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# *Communications to the Editor*

## An Efficient and Impurity-Free Process for Telmisartan: An Antihypertensive Drug§

Kikkuru Srirami Reddy,† Neti Srinivasan,† Chinta Raveendra Reddy,† Naveenkumar Kolla,† Yerremilli Anjaneyulu,‡ Sundaram Venkatraman,† Apurba Bhattacharya,† and Vijayavitthal T. Mathad*,†

*Department of Research and Development, Dr. Reddy's Laboratories Ltd., IPD, Unit-III, Bollaram, Medak-502325, Andhrapradesh, India, and Center for Atmospheric Science, J.N.T. University, Kukatpally, Hyderabad-500072, Andhrapradesh, India*

**Abstract:**

**Telmisartan (1), a substituted dibenzimidazole derivative, is an antihypertensive drug, essentially used to control blood pressure. An improved, cost-effective, and impurity-free process for telmisartan (1) 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).**

### Introduction

Telmisartan (**1**) is an angiotensin II receptor antagonist useful in the treatment of hypertension, heart diseases, heart strokes, and bladder diseases.[1] Telmisartan (**1**) is currently available in the market as an antihypertensive drug[2] under the brand name of MICARDIS. The first reported synthetic method[3] for this molecule consists of 8 steps (Scheme 1) involving condensation of 4-amino-3-methyl benzoic acid methyl ester (**2**) with butyryl chloride (**3**) in chlorobenzene to yield **4**. Nitration of **4** followed by reduction of the resulting 5-substituted nitro compound **5** over Pd−C in methanol yielded amine **6**. Cyclisation of **6** in acetic acid reflux affords the monobenzimidazole derivative **7**, which upon further hydrolysis yielded an acid intermediate **8** by a saponification process. Condensation of compound **8** with diamine derivative **9** in polyphosphoric acid yielded the dibenzimidazole compound **10**, which was further alkylated with 4′-bromomethyl-biphenyl-2-carboxylic acid *tert*-butyl ester (**11**)[4] to afford product **12**. Finally, hydrolysis of ester **12** in trifluoracetic acid yielded telmisartan (**1**) in an overall yield of around 21% with several impurities.

This process suffers from disadvantages such as (a) a multistep synthesis for compound **8** (3 steps from compound **5**); (b) the solvents dimethyl formamide (DMF) or dimethylsulfoxide (DMSO) used in the penultimate stage are unrecoverable, while the use of potassium *tert*-butoxide resulted in high organic volatile impurities (OVI) in telmisartan; (c) deprotection of the *tert*-butyl group using trifluoroacetic acid in DMF lead to the formation of several byproducts; (d) residue on ignition (ROI) in API obtained from this process is always >1.0% (ICH limit <0.1%), and there is no specified process mentioned in the literature to control the ash content. This is mainly due to very poor solubility of the telmisartan in most of the solvents including water; and (e) the overall yield (21%) of this process is discouraging, which makes the process less viable for commercial production. Herein, we report an economic, efficient, and impurity-free synthesis of telmisartan having regulatory quality[5] with an overall yield of 50% which has been accomplished by modifying the original process.

### Results and Discussion

Our efforts to develop a robust and economic route for telmisartan (**1**) are described below in greater detail.

**Process for Dibenzimidazole Intermediate 10 via One Pot Synthesis of 8.** We opted for 4-butyrylamino-3-methyl-5-nitro-benzoic acid methyl ester (**5**) as a starting material due to its commercial availability. In our approach, after the reduction of nitro compound **5** to obtain amine **6**, the resulting reaction mass was filtered to remove Pd−C catalyst and the filtrate was concentrated to a thick syrup which was directly treated with aqueous sodium hydroxide to furnish benzimidazole intermediate **8** in a single step with 92−95% yield (Scheme 2). The workup involves cooling the reaction mass to room temperature followed by adjusting the pH of the reaction mass between 4.5 and 5.0 with concd HCl to afford compound **8** as crystalline solid powder. The intermediate **8** was then condensed with *N*-methyl-benzene-1,2-

* Corresponding author. Telephone: 91 9822581611. Fax: +91 8458 279619. E-mail: drvtmathad@yahoo.co.in.

