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RECENT ADVANCES IN THE SYNTHESIS OF TELMISARTAN: A REVIEW

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ABSTRACT

Telmisartan is an effective, long-lasting, nonpeptide antagonist of the angiotensin II type-1 (AT_1) receptor that is indicated for the treatment of essential hypertension. It selectively inhibits stimulation of the AT_1 receptor by angiotensin II without affecting other receptor systems involved in cardiovascular regulation. Very high lipophilicity a unique feature of telmisartan attached with a high volume of distribution indicate that the compound offers the clinically important advantage of good tissue penetration. It also activates peroxisome proliferator–activated receptor c (PPAR-c) and increase adiponectin protein content in adipocytes. As a result they may develop insulin sensitivity. It belongs to a class II drug in BCS categorization i.e. low solubility and high permeability. One of the major troubles with this drug is its low solubility in biological fluids which results into poor bioavailability after oral administration to improve the aqueous solubility and dissolution rate of the telmisartan solid dispersions of drug using different methods were prepared and investigated.

KEYWORDS: Telmisartan was discovered and commercialized by Boehringer Ingelheim.

INTRODUCTION

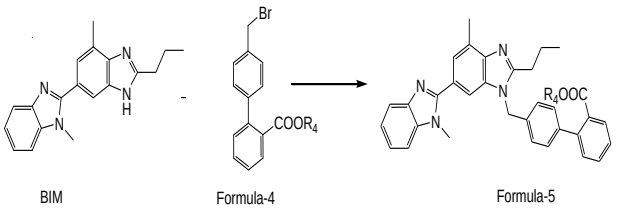
Telmisartan was discovered and commercialized by Boehringer Ingelheim.[1] Under the trademarks MICARDIS^R and MICARDISPLUS^R, this is in combination with hydrochlorothiazide. The company sells the telmisartan in 84 countries around the world, excluding the USA, Japan and European countries. Telmisartan is a component of the angiotensin II receptor blocker (ARB) class and is being investigated in the most determined and significant research programmed conducted with an angiotensin II receptor blocker. In the medical trial involuntary ONTARGET, PROTECTION and PROFESS, over 58,000 patients have been enrolled to study the cardiovascular defensive effects of MICARDIS^R.

In the industrial production of telmisartan, commercially available free acid formulations of telmisartan are prepared by direct contact of telmisartan with a strong base such as sodium hydroxide. Such a production process is potentially harmfully to human health. In addition, quality reproducibility of the final formulation may vary depending on a period of reaction time. Physicochemical properties of telmisartan in the solid free acid form may also cause difficulties of direct application thereof to the human body; so many scientists have been aggressively conducted to overcome the limited applicability of telmisartan.

The improvement of telmisartan relates to a process for preparing telmisartan or its pharmaceutically acceptable salts. It further relates to a process for isolating telmisartan or its pharmaceutically acceptable salts. Besides, The synthesis of telmisartan has been described in the prior art by various reaction pathways including reacting 2-n-propyl-4-methyl-6-(methylbenzimidazol-2'-yl)benzimidazole with either 4'-bromomethylbiphenyl-2-carboxylic acid alkyl ester or 4'-halomethyl cyano biphenyl, specifically the 4'-bromomethyl derivative. Several patents have been reported with different routes to prepare process of Telmisartan as follows.

1. US 5591762[2]

General process for the preparation of compound formula-V

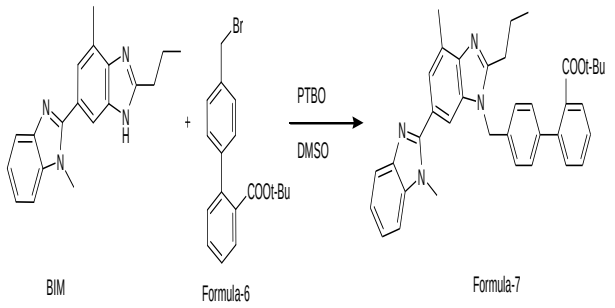


BIM Formula-4 Formula-5

Wherein bromine in structure IV is leaving group there are several other leaving groups such as chlorine, iodine, a substituted sulphonyloxy group, e.g. a methane sulphonyloxy, phenylsulphonyloxy or p-toluenesulphonyloxy group are reported.

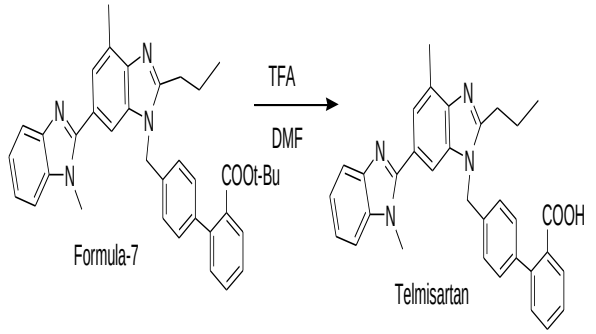
2. Preparation of Telmisartan tert. butyl ester[3]

Preparation of Telmisartan tert. butyl ester is described using BIM and 2-(4'bromomethyl phenyl) tert. butyl benzoate using pot. Tert butoxide as a base in DMSO as solvent.



Potassium tert-butoxide was added to the solution of BIM in DMSO at room temperature followed by the addition of the compound of formula Vl. Upon stirring for 14 hrs, the mixture was poured into water and extracted with ethyl acetate, the combined extract was dried on $MgSO_4$ and evaporated. Residue was purified by silica gel column chromatography to give compound of formula-VII. The above mentioned process uses chromatographic purification, which is generally cumbersome and time consuming process and also requires solvents in high volume.

Preparation of Telmisartan from Telmisartan tert. butyl ester is described using trifluoroacetic acid in DMF as a solvent in 63.9 % yield. (Exam.-9) The resulting product had a melting point of 261-263^{0}C.

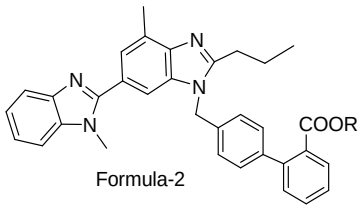


The process for the preparation of tert Butyl ester of Telmisartan is not commercially viable and deprotection involving the use of trifluoro acetic acid is not eco-friendly.

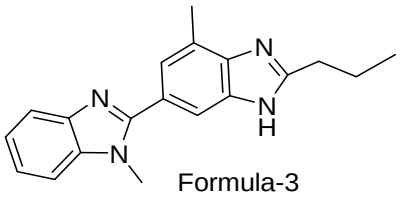
Preparation of telmisartan later on has been reported by 4′-bromomethyl-biphenyl-2-carboxylic acid methyl ester (or ethyl ester) (VI) or 4′-bromomethyl-biphenyl-2-carbonitrile (VII) Preparation of telmisartan (CN01126367, CN01131915).

