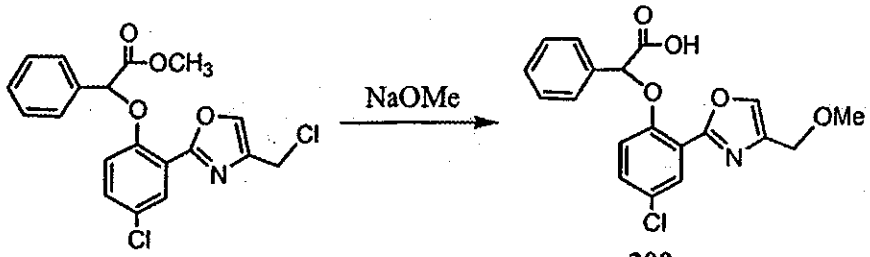
Example 299



[0557] A mixture of **299-S1**, dichloroacetone in a pressure vessel was stirred for several hours at 120 °C. The resulting solid was dissolved in ethyl acetate. Purification with chromatography (hexanes/ethyl acetate 10/1) gave **299-S2** (6.2 g) as a white solid.

[0558] In the same manner as that described in **Example 28** compound **299** was prepared from **299-S3** and **299-S2.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 – 6.72 (m, 9H), 5.62 (s, 1H), 4.60 (s, 2H).

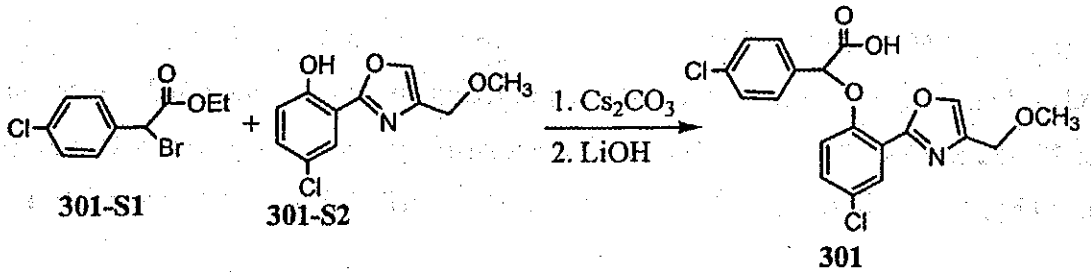
Example 300



300-S1 **300**

[0559] **300-S1** (0.26 g) in DMF and 0.5 g NaOMe was stirred for one hour, quenched with HCl solution (1 N), diluted with water, extracted with ethyl acetate. The solvent was removed, and the residue was purified with chromatography (ethyl acetate) to give the acid product (0.23 g) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 – 6.50 (m, 9H), 5.62 (s, 1H), 4.54 (s, 2H), 3.50 (s, 3H).

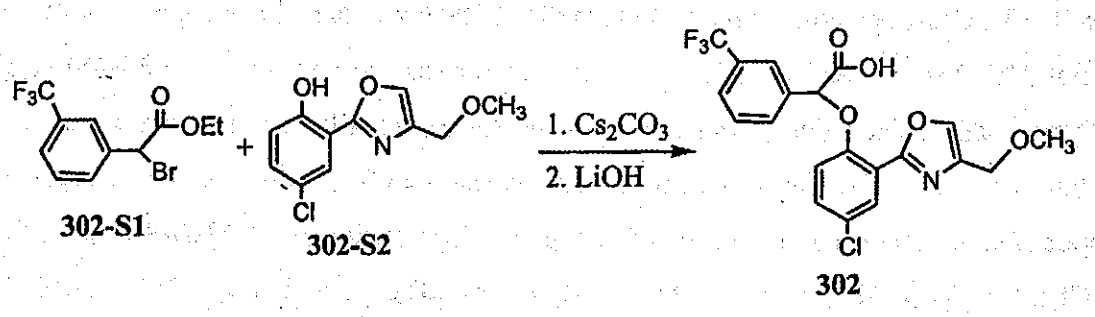
Example 301



301-S1 **301-S2** **301**

[0560] In the same manner as that described in **Example 28** compound **301** was prepared from **301-S1** and **301-S2.** ^{1}H NMR (400 MHz, DMSO): δ 13.48 (br, 1H), 8.23 – 7.12 (m, 8H), 6.12 (s, 1H), 4.39 (s, 2H), 3.25 (s, 3H).

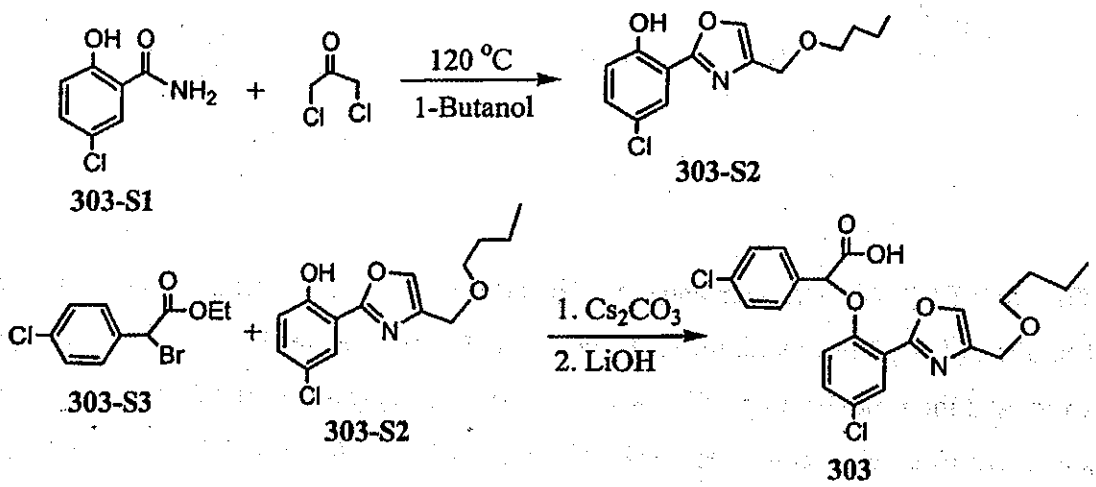
Example 302



302-S1 **302-S2** **302**

[0561] In the same manner as that described in **Example 28** compound **302** was prepared from **302-S1** and **302-S2.** ^{1}H NMR (400 MHz, DMSO): δ 8.17 – 7.16 (m, 8H), 6.29 (s, 1H), 4.39 (s, 2H), 3.45 (s, 3H).

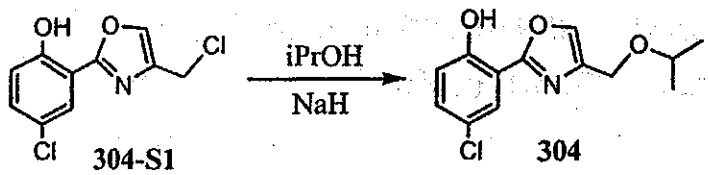
Example 303



[0562] A mixture of **303-S1**, dichloroacetone in 1-butanol was refluxed overnight. The solution was concentrated, and purified with chromatography (hexanes/ethyl acetate 5:1) to give **303-S2** (7.0 g) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.02 (s, 1H), 7.80 – 7.01 (m, 4H), 4.50 (s, 2H), 3.58 (t, 2H), 1.57 (m, 2H), 1.40 (m, 2H), 0.95 (t, 3H).

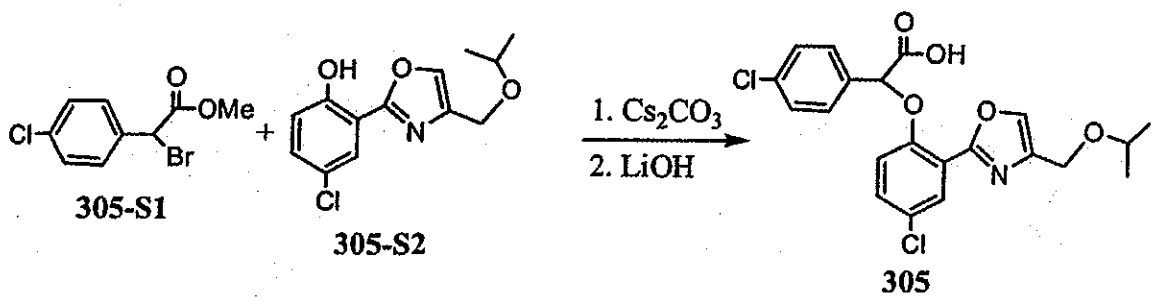
[0563] In the same manner as that described in **Example 28** compound **303** was prepared from **303-S2** and **303-S3**. ^{1}H NMR (400 MHz, DMSO): δ 8.17 – 7.02 (m, 8H), 5.32 (s, 1H), 4.42 (s, 2H), 3.58 (m, 2H), 2.47 (m, 2H), 1.72 (m, 2H), 1.32 (m, 2H), 0.85 (t, 3H).

Example 304



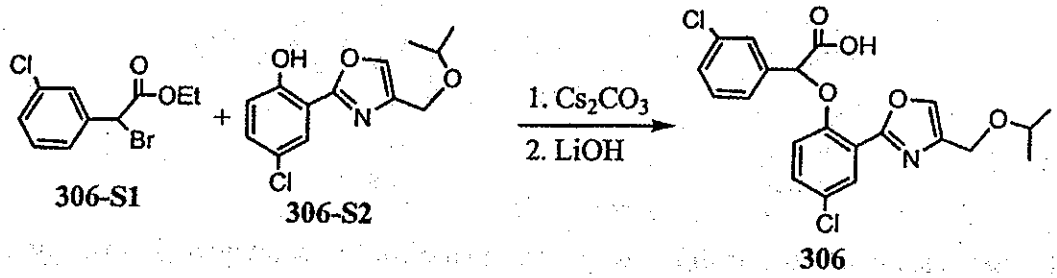
[0564] To a suspension of NaH (2.09 g, 60%) in DMF was added isopropanol (4 mL) drop wise at 0 °C. The mixture was stirred for half an hour, and then a solution of **304-S1** (6 g) in DMF was added. The solution was stirred for several hours, diluted with ethyl acetate, washed with brine. The solvent was removed, the residue was purified with chromatography (hexanes/ethyl acetate 10:1) to give **304** (2.9 g) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.07 (s, 1H), 7.79 – 6.99 (m, 4H), 4.51 (s, 2H), 3.78 (m, 1H), 1.24 (m, 6H).

Example 305



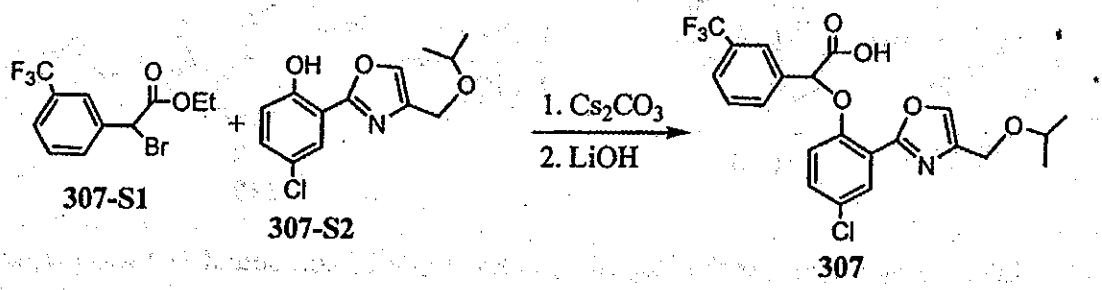
[0565] In the same manner as that described in **Example 28** compound **305** was prepared from **305-S1** and **305-S2.** ^{1}H NMR (400 MHz, DMSO): δ 8.18 – 7.12 (m, 8H), 6.11 (s, 1H), 4.42 (s, 2H), 3.71 (m, 1H), 1.14 (d, 6H).

Example 306



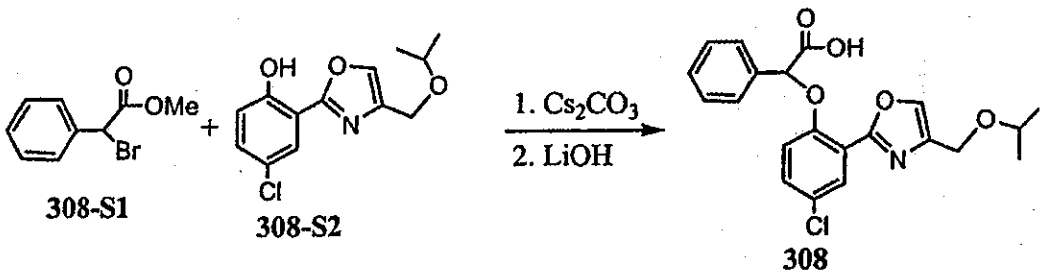
[0566] In the same manner as that described in **Example 28** compound **306** was prepared from **306-S1** and **306-S2.** ^{1}H NMR (400 MHz, DMSO): δ 8.15 – 7.13 (m, 8H), 6.15 (s, 1H), 4.45 (s, 2H), 3.71 (m, 1H), 1.13 (d, 6H).

Example 307



[0567] In the same manner as that described in **Example 28** compound **307** was prepared from **307-S1** and **307-S2.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 – 6.66 (m, 8H), 5.64 (s, 1H), 4.57 (s, 2H), 3.81 (m, 1H), 1.26 (d, 6H).

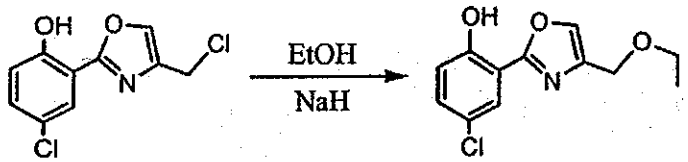
Example 308



308-S1 **308-S2** **308**

[0568] In the same manner as that described in **Example 28** compound **308** was prepared from **308-S1** and **308-S2.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 – 6.70 (m, 9H), 5.61 (s, 1H), 4.57 (s, 2H), 3.81 (m, 1H), 1.27 (d, 6H).

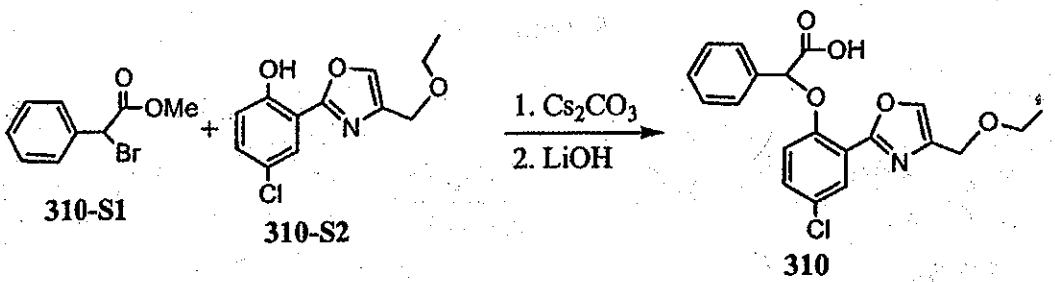
Example 309



309-S1 **309**

[0569] In the same manner as that described in **Example 304** compound **309** was prepared from **309-S1.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.03 (s, 1H), 7.79 – 6.99 (m, 4H), 4.50 (s, 2H), 3.64 (q, 2H), 1.25 (t, 3H).

