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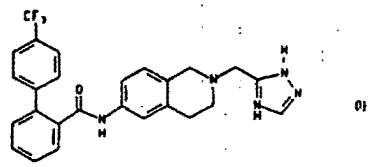
(54) Title: PROCESSES AND INTERMEDIATES FOR PREPARING 4'-TRIFLUOROMETHYLBIPHENYL-2-CARBOXYLIC ACID [2-(2H-[1,2,4]TRIAZOL-3-YLMETHYL)-1,2,3,4-TETRAHYDRO-ISOQUINOLIN-6-YL]-AMIDE

(57) Abstract

A process for preparing the compound of formula (I) which comprises treating the compound of formula (III) wherein R is H or R^2 and R^2 is selected from the group comprising allyl or a substituted methyl group wherein the substituents comprise one to three (C_6-C_{10})aryl groups wherein the aryl groups are further optionally substituted with one or more substituents selected from nitro and (C_1-C_6)alkoxy; a) with a compound of formula (X) wherein J is a leaving group such as a halogen atom, an azido group, a (C_1-C_6)acyloxy group or a (C_6-C_{10})aroyloxy group, preferably a chlorine or bromine atom; and b) when R is R^2 further treating the product of step a) with an acid. A compound of formula (II) wherein R is R^2 and R^2 is as defined above and is, preferably, $CH_3OC_6H_4CH_2$-.



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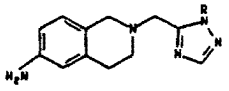

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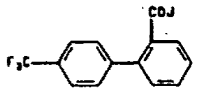

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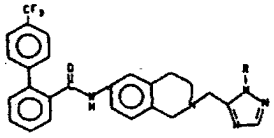

(I)

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PROCESSES AND INTERMEDIATES FOR PREPARING 4'-TRIFLUOROMETHYLBIPHENYL-2-CARBOXYLIC ACID [2-(2H-[1,2,4] TRIAZOL-3-YLMETHYL)-1,2,3,4-TETRAHYDRO-ISOQUINOLIN-6-YL]-AMIDE

Field Of The Invention

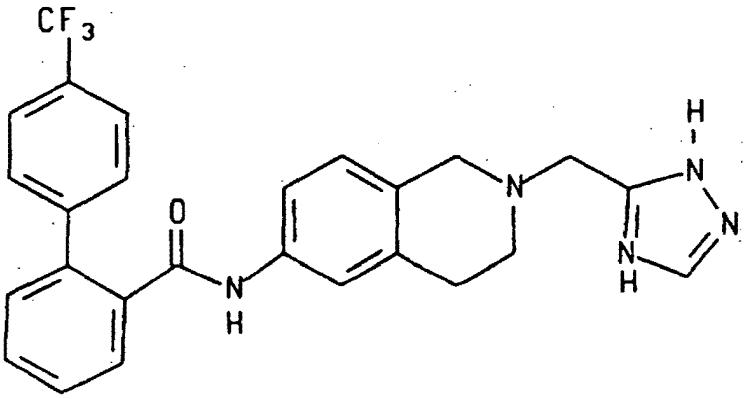
This invention relates to 4'-trifluoromethylbiphenyl-2-carboxylic acid [2-(2H-[1,2,4]triazol-3-ylmethyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl]-amide of formula I below. More particularly it relates to an improved method, and intermediates, for the preparation of compound I. Compound I is an inhibitor of microsomal triglyceride transfer protein C and/or apolipoprotein B (Apo B) secretion and is, accordingly, useful for the prevention and treatment of atherosclerosis and its clinical sequelae, for lowering serum lipids, and related diseases.