3. US 20060094883[4]

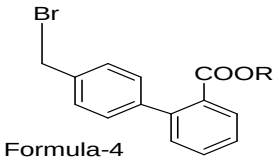
Process for the preparing Telmisartan, wherein Telmisartan alkyl ester compound of formula-2 is prepared,



Comprising the steps of: (a) combining i. BIM of formula 3,



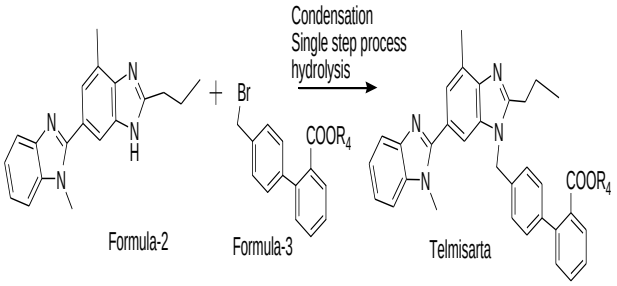
Formula 3 with 4′-bromomethyl-biphenyl-2-carboxylic acid alkyl ester (referred to as BMBP alkyl ester) of formula 4.



Formula 4 an inorganic base and a low boiling point organic solvent, to obtain a mixture;
(b) heating the mixture obtained in step (a) to a temperature of about 55°C. to about 120^{0}C;
(c) maintaining the mixture obtained in step (b) for about 1 hour to about 8 hours, to obtain Telmisartan alkyl ester of formula II; and (d) Recovering Telmisartan alkyl ester of formula II, wherein, R is a straight or branched chain C_1-C_4 alkyl.

4. WO 2005108375[5]

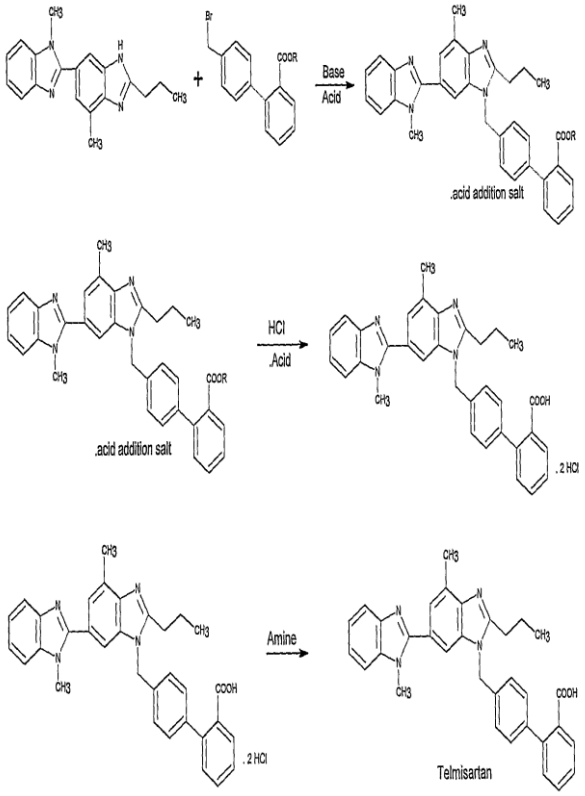
Describes process for the preparation of Telmisartan, characterized in that 1H-Benzimidazole-2-n-propyl-4-methyl-6-(1 '-methyl benzimidazole- 2'yl) of formula (II) and methyl-4- (bromo methyl)biphenyl 2-carboxylate of formula (III) are subjected to



5. WO 2007010558[6]

Method for the preparation of Telmisartan involving Telmisartan dihydrochloride which comprises, i) condensing 4-Methyl-2-n-propyl-IH- benzimidazole-6-carboxylic acid with N-Methyl- O-phenylene diamine dihydrochloride to yields 4-methyl-6 (1 -methyl benzimidazol-2- yl)-2-n-propyl IH- benzimidazole, ii)

treating 4- methyl-6-(l -methyl benzimidazol-2-yl)-2-n-propyl-IH-benzimidazole with 4– (bromomethyl)-2-biphenyl-2-carboxylate in presence of a base in an organic solvent and isolating the ester as acid addition salt, iii) converting ester acid addition salt to Telmisartan dihydrochloride and iv) converting Telmisartan dihydrochloride to Telmisartan.



6. WO /2010/018441 (CN1344712)[7]

Method comprising reaction of 4-methyl-6-(1-methyl-2(1H)- benzimidazolyl)-1H-benzimidazole with 4′-bromomethyl-biphenyl-2-carboxylic acid alkyl ester [wherein alkyl is methyl or ethyl] in solvent i.e. DMF, DMSO, THF, dioxane, chloroform, dichloroethane, etc. in the presence of base [such as Na alcoholate, triethylamine, tributylamine, tripropylamine, KOH, NaOH, CsOH, $Ba(OH)_2$ etc.] as acid capturer at 20-100^0C for 8-10 hrs, and then hydrolyzing with acid (such as H_2SO_4, HCI, HBr, HOAc, etc) at room temp, to reflux temp, or with base in water at 20-160^0C for 1-10 hour.

7. WO 2006/125592[8]

A new process for the preparation of Telmisartan is described 2-butyl-3- [[2″-[1 -(triphenylmethyl)-i H-tetrazol-5-yl][1, 1 ‘-biphenyl]-4-yl]methyl]-1, 3-diazaspiro[4.4] non- 1-en-4-one is disclosed, which proceeds via novel intermediate, 4-[(2-butyl-4-oxo-1 ,3-diazaspiro[4.4]non-1-en-3-yl)methyl]phenylboronic acid (Formula (H)) or its analogs. Compound (II) reacts with 5-(2-bromophenyl)-1-(triphenylmethyl)-1H-tetrazole (III) in the presence of catalyst, using conditions of Suzuki reaction, to give trityl irbesartan (I), whereas analogs to compound (II) may give candesartan, valsartan, Telmisartan, losartan and olmesartan.

8. WO 2006/050509[9]

The amorphous form of Telmisartan sodium and the preparation thereof. Also provided are the Telmisartan sodium polymorph crystal Forms 0 to

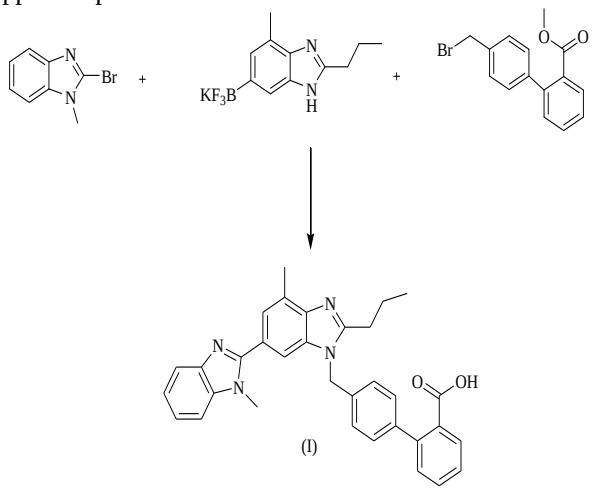
XIII and XV to XX and preparations thereof. Also provided are pharmaceutical composition of amorphous and polymorphic forms of Telmisartan sodium or mixtures thereof and methods of treatment of a mammal in need thereof.

9. WO 2004/087676[10]

A novel method for the production of Telmisartan is described by reacting 2-n-propyl-4-methyl-6-(1′-methylbenzimidazol-2’-yl)-benzimidazol with a compound of general formula $(IV)_1$ in which Z is a leaving group, wherein the compound 2-cyano-4′-[2″- n-propyl-4″-methyl-6″-(1 “’-methylbenzimidazol-2^{l}“-yl)benzimidazol-1 “-ylmethyl]biphenyl is obtained, and subsequently conducting hydrolysis of the nitrile to acid function.