† Dr. Reddy's Laboratories Ltd.

‡ J.N.T. University.

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(1) (a) Battershill, A. J.; Scott, L. J. *Drugs* **2006**, *66* (1), 51−83. (b) Norbert, H.; Berthold, N.; Uwe, R.; Jacobus, C. A.; Van, M.; Wolfgang, W.; Michael, E. U.S. Patent 5,591,762, 1997. (c) Ruth, R. W.; William, J. C.; John, D. I.; Michael, R. C.; Kristine, P.; Ronald, D. S.; Pieter, B. M. W. M. T. *J. Med. Chem*. **1996**, *39* (3), 625−656.

(2) http://www.rxlist.com/cgi/generic2/telmisartan.htm.

(3) (a) Uwe, J. R.; Gerhard, B. N.; Kai, M. H.; Helmut, W.; Michael, E.; Jacobus, C. A.; Van, M.; Wolfgang, W.; Norbert, H. H. *J. Med. Chem*. **1993**, *36*, 4040−4051. (b) Merlos, M.; Casas, A.; Castaner, J. *Drugs Future* **1997**, *22* (10), 1112−1116.

(4) Carini, D. J.; Dunicia, J. V. Eu. Patent 2,53,310, 1988.

(5) Venkataraman, S.; Mathad, V. T.; Kikkuru, S. R.; Neti, S.; Chinta, R. R.; Arunagiri, M.; Routhu, L. K PCT WO 06/044754A2, 2006.

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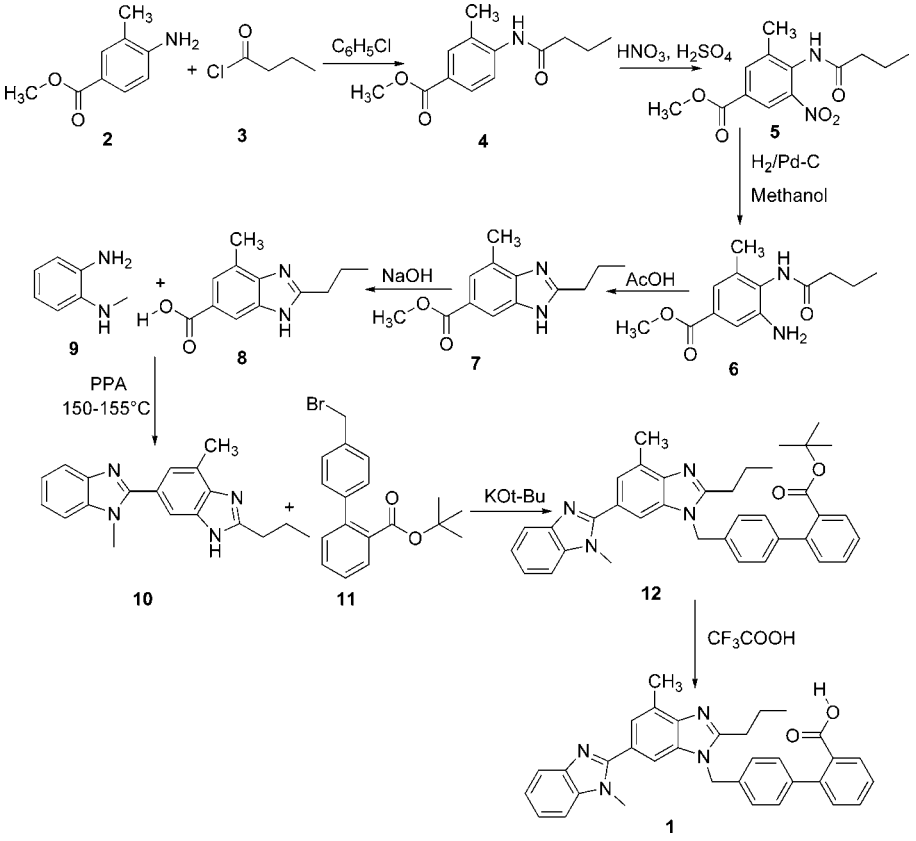
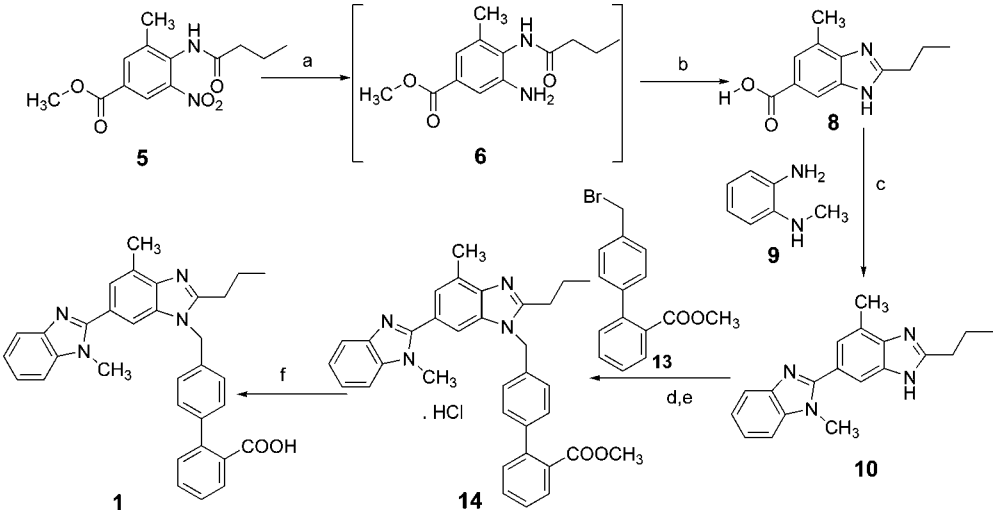
***Scheme 1.*** **Reported synthetic scheme of telmisartan**