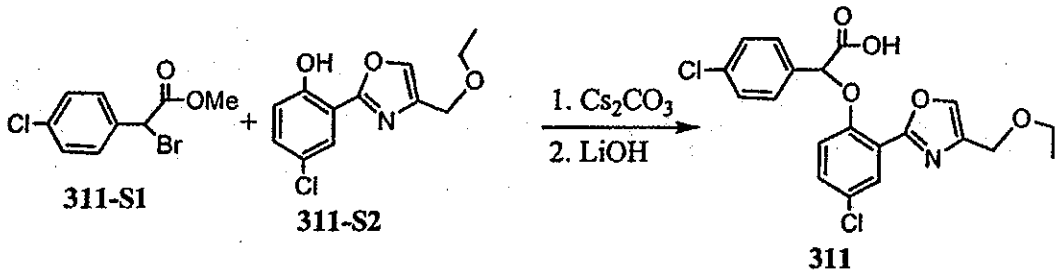
Example 310



310-S1 **310-S2** **310**

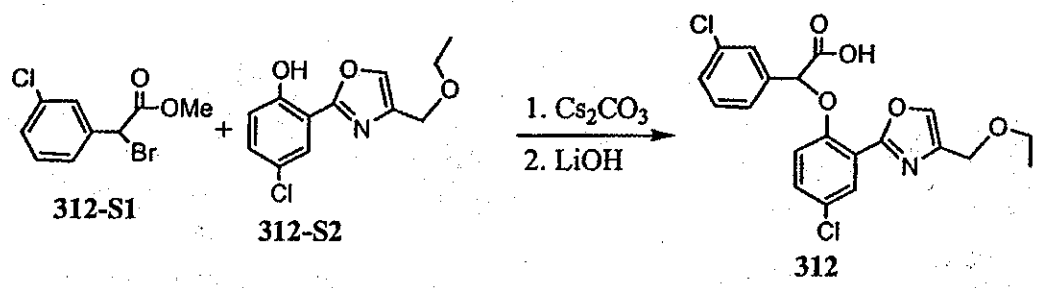
[0570] In the same manner as that described in **Example 28** compound **310** was prepared from **310-S1** and **310-S2.** ^{1}H NMR (400 MHz, DMSO): δ 13.37 (br, 1H), 8.21 – 7.14 (m, 9 H), 6.07 (s, 1H), 4.41 (s, 2H), 3.54 (q, 2H), 1.13 (t, 3H).

Example 311



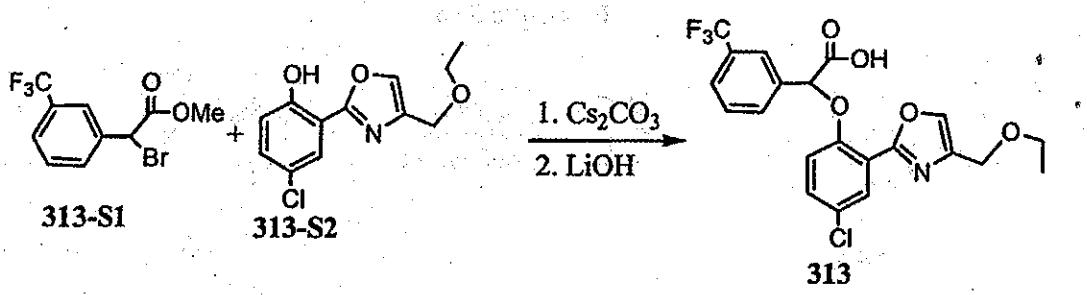
[0571] In the same manner as that described in **Example 28** compound **311** was prepared from **311-S1** and **311-S2.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 – 6.69 (m, 8H), 5.57 (s, 1H), 4.56 (s, 2H), 3.68 (q, 2H), 1.27 (t, 3H).

Example 312



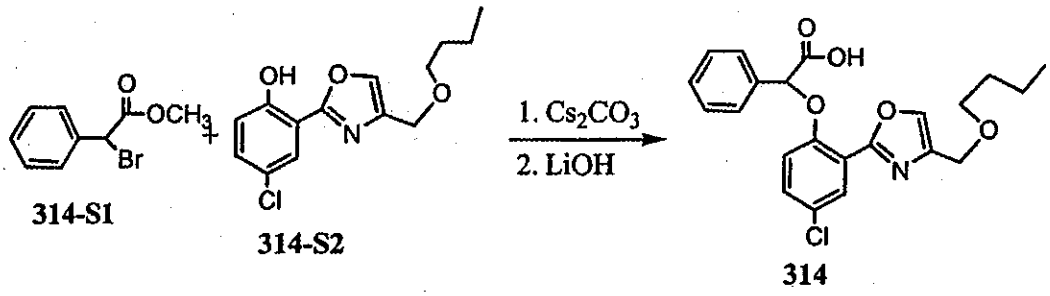
[0572] In the same manner as that described in **Example 28** compound **312** was prepared from **312-S1** and **312-S2.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 – 6.69 (m, 8H), 5.56 (s, 1H), 4.57 (s, 2H), 3.68 (q, 2H), 1.28 (t, 3H).

Example 313



[0573] In the same manner as that described in **Example 28** compound **313** was prepared from **313-S1** and **313-S2.** ^{1}H NMR (400 MHz, DMSO): δ 8.15 – 7.16 (m, 8H), 6.29 (s, 1H), 4.42 (s, 2H), 3.53(q, 2H), 1.12 (t, 3H).

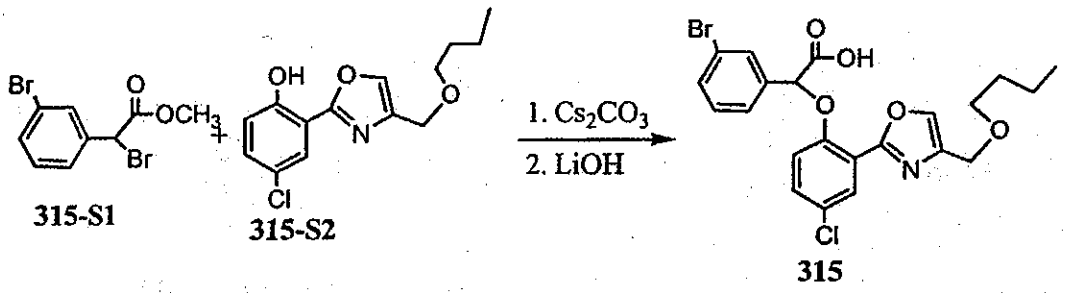
Example 314



314-S1 **314-S2** **314**

[0574] In the same manner as that described in **Example 28** compound **314** was prepared from **314-S1** and **314-S2.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 – 6.71 (m, 9H), 5.61 (s, 1H), 4.57 (s, 2H), 3.61 (t, 2H), 1.63 (m, 2H), 1.39 (m, 2H), 0.95 (t, 3H).

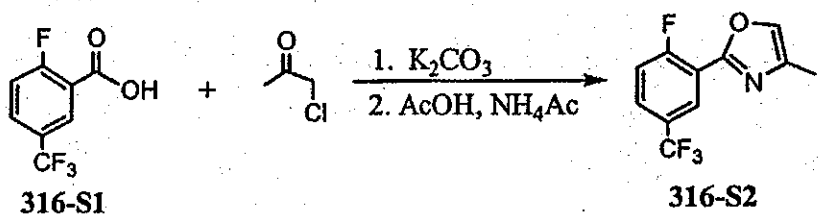
Example 315



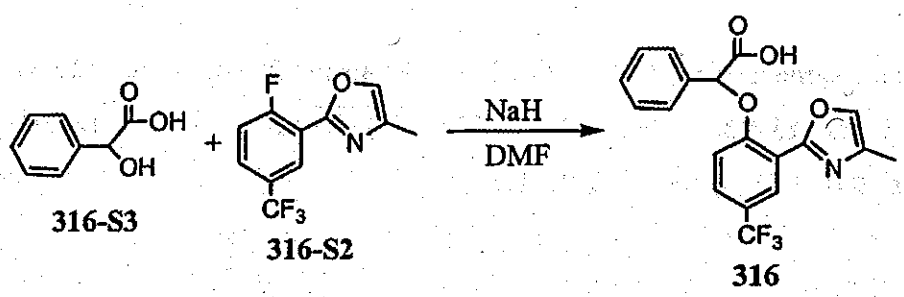
315-S1 **315-S2** **315**

[0575] In the same manner as that described in **Example 28** compound **315** was prepared from **315-S1** and **315-S2.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 – 6.69 (m, 8H), 5.55 (s, 1H), 4.56 (s, 2H), 3.60 (t, 2H), 1.63 (m, 2H), 1.39 (m, 2H), 0.93 (t, 3H).

Example 316



316-S1 **316-S2**

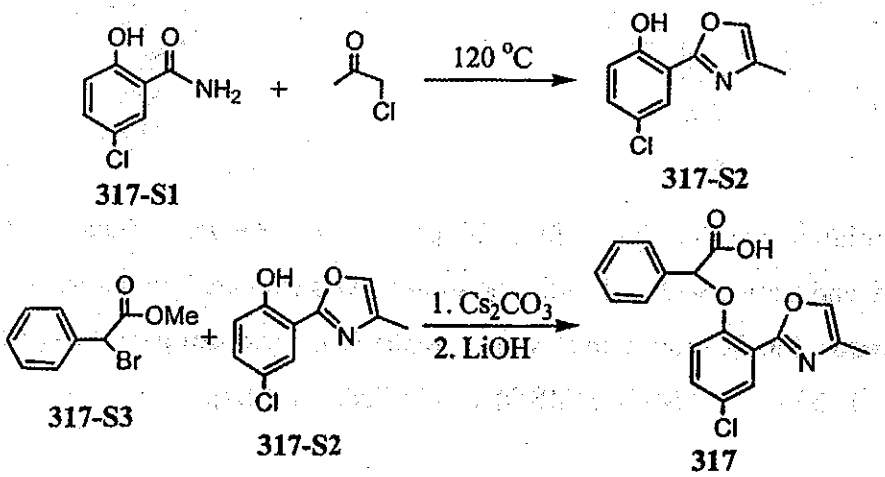


316-S3 **316-S2** **316**

[0576] A mixture of acid **316-S1** (5 g), chloroacetone (2.3 mL) in DMF with K_2CO_3 (3.32 g) was stirred for several hours, diluted with ethyl acetate, washed with brine and dried. The solvent was removed, and the residue was dissolved in toluene. The solution was refluxed with NH_4Ac (4.6 g), AcOH (50 mL) overnight. The solvent was removed. Purification with chromatography (hexanes/ethyl acetate 10:1) gave **316-S2** (0.45 g) as colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 8.35 – 7.26 (m, 4H), 2.28 (s, 3H).

[0577] To a suspension of NaH (0.13 g) in DMF (20 mL) was added drop wise a solution of **316-S3** (0.48 g) in DMF (20 mL) at 0 °C. The mixture was stirred for half an hour, and was added the **316-S2** (0.43 g) in DMF (10 mL) solution. The solution was stirred for one hour, quenched with water, extracted with ethyl acetate, concentrated. Purification with chromatography (ethyl acetate) gave the acid (0.13 g) as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ 8.28 – 6.92 (m, 9H), 5.73 (s, 1H), 2.37 (s, 3H).

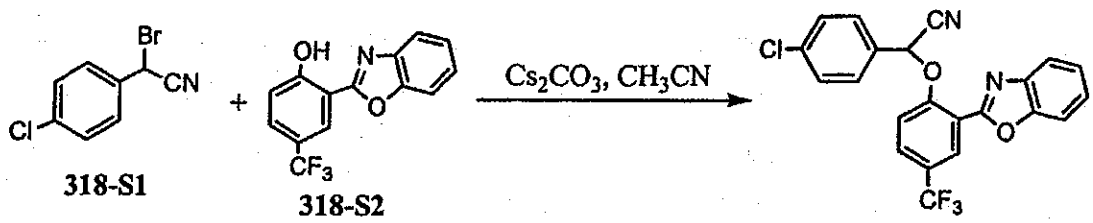
Example 317



[0578] A mixture of **317-S1** (6.0 g), chloroacetone (10 mL) in a pressure vessel was stirred at 120 °C for several hours. The mixture turned to dark mud, which was dissolved in ethyl acetate. The solid left was filtered off. The solution was concentrated, and purified with chromatography (hexanes/ethyl acetate 20:3) to give **317-S2.**

[0579] **317-S2** was reacted with 1.5 g of **317-S3** and 1 g of Cs_2CO_3 in CH_3CN. The mixture was stirred for two hours. The solid was filtered off. The solution was concentrated and purified with chromatography (hexane/ethyl acetate 5:1) to give the ester. Hydrolysis with 1 N LiOH (20 mL) gave **317** (0.25 g) as a light yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.95 – 6.72 (m, 9H), 5.61 (s, 1H), 2.33 (s, 3H).

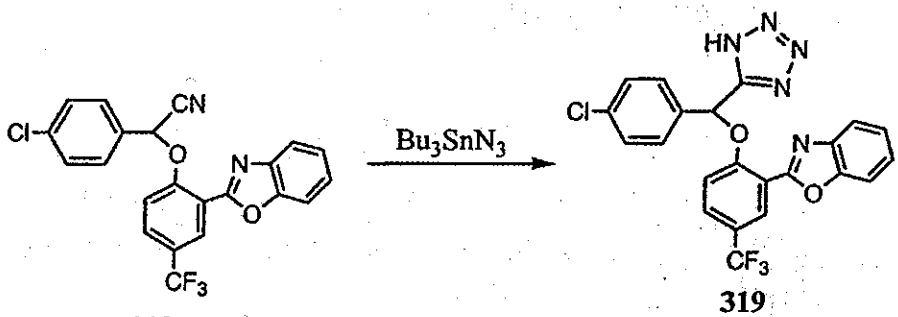
Example 318



318-S1 **318-S2** **318**

[0580] In the same manner as that described in **Example 28** compound **318** was prepared from **318-S1** and **318-S2.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 -7.26 (m, 11H), 6.11(s, 1H).

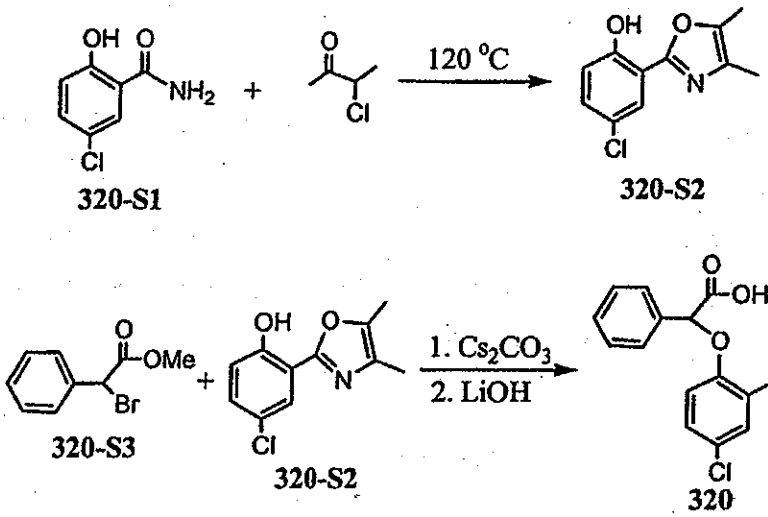
Example 319



318 **319**

[0581] A solution of **318** (0.73 g), Bu_3SnN_3 (0.7 mL) in THF was refluxed overnight, then concentrated, and treated with 1N HCl. The solution was extracted with ethyl acetate, dried and concentrated. Purification with chromatography (ethyl acetate) gave **319** (0.43 g) as a white solid. ^{1}H NMR (400 MHz, DMSO): δ 8.37-7.42 (m, 12H).

Example 320

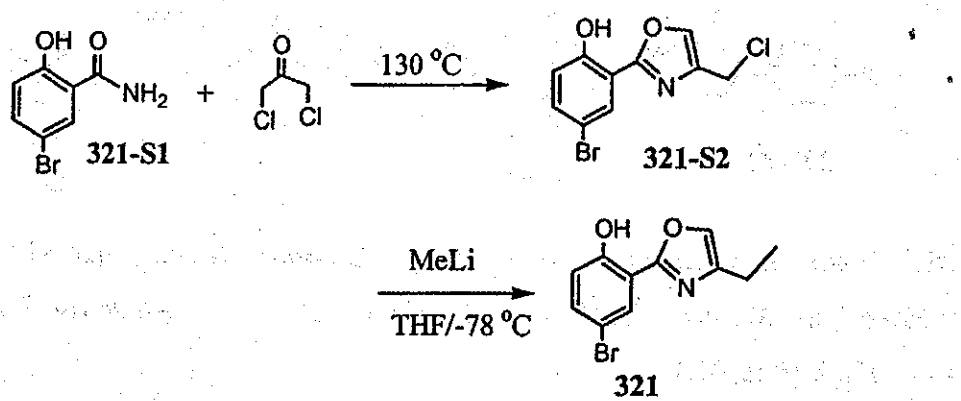


[0582] A mixture of **320-S1** (5.0 g), chlorobutanone (20 mL) in a pressure vessel was stirred at 120 °C for several hours. The mixture turned to dark mud, which was dissolved in ethyl acetate. The solid left was filtered off. The solution was concentrated, and purified with chromatography (hexanes/ethyl acetate 20:3) to give **320-S2** (0.19 g) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.36 (s, 1H), 7.73 – 6.96 (m, 3H), 2.33 (s, 3H), 2.15 (s, 3H).