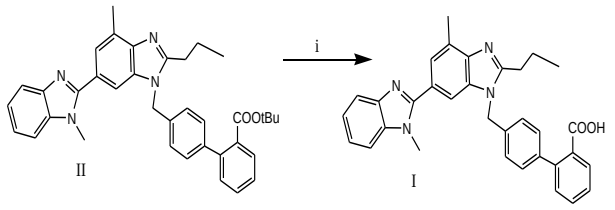
10. Synthesis Using Suzuki reaction

Total synthesis has been developed for telmisartan, a commonly used treatment for hypertension. This approach brings together two functionalized benzimidazoles using a Suzuki reaction that can be catalyzed by either a homogeneous palladium source or graphene-supported palladium nanoparticles. The ability to perform the cross-coupling reaction was facilitated by the regio-controlled preparation of the 2-bromo-1-methylbenzimidazole precursor. This convergent approach provides telmisartan.[11]

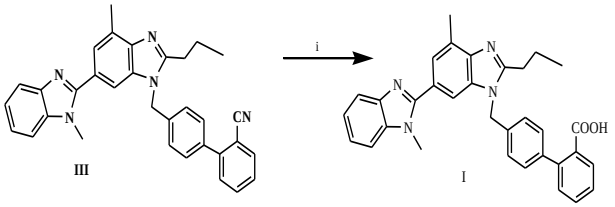


11. WO 2009006860A2[12]

Telmisartan (I) is produced in accordance with the original patent of Boehringer Ingelheim (US 5 591 762) from telmisartan tert-butyl ester (II). The hydrolysis is carried out using of trifluoroacetic acid in the toxic solvent N, N-dimethylformamide.

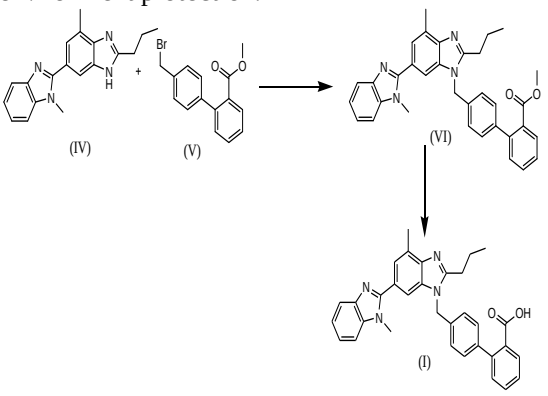


According to another patent applied by the same company (US 2004 236113) the manufacture was problematic and this is why this procedure was replaced with hydrolysis of the corresponding nitrile (III). However, during the hydrolysis, which is carried out with potassium hydroxide in ethylene glycol, a high temperature (160 ^{0}C) is used, which causes browning of the product, which must be subsequently purified by means of activated carbon. Also, the energy demands of several-ton production would be considerably high.



12. US 20100222402[13]

Two synthetic steps (iii+iv) are combined and telmisartan is isolated after alkaline hydrolysis by acidifying of the reaction mixture in water or extraction with dichloromethane and precipitation with acetone. Both the ways of isolation are unsuitable for industrial production. In the case of telmisartan of crystalline form A its isolation from water or aqueous solutions of organic solvents is very difficult since a hardly filterable product is formed. Extraction of the product with dichloromethane and precipitation with acetone brings a well-filterable product, but the use of dichloromethane is virtually impossible from the point of view of environment protection.



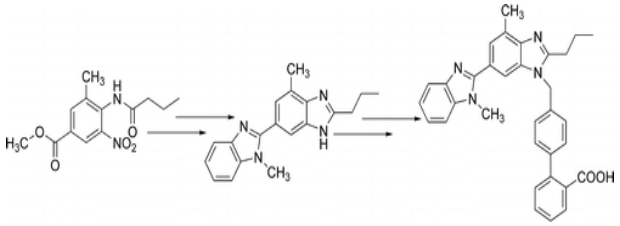
13. WO 2006/044754[14]

Process starts from telmisartan methyl ester hydrochloride, which is hydrolyzed to produce the potassium salt of telmisartan, which is further acidified in aqueous acetonitrile; after isolation it crystallizes from a methylene dichloride/methanol mixture and finally from methanol alone, and wherein a pressure apparatus is used for the dissolution in methanol at a temperature above its boiling point (80 °C). The result of this complex procedure, which manifests the already above mentioned shortcomings, is a low yield of the product.

14. WO 2006/044648[15]

Mentioned procedure of Cipla, wherein the last two steps of the synthesis are also combined. The method comprises phase separations, which lead to low yields (69 % – 80 %) besides increased tediousness. Matrix starts from telmisartan tert-butyl ester (II), which is first converted to telmisartan dihydrochloride, which in turn, by action of aqueous ammonia in methanol, provides telmisartan with a low total yield of 73%.

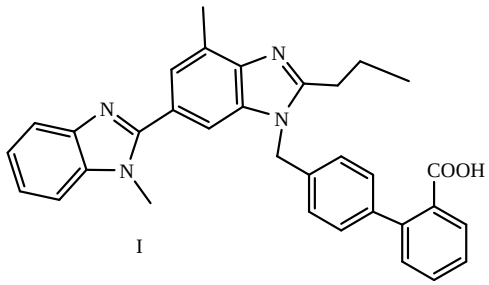
15. Dibenzimidazole derivative of Telmisartan[16]



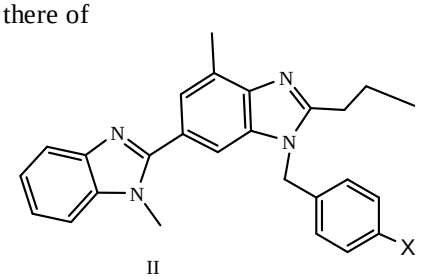
Telmisartan a substituted dibenzimidazole derivative, is an antihypertensive drug, essentially used to control blood pressure. An improved, cost-effective, and impurity-free process for telmisartan suitable for large-scale production is described here by addressing various process development issues. The overall yield obtained from this newly developed process is around 50% (over five steps) compared to the literature reported process (21%, over eight steps).

16. EP 1719766A2[17]

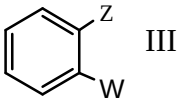
The Present invention provides a process for the preparation of a compound of formula (I) or a salt thereof



Comprising the reaction of a compound of formula (II) or a salt there of

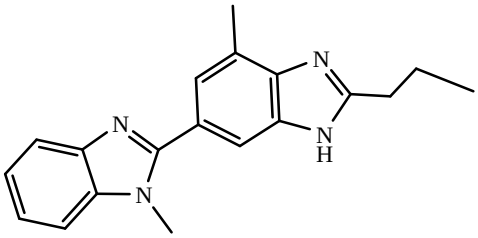


With a synthon of formula (III) or a salt there of

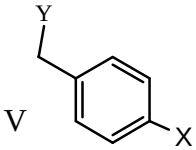


III

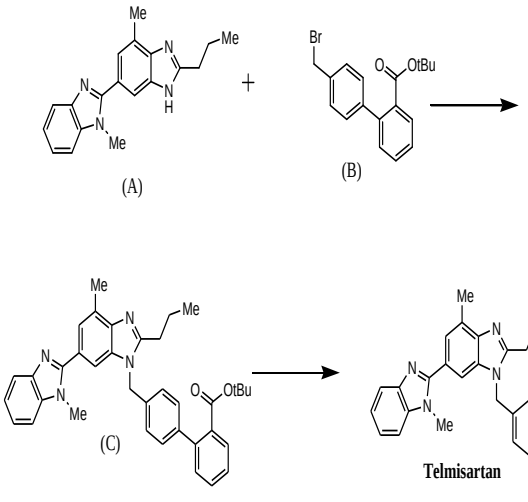
Prepared by reaction of a compound of formula (IV)