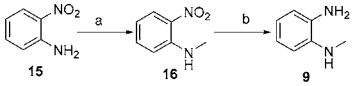

***Scheme 2.*** **Modified synthetic schme of telmisartan**[a]




[a] Reagents and conditions: (a) Pd−C/methanol/$H_2$ gas/25−35 °C/3−4 h. (b) NaOH/methanol and water/4−5 h. (c) Polyphosphoric acid/150−155 °C/4−5 h. (d) KOH flakes/acetone/25−35 °C/1.5−2 h. (e) Methanolic HCl(30%)/methanol/acetonitrile. (f) KOH flakes/ $CH_3CN$/80−85 °C/1.5−2 h.

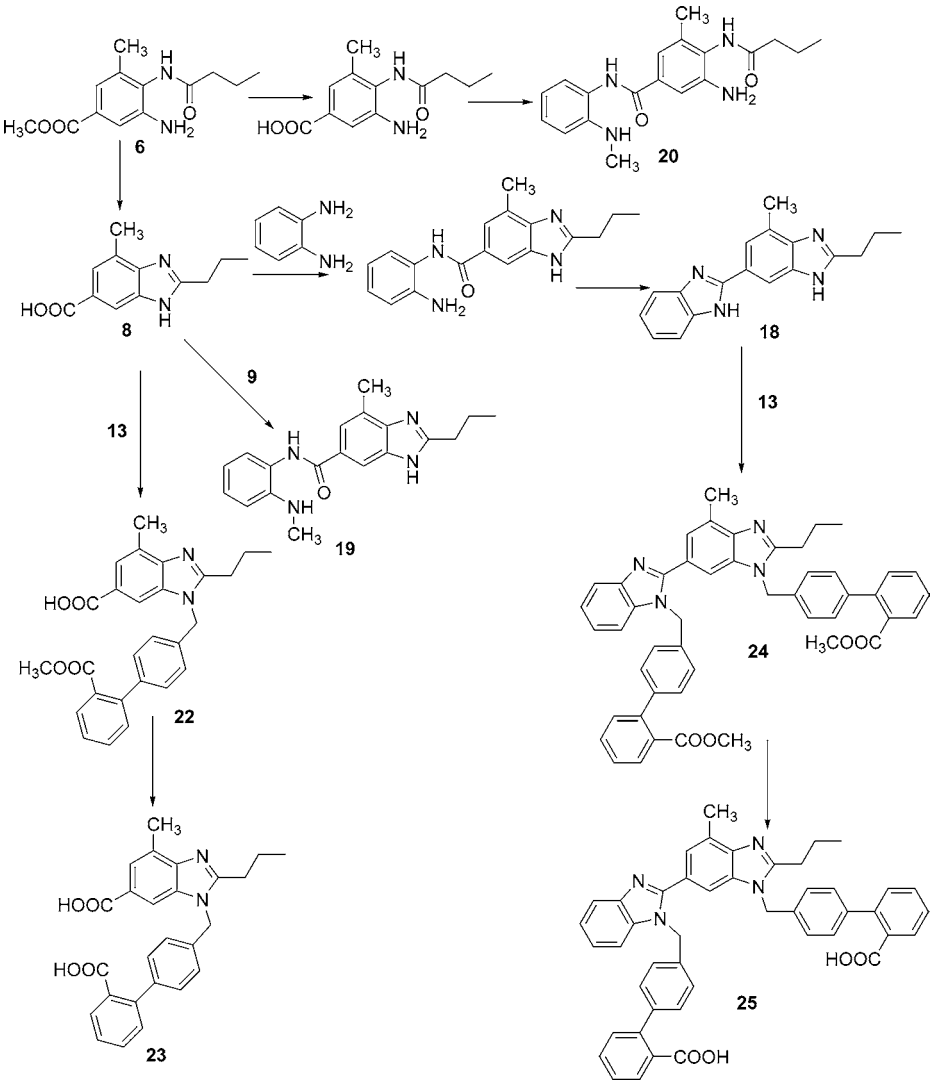
diamine (**9**)[6] in polyphosphoric acid at 150−155 °C to obtain the dibenzimidazole intermediate **10**. The major impurities found in **10** were desmethyl dibenzimidazole (**18**) which may be due to the presence of traces of benzene-1,2-diamine in **9**, 7-methyl-2-propyl-3*H*-benzoimidazole-5-carboxylic acid (2-methylaminophenyl)amide (**19**), and 3-amino-4-butyrylamino-5-methyl-*N*-(2-methylaminophenyl)benzamide (**20**) (Scheme 3). A robust purification method has been developed to control all these impurities in **10**, in order to avoid the formation of corresponding byproducts in the subsequent stages. These impurities are very difficult to wash out at either the penultimate or final step. These impurities were

