Drugs of the Future 2000, 25(11): 1138-1144

CCC: 0377-8282/2000

C30

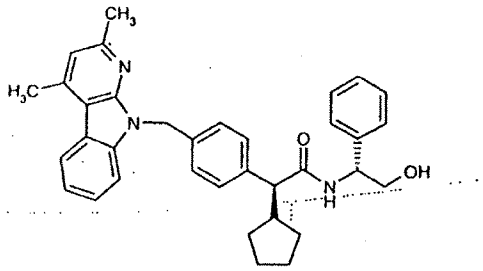
Implitapide

Prop INN

Hypolipidemic
Treatment of Atherosclerosis
MTP Inhibitor
ApoB Secretion Inhibitor

BAY-13-9952

2(*S*)-Cyclopentyl-2-[4-(2,4-dimethyl-9*H*-pyrido[2,3-*b*]indol-9-ylmethyl)phenyl]-*N*-[2-hydroxy-1(*R*)-phenylethyl]acetamide



$C_{35}H_{37}N_3O_2$ Mol wt: 531.7040

CAS: 177469-96-4

EN: 236417

Synthesis

Implitapide has been obtained by two related ways:

1) Reaction of 4,6-dimethylpyridin-2-amine (I) with isoamyl nitrite and HCl gives 2-chloro-4,6-dimethylpyridine (II), which is treated with hydrazine in diethylene glycol at 140 °C yielding 2-hydrazino-4,6-dimethylpyridine (III). Cyclization of (III) with cyclohexanone (IV) in refluxing diethylene glycol affords the tetrahydro-α-carboline (V), which is dehydrogenated with Pd in refluxing diethylene glycol, giving the α-carboline (VI). The alkylation of (VI) with the benzyl bromide (VII) by means of potassium *tert*-butoxide in DMF yields the adduct (VIII), which is hydrolyzed with concentrated H_2SO_4 to provide the carboxylic acid (IX). Finally, this acid is condensed with (*R*)-2-hydroxy-1-phenylethylamine (X) by means of HOBT and EDC in dichloromethane, giving a diastereomeric mixture of the corresponding amides that is resolved by column chromatography (1). Scheme 1.

The benzyl bromide intermediate (VII) has been obtained as follows: Esterification of 2-(4-methylphenyl)acetic acid (XI) with *tert*-butanol and DCC and DMAP in dichloromethane gives the corresponding *tert*-butyl ester (XII), which is condensed with cyclopentyl bromide (XIII) by means of potassium *tert*-butoxide in DMF to yield racemic 2-cyclopentyl-2-(4-methylphenyl)-acetic acid *tert*-butyl ester (XIV). Finally, this compound is brominated with NBS and AIBN in refluxing CCl_4 (1). Scheme 1.

2) Esterification of 2-(4-methylphenyl)acetic acid (XI) with L-menthol (XV) by means of $MeSO_3H$ in refluxing toluene gives the ester (XVI), which is diastereoselectively condensed with cyclopentyl bromide (XIII) by means of *t*-BuOK in DMF, affording 2(*S*)-cyclopentyl-2-(4-methylphenyl)acetic acid L-menthyl ester (XVII). Bromination of (XVII) with 1,3-dibromo-5,5-dimethylhydantoin (DBMH) in hot chlorobenzene gives the chiral benzyl bromide (XVIII), which is condensed with the already described α-carboline (VI) by means of *t*-BuOK in DMF to yield the adduct (XIX). Hydrolysis of (XIX) with HBr in formic acid affords the chiral cyclopentylacetic acid (XX), which is treated with $SOCl_2$ in refluxing dichloromethane to provide the corresponding acyl chloride (XXI). Finally, this compound is condensed with (*R*)-2-hydroxy-1-phenylethylamine (X) by means of TEA in hot toluene (2). Scheme 2.

Description

Crystals, m.p. 221 °C (2).