With a compound of formula (V)

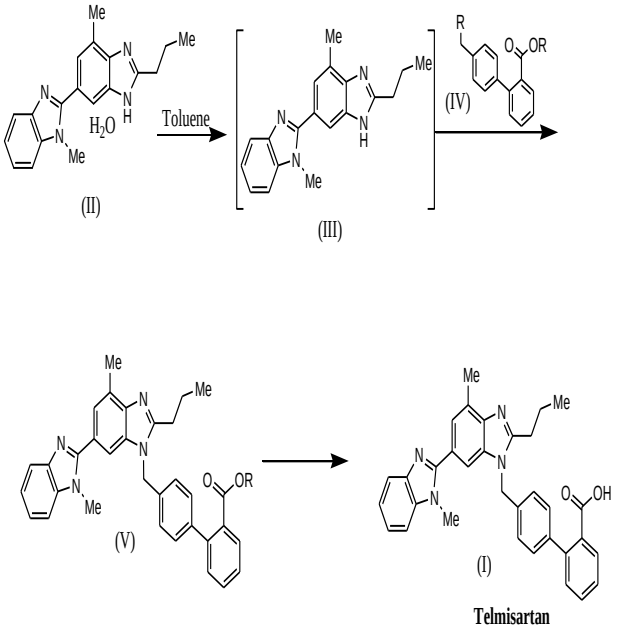


Telmisartan, 4′-[(1,7′ -dimethyl-2′ -propyl[2,5′ -bis-l H-benzimidazol]-3′-yl)methyl][1,1′-biphenyl]-2-carboxylic acid is a known ACE inhibitor useful in therapy as antihypertensive agent. Its preparation is disclosed in EP 502314 and comprises the alkylation of 4-methyl-6-(1-methyl-benzimidazol-2-yl)-2-propylbenzimidazole (A) with t-butyl 4′-(bromomethyl) biphenyl-2-carboxylate (B).



However, compound (B) is not commercially available and its synthesis requires a number of steps, among them the protection of the carboxylic function which is finally removed by hydrolysis. Therefore there is the need for an alternative synthesis for the industrial preparation of telmisartan, which makes use of commercially available or easy to prepare intermediates and which, if possible, avoids the additional steps of protection and deprotection of the carboxylic function.

17. EP 2305650A1[18]

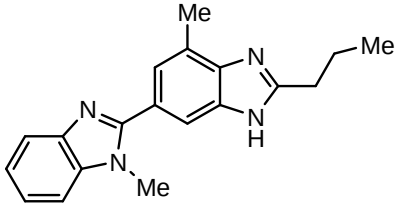


Telmisartan is a compound of formula (I)

Chemically known as 4′-((1, 7′-dimethyl-2′-propyl-1H,3′H-2,5′,-bibenzo[d]imidazol-3′-yl)methyl)biphenyl-2-carboxylic acid, which is disclosed in EP 502314 B1 and marketed under the trade name Micardis®.

18. EP 502314 B1[19]

The process described in comprises the alkylation of 4-methyl-6-(1-methyl-benzimidazol-2-yl)-2-propylbenzimidazole (III).



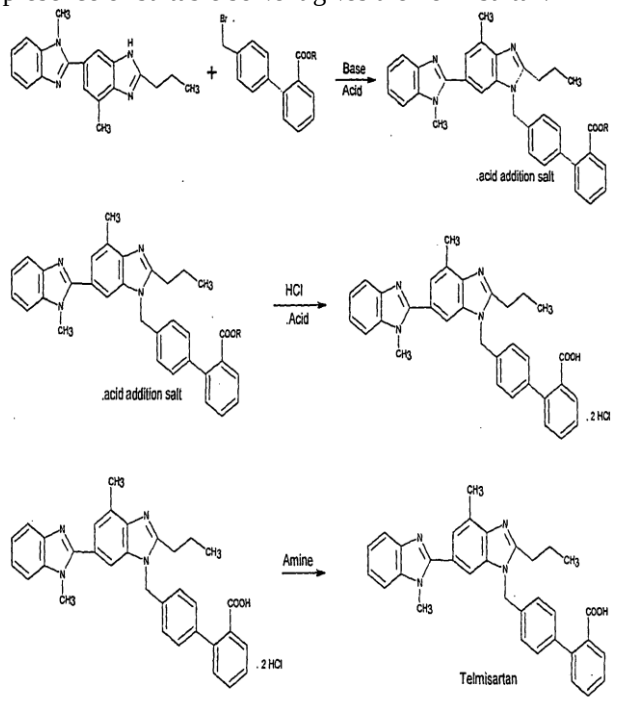
(III)

With t-butyl 4′-(bromomethyl) biphenyl-2-carboxylate and subsequently hydrolysis to Telmisartan. t-Butyl 4′-(bromomethyl)biphenyl-2-carboxylate is not commercially available and its synthesis requires a number of steps, among them the protection of the carboxylic function which is finally removed by hydrolysis.

19. EP1912975B1[20]

Accordingly this invention 4-methyl- 6(1-methyl benzimidazol-2-yl)-2-n-propyl 1H-benzimidazole which on condensation with 4'-(bromo methyl)-2-biphenyl- 2-carboxylate esters in the presence of base followed by acidification gives 4'-[4-Methyl-6-(1-methyl-1H-benzimidazol- 2-yl)-2-n-propyl-1H-benzimidazol-1-yl-methyl] biphenyl-2-carboxylate ester acid addition salt

(acid addition salts of Telmisartan ester), on hydrolysis with hydrochloric acid gives the 4'-[4-Methyl-6-(1-methyl-1H-benzimidazol-yl)-2-n-propyl- 1H-benzimidazol-1-yl-methyl]biphenyl-2-carboxylic acid dihydrochloride salt (Telmisartan dihydrochloride). Telmisartan dihydrochloride on treatment with a base in presence of suitable solvent gives the Telmisartan.



Scheme-2

20. WO 2000043370A1[21]

The patent application relates to a method for the production of Telmisartan by reacting 4-methyl-6-(1-methyl-benzimidazol-2-yl)-2-propylbenzimidazole (III) with 4-bromomethyl-2′-cyanobiphenyl and subsequently hydrolysis of the nitrile to the acid function.

21. WO 2010146187A2[22]

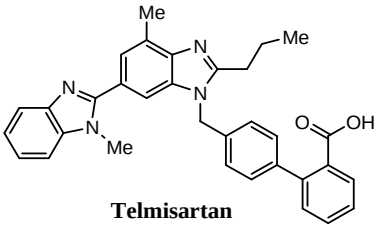
The patent application relates to a method for the production of Telmisartan, by coupling with a Suzuki reaction the N-4-bromobenzyl derivative of the compound of formula (III) with 2-carboxylphenyl boronic acid.