(6) The intermediate **9** is prepared via monomethylation of *o*-nitroaniline (**15**) using dimethylsulfate followed by hydrogenation over Pd−C catalyst in methanol with 75% of overall yield. Of the several methylating agents such as $CH_3I$, DMS, HCOOH, and $H_2CO$ explored for monomethylation of **15**, DMS was found to be superior to obtain **15**.




[a]Reagents and conditions: a) KOH flakes/ DMA/DMS/25-35°C/1.5-2 hrs.
b) Pd-C/ methanol/ $H_2$-pressure/5.0-5.5 Kg/$Cm^2$/25-35°C/4-5 hrs

***Scheme 3.*** **Synthetic scheme of telmisartan impurities**

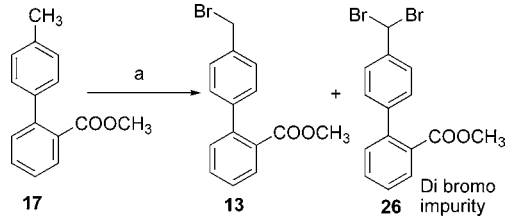



synthesized, characterized, and confirmed to be present in our sample by HPLC.[7]

**Synthesis of 4′-Bromomethylbiphenyl-2-carboxylic Acid Methyl Ester (13).** 4′-Methylbiphenyl-2-carboxylic acid is one of the key fragments of the telmisartan (**1**), and this is constructed on telmisartan through alkylation of **10** with the *tert*-butyl methyl ester **11**. As we experienced the problem in the deprotection of the *tert*-butyl group in the original route (Scheme 1), this small change to methyl ester (**13**)[8] in the route (Scheme 2) avoided the usage of hazardous reagent trifluoroacetic acid and high boiling liquid DMF for this reaction. Methyl ester **13** has been synthesized through bromination of commercially available 4′-methylbiphenyl-2-carboxylic acid methyl ester (**17**)[9] (Scheme 4).