[0583] In the same manner as that described in **Example 28** compound **320** was prepared from **320-S3** and **320-S2.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 – 6.68 (m, 8H), 5.57 (s, 1H), 2.38 (s, 3H), 2.23 (s, 3H).

[0584] The two enantiomers were separated by HPLC. Column: PIRKLE COVALENT, (R, R) Whelk-O 2 10/100, 25 cm x 21.1 mm. Flow: 30 ml/min, 40% iPrOH/Hexanes-0.1% TFA.

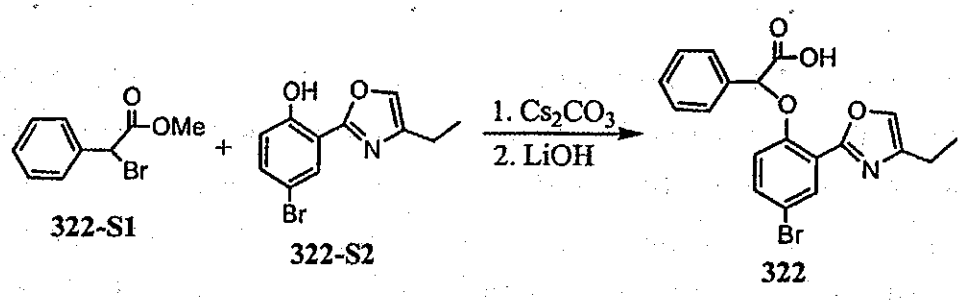
Example 321



[0585] In the same manner as that described in **Example 299** compound **321-S2** was prepared from **321-S1.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.84 (s, 1H), 7.93 – 6.96 (m, 4H), 4.56 (s, 2H).

[0586] To a solution of **321-S2** (1.2 g) in THF was added drop wise 6.2 mL MeLi (1.5 M) at -78 °C. The solution was stirred for 30 mins, quenched with aqueous NH_4Cl solution, extracted with ethyl acetate, and dried. Purification with chromatography (hexanes/ethyl acetate 5:1) gave **321** (0.72 g) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.35 (s, 1H), 7.90 – 6.93 (m, 4H), 2.62 (q, 2H), 1.27 (t, 3H).

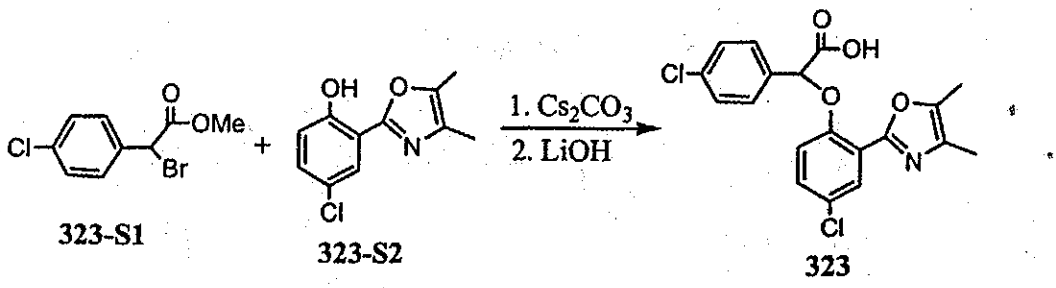
Example 322



322-S1 **322-S2** **322**

[0587] In the same manner as that described in **Example 28** compound **322** was prepared from **322-S1** and **322-S2.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 – 6.67 (m, 9H), 5.62 (s, 1H), 2.72 (q, 2H), 1.33 (t, 3H).

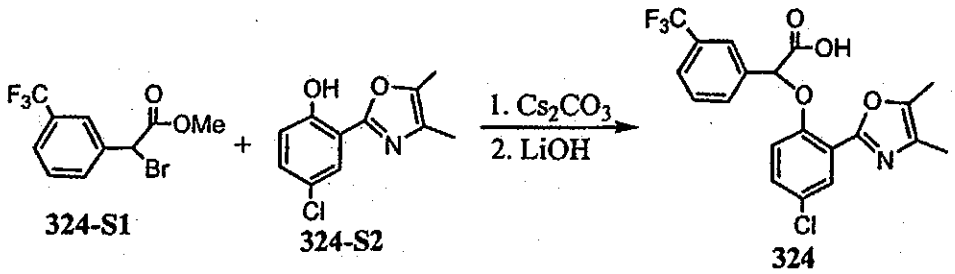
Example 323



323-S1 **323-S2** **323**

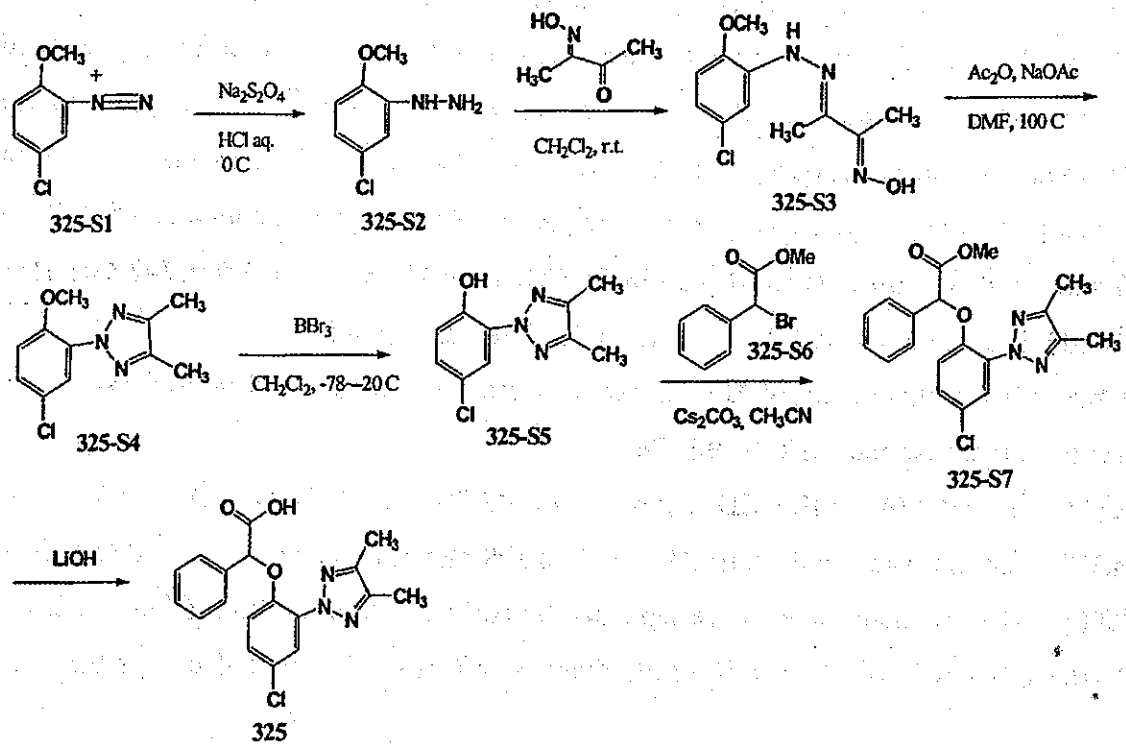
[0588] In the same manner as that described in **Example 28** compound **323** was prepared from **323-S1** and **323-S2.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 – 6.96 (m, 7H), 6.07 (s, 1H), 2.31 (s, 3H), 2.10 (s, 3H).

Example 324



[0589] In the same manner as that described in **Example 28** compound **324** was prepared from **324-S1** and **324-S2.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 – 6.65 (m, 7H), 5.63 (s, 1H), 2.36 (s, 2H), 2.22 (s, 3H).

Example 325



[0590] To a solution of diazo compound **325-S1**(0.826 g, 3.02 mmol) in 1.5 N HCl (36 mL) was added slowly solid $Na_2S_2O_4$ (619 mg, 3.02 mmol) at 0 °C. The mixture was stirred at 0 °C for 20 min, and quenched carefully with saturated aqueous $NaHCO_3$ solution. The mixture was extracted with EtOAc, washed with brine, dried and concentrated to give the phenyl hydrazine derivative **325-S2** as brown oil (156mg) which was used for next reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96 (d,J=2.0Hz,1H), 6.71(dd, J=2.0 and 8.4 Hz,1H), 6.66 (d,J=8.4Hz,1H).

[0591] A mixture of the above hydrazine derivative (177 mg, 1.03 mmol) and diacetyl mono-oxime (104 mg, 1.03 mmol) in CH_2Cl_2 (5 mL) was stirred overnight at room temperature. The mixture was diluted with hexanes, and white solids were formed. After filtration and washing with hexanes, a white solid (138 mg) was obtained **(325-S3)**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (bs, 1H), 7.44 (d,J=2.4Hz,1H), 6.79(dd, J=2.8 and 8.8 Hz,1H), 6.73 (d,J=8.8Hz,1H), 3.88 (s,3H), 2.22(s,3H), 2.08 (s,3H).

[0592] A mixture of the above white solid (130 mg), acetyl anhydride (1 mL), and NaOAc (42 mg) in DMF (3 mL) was heated at 100 °C overnight. The mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ solution and brine, dried and concentrated. Purification *via* flash column (5% to 30% EtOAc in hexanes) gave the triazole compound **325-S4** as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d,J=2.8Hz,1H), 7.34 (dd, J=2.8 and 8.8 Hz,1H), 6.98 (d,J=8.8Hz,1H), 3.87 (s,3H), 2.33 (s,6H).

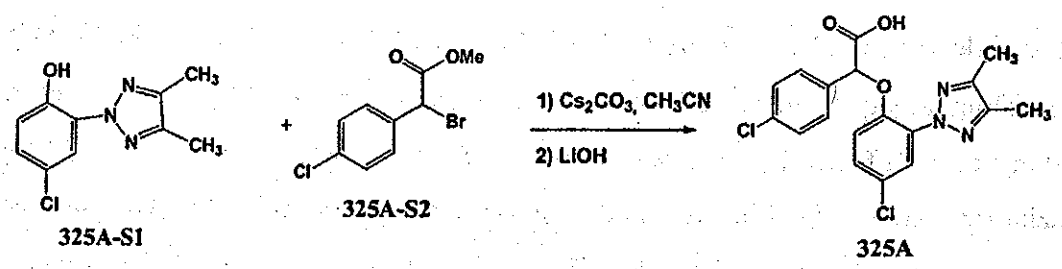
[0593] To a solution of the above triazole compound (90 mg) in CH_2Cl_2 (5 mL) was added drop wise BBr_3 (0.15 mL) at –78 °C. The mixture was warmed to –20 °C over 2 hours, and quenched with saturated aqueous $NaHCO_3$ solution. The mixture was extracted with EtOAc, washed with brine, dried and concentrated to give the triazole phenol compound **325-S5** as an off-white solid (80 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.75 (s,1H), 8.0 (d,J=2.4Hz,1H), 7.14 (dd, J=2.8 and 8.8 Hz,1H), 7.01 (d,J=8.8Hz,1H), 2.38 (s,6H).

[0594] The target compound **325** was prepared from **325-S5** and **325-S6** in the same manner as that described in **Example 28.**

[0595] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d,J=2.8Hz,1H), 7.47 (m,2H), 7.36-7.32 (m,3H), 7.08 (dd, J=2.8 and 8.8 Hz,1H), 6.77 (d,J=8.8Hz,1H), 5.63 (s,1H), 2.33 (s,6H).

[0596] The two enantiomers were separated by HPLC. Column: PIRKLE COVALENT, (R, R) Whelk-O 2 10/100, 25 cm x 21.1 mm. Flow: 30 ml/min, 25% iPrOH/Hexanes-0.1% TFA.

Example 325A

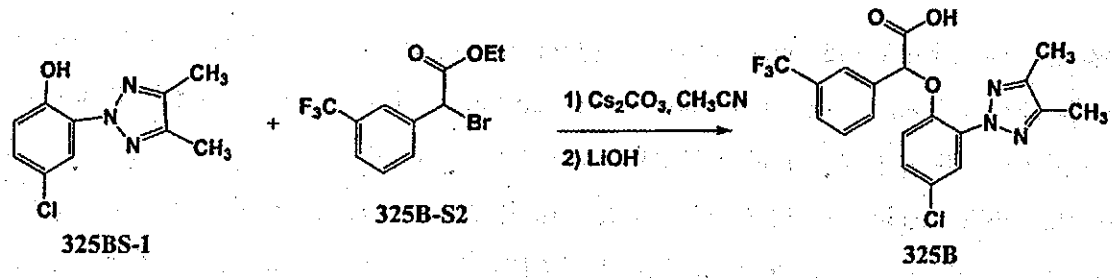


325A-S1 **325A-S2** **325A**

[0597] Compound **325A** was prepared from **325A-S1** and **325A-S2** in the same manner as that described in **Example 28.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.60 (d,J=2.8Hz,1H), 7.54-7.44 (m,5H), 7.15 (d,J=9.2Hz,1H), 5.96 (s,1H), 2.26 (s,6H).

[0598] The two enantiomers were separated by HPLC. Column: PIRKLE COVALENT, (R, R) Whelk-O 2 10/100, 25 cm x 21.1 mm. Flow: 30 ml/min, 30% iPrOH/Hexanes-0.1% TFA.

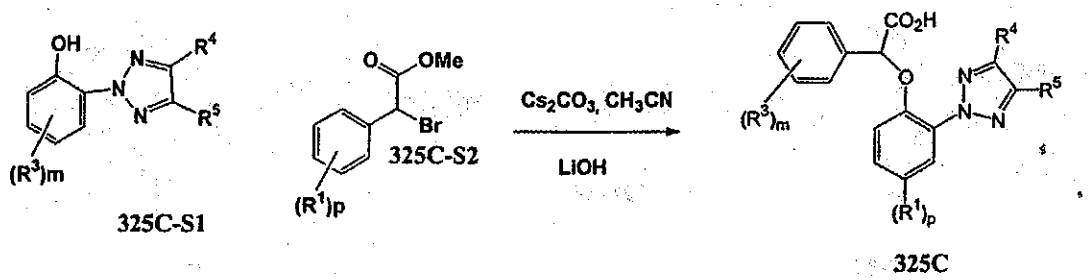
Example 325B



[0599] Compound **325B** was prepared from **325B-S1** and **325B-S2** in the same manner as that described in **Example 28.** ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.94 (d,J=2.4Hz,1H), 7.79-7.55 (m,5H), 7.20 (dd, J=2.8 and 9.2 hz,1H), 6.83 (d, J=9.2Hz,1H), 5.78 (s,1H), 2.42 (s, 6H).

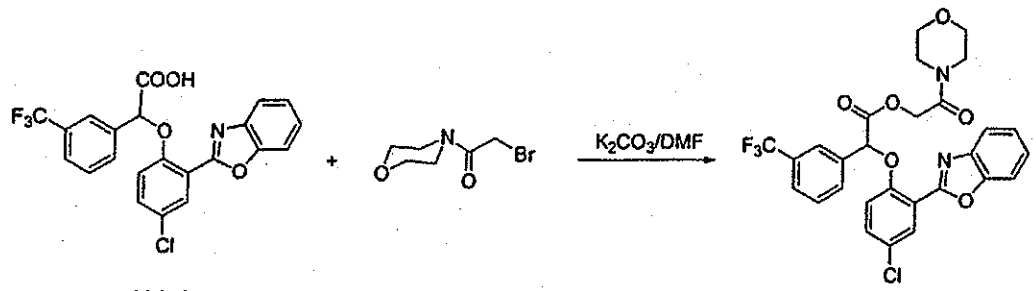
[0600] The two enantiomers were separated by HPLC. Column: PIRKLE COVALENT, (R, R) Whelk-O 2 10/100, 25 cm x 21.1 mm. Flow: 30 ml/min, 30% iPrOH/Hexanes-0.1% TFA.