22. EP 1878735[23]

As described in 2-carboxyphenyl boronic acid requires a very laborious process to separate it, since it is extremely soluble in water, making the process unattractive for an industrial application. Thus, the active substance prepared by the process known up till now can only be obtained in a satisfactory quality after running through a number of process steps, wherein additional steps of protection and deprotection of the carboxylic function or additional steps to obtain the carboxylic function are often present.

23. WO2014067237A1[24]

Telmisartan is a novel non-peptide angiotensin Π (AT Π) receptor antagonist, for the clinical treatment of hypertension, its chemical name is 4 '- [(1,4′-dimethyl – 2′-propyl [2,6'- two -1H- benzoimidazol] -Γ–yl) methyl] biphenyl] -2-carboxylic acid, knot.

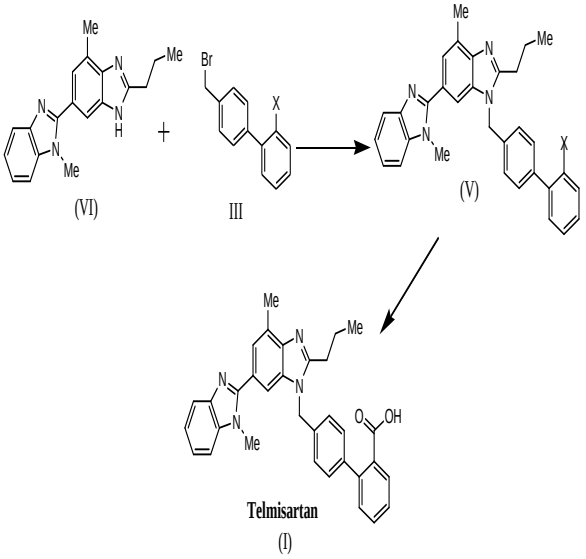


Telmisartan

Telmisartan synthetic route has mainly 3-methyl-4-amino-benzoic acid methyl ester as the starting material by N- acylation, nitration, reduction, cyclization, ester hydrolysis and condensation reaction intermediates 2-n-propyl-4-methyl – 6 – (1 – methyl-benzimidazol-2-yl) benzimidazole-α), Ï with 4′-bromomethyl-biphenyl-2-carboxylate (V) via nucleophilic substitution, hydrolysis reaction to give the final product two Bu telmisartan (reaction formula 1)

24. EP 2149566[25]

A purpose of the present invention is to describe commercially useful process for the preparation of Telmisartan, which avoids the identified problems. This development also relates to intermediates of formula (V) and to a process for preparing them.



25. WO 2011077444A1[26]

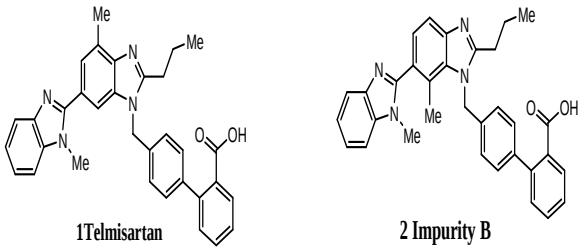
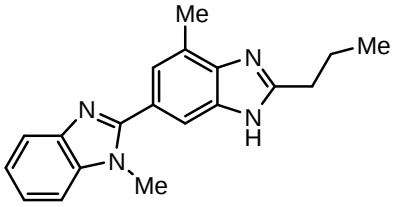


Table 1: Preparation of Telmisartan and 2 with reported synthetic schemes.

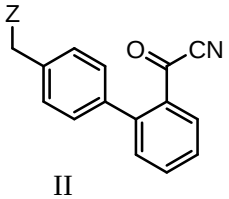
Entry	Process reference	Condensation		Hydrolysis		Yield (%)
		N-3 isomer	Purity	Impurity-B	Purity	
1	EP502314B1	0.5	93.3	0.30	98.1	67
2	US20060264491 A1	1.3	94.7	0.63	97.2	65
3	US7193089B2	0.8	93.2	0.45	97.6	70

Process for the preparation of telmisartan, comprising: condensation of -n-propyl-4-methyl-6-(l'-methylbenzimidazol-2′-yl) benzimidazole (I)



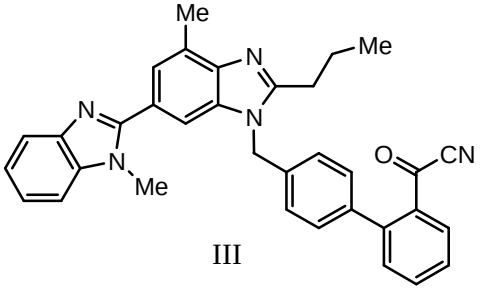
I

With a compound of general formula II)



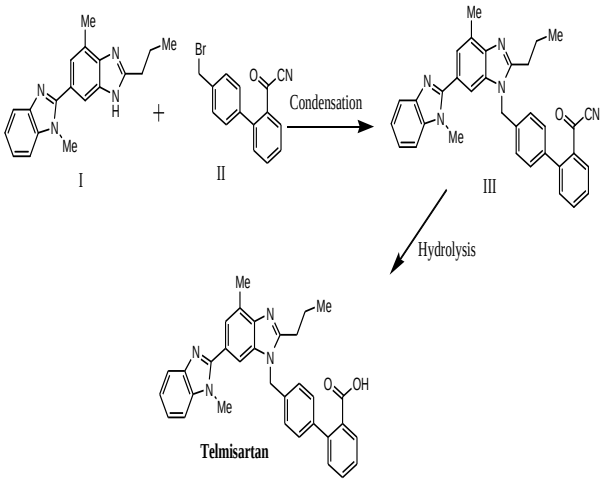
II

Wherein Z denotes a leaving group such as a halogen atom, for example, a chlorine, bromine, or iodine atom to obtain the compound 2-cyano-4′-[2″-n-propyl-4″-methyl-6″-(1 ‘“-methylbenzimidazol-2″‘-yl)benzimidazol- 1 “-ylmethyl] biphenyl (III), and subsequent



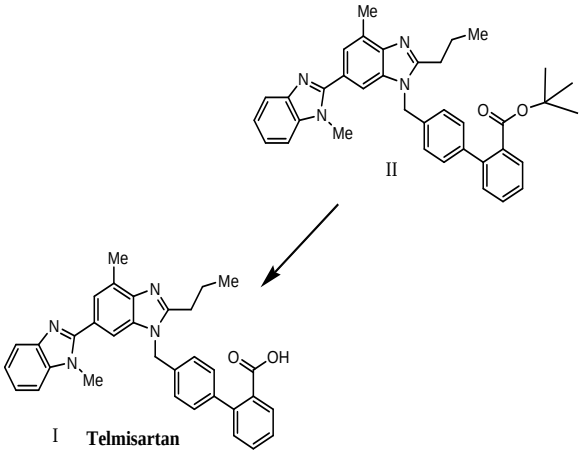
III

Hydrolysis of nitrile in the presence of excess base and solvent followed by acid/base purification to obtain pure telmisartan.