Background Of The Invention

Microsomal triglyceride transfer protein (MTP) catalyzes the transport of triglyceride, cholesteryl ester, and phospholipids. It has been implicated as a probable agent in the assembly of Apo B-containing lipoproteins, biomolecules which contribute to the formation of atherosclerotic lesions. See European Patent application publication no. 0 643 057 A1, European Patent application publication no. 0 584 446 A2, and Wetterau et al., Science, 258, 999-1001, (1992). Compounds which inhibit MTP and/or otherwise inhibit Apo B secretion are, therefore, useful in the treatment of atherosclerosis. Such compounds are also useful in the treatment of other diseases or conditions in which, by inhibiting MTP and/or Apo B secretion, serum cholesterol and triglyceride levels can be reduced. Such conditions include hypercholesterolemia, hypertriglyceridemia, pancreatitis, and obesity; and hypercholesterolemia, hypertriglyceridemia, and hyperlipidemia associated with pancreatitis, obesity, and diabetes.

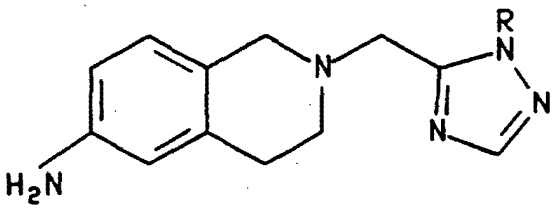
Summary Of The Invention

This invention provides a method for preparing the compound of formula



I

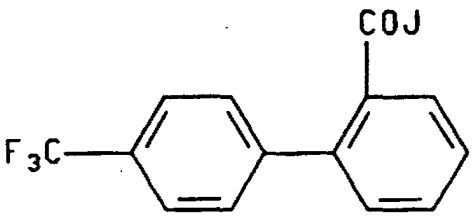
which comprises treating the compound of the formula



III

wherein R is H or R^2 and R^2 is selected from allyl and a substituted methyl group wherein the substituents comprise one to three (C_6-C_{10})aryl groups wherein the aryl groups are optionally substituted with one or more substituents selected from nitro and (C_1-C_6)alkoxy;

a) with a compound of the formula



X

wherein J is a leaving group such as a halogen atom, an azido group, a (C_1-C_6)acyloxy group or a (C_6-C_{10})aroyloxy group, preferably a chlorine or bromine atom; and

b) when R is R^2 further treating the product of step a) with an acid such as trifluoroacetic acid (TFA), p-toluenesulfonic acid (PTSA), methane- or

trifluoromethanesulfonic acid and HBr in acetic acid, preferably trifluoroacetic acid.

Reference to a moiety as "heterocyclic" means any single ring or fused ring system containing at least one ring heteroatom independently selected from O, N, and S. Thus a polycyclic fused ring system containing one or more carbocyclic fused saturated, partially unsaturated, or aromatic rings (usually benzene rings) is within the definition of heterocyclyl so long as the system also contains at least one fused ring which contains at least one of the aforementioned heteroatoms. As a substituent, such heterocyclic rings may be attached to the remainder of the molecule from either a carbocyclic (e.g., benzene) ring or from a heterocyclic ring.

Reference to a moiety containing "one or more rings" is intended to mean that said moiety contains a single or fused cyclic moiety or moieties. The rings may be carbocyclic or heterocyclic, saturated or partially unsaturated, and aromatic or non-aromatic.

Reference to a fused polycyclic ring system or radical means that all rings in the system are fused.

Reference to "halo" in this specification is inclusive of fluoro, chloro, bromo, and iodo unless noted otherwise.

Reference to an "aryl" substitutent (e.g. (C_6-C_{10})aryl) means the ring or substitutent is carbocyclic. Aromatic moieties which contain one or more heteroatoms are included as a subset of the term "heterocyclic", as discussed above.

Reference to an "acyl" substituent refers to an aliphatic or cyclic hydrocarbon moiety attached to a carbonyl group through which the substituent bonds.

Reference to "alkyl" and "alkoxy" include both straight and, when the moiety contains more than two carbon atoms, branched of cyclic chain radicals, but it is to be understood that references to individual radicals such as "propyl" or "propoxy" embrace only the straight chain ("normal") radical, branched chain isomers such as "isopropyl" or "isopropoxy" being referred to specifically.

Certain intermediates of the formula

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