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# An improved and efficient synthesis of Irbesartan, an antihypertensive drug

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**Abstract:** Development of a new improved and efficient process suitable for the large-scale production of Irbesartan has been described. The key steps are tetrazole formation from secondary amide for the preparation of the key intermediate 1-Benzyl-5-(4'-bromomethyl-biphenyl-2-yl)-1*H*-tetrazole (**9**), *N*-alkylation and debenzylation.

**Key words:** Irbesartan; antihypertensive drug; tetrazole formation; debenzylation.

## 1. Introduction

Irbesartan **1** is a non-peptide angiotensin II receptor antagonist used in the management of hypertension, heart diseases, heart strokes, diabetic neuropathy and congestive heart diseases.[1] Irbesartan is currently available in the market as an antihypertensive drug under the brand name of Avapro.[2] The metabolism of Irbesartan, a highly selective and potent nonpeptide angiotensin II receptor antagonist, has been investigated in humans.[3] Irbesartan inhibits the activity of angiotensin II (AII) via specific, selective noncompetitive antagonism of the AII receptor subtype 1 (AT1) which mediates most of the known physiological activities of AII.[4]

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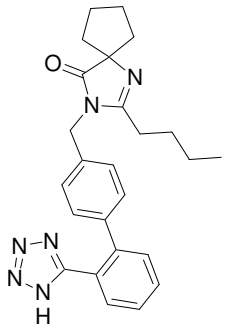
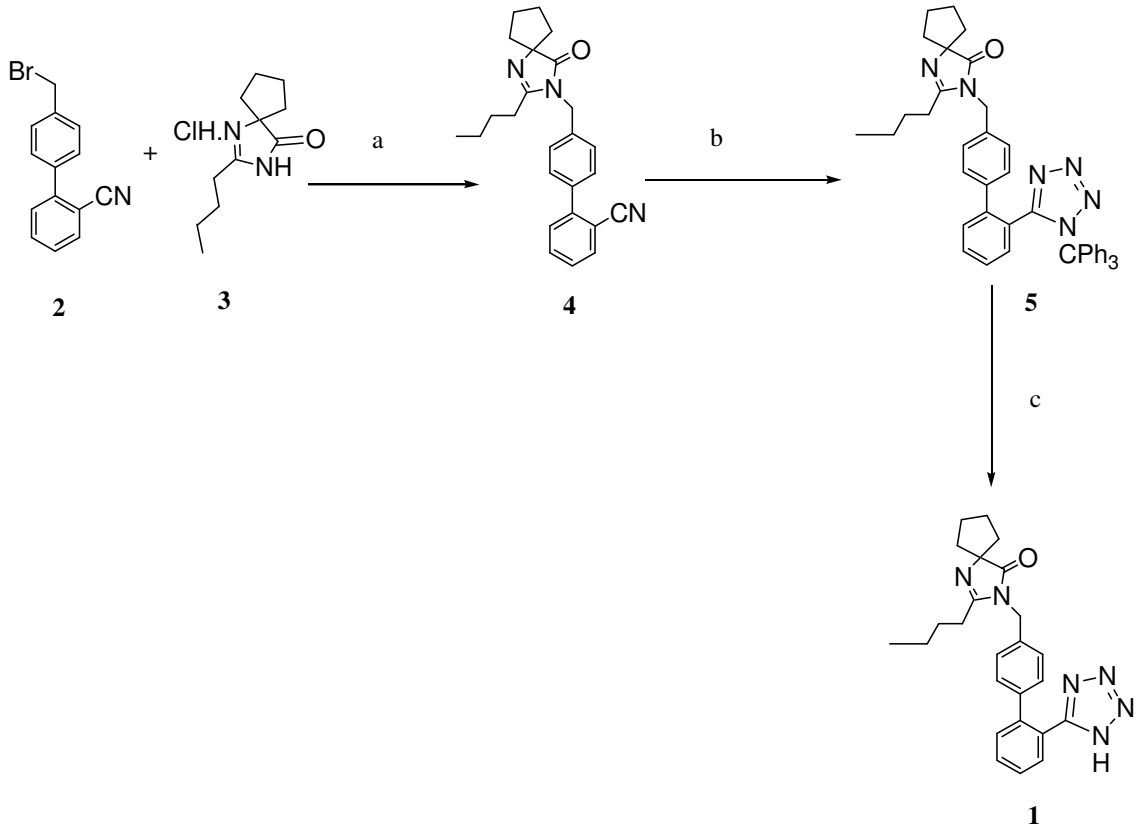