Example 325C



[0601] In the same manner as that described in **Example 28** compound **325C** was prepared from **325C-S1** and **325CA-S2.**

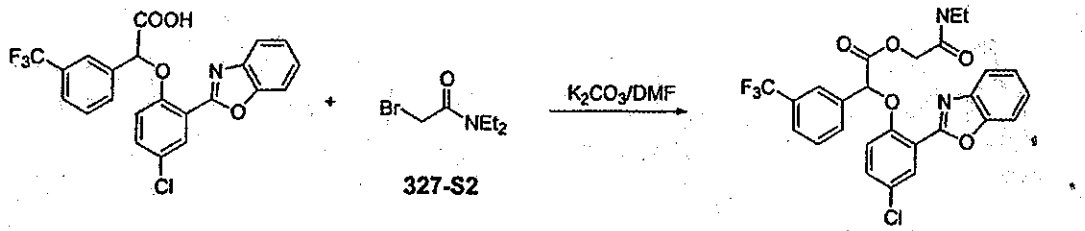
Example 326



326-S1 326-S2 326

[0602] Bromide **326-S2** was prepared by reaction of bromoacetyl bromide (1.0 eq.) and morpholine (1.0 eq.) with triethylamine (1.02 eq.) in CH_2Cl_2 at 0 °C for 1.5 h. To a solution of **326-S1** (1.99 g, 4.44 mmol) in DMF (10 mL) at rt was added K_2CO_3 (0.64 g, 9.30 mmol), and then followed by **326-S2** (1.55 g, 7.45 mmol). After stirring for 40 min at rt, the reaction mixture was diluted with EtOAc and aq. NH_4Cl/H_2O. The organic layer was washed with aq. NH_4Cl/H_2O, and then brine/water, dried over Na_2SO_4, concentrated *in vacuo*. Purification *via* chromatography with EtOAc/hexanes (30% to 50%) to afforded **326** (1.34 g, 52%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (1H, s), 8.25 (1H, s), 7.99 (1H, d, J = 7.2 Hz), 7.81 (1H, m), 7.68 (1H, d, J = 7.2 Hz), 7.56 (2H, m), 7.48 (1H, m), 7.38 (2H, m), 7.28 (1H, m), 6.02 (1H, s), 4.92 (1H, d, J = 14.0 Hz), 4.64 (1H, d, J = 14.0 Hz), 3.60–3.66 (6H, m), 3.27 (2H, m) ppm.

Example 327

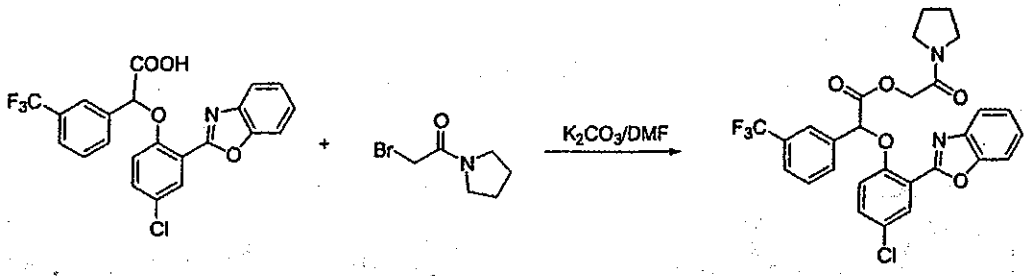


327-S1 327-S2 327

[0603] To a solution of **327-S1** (2.16 g, 4.82 mmol) in DMF (10 mL) at rt was added K_2CO_3 (0.50 g, 3.62 mmol), and then followed by **327-S2** (1.42 g, 7.32 mmol). After stirring for 30 min at rt, the reaction mixture was diluted with EtOAc and aq. NH_4Cl/H_2O. The organic layer was washed with aq. NH_4Cl/H_2O, and then brine/water, dried over Na_2SO_4, concentrated *in vacuo*. Purification *via* chromatography with EtOAc/hexanes (30% to 50%) to afforded **327** (2.05 g, 76%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (1H, s), 8.24 (1H, d, J = 2.8 Hz), 8.00 (1H, d, J = 7.8 Hz), 7.81 (1H, m), 7.67 (1H, d, J = 7.8 Hz),

7.46–7.59 (3H, m), 7.30–7.39 (2H, m), 7.31 (1H, d, J = 8.8 Hz), 6.03 (1H, s), 4.97 (1H, d, J = 14.2 Hz), 4.59 (1H, d, J = 14.2 Hz), 3.45 (1H, m), 3.32 (1H, m), 3.15–3.31 (2H, m), 1.15 (6H, m) ppm.

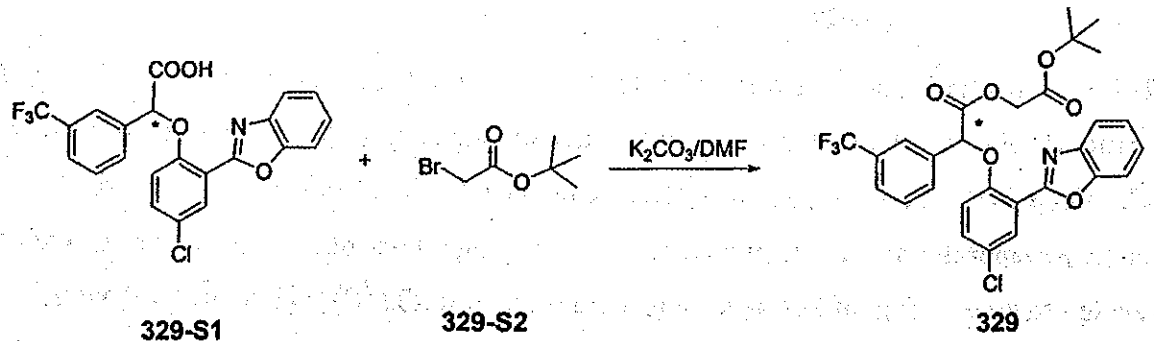
Example 328



328-S1 **328-S2** **328**

[0604] Bromide **328-S2** was prepared by reaction of bromoacetyl bromide (1.0 eq.) and pyrrolidine (1.0 eq.) with triethylamine (1.01 eq.) in CH_2Cl_2 at –5 °C for 1.5 h. To a solution of **328-S1** (2.19 g, 4.90 mmol) in DMF (20 mL) at rt was added K_2CO_3 (0.66 g, 4.78 mmol), and then followed by bromide (1.41 g, 7.39 mmol). After stirring for 1 h at rt, the reaction mixture was diluted with EtOAc and aq. NH_4Cl/H_2O. The organic layer was washed with aq. NH_4Cl/H_2O, and then brine/water, dried over Na_2SO_4, concentrated *in vacuo*. Purification *via* chromatography with EtOAc/hexanes (30% to 50%) to afforded **328** (1.91 g, 70%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (1H, s), 8.24 (1H, d, J = 2.8 Hz), 8.01 (1H, d, J = 7.4 Hz), 7.81 (1H, m), 7.68 (1H, d, J = 7.4 Hz), 7.50–7.59 (3H, m), 7.37–7.39 (2H, m), 7.30 (1H, d, J = 9.2 Hz), 6.04 (1H, s), 4.86 (1H, d, J = 14.4 Hz), 4.53 (1H, d, J = 14.4 Hz), 3.49 (2H, m), 3.28 (2H, m), 1.94 (2H, m), 1.84 (2H, m) ppm.

Example 329

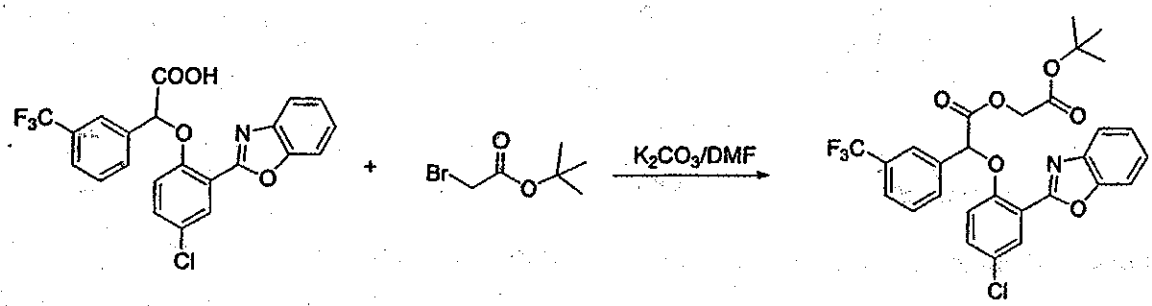


329-S1 **329-S2** **329**

[0605] In the same manner as that described in **Example 328** compound **329** was prepared from **329-S1** and **329-S2.** (m.p. 80-82 °C). ^{1}H-NMR (400 MHz, d_6-DMSO) δ 8.31 (s,

1H), 8.12 (d, 1H, J=2.4), 8.04 (d, 1H, J=7.6), 7.66-7.82 (m, 5H), 7.43-7.49 (m, 2H), 7.34 (d, 1H, J=9.2), 6.65 (s, 1H), 4.61 (s, 2H), 1.23 (s, 9H). Chiral HPLC conditions: 4.6 x 250 mm Regis Whelk-O-1 column; 970:30:1 hexanes/IPA/TFA @ 1.5 mL/min @ r.t.; detection at 220 nm. Retention time of major enantiomer: 7.8 minutes. Retention time of the minor enatiomer: 8.2 minutes.

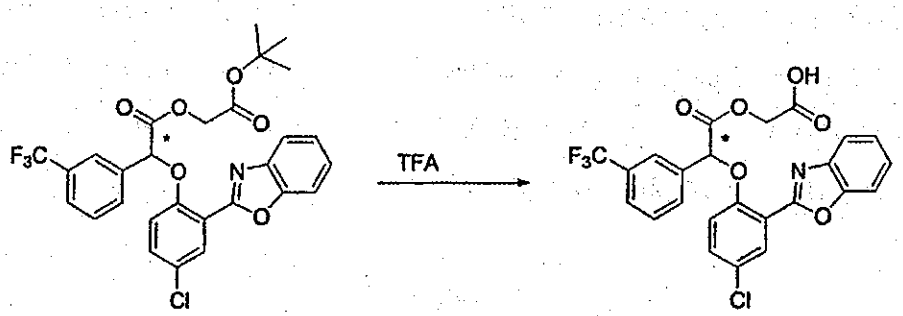
Example 330



330-S1 **330-S2** **330**

[0606] In the same manner as that described in **Example 329** compound **330** was prepared from **330-S1** and **329-S2.** Melting point: 93-95 °C.

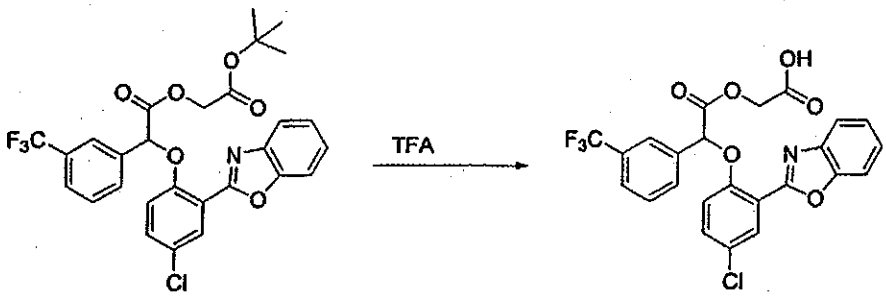
Example 331



331-S1 **331**

[0607] To a flask under air was added 15.2 g (33.9 mmol) of **331-S1**, 80 mL of CH_2Cl_2 and 80 mL of TFA (1040 mmol; 30.6 equiv.). After stirring at room temperature for 2 hours, 500 mL of heptane was added to the reaction mixture and the volatiles were removed via a rotatory evaporator at room temperature. The resulting white solid was further dried under vacuum to give 13.9 g of **331** as a white solid (m.p. 200-202 °C). ^{1}H-NMR (400 MHz, d_6–DMSO) δ 13.2 (br, 1H), 8.31 (s, 1H), 8.12 (d, 1H, J=2.8), 8.03 (d, 1H, J=8.0), 7.63-7.81 (m, 5H), 7.42-7.49 (m, 2H), 7.36 (d, 1H, J=9.2), 6.65 (s, 1H), 4.66 (s, 2H).

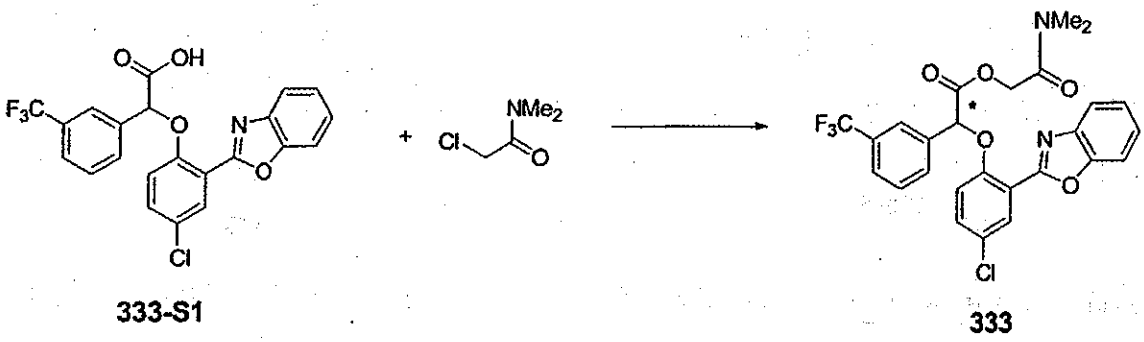
Example 332



332-S1 332

[0608] With the exception that **332-S1** (the racemic compound) was used as the starting material , this compound was synthesized via a procedure analogous to that used in the preparation of **331**. 89% yield. Melting point: 208-210 °C.

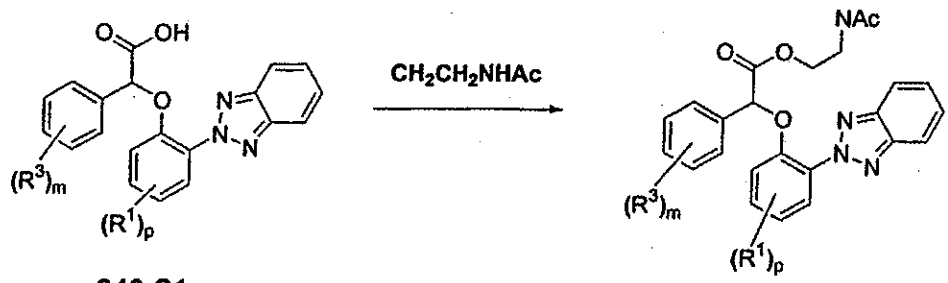
Example 333



333-S1 333

[0609] To a flask was added 3.08 g (22.3 mmol; 1.00 equiv.) of K_2CO_3, 50 mL of DMF, 10.0 g (22.3 mmol) of **333-S1** and 5.0 mL (48.4 mmol; 2.17 equiv.) of 2-chloro-*N,N*-dimethylacetamide. After stirring at room temperature for 6 hours, the reaction mixture was poured into 300 mL of EtOAc and washed with water 2 x 200 mL. To the organic phase was added 300 mL of heptane. The organic phase was concentrated to ~300 mL via a rotatory evaporator and the resulting precipitate was collected in a filter funnel. After air drying, 10.6 g (89% yield) of a white solid (m.p. 145-147 °C) was obtained. ^{1}H-NMR (400 MHz, d_6-DMSO) δ 8.30 (s, 1H), 8.13 (d, 1H, J=2.4), 8.06 (d, 1H, J=8.4), 7.67-7.76 (m, 5H), 7.43-7.47 (m, 3H), 6.62 (s, 1H), 4.92 (d, 1H, J=14.8), 4.85 (d, 1H, J=14.8), 2.83 (s, 3H), 2.77 (s, 3H).