**Condensation of 10 and 13 Followed by Telmisartan (1) Synthesis.** Our attempts to telescope the alkylation and hydrolysis steps (steps 3 and 4, Scheme 2) to achieve telmisartan in a single pot was unsuccessful due to formation

***Scheme 4.*** **Synthesis of 4′-bromomethylbiphenyl-2-carboxylic acid methyl ester 13**[a]




[a] Reagents and conditions: (a) DBDMH/AIBN/$CHCl_3$/60−65 °C/1−2 h.

of several impurities which were difficult to wash out by crystallization in various solvents. The telimisartan (**1**) obtained by this process also showed the high ash content. Hence, the bromo compound **13** is first alkylated with **10** in acetone in the presence of KOH, and the product precipitated

(7) Structures of these impurities were tentatively proposed based on MS−MS data and a probable reaction mechanism and then synthesized as shown in Scheme 3. These impurities were characterized by NMR, mass, and IR techniques and further confirmed to be present in the sample by HPLC coinjection and spiking methods (0.1%).

(8) Shen, J.; Li, J.; Yan, T.; Li, H.; Ji, R. CN 1,344,712, 2002.

(9) Several brominating agents such as molecular bromine, *N*-bromosuccinimide (NBS), and 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) resulted in **13** along with the dibromo impurity **26**. The formation of the dibromo impurity **26** is varying from 20−45% by HPLC. The content of **26** is nearly 45% in the case of NBS bromination, whereas the same is in the range of 15%−20% in the case of DBDMH. Hence, DMDBH has been utilized as the brominating agent in the process. However impurity **26** did not participated in the next step and was easily washed out to a nondetected level during the isolation of **14** in the condensation step.

***Table 1.*** **Content of impurities in the telmisartan (1)[a]**

| expmt no. | purity of **1** by HPLC % | content of impurities by HPLC | | | | | ash content | overall yield (%) |
|---|---|---|---|---|---|---|---|---|
| | | **14** | **22** | **23** | **24** | **25** | | |
| 1 | 99.98 | ND | ND | 0.01 | ND | ND | 0.02 | 51.6 |
| 2 | 99.97 | 0.01 | ND | ND | ND | ND | 0.04 | 50.8 |
| 3 | 99.99 | ND | ND | ND | 0.01 | ND | 0.01 | 50.2 |

[a] ND = Not detectable level.

was further converted to a hydrochloride salt in methanol. Distillation of methanol followed by isolation of the salt in acetonitrile afforded the HCl salt of methyl ester (**14**) with 85% yield and >99.5% purity by HPLC. This process efficiently removed the crucial impurities **22**, **23**, **24**, and **25** to a negligible amount (Scheme 3) in API.

In the next step, HCl salt **14** was hydrolyzed to telmisartan (**1**) via a saponification process using potassium hydroxide as a base in acetonitrile. The telmisartan potassium salt precipitated directly as a crystalline solid was collected by filtration and dissolved in water and acetonitrile. The pH of the resulting solution is adjusted to 5.0−5.5 using a 5% solution of acetic acid. The precipitated telmisartan (**1**) was separated by filtration and washed with water. The telmisartan obtained as per this process matches with the desired polymorphic form A reported in the literature[10] and fulfills all regulatory specifications except for the ash content (1.0−3.0%). Several attempts to remove the ash content of telmisartan by making slurries in various solvents including water at different reaction conditions were unsuccessful. Various options explored to remove the ash during optimization lead to the following final process.