**1**

To meet the Irbesartan drug demand of the market, there is a need to develop an ideal commercial process, which is a safe, ecologically sound, economic and meets the quality specifications. The first reported synthetic method [5, 6] for the preparation of Irbesartan as shown in Scheme 1 consists of the condensation of 4'-Bromomethyl-biphenyl-2-carbonitrile (**2**) with 2-butyl-1,3-diaza-spiro[4,4]non-1-en-4-one hydrochloride (**3)** using sodium hydride (NaH) as a base and dimethyl formamide (DMF) as solvent medium. The second step involves the tetrazole formation by treating tributyltinazide in xylene followed by trityl protection to obtain Trityl Irbesartan. The trityl group was cleaved by treating with aqueous hydrochloride in methanol and tetrahydrofuran mixture.



**2** **3** **4** **5** **1**

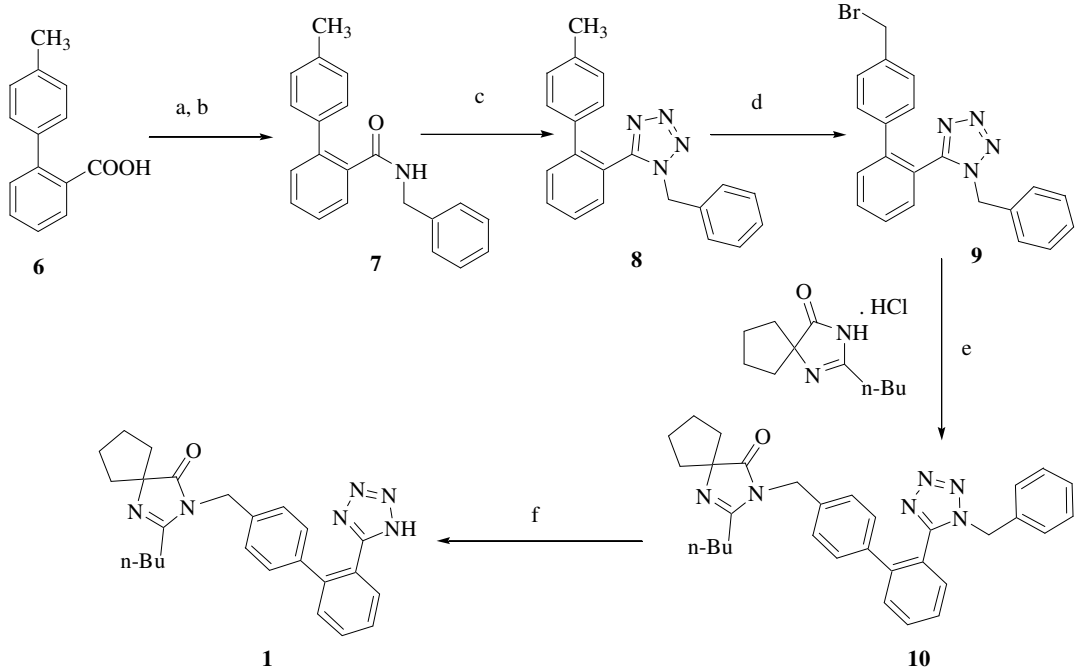
**Scheme 1.** *Reagents and conditions:* (a) NaH, DMF, rt, 1 h, 79%. (b) tributyltin azide, xylene, reflux, 66 h, trityl chloride, 26 h, 72%. (c) 4N HCl, methanol, THF, rt, 4 h, 67%.