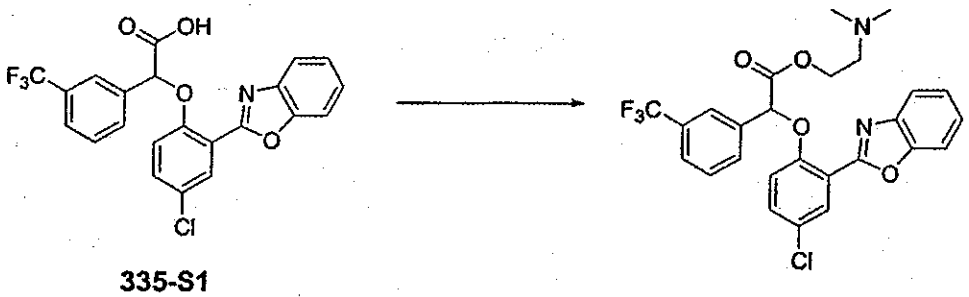
Example 334



340-S1 **340**

[0610] In the same manner as that described in **Example 136** compound **340** was prepared from **340-S1**.

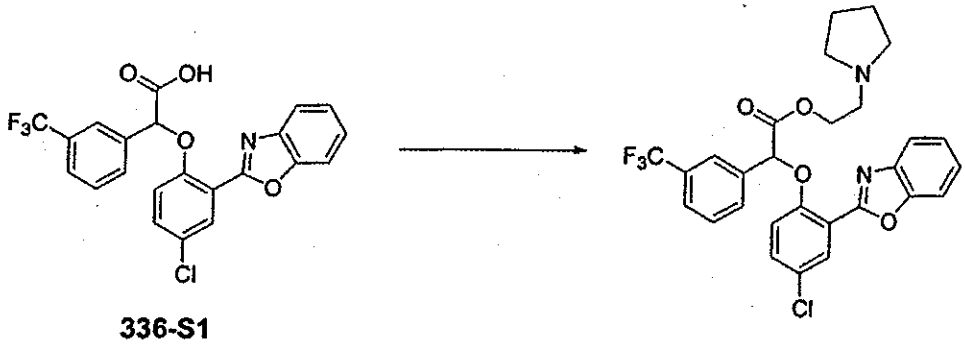
Example 335



335-S1 **335**

[0611] To a flask under air was added 8.96 g (20.0 mmol) of **335-S1**, 100 mL of anhydrous DMF and 4.05 g (25.0 mmol; 1.25 equiv.) of 1,1'-carbonyldiimidazole. After stirring at room temperature for 30 minutes, 6.6 mL (49.9 mmol; 2.50 equiv.) of 2-dimethylamino-ethanol was added. After stirring for an additional 2 hours at room temperature, the reaction mixture was poured into 500 mL of EtOAc and rinsed with water 3 x 250 mL. After phase separation, 500 mL of heptane was added to the organic phase. The organic phase was concentrated to ~ 200 mL via a rotaotory evaporator. The resulting precipitate was collected in a filter funnel and rinsed with heptane 2 x 50 mL. After air drying, 6.62 g (61% yield) of a white solid (m.p. 78-80 °C) was obtained. ^{1}H-NMR (400 MHz, d_6-DMSO) δ 8.29 (s, 1H), 8.12 (d, 1H, J=2.4), 8.02 (d, 1H, J=8.0), 7.66-7.83 (m, 5H), 7.43-7.49 (m, 2H), 7.31 (d, 1H, J=8.8), 6.52 (s, 1H), 4.09 (m, 2H), 2.46 (m, 2H), 2.27 (q, 4H, J=7.2), 0.71 (t, 6H, J=7.2).

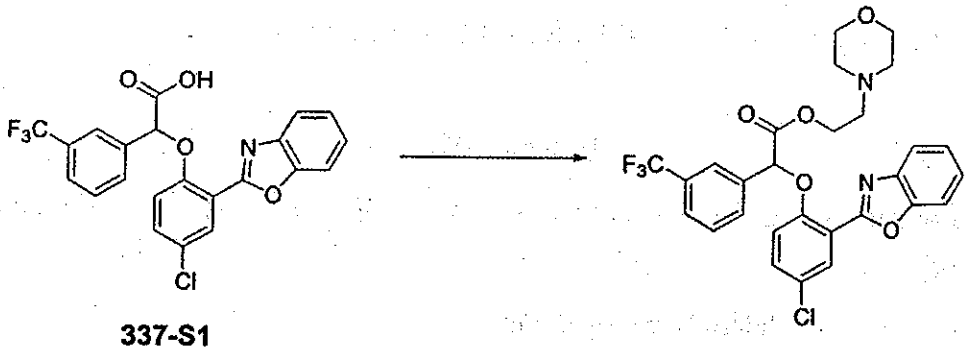
Example 336



336-S1 **336**

[0612] This compound was synthesized via a procedure analogous to that used in the preparation of **335** with the exception that 2.50 equiv. of 2-pyrrolidin-1-yl-ethanol was used instead. 77% yield. Melting point: 97-99 °C. ^{1}H-NMR (400 MHz, d_6-DMSO) δ 8.30 (s, 1H), 8.13 (d, 1H, J=2.4), 8.02 (d, 1H, J=7.6), 7.65-7.83 (m, 5H), 7.45-7.48 (m, 2H), 7.31 (d, 1H, J=8.8), 6.55 (s, 1H), 4.13 (m, 2H), 2.46 (m, 2H), 2.21 (m, 4H), 1.46 (m, 4H).

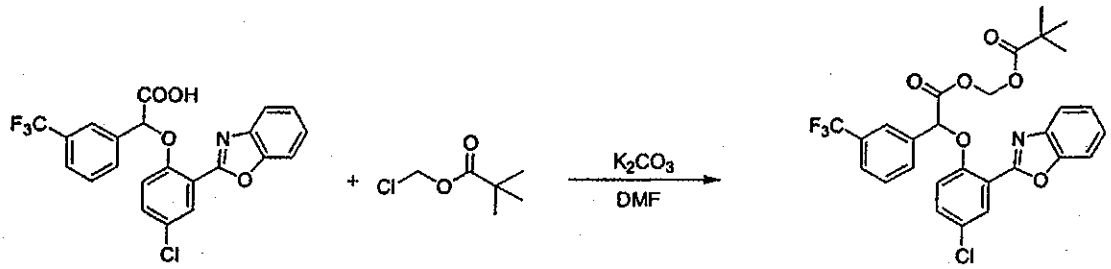
Example 337



337-S1 **337**

[0613] This compound was synthesized via a procedure analogous to that used in the preparation of **335** with the exception that 2.50 equiv. of 2-morpholin-4-yl-ethanol was used instead. 82% yield. Melting point: 93-95 °C. ^{1}H-NMR (400 MHz, d_6-DMSO) δ 8.30 (s, 1H), 8.13 (d, 1H, J=2.4), 8.02 (d, 1H, J=8.0), 7.67-7.82 (m, 5H), 7.45-7.50 (m, 2H), 7.31 (d, 1H, J=9.2), 6.55 (s, 1H), 4.19 (m, 1H), 4.11 (m, 1H), 2.46 (m, 2H), 3.28 (m, 4H), 2.32 (m, 2H), 2.10 (m, 4H).

Example 338



338-S1 338

[0614] To a solution of **338-S1** (2.35 g, 5.25 mmol) in DMF (15 mL) at rt was added K_2CO_3 (1.06 g, 7.67 mmol), and then followed by chloromethyl pivalate (2.0 mL, 13.5 mmol). After stirring for 1 h at 40 °C, the reaction mixture was diluted with EtOAc and aq. NH_4Cl/H_2O. The organic layer was washed with aq. NH_4Cl/H_2O, and then brine/water, dried over Na_2SO_4, concentrated *in vacuo*. Purification *via* chromatography with EtOAc/hexanes (10% to 20%) to afforded **338** (1.19 g, 40%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (1H, s), 8.27 (1H, d, J = 2.8 Hz), 7.92 (1H, d, J = 7.2 Hz), 7.82 (1H, m), 7.68 (1H, d, J = 7.2 Hz), 7.54–7.58 (2H, m), 7.38–7.43 (3H, m), 6.97 (1H, d, J = 8.8 Hz), 5.89 (1H, s), 5.81 (1H, d, J = 5.4 Hz), 5.72 (1H, d, J = 5.4 Hz), 1.04 (9H, s) ppm.

In vivo Activities

[0615] The anti-diabetic activities of the compounds were evaluated in the C57BL/6j ob/ob Mice model.

A. Materials and methods

[0616] Male, 7-9 weeks old, C57BL/6J ob/ob mice were purchased from The Jackson Laboratory (Bar Harbor, ME, USA). Animals were housed (4-5 mice/cage) under standard laboratory conditions at 22 ± 3^{0}C temperature and 50 ± 20% relative humidity, and were maintained on a diet of Purina rodent chow and water *ad libitum*. Prior to treatment, blood was collected from the tail vein of each animal. Mice that had non-fasting plasma glucose levels between 250 and 500 mg/dl were used. Each treatment group consisted of 8-10 mice that were distributed so that the mean glucose levels were equivalent in each group at the start of the study. Mice were dosed orally by gavage once a day for 1-4 days with vehicle and one or more dose of test compound at a dose ranging from 5 to 125 mg/kg. Compounds were delivered in a liquid formulation containing 5% (v/v) dimethyl sulfoxide (DMSO), 1% (v/v) Tween 80® and 0.9% (w/v) methylcellulose. The gavage volume was 10 ml/kg. Blood

samples were taken at 6 hours after the each dose and analyzed for plasma glucose. Food intake and body weight were measured daily. Plasma glucose concentrations were determined colorimetrically using a commercial glucose oxidase method (Sigma Chemical Co, St. Louis, MO, USA). Significant difference between groups (comparing drug-treated to vehicle-treated) was evaluated using the Student unpaired t-test.

B. Results

[0617] **Figure 6** illustrates the anti-diabetic effects of selected compounds of the present invention. **Table 15** provides the relative potency of some of these selected compounds. Compounds that are effective for glucose lowering at the dose of ≥125 mg/kg are assigned a potency of +; compounds that are effective for glucose lowering at a dose of >25 mg/kg but <125 mg/kg are assigned a potency of ++; compounds that are effective for glucose lowering at a dose of ≤25 mg/kg are assigned a potency of +++. For example, a compound at 25 mg/kg that lowered the animal glucose level from 400 mg/dL (vehicle group value) to 250 mg/dL, is assigned the potency of +++.

Table 13. Potency of Invention Compounds

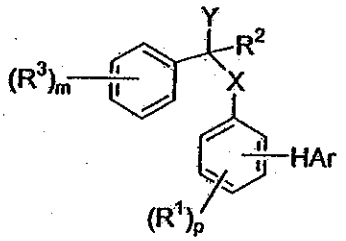
Number	Compound #	Potency	Insulin Level compared with vehicle
1	I-1	++	Lower
2	I-3	+	Lower
3	I-89	+++	Lower
4	I-92	+++	Lower
5	I-190	+++	Lower
6	I-191	+++	Lower
7	I-193	+++	Lower
8	I-194	+++	Lower

9	I-369	+++	Lower
10	I-372	+++	Lower
11	Ia-365	+++	Lower
12	Ia-366	+++	Lower
13	IX-2	++	Lower
14	IX-5	++	Lower
15	XI-2	+++	Lower
16	XI-6	+++	Lower
17	XI-24	+++	Lower
18	XI-47	+++	Lower
19	XI-51	+++	Lower
20	XIa-5	+++	Lower
21	XIa-51	+++	Lower

[0618] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

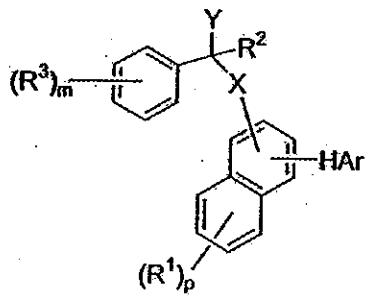
CLAIMS:

1. A compound having a formula selected from the group consisting of:



Ia

and



Ib

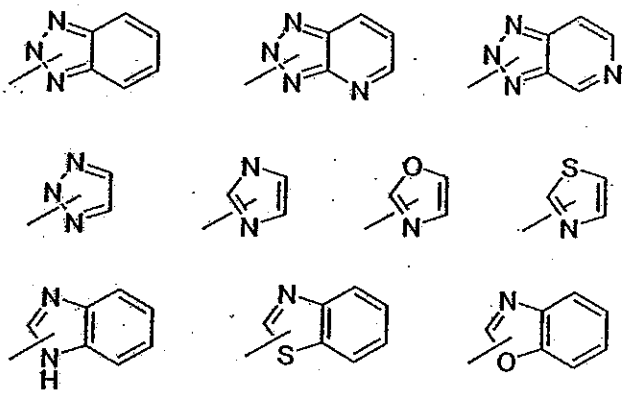
wherein

X is a member selected from the group consisting of O, S, SO and SO_2;

Y is a member selected from the group consisting of CH_2OR^c, CO_2R^c, CHO, $CONR^cR^m$, $CH(=NR^c)$, $CH(=NOR^c)$, $C(O)NHSO_2R^n$, sulfonic acids, sulfinic acids, phosphonic acids, phosphinic acids, activated carboxamides, hydroxamic acids, tetrazol-5-yl, triazole, hydroxypyrazole, hydroxyoxazole, acidic alcohols and SO_2NHX^1, wherein X^1 is an electron withdrawing group relative to an alkyl group, R^c is a member selected from the group consisting of H, $(C_1$-$C_8)$alkyl, $(C_3$-$C_8)$alkenyl, $(C_3$-$C_8)$alkynyl, $(C_3$-$C_7)$cycloalkyl, $(C_4$-$C_8)$cycloalkyl-alkyl, aryl, aryl$(C_1$-$C_8)$alkyl and $(C_1$-$C_8)$alkylene-Z, wherein Z is selected from the group consisting of COR^d, $COOR^d$, NR^dR^e, $NR^dCONR^eR^f$, NR^dCOR^e, NR^dCOOR^e and $CONR^dR^e$ wherein R^d, R^e and R^f are each independently selected from the group consisting of H, $(C_1$-$C_8)$alkyl and phenyl, or optionally two of R^d, R^e and R^f when attached to the same nitrogen atom are combined to form a five- or six-membered ring; and wherein R^m is selected from the group consisting of H, $(C_1$-$C_8)$alkyl, aryl, OH and SO_2R^n, wherein R^n is selected from the group consisting of $(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$haloalkyl, aryl$(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$heteroalkyl, aryl, heteroaryl, $(C_1$-$C_8)$alkoxy, aryloxy, alkylamino, dialkylamino, arylamino, diarylamino, haloalkylamino and di(haloalkyl)amino, and R^m and R^c are optionally combined

with the nitrogen atom to which each is attached to form a five- or six-membered ring;

HAr is selected from the group consisting of



optionally substituted with from one to three substituents independently selected from the group consisting of halogen, hydroxy, $(C_1\text{-}C_8)$alkyl, aryl$(C_1\text{-}C_8)$alkyl, $(C_1\text{-}C_8)$alkoxy, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_4\text{-}C_8)$cycloalkyl-alkyl, $(C_1\text{-}C_8)$heteroalkyl, $(C_2\text{-}C_5)$heterocyclyl, aryl, aryloxy, heterosubstituted$(C_3\text{-}C_7)$cycloalkyl, heteroalkyl substituted $(C_3\text{-}C_7)$cycloalkyl, $(C_1\text{-}C_8)$haloalkyl, O$(C_1\text{-}C_8)$haloalkyl, nitro, cyano, CO_2R^g, COR^g, NR^gR^h, $S(O)_qR^g$, $SO_2NR^gR^h$, $NR^gCONR^hR^i$, NR^gCOR^h, NR^gCOOR^h and $CONR^gR^h$, wherein R^g, R^h and R^i are each independently selected from the group consisting of H and $(C_1\text{-}C_8)$alkyl, or optionally two of R^g, R^h and R^i when attached to the same nitrogen atom are combined to form a five- or six-membered ring, and the subscript q is an integer of from 0 to 2;

each R^1 and R^3 is a member independently selected from the group consisting of halogen, hydroxy, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $(C_1\text{-}C_8)$alkoxy, $(C_3\text{-}C_7)$cycloalkyl, $(C_4\text{-}C_8)$cycloalkyl-alkyl, $(C_1\text{-}C_8)$haloalkyl, $(C_1\text{-}C_8)$heteroalkyl, $(C_2\text{-}C_5)$heterocyclyl, heterosubstituted$(C_3\text{-}C_7)$cycloalkyl, heteroalkyl substituted $(C_3\text{-}C_7)$cycloalkyl, O$(C_1\text{-}C_8)$haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl, $S(O)_r$-phenyl, COR^j, $COOR^j$, NR^jR^k, $S(O)_rR^j$, $SO_2NR^jR^k$, $NR^jCONR^kR^l$, NR^jCOR^k, NR^jCOOR^k and $CONR^jR^k$ wherein the phenyl ring is optionally substituted and R^j, R^k and R^l are each independently selected from the group consisting of H, $(C_1\text{-}C_8)$alkyl and $(C_1\text{-}C_8)$haloalkyl, or optionally two of R^j, R^k

and R^1 when attached to the same nitrogen atom are combined to form a five- or six-membered ring, and the subscript r is an integer of from 0 to 2;

R^2 is a member selected from the group consisting of H, $(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$haloalkyl, aryl$(C_1$-$C_8)$alkyl and $(C_1$-$C_4)$alkylene-Z, wherein Z is as defined above;

the subscript m is an integer of from 0 to 4;

the subscript p is an integer of from 0 to 3; and

pharmaceutically acceptable salts thereof.