Introduction

Hypercholesterolemia and hyperlipidemia are considered the major risk factors for the development of coronary heart disease (3-5) and reduction of serum cholesterol levels has been shown to be an effective treatment of atherosclerotic disease (6, 7). Thus, research has focused on the discovery of agents which effectively control plasma lipid levels (8).

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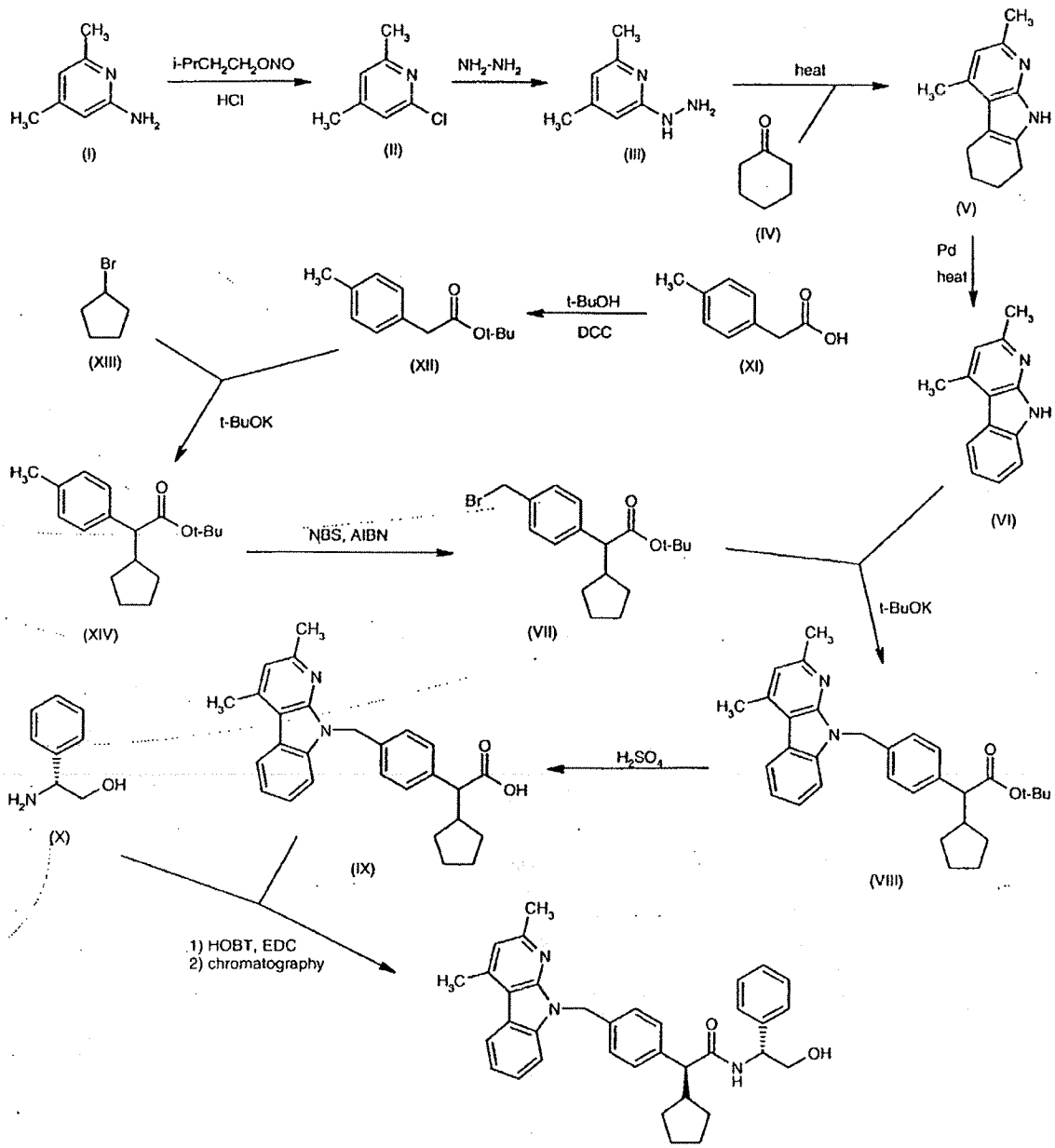
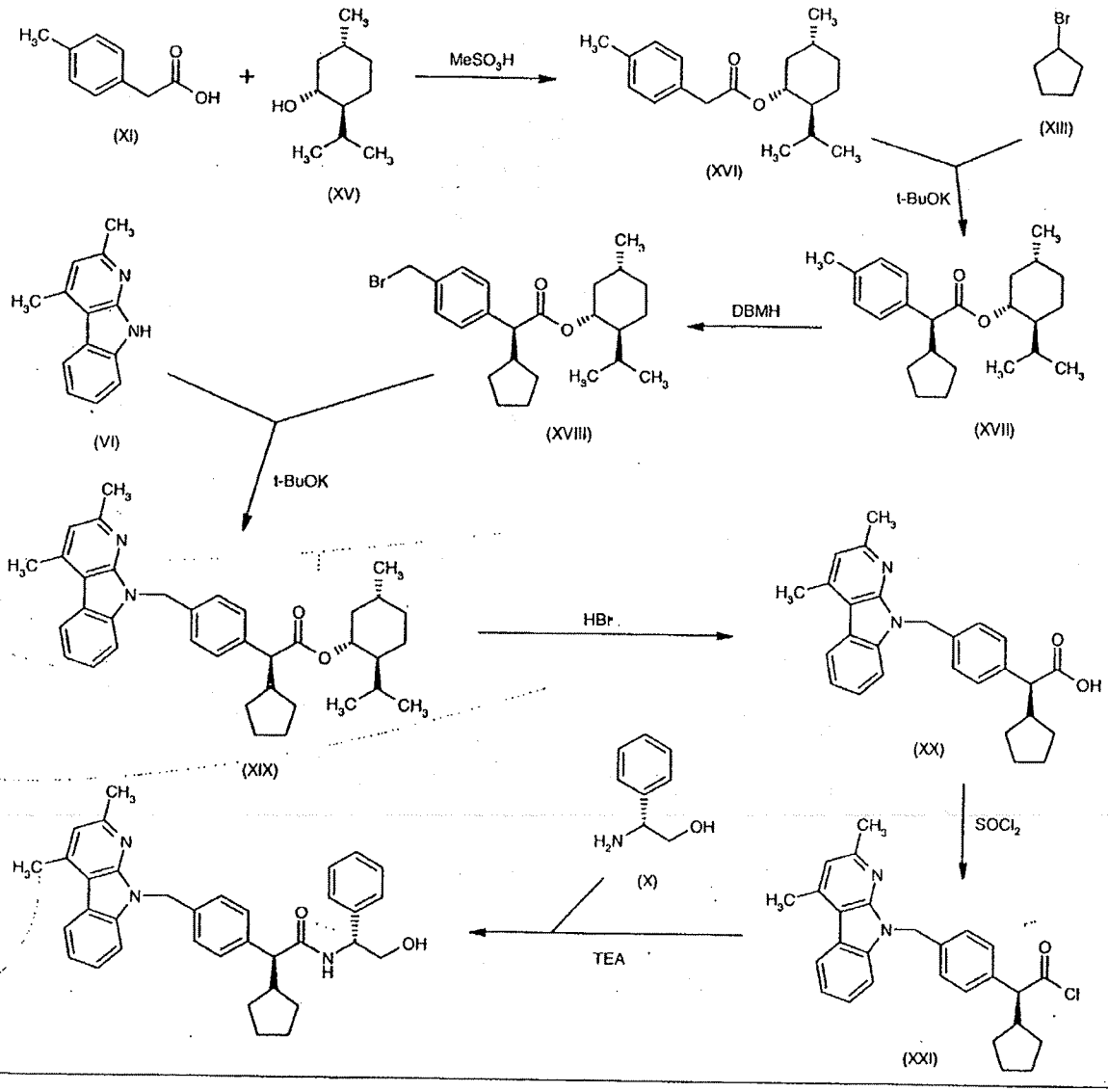
Scheme 1: Synthesis of Implitapide