The dissolution of telmisartan containing around 1.0−3.0% of ash content in methanol in a closed vessel at 80−85 °C under in built pressure of 2.0−2.2 kg/cm$^2$ was allowed to crystallize at room temperature. The telmisartan obtained from this process consistently produced the telmisartan having ROI always less than 0.1%. The overall yield obtained from this improved process is around 50% (Scheme 2). The overall yield and quality of the telmisartan obtained from this process at scale-up were tabulated below in Table 1.

## Conclusion

We have provided an improved, cost-effective, and industrially feasible manufacturing process for telmisartan that is substantially free from impurities and meets the regulatory norms in terms of quality with an overall yield of around 50%.

## Experimental Section

The $^1$H and $^{13}$C NMR spectra were measured in $CDCl_3$ and DMSO-$d_6$, using 200 and 50 MHz, respectively on a Varian Gemini 200 MHz FT NMR spectrometer; the chemical shifts are reported in $\delta$ ppm relative to TMS. The FT−IR spectra were recorded in the solid state as a KBr dispersion using a Perkin-Elmer 1650 FT−IR spectrophotometer. The mass spectrum (70 eV) was recorded on an HP-5989A LC-MS spectrometer. The CHN analysis was carried out on a Perkin-Elmer model 2400S analyzer. The melting points were determined by using the capillary method on a POLMON (model MP-96) melting point apparatus. The PXRD studies were demonstrated on a BRUKER axs D8 advanced wide-angle X-ray diffractometer. The DSC analysis was performed on a DSC Q 1000 (TA instruments) under a nitrogen atmosphere. The solvents and reagents were used without further purification.

**7-Methyl-2-propyl-3*H*-benzimidazole-5-carboxylic Acid (8).** A solution of 4-butyrylamino-3-methyl-5-nitro benzene acid methyl ester (**5**, 50.0 g, 0.178 mol), methanol (750 mL), and Pd−C (2.5 g) was placed in an autoclave system under hydrogen pressure (3.4 kg/cm$^2$) at 25−35 °C for 4 h. The reaction mass was filtered through a hyflowbed, and the catalyst was washed with methanol (100 mL). The combined filtrates were concentrated to obtain 42 g of **6** as a thick residue. Water (400 mL) was added followed by sodium hydroxide (14.3 g, 0.357 mol) and heated to reflux temperature for about 5 h. After completion, the reaction mass was cooled to 25−35 °C, the pH of the reaction mass was adjusted to 4.5−5.0 using concentrated hydrochloric acid (34 mL), and then the reaction mass continued stirring for 45−60 min. The crystalline solid obtained was filtered, washed with water (200 mL), and dried at 55−60 °C for 2−3 h to obtain **8** as a white crystalline powder. Yield 36 g (92.54%); mp 295−297 °C; MS *m*/*z* 219 $M^+ + H$; $^1$H NMR ($CDCl_3$) $\delta$ 8.1 (s, 1H), 7.6−7.8 (m, 2H), 2.95 (t, $J$ = 7.6, 2H), 2.90 (s, 3H), 1.90 (q, $J$ = 7.5, 2H), 1.02 (t, $J$ = 7.3, 3H).

**1,4′-Dimethyl-2′-propyl-1*H*,3′*H*-2,5′-dibenzimidazole (10).** A mixture of 7-methyl-2-propyl-3*H*-benzimidazole-5-carboxylic acid (**8**, 10.0 g, 0.045 mol), *N*-methylbenzene-1,2-diamine (**9**, 8.0 g, 0.05 mol), and polyphosphoric acid (30.0 g) was heated at 150−155 °C for 4−5 h. The reaction mass was cooled to 70−80 °C and decomposed slowly with water (100 mL) at 70−80 °C. The pH of the reaction mass was adjusted to 4.5−5.0 using 20% NaOH solution, and the reaction mass continued stirring at the same temperature (70−80 °C) for 4−5 h to precipitate **10** as a crystalline solid. The crystalline solid obtained was filtered, washed thoroughly with water (50 mL), and then recrystallised from THF (90 mL) to obtain **10** in 11.7 g, 84% yield; mp 130−135 °C; MS *m*/*z* 305 ($M^+ + H$); $^1$H NMR ($CDCl_3$) $\delta$ 7.8 (s, 1H), 7.2−7.7 (m, 6H), 3.89 (s, 3H), 2.80 (t, $J$ = 7.4, 2H), 2.05 (s, 3H), 1.86 (q, $J$ = 7.3, 2H), 0.99 (t, $J$ = 7.4, 3H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 13.7, 16.8, 21.0, 30.6, 31.7, 110.2, 113.4, 118.6, 121.7, 121.9, 122.9, 123.1, 136.6, 142.5, 154.3, 156.2.