2. A compound of claim 1, wherein Y is selected from the group consisting of CH_2OR^c, CO_2R^c, tetrazol-5-yl, $CONHSO_2R^n$ and CHO.

3. A compound of claim 1, wherein Y is selected from the group consisting of CH_2OR^c, tetrazol-5-yl, $CONHSO_2R^n$ and CO_2R^c.

4. A compound of claim 3, wherein HAr is optionally substituted with from one to three substituents independently selected from the group consisting of halogen, $(C_1$-$C_4)$alkyl, aryl, aryloxy, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$haloalkyl, $O(C_1$-$C_4)$haloalkyl, nitro, cyano, CO_2R^g, COR^g and $CONR^gR^h$.

5. A compound of claim 4, wherein X is selected from the group consisting of O and S.

6. A compound of claim 5, wherein R^2 is selected from the group consisting of H, CH_3 and CF_3.

7. A compound of claim 6, wherein HAr is attached to the 2- or 3-position of the ring bearing X and, is optionally substituted with from one to three substituents independently selected from the group consisting of halogen, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$haloalkyl, $O(C_1$-$C_4)$haloalkyl, nitro, cyano, CO_2R^g, COR^g and $CONR^gR^h$.

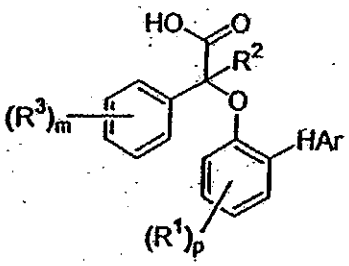
8. A compound of claim 7, wherein the subscript m is an integer of from 0 to 2 and each R^3 when present is independently selected from the group consisting of halogen, $(C_1$-$C_4)$ alkyl,

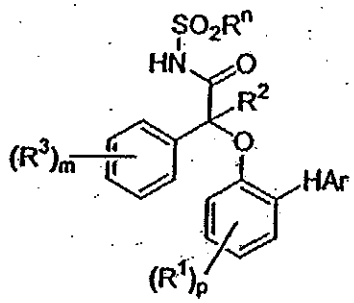
(C_1-C_4)alkoxy, (C_1-C_4)haloalkyl, O(C_1-C_4)haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl and $S(O)_r$-phenyl.

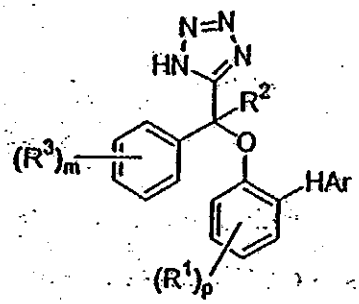
9. A compound of claim 8, wherein p is an integer of from 0 to 2 and each R^1 when present is independently selected from the group consisting of halogen, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)haloalkyl, O(C_1-C_4)haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl and $S(O)_r$-phenyl.

10. A compound of claim 1, wherein m is an integer of from 0 to 2; each R^3 when present is independently selected from the group consisting of halogen, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)haloalkyl, O(C_1-C_4)haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl and $S(O)_r$-phenyl; p is an integer of from 0 to 2; and each R^1 is independently selected from the group consisting of halogen, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)haloalkyl, O(C_1-C_4)haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl and $S(O)_r$-phenyl.

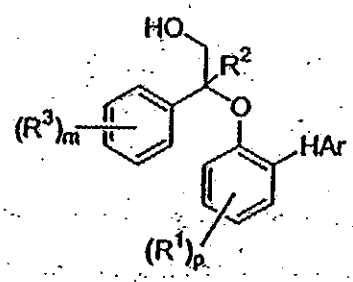
11. A compound of claim 7, having a formula selected from the group consisting of:







and

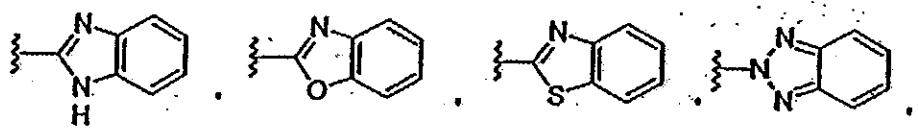


wherein the subscript m is an integer of from 0 to 2, the subscript p is an integer of from 0 to 2, and R^1 and R^3 are each independently selected from the group consisting of halogen, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)haloalkyl, O(C_1-C_4)haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl and $S(O)_r$-phenyl; and R^n is selected from the group consisting of (C_1-C_8)alkyl, (C_1-C_8)haloalkyl, aryl(C_1-C_8)alkyl, (C_1-C_8)heteroalkyl, aryl, heteroaryl, (C_1-

C_8)alkoxy, aryloxy, alkylamino, dialkylamino, arylamino, diarylamino, haloalkylamino and di(haloalkyl)amino.

12. A compound of claim 11, wherein HAr is and is optionally substituted with from one to three substituents independently selected from the group consisting of halogen, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)haloalkyl, O(C_1-C_4)haloalkyl, nitro, cyano, CO_2R^g, COR^g and $CONR^gR^h$.

13. A compound of claim 10, wherein HAr is selected from the group consisting of



wherein each of said HAr groups is optionally substituted with from one to three substituents independently selected from the group consisting of halogen, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)haloalkyl, O(C_1-C_4)haloalkyl, nitro, cyano, CO_2R^c, COR^c and $CONR^cR^d$.

14. A compound of claim 13, wherein HAr is 2-benzoxazolyl; R^2 is H or CH_3; the subscript m is 0 or 1, and p is 1 or 2; and R^1 and R^3 are each independently selected from the group consisting of halogen, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)haloalkyl, O(C_1-C_4)haloalkyl, nitro, cyano, CO_2R^g, COR^g and $CONR^gR^h$.

15. A compound of claim 13, wherein HAr is 2-benzothiazolyl; R^2 is H or CH_3; the subscript m is 0 or 1, and p is 1 or 2; and R^1 and R^3 are each independently selected from the group consisting of halogen, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)haloalkyl, O(C_1-C_4)haloalkyl, nitro, cyano, CO_2R^g, COR^g and $CONR^gR^h$.

16. A compound of claim 13, wherein HAr is 2-benzotriazolyl; R^2 is H or CH_3; the subscript m is 0 or 1, and p is 1 or 2; and R^1 and R^3 are each independently selected from the group consisting of halogen, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)haloalkyl, O(C_1-C_4)haloalkyl, nitro, cyano, CO_2R^g, COR^g and $CONR^gR^h$.

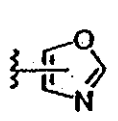
17. A compound of claim 11, wherein R^2 is H or CH_3; the subscript m is 0 or 1, and p is 1 or 2; and R^1 and R^3 are each independently selected from the group consisting of halogen, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)haloalkyl, O(C_1-C_4)haloalkyl, nitro and cyano.

18. A compound of claim 3, wherein HAr is a monocyclic heteroaryl moiety, wherein each of said HAr groups is optionally substituted with from one to three substituents independently selected from the group consisting of halogen, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_8)$heteroalkyl, $(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_4)$haloalkyl, $O(C_1\text{-}C_4)$haloalkyl, aryl$(C_1\text{-}C_4)$alkyl, aryl, heteroaryl, nitro, cyano, CO_2R^g, COR^g and $CONR^gR^h$.

19. A compound of claim 18, wherein X is selected from the group consisting of O and S.

20. A compound of claim 19, wherein R^2 is selected from the group consisting of H, CH_3 and CF_3.

21. A compound of claim 20, wherein HAr is attached to the 2- or 3-position of the phenyl ring bearing X and is selected from the group consisting of



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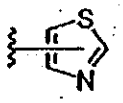
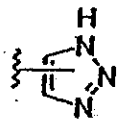


and


.

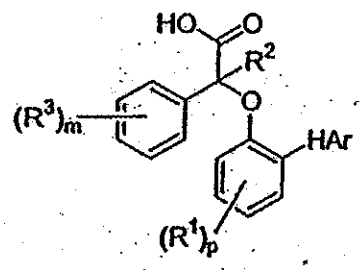
wherein each of said HAr groups is optionally substituted with from one to three substituents independently selected from the group consisting of halogen, $(C_1$-$C_4)$alkyl, $(C_1$-$C_8)$heteroalkyl, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$haloalkyl, $O(C_1$-$C_4)$haloalkyl, aryl$(C_1$-$C_4)$alkyl, aryl, heteroaryl, nitro, cyano, CO_2R^g, COR^g and $CONR^gR^h$, and the wavy line indicates the attachment to the ring bearing X.

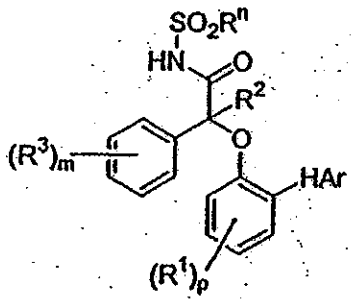
22. A compound of claim 21, wherein m is 0 to 2 and each R^3 when present is independently selected from the group consisting of halogen, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$haloalkyl, $O(C_1$-$C_4)$haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl and $S(O)_r$-phenyl.

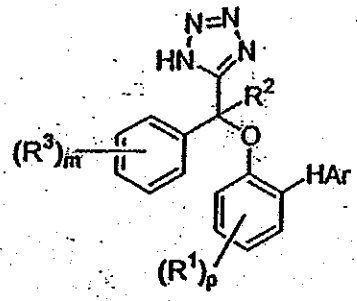
23. A compound of claim 22, wherein p is 0 to 2 and each R^1 when present is independently selected from the group consisting of halogen, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$haloalkyl, $O(C_1$-$C_4)$haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl and $S(O)_r$-phenyl.

24. A compound of claim 23, wherein m is an integer of from 0 to 2; each R^3 is independently selected from the group consisting of halogen, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$haloalkyl, $O(C_1$-$C_4)$haloalkyl, nitro and cyano; p is an integer of from 0 to 2; and each R^1 is independently selected from the group consisting of halogen, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$haloalkyl, $O(C_1$-$C_4)$haloalkyl, nitro and cyano.

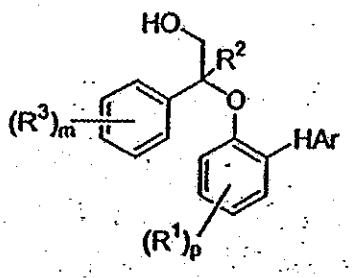
25. A compound of claim 21, having a formula selected from the group consisting of:





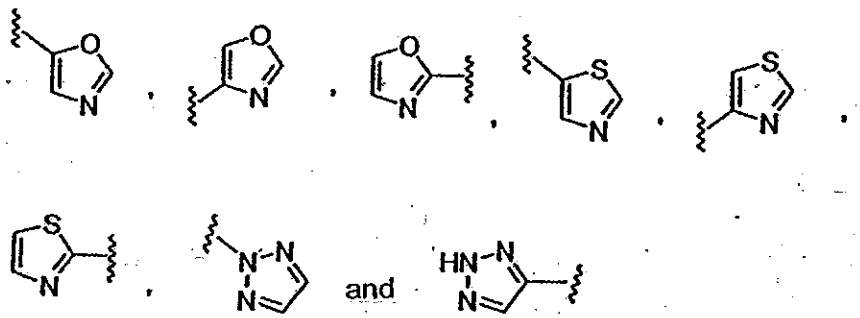


and



wherein m is an integer of from 0 to 2, p is an integer of from 0 to 2, and R^1 and R^3 are each independently selected from the group consisting of halogen, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)haloalkyl, $O(C_1-C_4)$haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl and $S(O)_r$-phenyl; and R^n is selected from the group consisting of (C_1-C_8)alkyl, (C_1-C_8)haloalkyl, aryl(C_1-C_8)alkyl, (C_1-C_8)heteroalkyl, aryl, heteroaryl, (C_1-C_8)alkoxy, aryloxy, alkylamino, dialkylamino, arylamino, diarylamino, haloalkylamino and di(haloalkyl)amino.

26. A compound of claim 25, wherein HAr is selected from the group consisting of



wherein each of said HAr groups is optionally substituted with from one to two substituents independently selected from the group consisting of halogen, (C_1-C_4)alkyl, (C_1-C_8)heteroalkyl, (C_1-C_4)alkoxy, (C_1-C_4)haloalkyl, $O(C_1-C_4)$haloalkyl, aryl(C_1-C_4)alkyl, aryl, heteroaryl, nitro, cyano, CO_2R^g, COR^g and $CONR^gR^h$.

27. A compound of claim 26, wherein m is an integer of from 0 to 2, p is an integer of from 0 to 2, R^1 and R^3 are each independently selected from the group consisting of F, Cl, Br, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)haloalkyl, $O(C_1-C_4)$haloalkyl, CN, NO_2 and phenyl.

28. A compound of claim 27, wherein HAr is optionally substituted 2-, 4- or 5-thiazolyl wherein the thiazolyl is optionally substituted with from one to two substituents selected from the group consisting of F, Cl, Br, (C_1-C_4)alkyl, aryl(C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)haloalkyl, $O(C_1-C_4)$haloalkyl, CN and phenyl; R^2 is H or CH_3; the subscript m is 0 or 1 and p is 1 or 2; and R^1 and R^3 are each independently selected from the group consisting of F, Cl, Br, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)haloalkyl, $O(C_1-C_4)$haloalkyl, CN, NO_2 and phenyl.

29. A compound of claim 27, wherein HAr is optionally substituted 2-, 4- or 5-oxazolyl wherein the oxazolyl is optionally substituted with from one to two substituents selected from the group consisting of F, Cl, Br, $(C_1$-$C_4)$alkyl, aryl$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$haloalkyl, O$(C_1$-$C_4)$haloalkyl, CN and phenyl; R^2 is H or CH_3; the subscript m is 0 or 1 and p is 1 or 2; and R^1 and R^3 are each independently selected from the group consisting of F, Cl, Br, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$haloalkyl, O$(C_1$-$C_4)$haloalkyl, CN, NO_2 and phenyl.

30. A compound of claim 27, wherein Har is optionally substituted 1,2,3-triazol-2-yl wherein the 1,2,3-triazol-2-yl is optionally substituted with from one to two substituents selected from the group consisting of F, Cl, Br, $(C_1$-$C_4)$alkyl, aryl$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$haloalkyl, O$(C_1$-$C_4)$haloalkyl, CN and phenyl; R^2 is H or CH_3; the subscript m is 0 or 1 and p is 1 or 2; and R^1 and R^3 are each independently selected from the group consisting of F, Cl, Br, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$haloalkyl, O$(C_1$-$C_4)$haloalkyl, CN, NO_2 and phenyl.

31. A composition comprising a pharmaceutically acceptable excipient and a compound in accordance with any one of claims 1-30.

32. A composition in accordance with claim 31, wherein Y is selected from the group consisting of CH_2OR^c, CO_2R^c, tetrazol-5-yl, $CONHSO_2R^n$ and CHO.

33. A composition in accordance with claim 32, wherein Y selected from the group consisting of CH_2OR^c, tetrazol-5-yl, $CONHSO_2R^n$ and CO_2R^c.