I II III

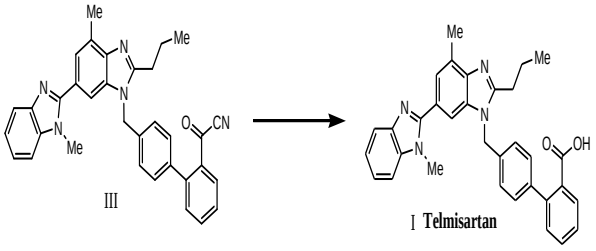
26. US 6358986[27]



II I **Telmisartan**

27. US 2004 236113[28]

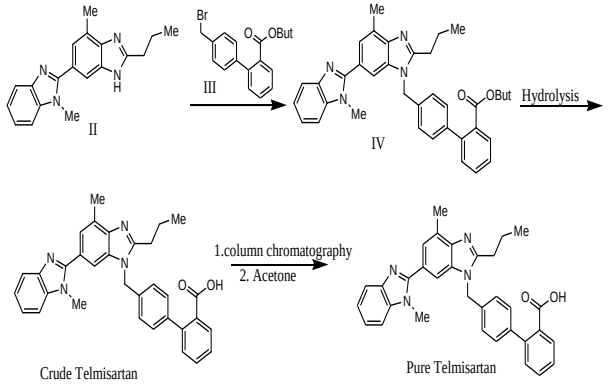
According to this patent the manufacture was problematic and this is why this procedure was replaced with hydrolysis of the corresponding nitrile (III). However, during the hydrolysis, which is carried out with potassium hydroxide in ethylene glycol, a high temperature (160 ^{0}C) is used, which causes browning of the product, which must be subsequently purified by means of activated carbon. Also, the energy demands of several-ton production would be considerably high.



III I **Telmisartan**

28. WO 2010004385[29]

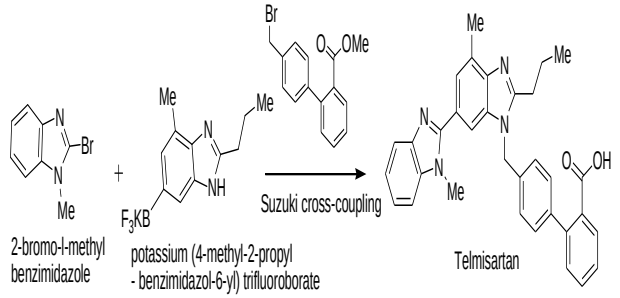
Telmisartan was first disclosed in US 5,591,762. US 5,591,762 also discloses a process for the preparation of Telmisartan by reacting l,4′-dimethyl-2′-propyl[2,6′-bi-lH- benzimidazole (II) with 4′-(bromomethyl)[l,r-biphenyl]-2-carboxylic acid 1,1- dimethylethyl ester (III) in a solvent optionally in the presence of an acid binding agent to produce the intermediate 4′-[(l,4′-dimethyl-2′-propyl[2,6[1]-bi-lH-benzimidazol]-l- yl)methyl]-[l,l'-biphenyl]-2-carboxylic acid 1,1-dimethylethyl ester (IV), which is further hydrolysed to produce crude Telmisartan. The crude product obtained is purified over a silica gel column and finally crystallized from acetone.



The drawback with the above process is the use of column chromatography in the purification of Telmisartan. Employing column chromatography technique is tedious and laborious and also involves use of large quantities of solvents, and hence is not suitable for industrial scale operations.

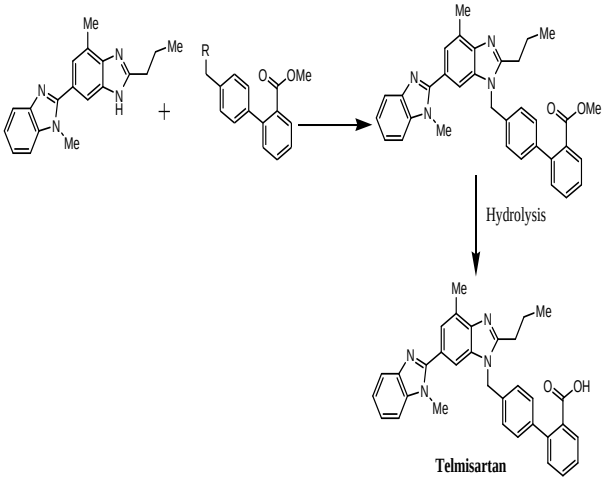
29. WO 2016089845[30]

According to the synthesis, there are 2-bromo-l-methyl benzimidazole and potassium (4-methyl-2-propyl-benzimidazol-6-yl) trifluoroborate and methyl 4'-bromomethyl-biphenyI-2-carboxylate are coupled. followed by a saponification to the desired carboxylic acid. A Suzuki cross-coupling reaction is then used to get a new carbon-carbon bond between the two differentially substituted benzimidazole derivatives to get target molecule.



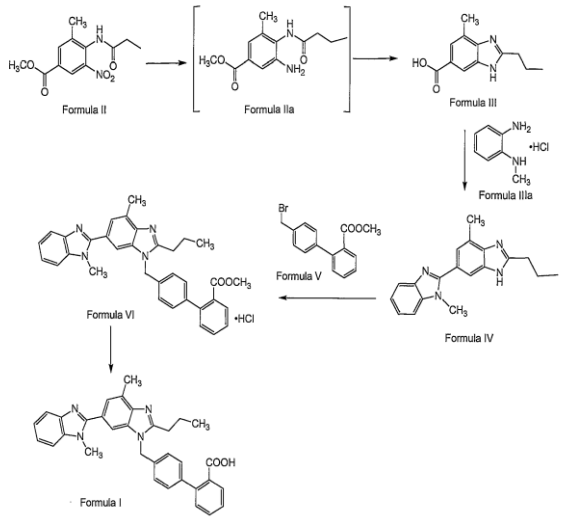
30. US 20070287840[31]

2-n-propyl-4-methyl-6-(1-methyl benzimidazole-2-yl)benzimidazole of methyl 4′-(bromomethyl)-biphenyl-2-carboxylate, and potassium hydroxide in presence of acetone and stirred at 25-35° C. to get stage-A with acetonitrile. 4′-[[(2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylate hydrochloride was hydrolyzed with potassium hydroxide in acetonitrile 70-75° C. Cool reaction mass and filter. Then wet material treatment with hot water to get telmisartan crude. Further Purified with methanol and MDC adjust pH 5 to 5.5 with acetic acid to get pure telmisaran.



31. EP 1805146 A2[32]

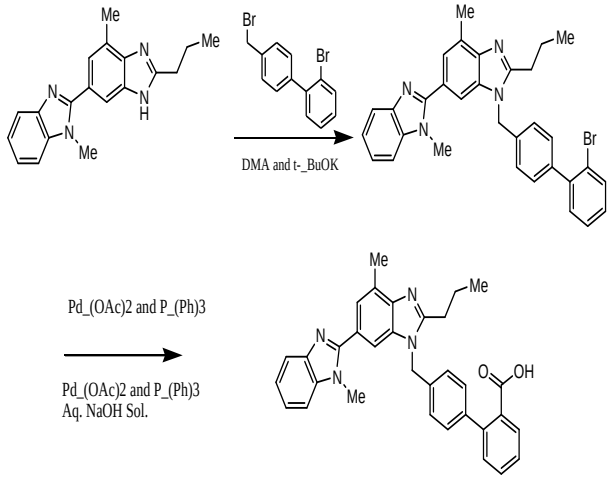
According to this development provides reduction of methyl 4-butyramido-3-methyl-5-nitrobenzoate to get methyl 3-amino-4-butyramido-5-methylbenzoate, which is hydrolysis to gets 2-n-propyl-4-methyl-benzimidazole-6- carboxylic acid. It is coupled with N-methyl-o-phenylenediamine hydrochloride to get 2-n-propyl-4-methyl-6- (1 -methyl benzamidazole-2-yl) benzamidazole. It further condensation with methyl 4'-(bromomethyl)biphenyl-2-carboxylate in the presence of a base to form methyl-4'-[(2 n-propyl-4-methyl-6-(1-methylbenzimidazol-2yl)-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylate; which is hydrolysis of methyl-4'-[[(2 n-propyl-4-methyl-6-(1-methylbenzimidazol-2yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylate, or its acid addition salt, with a base to form telmisartan; and e) purifying to afford pure telmisartan.