Much of the design and identification of antilipidemic agents has focused on acyl-CoA:cholesterol *O*-acyltransferase (ACAT; EC 2.3.1.26), the enzyme located in the endoplasmic reticulum that is responsible for catalyzing the esterification of free cholesterol with acetyl CoA resulting in cholesteryl esters (8). However, recently, another therapeutic target microsomal triglyceride transfer protein (MTP) has been identified. MTP is a heterodimeric transfer protein which limits the production of atherogenic apolipoprotein B (apoB)-containing lipoproteins (10). MTP is therefore an attractive target for the treatment of dyslipidemias and prevention of atherosclerosis.

Interest in designing MTP inhibitors began in 1995. Compounds currently under development and those

Scheme 2: Synthesis of Implitapide



described in patent literature are shown in Tables I and II, respectively. Implitapide (Bay-13-9952) is one such compound that has been shown to inhibit apoB-lipoprotein secretion from liver cells and diasteroselectively inhibit MTP-catalyzed transport of lipids (11). At present, implitapide, BMS-201038 and avasimibe are the only compounds in clinical stages of development.

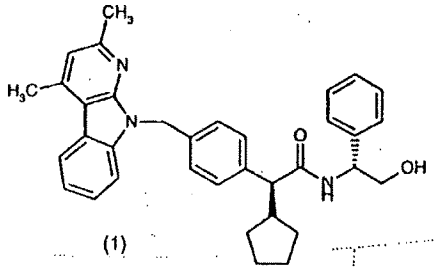
Pharmacological Actions

Implitapide is a blocker of MTP that potently inhibited secretion of apoB-containing VLDL-like lipoproteins from a human hepatoma cell line (HepG2) with an IC_{50} value of 1.1 nM. α-2-Macroglobulin secretion was not affected by the agent, indicating that cell viability was maintained and other secretory processes remained intact. Implitapide was shown to suppress MTP-catalyzed transport of triglycerides between synthetic unilamellar vesicles in an *in vitro* assay using MTP from both porcine liver (IC_{50} = 27 nM) and a recombinant human form complexed with protein disulphide isomerase (IC_{50} = 10 nM) (12). Table III presents pharmacological data of selected MTP inhibitors under development.

Implitapide showed efficacy in several *in vivo* animal models. Treatment of olive oil-loaded (2.5 mg/kg) normal

Table I: MTP inhibitors in development (Prous Science Ensemble database).