***N*-Methylbenzene-1,2-diamine (9).** To a stirred solution of *o*-nitroaniline (**15**, 100 g, 0.72 mol), KOH flakes (101.4 g, 1.81 mol), and DMA (350 mL) was slowly added dimethylsulfate (85.6 g, 0.904 mol) at below 35 °C, and the solution stirred for about 1−2 h. The reaction mass was filtered through hyflow, and the filtered cake was thoroughly washed with 1000 mL of $CH_2Cl_2$. The combined filtrates were washed with water (2 × 1000 mL) and distilled under reduced pressure to give 108 g of **16** as a syrup. Methanol

(10) Robert, E. D.; Peter, S.; Herbert, N.; Kenneth, S.; William, I. F. D. *J. Pharm. Sci*. **2000**, *89* (11), 1465−1479.

(1 L) was added and hydrogenated over 5% Pd−C (4 g) in a closed autoclave system at 25−35 °C under 5.5 kg/cm$^2$ of hydrogen pressure for 4−5 h. The reaction mass was filtered through hyflow at 25−35 °C, and the catalyst was washed with methanol (200 mL). The pH of the combined filtrates was adjusted to 1.0−2.0 with concentrated hydrochloric acid (60 mL) and stirred for 15 min. The solvent was distilled off under reduced pressure to obtain crude, and the obtained crude was crystallized from acetonitrile (500 mL). The crystalline solid obtained was filtered, washed with chilled acetonitrile (200 mL), and dried at 50−55 °C for 5−6 h to obtain the HCl salt of **9** as a white crystalline material. Yield 85 g (74%); mp 170−175 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.2−7.5 (m, 4H), 6.80 (s, 1H), 6.7 (s, 2H), 3.01 (s, 3H); MS *m*/*z* 123 ($M^+ + H$).

**4′-Bromomethylbiphenyl-2-carboxylic Acid Methyl Ester (13).** A mixture of 4′-methylbiphenyl-2-carboxylic acid methyl ester (**17**, 10.0 g, 0.044 mol), 1,3-dibromo-5,5-dimethylhydantoin (9.0 g, 0.031 mol), and 2,2-azobisisobutyronitrile (0.5 g, 0.003 mol) in chloroform (100 mL) was heated to reflux (60−65 °C) for 1−2 h. The reaction mixture was cooled to 25−35 °C, the formed byproduct was filtered, and the filtrate was washed with water (200 mL). The organic layer was separated and concentrated under a vacuum. The obtained residue was triturated with *n*-hexane (50 mL), and the obtained solid was filtered and dried under a vacuum: yield 12.5 g, 92.6%; mp 40−42 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.2−7.8 (m, 8H), 4.5 (s, 2H), 3.6 (s, 3H); MS *m*/*z* 306 ($M^+ + H$).