Scheme A

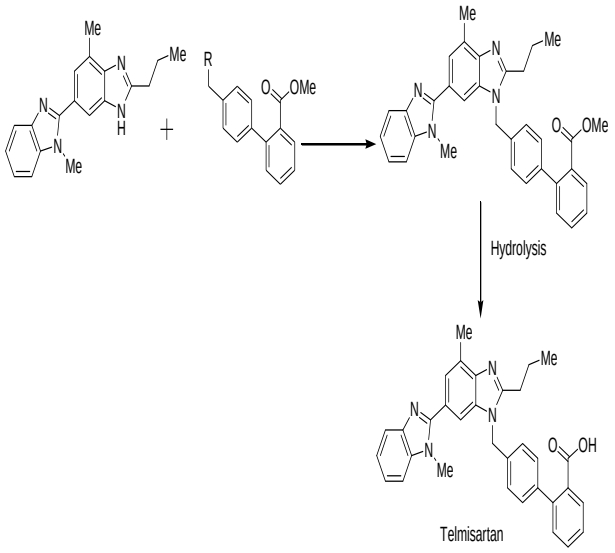
32. EP 2149566[33]

According to this invention provide coupling of 2-Bromo-4'-(bromomethyl)biphenyl with 4-methyl-6-(1-methyl-benzimidazol-2-yl)-2-propylbenzimidazole in presence of DMA and t-_BuOK to get 3'-((2'-bromobiphenyl-4-yl)methyl)-1,7'-dimethyl-2'-propyl-1H,3H-2,5'-bibenzo[d]imidazole. Which is react with Under CO atmosphere (1 atm) in presence of Pd_(OAc)2 and P_(Ph)3 then react with CsOAc in DMF, water and Bu3N and further hydrolysed with a solution of NaOH to form telmisartan; and purifying to afford pure telmisartan.



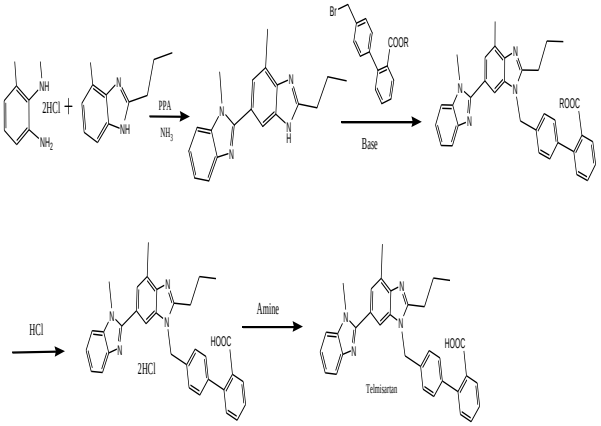
33. US 20060211866[34]

A process of the present invention produces an intermediate of telmisartan which includes at least reacting 1,4′-dimethyl-2′-propyl[2,6′-bi-1H-benzimidazole] (1) with methyl 4′-(bromomethyl)[1,1′-biphenyl]-2-carboxylate (2) in a biphasic solvent system in the presence of an acid binding agent and a phase transfer catalyst to provide intermediate methyl 4′-[(1,4′-dimethyl-2′-propyl[2,6′-bi-1H-benzimidazol]-1′-yl)methyl]-[1,1′-biphenyl]-2-carboxylate (3) as generally shown below in Scheme : the intermediate of formula 3, the intermediate can then be hydrolyzed to provide telmisartan.



34. US 20090023932[35]

The present invention encompasses a method for the preparation of Telmisartan comprises, through Telmisartan dihydrochloride comprises i) Condensing 4-Methyl-2-n-propyl-1H-benzimidazole-6-carboxylic acid with N-Methyl-O-phenylenediamine dihydrochloride to yields 4-methyl-6 (1-methyl benzimidazol-2-yl)-2-n-propyl 1H-benzimidazole ii) Treating 4-methyl-6-(1-methylbenzimidazol-2-yl)-2-n-propyl-1H-benzimidazole with 4′-(bromomethyl)-2-biphenyl-2-carboxylate in presence of a base in an organic solvent and isolating the ester as acid addition salt iii) Converting ester acid addition salt to Telmisartan dihydrochloride and iv) Converting Telmisartan dihydrochloride to Telmisartan.

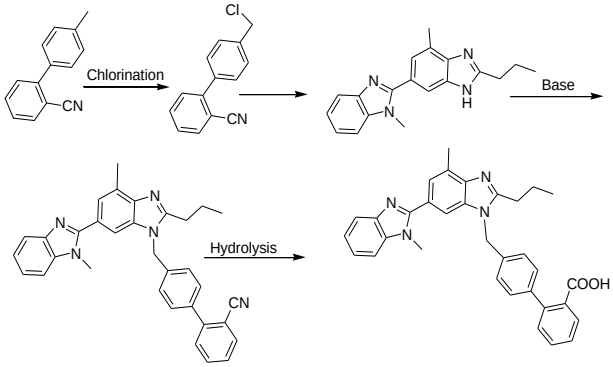


35. WO 2005108375[36]

According to this invention process preparation of telmisartan, or a pharmaceutically salt acceptable salt thereof, comprises subjecting 1H-Benzimidazole-2-n-propyl-4-methyl-6-(1'methyl benimidadazole-2'yl) of formula (II) and methyl-4-(bromomethyl) biphenyl-2-carboxylate of formula (III) to condensation and hydrolysis in single steps

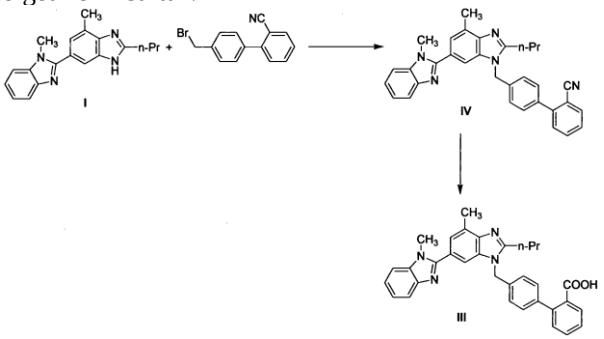
36. US 20150197495A1[37]

According to this invention a process for the preparation of bromine frees telmisartan in one pot starting from 2-cyano-4′-methyl biphenyl. The process can also be carried out in multiple steps by isolation of the intermediate compounds. The intermediate compound 4-chloromethyl-2′-cyanobiphenyl can also be used for the preparation of Telmisartan and other sartans.