Drug name	Company	Status
1. Implitapide	Bayer	Phase II
2. BMS-201038[1]	Bristol-Myers Squibb	Phase II
3. Avasimibe[2]	Warner-Lambert	Phase II
4. GW-328713	Glaxo Wellcome	Discontinued[3]
5. R-103757	Janssen	Preclinical
6. CP-467688	Pfizer	Preclinical
7. CP-319340	Pfizer	Preclinical
8. CP-346086[c]	AstraZeneca, Pfizer	Preclinical
9. BMS-192951	Bristol-Myers Squibb	Preclinical
10. BMS-200150	Bristol-Myers Squibb	Preclinical
11. BMS-212122	Bristol-Myers Squibb, Novartis	Preclinical
12. BMS-197636[2]	Bristol-Myers Squibb	Preclinical
13. Biphenylcarboxamide derivative	Wakunaga	Preclinical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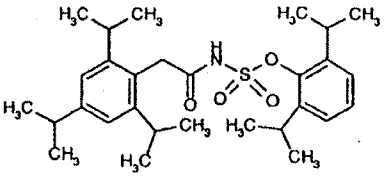
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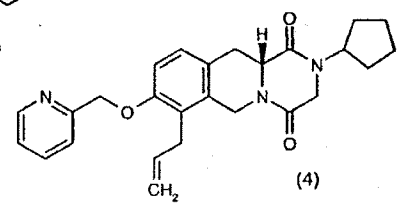
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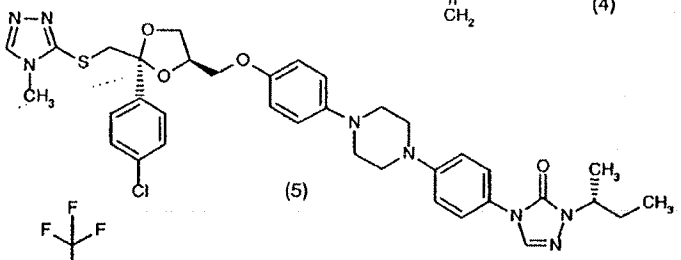
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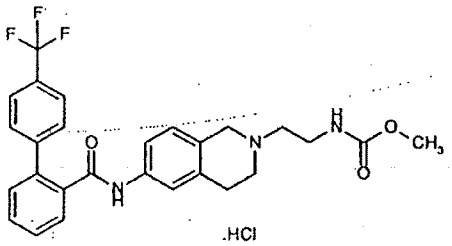
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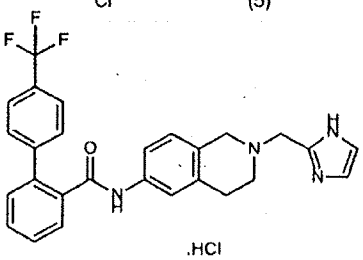
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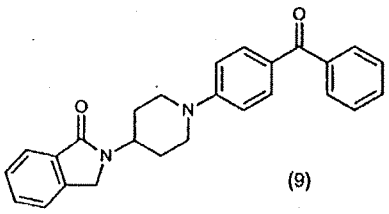
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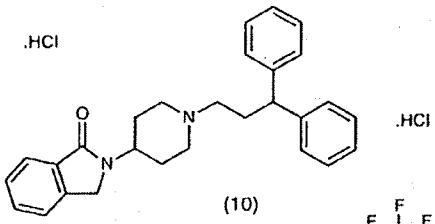
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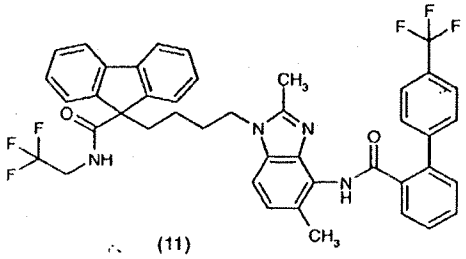
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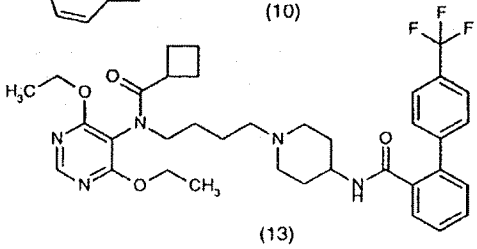
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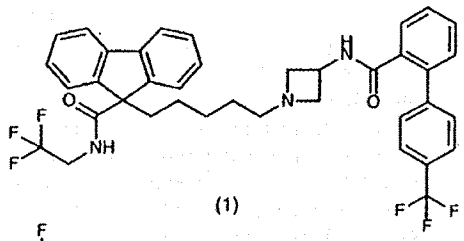
[1]Chemical structure not yet detected. [2]ACAT inhibitor which also decreases the expression of MTP. [3]Discontinued in phase I clinical trials.

Table II: Recent patents on MTP inhibitors (Prous Science Ensemble database).