**4′-(1,4′-Dimethyl-2′-propyl-1*H*-[2,5′]bibenzimidazolyl-3′-ylmethyl)biphenyl-2-carboxylic Acid Methyl Ester (14).** A mixture of 1,4′-Dimethyl-2′-propyl-1*H*,3′*H*-2,5′bibenzimidazole (**10**, 10.0 g, 0.032 mol), KOH flakes (2.8 g, 0.05 mol), and 4′-bromomethylbiphenyl-2-carboxylic acid methyl ester (**13**, 16.2 g, 0.053 mol) in acetone was stirred at 25−35 °C for 1.5−2.0 h. The product thus obtained was separated by filtration, and the filtered solid was washed with 20 mL of chilled acetone. The wet solid obtained was directly dissolved in methanol (50 mL), and the pH of the resulting solution was adjusted to 1−2 using 30% methanolic HCl (27 mL). Solvent was distilled off under reduced pressure, and the resulting crude was isolated as a crystalline solid material from acetonitrile (90 mL). The crystalline solid obtained was filtered, washed with chilled acetonitrile (20 mL), and dried at 50−55 °C for 3−4 h to obtain **14** as a white crystalline powder. Yield 14.8 g (85%); mp 170−175 °C; MS; *m*/*z* 529 ($M^+ + H$). $^1$H NMR ($CDCl_3$) $\delta$ 7.2−7.9 (m, 14H), 5.7 (s, 2H), 4.10 (s, 3H), 3.59 (s, 2H), 3.28 (t, $J$ = 7.8, 2H), 2.88 (s, 3H), 2.01 (q, $J$ = 7.7, 2H), 1.14 (t, $J$ = 7.4, 3H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 13.7, 16.4, 20.6, 28.7, 31.6, 46.0, 51.7, 109.1, 110.2, 118.6, 121.7, 121.9, 123.1, 123.3, 126.4, 127.4, 128.2, 128.5, 129.2, 130.4, 130.6, 131.4, 134.7, 136.1, 136.6, 139.7, 140.7, 142.5, 154.0, 156.1, 168.2.

**4′-[(1,4′-Dimethyl-2′-propyl-[2,6′-bi-1*H*-benzimidazol]-1′-yl)methyl]-[1,1′-biphenyl]-2-carboxylic Acid (1).** A mixture of **14** (10 g, 0.017 mol), acetonitrile (150 mL), and KOH flakes (4.5 g, 0.08 mol) was heated to reflux for about 2 h. The reaction mass was cooled to 25−35 °C, and the potassium salt thus obtained was separated by filtration and washed with acetonitrile (20 mL). The wet solid was dissolved in a mixture of water (150 mL) and acetonitrile (50 mL) and then heated to 60−65 °C under stirring. The pH of the resulting clear solution was adjusted to 5.0−5.5 using 5% acetic acid (4 mL), and stirring continued for 2 h. The crystalline solid was filtered and washed with water (50 mL). The wet solid obtained was transferred to a closed autoclave system, methanol (80 mL) was added, and the system was heated to 80−85 °C until dissolution under inbuilt pressure (2.0−2.2 kg/cm$^2$). The reaction mass was allowed to cool to room temperature and then stirred for 1−2 h. The precipitated solid was filtered, washed with chilled methanol (10 mL), and dried at 70−75 °C for 4−5 h under a vacuum to obtain Telmisartan (**1**) as a white crystalline powder. Yield 7 g (77%); purity by HPLC 99.9%; mp 260−262 °C; Pd content not detected; Heavy metals <10 ppm; MS *m*/*z* 515 ($M^+ + H$); $^1$H NMR ($CDCl_3$) $\delta$ 12.8 (s, 1H), 7.05−7.5 (m, 14H), 5.60 (s, 2H), 3.82 (s, 3H), 2.97 (t, $J$ = 7.5, 2H), 2.63 (s, 3H), 1.88 (q, $J$ = 7.3, 2H), 1.04 (t, $J$ = 7.3, 3H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 13.5, 16.7, 20.6, 27.6, 32.7, 47.1, 51.7, 112.0, 112.7, 114.7, 118.6, 125.3, 125.7, 125.8, 127.0, 127.4, 128.6, 129.3, 130.4, 130.6, 131.5, 132.3, 133.1, 133.7, 134.5, 140.2, 140.5, 150.2, 157.3, 168.1. Anal. Calcd for $C_{33}H_{30}N_4O_2$: C, 77.02; H, 5.88; N, 10.89; O, 6.22. Found: C, 77.0; H, 5.82; N, 10.89; O, 6.20.

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