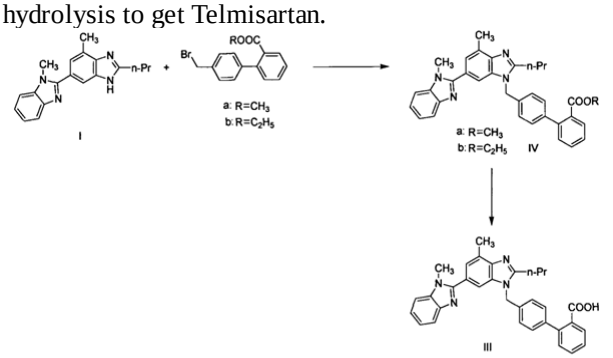
37. CN 1412183[38]

Chinese patent application describes a process for preparing Telmisartan, which includes reacting 2-n-propyl-4-methyl- 6-(l-methylbenzimidazol-2-yl)benzimidazole with 4'-(bromomethyl)-[l,l '- biphenyl]-2 -carbonitrile to afford the carbonitrile derivative of Telmisartan, i.e., 4'- [1 ,4 ' -dimethyl-2 ' -propyl [2,6' -bi- 1 H-benzimidazol] - 1 ' -yl-) methyl] -[1,1 '-biphenyl] - -carbonitrile, followed by hydrolysis of the cyano group to get Telmisartan.



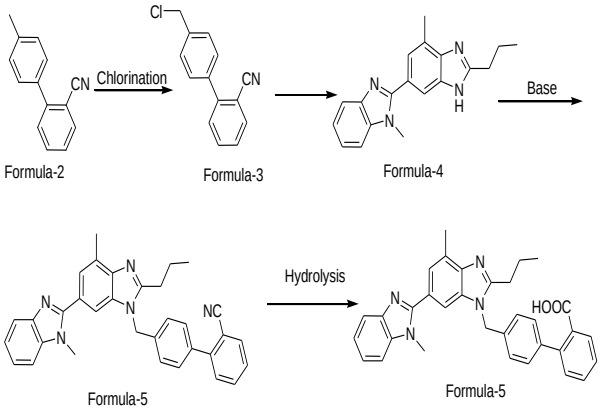
38. CN 1344712[39]

Chinese patent application describes the preparation of Telmisartan by reacting 2-n-propyl-4-methyl-6-(l-methylbenzimidazol-2-yl)benzimidazole with 4'-(bromomethyl)-[l,r-biphenyl]-2- carboxylic acid methyl or ethyl ester via nucleophilic substitution, to give the carboxylic ester derivatives of Telmisartan, followed by hydrolysis to get Telmisartan.



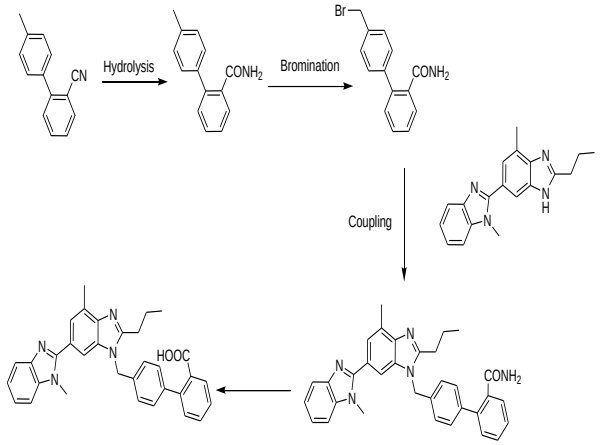
39. WO 2014027280[40]

The object of the development is to describe a one pot synthesis for the industrial scale produce of telmisartan. This development relates to the use of raw materials which are readily available to yield telmisartan, its salts and derivatives thereof, which are bromine free and potentially less genotoxic, since there is no bromine atom in any of the raw materials used in this invention.



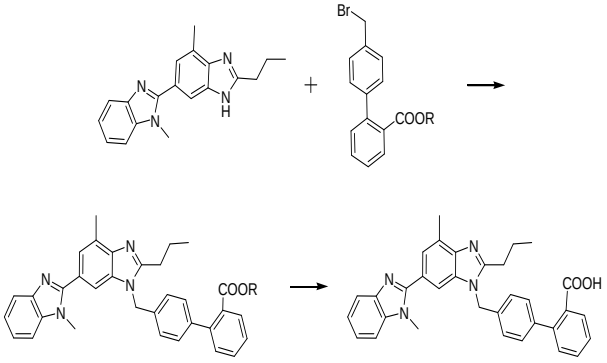
40. US 20060264491[41]

The present inventions have described a novel process for preparing highly pure Telmisartan in high yield, which overcomes the limitations of reported methods for preparing Telmisartan. The process of the present invention preferably includes converting 4′-[(1,4′-dimethyl-2′-propyl[2,6′-bi-1H-benzimidazol]-1′-yl)methyl]-[1,1′- biphenyl]-2-carboxamide (compound VII) into Telmisartan. In one embodiment, the process of the present invention includes hydrolyzing compound VII, preferably using a mixture of a base and propylene glycol, which is an environmentally friendly ICH class 3 solvent.



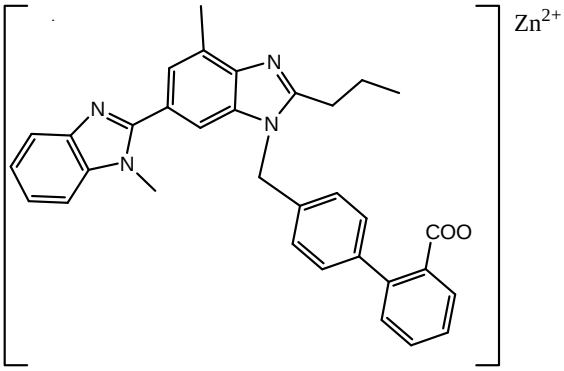
41. US 7501448 B2[42]

The aim of the present invention is therefore to provide an alternative method of preparing telmisartan, which can be used on a large scale and allows telmisartan to be easily worked up, purified, and isolated.



42. WO 2010053233[43]

The present invention describe preparation of a novel zinc salt of 2-[4-[[4-methyl-6-(1-methylbenzoimidazol-2-yl)-2-propylbenzoimidazol-1-yl] methyl] phenyl] benzoic acid (telmisartan). The telmisartan zinc salt exhibits excellent physicochemical properties as compared to reported telmisartan and addition salts thereof, as well as sufficient safety as a novel salt compound. Therefore, the telmisartan zinc salt of the present invention is useful as a compound having angiotensin II antagonistic activity.



Some structures of Piperidone, diazido, Glutarimides etc compounds are mentioned their clinical and preclinical studies followed Vilsmeier-Haack reaction.[44-48]

CONCLUSION

Telmisartan originated as lifesaving drugs by reducing the risk of heart diseases, they are also known to produce minor side effects such as hyperkalemia, renal failure, dizziness and hypotension. This article provides a way forward for new insights in design and development of new upcoming Telmisartan drugs. There also a broad scope in the development of Telmisartan drugs and further research is needed to come out with new Telmisartan drug hybrids which can reduce the risk of hypertension related heart diseases with minimal or zero side effects, caused with their intake.

ACKNOWLEDGEMENTS

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