Patent	Company
1. US 5885983, WO 9743255	Bristol-Myers Squibb
2. US 5827875, WO 9743257	Bristol-Myers Squibb
3. EP 0944602, JP 2000505810, WO 9823593	Pfizer
4. US 5965577, WO 9827979	Bristol-Myers Squibb
5. EP 0887345, JP 1999060557	Pfizer
6. JP 1999035555	Wakunaga
7. EP 1039915, US 5962440, WO 9921564	Bristol-Myers Squibb
8. JP 1999514964, US 5919795, WO 9640640	Pfizer
9. EP 0970954, JP 1999228569, WO 9931085	Japan Tobacco
10. WO 0005201	Novartis
11. WO 0037463	Janssen



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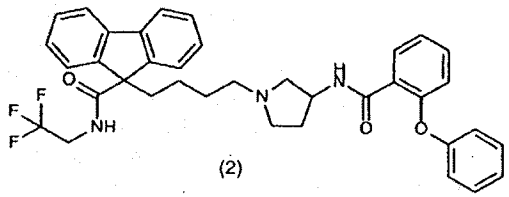

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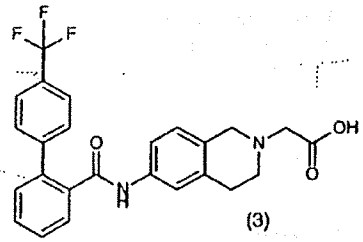

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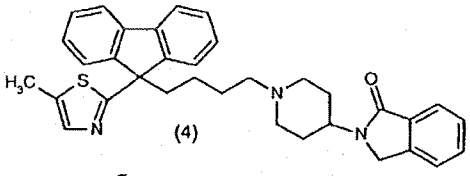

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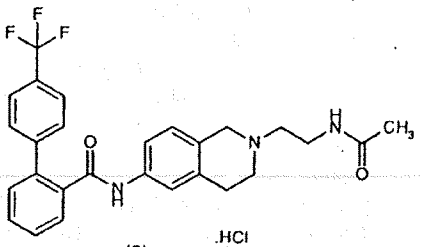

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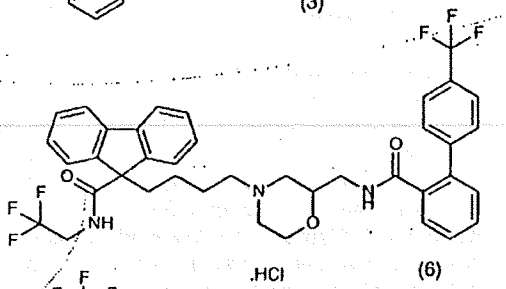

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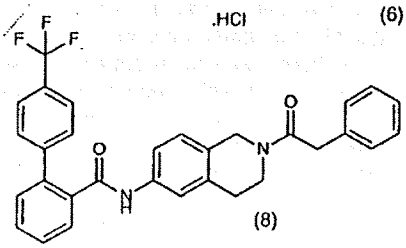

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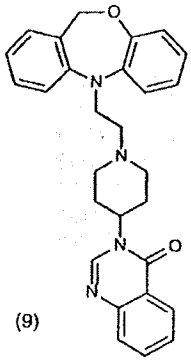

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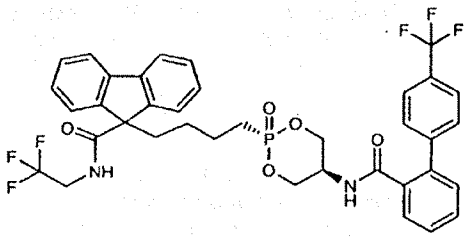

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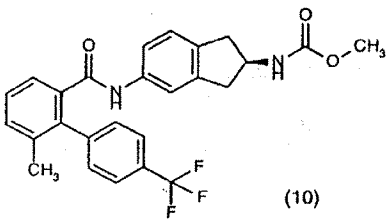

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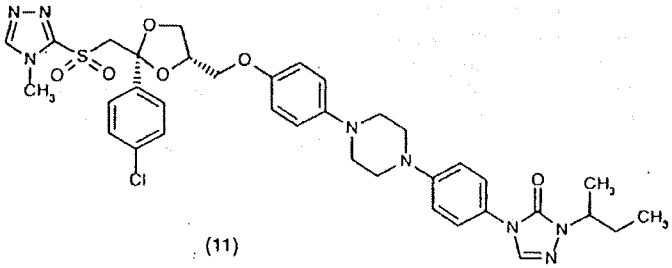

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