34. A composition in accordance with claim 33, wherein HAr is optionally substituted with from one to three substituents independently selected from the group consisting of halogen, $(C_1$-$C_4)$alkyl, aryl, aryloxy, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$haloalkyl, O$(C_1$-$C_4)$haloalkyl, nitro, cyano, CO_2R^g, COR^g and $CONR^gR^h$.

35. A composition in accordance with claim 34, wherein X is selected from the group consisting of O and S.

36. A composition in accordance with claim 35, wherein R^2 is selected from the group consisting of H, CH_3 and CF_3.

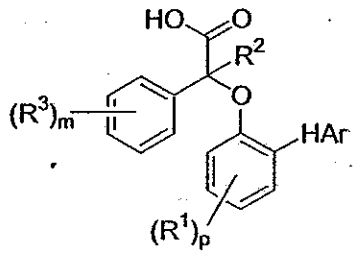
37. A composition in accordance with claim 36, wherein HAr is attached to the 2- or 3-position of the ring bearing X and is optionally substituted with from one to three substituents independently selected from the group consisting of halogen, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_4)$haloalkyl, $O(C_1\text{-}C_4)$haloalkyl, nitro, cyano, CO_2R^g, COR^g and $CONR^gR^h$.

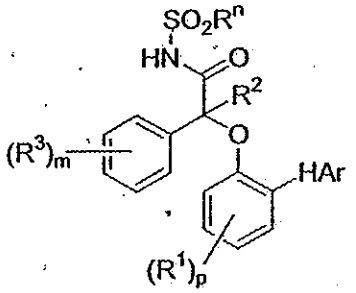
38. A composition in accordance with claim 37, wherein m is from 0 to 2; and each R^3 when present is independently selected from the group consisting of halogen, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_4)$haloalkyl, $O(C_1\text{-}C_4)$haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl and $S(O)_r$-phenyl.

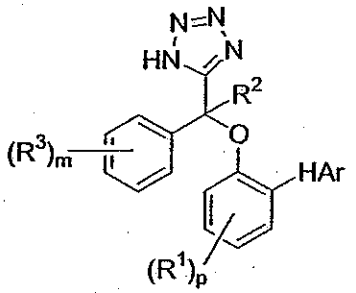
39. A composition in accordance with claim 38, wherein p is from 0 to 2; and each R^1 when present is independently selected from the group consisting of halogen, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_4)$haloalkyl, $O(C_1\text{-}C_4)$haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl and $S(O)_r$-phenyl.

40. A composition in accordance with claim 31, wherein m is an integer of from 0 to 2; each R^3 is independently selected from the group consisting of halogen, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$haloalkyl, $O(C_1$-$C_4)$haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl and $S(O)_r$-phenyl; p is an integer of from 0 to 2; and each R^1 is independently selected from the group consisting of halogen, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$haloalkyl, $O(C_1$-$C_4)$haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl and $S(O)_r$-phenyl.

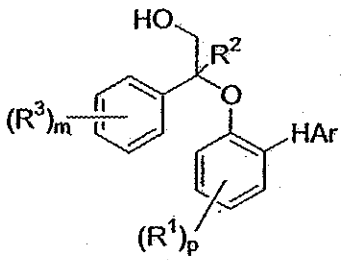
41. A composition in accordance with claim 37, having a formula selected from the group consisting of:







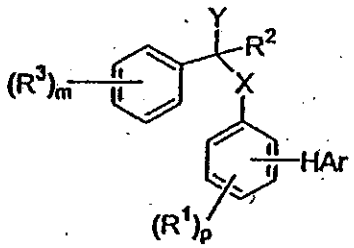
and



wherein the subscript m is an integer of from 0 to 2; the subscript p is an integer of from 0 to 2; R^1 and R^3 are each independently selected from the group consisting of halogen, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$haloalkyl, $O(C_1$-$C_4)$haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl and $S(O)_r$-phenyl; and R^n is selected from the group consisting of $(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$haloalkyl, aryl$(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$heteroalkyl, aryl, heteroaryl, $(C_1$-$C_8)$alkoxy, aryloxy, alkylamino, dialkylamino, arylamino, diarylamino, haloalkylamino and di(haloalkyl)amino.

42. A composition in accordance with claim 41, wherein HAr is optionally substituted with from one to three substituents independently selected from the group consisting of halogen, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$haloalkyl, $O(C_1$-$C_4)$haloalkyl, nitro, cyano, CO_2R^g, COR^g and $CONR^gR^h$.

43. A use of a compound having the formula:



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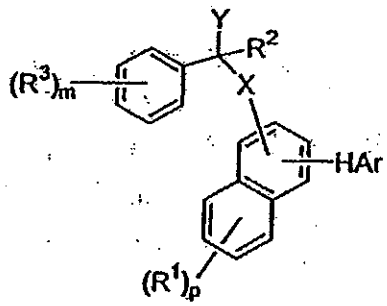
and



Ib

wherein

X is a member selected from the group consisting of O, S, SO, SO_2 and NR, wherein R is H, $(C_1$-$C_8)$alkyl, COR^a, $COOR^a$ and $CONR^aR^b$ wherein R^a and R^b are each independently selected from the group consisting of H and $(C_1$-$C_8)$alkyl;

Y is a member selected from the group consisting of CH_2OR^c, CO_2R^c, CHO, $CONR^cR^m$, $CH(=NR^c)$, $CH(=NOR^c)$ and carboxylic acid surrogates, wherein R^c is a member selected from the group consisting of H, $(C_1$-$C_8)$alkyl, $(C_3$-$C_8)$alkenyl, $(C_3$-$C_8)$alkynyl, $(C_3$-$C_7)$cycloalkyl, $(C_4$-$C_8)$cycloalkyl-alkyl, aryl, aryl$(C_1$-$C_8)$alkyl and $(C_1$-$C_8)$alkylene-Z, wherein Z is selected from the group consisting of COR^d, $COOR^d$, NR^dR^e, $NR^dCONR^eR^f$, NR^dCOR^e, NR^dCOOR^e and $CONR^dR^e$ wherein R^d, R^e and R^f are each independently selected from the group consisting of H, $(C_1$-$C_8)$alkyl and phenyl, or optionally two of R^d, R^e and R^f when attached to the same nitrogen atom are combined to form a five- or six-membered ring; and wherein R^m is selected from the group consisting of H, $(C_1$-$C_8)$alkyl, aryl, OH and SO_2R^n, wherein R^n is selected from the group consisting of $(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$haloalkyl, aryl$(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$heteroalkyl, aryl, heteroaryl, $(C_1$-$C_8)$alkoxy, aryloxy, alkylamino, dialkylamino, arylamino, diarylamino, haloalkylamino and

di(haloalkyl)amino, and R^m and R^c are optionally combined with the nitrogen atom to which each is attached to form a five- or six-membered ring;

HAr is heteroaryl moiety, optionally substituted with from one to three substituents independently selected from the group consisting of halogen, hydroxy, (C_1-C_8)alkyl, aryl(C_1-C_8)alkyl, (C_1-C_8)alkoxy, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_7)cycloalkyl, (C_4-C_8)cycloalkyl-alkyl, (C_1-C_8)heteroalkyl, (C_2-C_5)heterocyclyl, aryl, aryloxy, heterosubstituted(C_3-C_7)cycloalkyl, heteroalkyl substituted (C_3-C_7)cycloalkyl, (C_1-C_8)haloalkyl, O(C_1-C_8)haloalkyl, nitro, cyano, CO_2R^g, COR^g, NR^gR^h, $S(O)_qR^g$, $SO_2NR^gR^h$, $NR^gCONR^hR^i$, NR^gCOR^h, NR^gCOOR^h and $CONR^gR^h$, wherein R^g, R^h and R^i are each independently selected from the group consisting of H and (C_1-C_8)alkyl, or optionally two of R^g, R^h and R^i when attached to the same nitrogen atom are combined to form a five- or six-membered ring, and the subscript q is an integer of from 0 to 2;

each R^1 and R^3 is a member independently selected from the group consisting of halogen, hydroxy, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_1-C_8)alkoxy, (C_3-C_7)cycloalkyl, (C_4-C_8)cycloalkyl-alkyl, (C_1-C_8)haloalkyl, (C_1-C_8)heteroalkyl, (C_2-C_5)heterocyclyl, heterosubstituted(C_3-C_7)cycloalkyl, heteroalkyl substituted (C_3-C_7)cycloalkyl, O(C_1-C_8)haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl, $S(O)_r$-phenyl, COR^j, $COOR^j$, NR^jR^k, $S(O)_rR^j$, $SO_2NR^jR^k$, $NR^jCONR^kR^l$, NR^jCOR^k, NR^jCOOR^k and $CONR^jR^k$ wherein the phenyl ring is optionally substituted and R^j, R^k and R^l are each independently selected from the group consisting of H, (C_1-C_8)alkyl and (C_1-C_8)haloalkyl, or optionally two of R^j, R^k and R^l when attached to the same nitrogen atom are combined to form a five- or six-membered ring, and the subscript r is an integer of from 0 to 2;

R^2 is a member selected from the group consisting of H, (C_1-C_8)alkyl, (C_1-C_8)haloalkyl, aryl(C_1-C_8)alkyl and (C_1-C_4)alkylene-Z, wherein Z is as defined above;

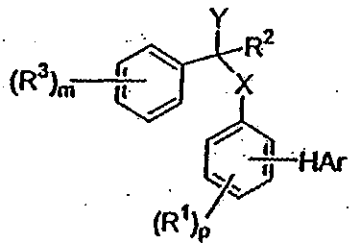
the subscript m is an integer of from 0 to 4;

the subscript p is an integer of from 0 to 3; and

pharmaceutically acceptable salts thereof in the manufacture of a medicament for treating Type 2 diabetes.

44. The use as claimed in claim 43, wherein said medicament is suitable for intravenous, transdermal or oral administration.

45. A use of a compound having the formula:



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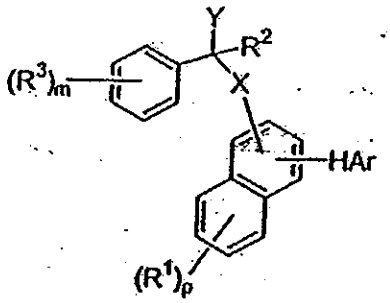


Ib

wherein

X is a member selected from the group consisting of O, S, SO, SO_2 and NR, wherein R is H, $(C_1$-$C_8)$alkyl, COR^a, $COOR^a$ and $CONR^aR^b$ wherein R^a and R^b are each independently selected from the group consisting of H and $(C_1$-$C_8)$alkyl;

Y is a member selected from the group consisting of CH_2OR^c, CO_2R^c, CHO, $CONR^cR^m$, $CH(=NR^c)$, $CH(=NOR^c)$ and carboxylic acid surrogates, wherein R^c is a member selected from the group consisting of H, $(C_1$-$C_8)$alkyl, $(C_3$-$C_8)$alkenyl, $(C_3$-$C_8)$alkynyl, $(C_3$-$C_7)$cycloalkyl, $(C_4$-$C_8)$cycloalkyl-alkyl, aryl, aryl$(C_1$-$C_8)$alkyl and $(C_1$-$C_8)$alkylene-Z, wherein Z is selected from the group consisting of COR^d, $COOR^d$, NR^dR^e, $NR^dCONR^eR^f$, NR^dCOR^e, NR^dCOOR^e and $CONR^dR^e$ wherein R^d, R^e and R^f are each independently selected from the group consisting of H, $(C_1$-$C_8)$alkyl and phenyl, or optionally two of R^d, R^e and R^f when attached to the same nitrogen atom are combined to form a five- or six-membered ring; and wherein R^m is selected from the group consisting of H, $(C_1$-$C_8)$alkyl, aryl, OH and SO_2R^n, wherein R^n is selected from the group consisting of $(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$haloalkyl, aryl$(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$heteroalkyl, aryl, heteroaryl, $(C_1$-$C_8)$alkoxy, aryloxy, alkylamino, dialkylamino, arylamino, diarylamino, haloalkylamino and di(haloalkyl)amino, and R^m and R^c are optionally combined with the nitrogen atom to which each is attached to form a five- or six-membered ring;

HAr is heteroaryl moiety, optionally substituted with from one to three substituents independently selected from the group consisting of halogen, hydroxy, $(C_1$-$C_8)$alkyl, aryl$(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$alkoxy, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl,

(C_3-C_7)cycloalkyl, (C_4-C_8)cycloalkyl-alkyl, (C_1-C_8)heteroalkyl, (C_2-C_5)heterocyclyl, aryl, aryloxy, heterosubstituted(C_3-C_7)cycloalkyl, heteroalkyl substituted (C_3-C_7)cycloalkyl, (C_1-C_8)haloalkyl, O(C_1-C_8)haloalkyl, nitro, cyano, CO_2R^g, COR^g, NR^gR^h, $S(O)_qR^g$, $SO_2NR^gR^h$, $NR^gCONR^hR^i$, NR^gCOR^h, NR^gCOOR^h and $CONR^gR^h$, wherein R^g, R^h and R^i are each independently selected from the group consisting of H and (C_1-C_8)alkyl, or optionally two of R^g, R^h and R^i when attached to the same nitrogen atom ~~are~~ combined to form a five- or six-membered ring, and the subscript q is an integer of from 0 to 2;

each R^1 and R^3 is a member independently selected from the group consisting of halogen, hydroxy, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_1-C_8)alkoxy, (C_3-C_7)cycloalkyl, (C_4-C_8)cycloalkyl-alkyl, (C_1-C_8)haloalkyl, (C_1-C_8)heteroalkyl, (C_2-C_5)heterocyclyl, heterosubstituted(C_3-C_7)cycloalkyl, heteroalkyl substituted (C_3-C_7)cycloalkyl, O(C_1-C_8)haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl, $S(O)_r$-phenyl, COR^j, $COOR^j$, NR^jR^k, $S(O)_rR^j$, $SO_2NR^jR^k$, $NR^jCONR^kR^l$, NR^jCOR^k, NR^jCOOR^k and $CONR^jR^k$ wherein the phenyl ring is optionally substituted and R^j, R^k and R^l are each independently selected from the group consisting of H, (C_1-C_8)alkyl and (C_1-C_8)haloalkyl, or optionally two of R^j, R^k and R^l when attached to the same nitrogen atom are combined to form a five- or six-membered ring, and the subscript r is an integer of from 0 to 2;

R^2 is a member selected from the group consisting of H, (C_1-C_8)alkyl, (C_1-C_8)haloalkyl, aryl(C_1-C_8)alkyl and (C_1-C_4)alkylene-Z, wherein Z is as defined above;

the subscript m is an integer of from 0 to 4;

the subscript p is an integer of from 0 to 3; and

pharmaceutically acceptable salts thereof in the manufacture of a medicament for modulating insulin resistance.

46. The use as claimed in claim 45, wherein said medicament is suitable for intravenous, oral or topical administration.

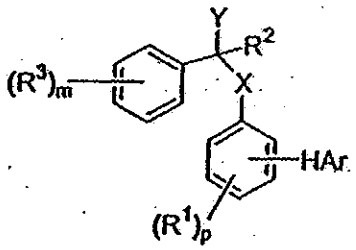
47. The use as claimed in claim 45 wherein said compound modulates a condition selected from the group consisting of polycystic ovarian syndrome, Impaired Glucose Tolerance, obesity, gestational diabetes, Syndrome X and atherosclerosis.

48. The use as claimed in claim 45, wherein said compound is suitable for administration in an amount of from about 1 mg to about 2000 mg per day.

49. The use as claimed in claim 45, wherein said compound is suitable for administration together with a pharmaceutically acceptable carrier.

50. The use as claimed claim 45, wherein said compound is suitable for administration in combination with a clinically effective agent selected from the group consisting of a sulfonylurea or other insulin secretogogue, a thiazolidinedione, a fibrate, a HMG-CoA reductase inhibitor, a biguanide, a bile acid binding resin, nicotinic acid, an α-glucosidase inhibitor and insulin.

51. A use of a compound having the formula:



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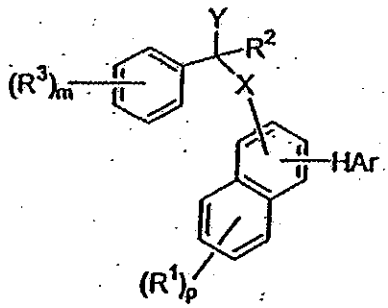


Ib

wherein

X is a member selected from the group consisting of O, S, SO, SO_2 and NR, wherein R is H, $(C_1$-$C_8)$alkyl, COR^a, $COOR^a$ and $CONR^aR^b$ wherein R^a and R^b are each independently selected from the group consisting of H and $(C_1$-$C_8)$alkyl;

Y is a member selected from the group consisting of CH_2OR^c, CO_2R^c, CHO, $CONR^cR^m$, $CH(=NR^c)$, $CH(=NOR^c)$ and carboxylic acid surrogates, wherein R^c is a member selected from the group consisting of H, $(C_1$-$C_8)$alkyl, $(C_3$-$C_8)$alkenyl, $(C_3$-$C_8)$alkynyl, $(C_3$-$C_7)$cycloalkyl, $(C_4$-$C_8)$cycloalkyl-alkyl, aryl, aryl$(C_1$-$C_8)$alkyl and $(C_1$-$C_8)$alkylene-Z, wherein Z is selected from the group consisting of COR^d, $COOR^d$, NR^dR^e, $NR^dCONR^eR^f$, NR^dCOR^e, NR^dCOOR^e and $CONR^dR^e$ wherein R^d, R^e and R^f are each independently selected from the group consisting of H, $(C_1$-$C_8)$alkyl and phenyl, or optionally two of R^d, R^e and R^f when attached to the same nitrogen atom are combined to form a five-

or six-membered ring; and wherein R^m is selected from the group consisting of H, (C_1-C_8)alkyl, aryl, OH and SO_2R^n, wherein R^n is selected from the group consisting of (C_1-C_8)alkyl, (C_1-C_8)haloalkyl, aryl(C_1-C_8)alkyl, (C_1-C_8)heteroalkyl, aryl, heteroaryl, (C_1-C_8)alkoxy, aryloxy, alkylamino, dialkylamino, arylamino, diarylamino, haloalkylamino and di(haloalkyl)amino, and R^m and R^c are optionally combined with the nitrogen atom to which each is attached to form a five- or six-membered ring;

HAr is heteroaryl moiety, optionally substituted with from one to three substituents independently selected from the group consisting of halogen, hydroxy, (C_1-C_8)alkyl, aryl(C_1-C_8)alkyl, (C_1-C_8)alkoxy, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_7)cycloalkyl, (C_4-C_8)cycloalkyl-alkyl, (C_1-C_8)heteroalkyl, (C_2-C_5)heterocyclyl, aryl, aryloxy, heterosubstituted(C_3-C_7)cycloalkyl, heteroalkyl substituted (C_3-C_7)cycloalkyl, (C_1-C_8)haloalkyl, O(C_1-C_8)haloalkyl, nitro, cyano, CO_2R^g, COR^g, NR^gR^h, $S(O)_qR^g$, $SO_2NR^gR^h$, $NR^gCONR^hR^i$, NR^gCOR^h, NR^gCOOR^h and $CONR^gR^h$, wherein R^g, R^h and R^i are each independently selected from the group consisting of H and (C_1-C_8)alkyl, or optionally two of R^g, R^h and R^i when attached to the same nitrogen atom are combined to form a five- or six-membered ring, and the subscript q is an integer of from 0 to 2;

each R^1 and R^3 is a member independently selected from the group consisting of halogen, hydroxy, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_1-C_8)alkoxy, (C_3-C_7)cycloalkyl, (C_4-C_8)cycloalkyl-alkyl, (C_1-C_8)haloalkyl, (C_1-C_8)heteroalkyl, (C_2-C_5)heterocyclyl, heterosubstituted(C_3-C_7)cycloalkyl, heteroalkyl substituted (C_3-C_7)cycloalkyl, O(C_1-C_8)haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl, $S(O)_r$-phenyl, COR^j, $COOR^j$, NR^jR^k, $S(O)_rR^j$, $SO_2NR^jR^k$, $NR^jCONR^kR^l$, NR^jCOR^k, NR^jCOOR^k and $CONR^jR^k$ wherein the phenyl ring is optionally substituted and R^j, R^k and R^l are each independently selected from the group consisting of H, (C_1-C_8)alkyl and (C_1-C_8)haloalkyl, or optionally two of R^j, R^k and R^l when attached to the same nitrogen atom are combined to form a five- or six-membered ring, and the subscript r is an integer of from 0 to 2;

R^2 is a member selected from the group consisting of H, (C_1-C_8)alkyl, (C_1-C_8)haloalkyl, aryl(C_1-C_8)alkyl and (C_1-C_4)alkylene-Z, wherein Z is as defined above;

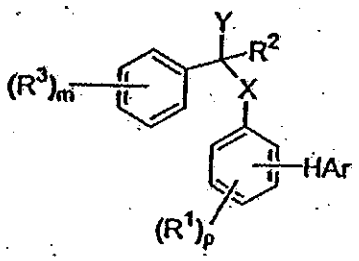
the subscript m is an integer of from 0 to 4;

the subscript p is an integer of from 0 to 3; and
pharmaceutically acceptable salts thereof in the manufacture of a medicament for alleviating hyperlipidemia.

52. The use as claimed in claim 51, wherein said compound lowers serum cholesterol levels, serum triglyceride levels, or a combination thereof.

53. The use as claimed in claim 51, wherein said compound is suitable for administration to a human subject in an amount of from about 1 mg to about 2000 mg per day.

54. A use of a compound having the formula:



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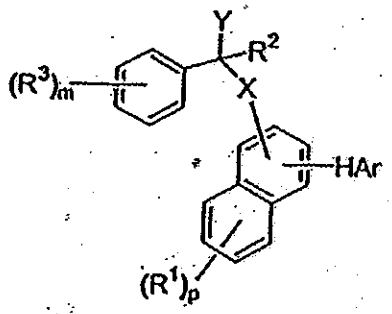
and



Ib

wherein

X is a member selected from the group consisting of O, S, SO, SO_2 and NR, wherein R is H, (C_1-C_8)alkyl, COR^a, $COOR^a$ and $CONR^aR^b$ wherein R^a and R^b are each independently selected from the group consisting of H and (C_1-C_8)alkyl;

Y is a member selected from the group consisting of CH_2OR^c, CO_2R^c, CHO, $CONR^cR^m$, $CH(=NR^c)$, $CH(=NOR^c)$ and carboxylic acid surrogates, wherein R^c is a member selected from the group consisting of H, (C_1-C_8)alkyl, (C_3-C_8)alkenyl, (C_3-C_8)alkynyl, (C_3-C_7)cycloalkyl, (C_4-C_8)cycloalkyl-alkyl, aryl, aryl(C_1-C_8)alkyl and (C_1-C_8)alkylene-Z, wherein Z is selected from the group consisting of COR^d, $COOR^d$, NR^dR^e, $NR^dCONR^eR^f$, NR^dCOR^e, NR^dCOOR^e and $CONR^dR^e$ wherein R^d, R^e and R^f are each independently selected from the group consisting of H, (C_1-C_8)alkyl and phenyl, or optionally two of R^d, R^e and R^f when attached to the same nitrogen atom are combined to form a five- or six-membered ring; and wherein R^m is selected from the group consisting of H, (C_1-C_8)alkyl, aryl, OH and SO_2R^n, wherein R^n is selected from the group consisting of (C_1-C_8)alkyl, (C_1-C_8)haloalkyl, aryl(C_1-C_8)alkyl, (C_1-

C_8)heteroalkyl, aryl, heteroaryl, (C_1-C_8)alkoxy, aryloxy, alkylamino, dialkylamino, arylamino, diarylamino, haloalkylamino and di(haloalkyl)amino, and R^m and R^c are optionally combined with the nitrogen atom to which each is attached to form a five- or six-membered ring;

HAr is heteroaryl moiety, optionally substituted with from one to three substituents independently selected from the group consisting of halogen, hydroxy, (C_1-C_8)alkyl, aryl(C_1-C_8)alkyl, (C_1-C_8)alkoxy, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_7)cycloalkyl, (C_4-C_8)cycloalkyl-alkyl, (C_1-C_8)heteroalkyl, (C_2-C_5)heterocyclyl, aryl, aryloxy, heterosubstituted(C_3-C_7)cycloalkyl, heteroalkyl substituted (C_3-C_7)cycloalkyl, (C_1-C_8)haloalkyl, O(C_1-C_8)haloalkyl, nitro, cyano, CO_2R^g, COR^g, NR^gR^h, $S(O)_qR^g$, $SO_2NR^gR^h$, $NR^gCONR^hR^i$, NR^gCOR^h, NR^gCOOR^h and $CONR^gR^h$, wherein R^g, R^h and R^i are each independently selected from the group consisting of H and (C_1-C_8)alkyl, or optionally two of R^g, R^h and R^i when attached to the same nitrogen atom are combined to form a five- or six-membered ring, and the subscript q is an integer of from 0 to 2;

each R^1 and R^3 is a member independently selected from the group consisting of halogen, hydroxy, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_1-C_8)alkoxy, (C_3-C_7)cycloalkyl, (C_4-C_8)cycloalkyl-alkyl, (C_1-C_8)haloalkyl, (C_1-C_8)heteroalkyl, (C_2-C_5)heterocyclyl, heterosubstituted(C_3-C_7)cycloalkyl, heteroalkyl substituted (C_3-C_7)cycloalkyl, O(C_1-C_8)haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl, $S(O)_r$-phenyl, COR^j, $COOR^j$, NR^jR^k, $S(O)_rR^j$, $SO_2NR^jR^k$, $NR^jCONR^kR^l$, NR^jCOR^k, NR^jCOOR^k and $CONR^jR^k$ wherein the phenyl ring is optionally substituted and R^j, R^k and R^l are each independently selected from the group consisting of H, (C_1-C_8)alkyl and (C_1-C_8)haloalkyl, or optionally two of R^j, R^k and R^l when attached to the same nitrogen atom are combined to form a five- or six-membered ring, and the subscript r is an integer of from 0 to 2;

R^2 is a member selected from the group consisting of H, (C_1-C_8)alkyl, (C_1-C_8)haloalkyl, aryl(C_1-C_8)alkyl and (C_1-C_4)alkylene-Z, wherein Z is as defined above;

the subscript m is an integer of from 0 to 4;

the subscript p is an integer of from 0 to 3; and

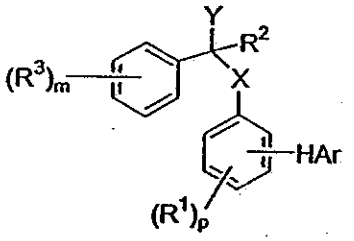
pharmaceutically acceptable salts thereof in the manufacture of a medicament for treating hyperuricemia.

55. The use as claimed in claim 54, wherein said compound is suitable for administration in an amount of from about 1 mg to about 2000 mg per day.

56. The use as claimed in claim 54, wherein said compound is suitable for administration together with a pharmaceutically acceptable carrier.

57. The use as claimed in claim 54, wherein said medicament is suitable for intravenous, oral or topical administration.

58. A prodrug agent having a formula selected from the group consisting of:



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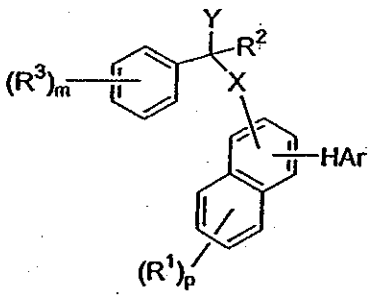
and



Ib

wherein

X is a member selected from the group consisting of O, S, SO, SO_2 and NR, wherein R is H, (C_1-C_8)alkyl, COR^a, $COOR^a$ and $CONR^aR^b$ wherein R^a and R^b are each independently selected from the group consisting of H and (C_1-C_8)alkyl;

Y is CO_2R'', wherein R" is selected from the group consisting of alkyl, heteroalkyl, aryl, heteroaryl, phenyl-lower alkyl, benzamido-lower alkyl, di-lower alkylamino-lower alkyl, ureido-lower alkyl, N'-lower alkyl-ureido-lower alkyl, carbamoyl-lower alkyl, halophenoxy substituted lower alkyl and carbamoyl substituted phenyl;

HAr is benzo-1,2,3-triazole, optionally substituted with from one to three substituents independently selected from the group consisting of halogen, hydroxy, (C_1-C_8)alkyl, aryl(C_1-C_8)alkyl, (C_1-C_8)alkoxy, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_7)cycloalkyl, (C_4-C_8)cycloalkyl-alkyl, (C_1-C_8)heteroalkyl, (C_2-C_5)heterocyclyl, aryl, aryloxy, heterosubstituted(C_3-C_7)cycloalkyl, heteroalkyl substituted (C_3-C_7)cycloalkyl, (C_1-C_8)haloalkyl, O(C_1-C_8)haloalkyl, nitro, cyano, CO_2R^g, COR^g, NR^gR^h, $S(O)_qR^g$, $SO_2NR^gR^h$, $NR^gCONR^hR^i$, NR^gCOR^h, NR^gCOOR^h and $CONR^gR^h$, wherein R^g, R^h and R^i are each independently selected from the group consisting of H and (C_1-C_8)alkyl, or optionally two of R^g, R^h and R^i when attached to the same nitrogen atom are combined to form a five- or six-membered ring, and the subscript q is an integer of from 0 to 2;

each R^1 and R^3 is a member independently selected from the group consisting of halogen, hydroxy, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_1-C_8)alkoxy, (C_3-C_7)cycloalkyl, (C_4-C_8)cycloalkyl-alkyl, (C_1-C_8)haloalkyl, (C_1-C_8)heteroalkyl, (C_2-C_5)heterocyclyl, heterosubstituted(C_3-C_7)cycloalkyl, heteroalkyl substituted (C_3-C_7)cycloalkyl, O(C_1-C_8)haloalkyl, nitro, cyano, phenyl, O-phenyl, NR^j-phenyl, $S(O)_r$-phenyl, COR^j, $COOR^j$, NR^jR^k, $S(O)_rR^j$, $SO_2NR^jR^k$, $NR^jCONR^kR^l$,

NR^jCOR^k, NR^jCOOR^k and $CONR^jR^k$ wherein the phenyl ring is optionally substituted and R^j, R^k and R^l are each independently selected from the group consisting of H, $(C_1$-$C_8)$alkyl and $(C_1$-$C_8)$haloalkyl, or optionally two of R^j, R^k and R^l when attached to the same nitrogen atom are combined to form a five- or six-membered ring, and the subscript r is an integer of from 0 to 2;

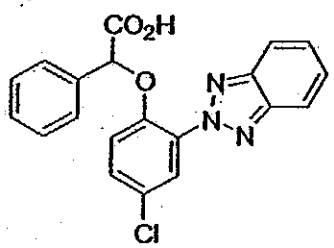
R^2 is a member selected from the group consisting of H, $(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$haloalkyl, aryl$(C_1$-$C_8)$alkyl and $(C_1$-$C_4)$alkylene-Z, wherein Z is as defined above;

the subscript m is an integer of from 0 to 4;

the subscript p is an integer of from 0 to 3; and

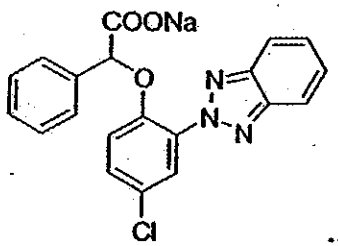
pharmaceutically acceptable salts thereof.

59. A compound of claim 1, having the structure



and pharmaceutically acceptable salts thereof.

60. A compound of claim 1, having the structure



61. A compound of claim 1, selected from the group consisting of (+)-(2-Benzotriazol-2-yl-4-chloro-phenoxy)-phenylacetic acid, (-)-(2-Benzotriazol-2-yl-4-chloro-phenoxy)-phenylacetic acid, and pharmaceutically acceptable salts thereof.

62. A compound of claim 61, which is (+)-(2-Benzotriazol-2-yl-4-chloro-phenoxy)-phenylacetic acid.

63. A compound of claim 61, which is (-)-(2-Benzotriazol-2-yl-4-chloro-phenoxy)-phenylacetic acid.