This process suffers from the disadvantages such as (a) NaH is used as base in the first step of the process for which utmost care should be taken to perform the reaction under inert atmosphere as it is an exothermic reaction, highly sensitive towards moisture, it is unsafe and not suitable for production on commercial scale (b) The purification of the compound **4** and compound **5** was done through column chromatography which is not commercially viable (c) Tri-n-butyltinazide was used as reagent for the tetrazole formation in the step 2. Toxicity of tin in humans is most frequently reported as the exposure to tin compounds will cause memory loss and insomnia as well as other symptoms like death.[7] Neurotoxicity and liver damage has been reported with tin compounds exposure in humans.[8] Considering the toxic effects of tin, this route is not suitable for the preparation of Irbesartan with respect to safety and health aspects (d) The temperature for the tetrazole formation step is high and the time cycle is more i.e. reflux in xylene (~150$^{o}$C) for 66 hours which is not a economic and ecofriendly process (e) The tetrazole group was protected by tritylation using trityl chloride. As the deprotection of the trityl group in the final step will give trityl alcohol as byproduct which is the potential impurity in this process and it is not removed easily (e) The over yield of the process is 38% only. Our quest to develop a more economic and cost effective process for important API`s prompted us to develop an efficient process for Irbesartan.

In the present communication, we report the preparation of Irbesartan using 1-benzyl-5-(4'-bromomethyl-biphenyl-2-yl)-1H-tetrazole **(9)** which has provided an advantage in improving the overall yield (66%) and also circumvented the repeated column chromatographic purifications.

## 2. Results and Discussion

Our research work focuses on the design of a new commercially viable process for the preparation of Irbesartan. Based on the literature search, we developed a five stage process which involves the preparation of the key intermediate, 1-Benzyl-5-(4'-bromomethyl-biphenyl-2-yl)-1*H*-tetrazole (**9**) starting from 4'-Methyl-biphenyl-2-carboxylic acid (**6**) and the subsequent condensation with 2-Butyl-1,3-diaza-spiro[4.4]non-1-en-4-one hydrochloride (**3**) and insitu debenzylation of the intermediate compound **10** to provide Irbesartan (**1**) (Scheme 2) in excellent yield as illustrated below,




**Scheme 2.** *Reagents and conditions*: (a) $SOCl_2$, TEA, toluene, 20-25$^{o}$C, 2 h. (b) benzylamine, 20-25$^{o}$C, 4h, 95% for two steps. (c) triphenylphosphine / diethyl azodicarboxylilate (DEAD) / trimethylsilylcyanide, THF, 20-25$^{o}$C, 24 h, 91%. (d) DBDMH, AIBN, EtOAc, reflux, 6 h, 89%. (e)

KOH, acetone, 25-30°C, 2 h. (f) 5% Pd/C, ammonium formate, isopropanol, water, 50-55°C, 15 h, 85% for two steps.

Accordingly, our first priority was to prepare the key intermediate **9**. There are some prior art procedures available in the literature for the preparation compounds **8** and **9** [9, 10], which involves the use of organo transition metals and harsh conditions and the yields reported are low. We have identified 4'-Methyl-biphenyl-2-carboxylic acid (**6**) as the starting material for the preparation of the key intermediate **9**. Compound **6** is treated with thionyl chloride to form acid chloride followed by the reaction with benzylamine to afford the amide compound **7** in 95% yield. We have screened different solvents and bases for the transformation of compound **6** to compound **7**. Optimum results were observed when triethylamine used as base in combination with toluene as solvent. The next task was the tetrazole formation from the amide compound **7**, which was a challenging part of the synthesis. There are few methods reported in the literature for the preparation of 1,5-substituted tetrazoles from secondary amides.[11-13] Initially we attempted the tetrazole formation using phosphorous pentachloride/sodium azide. This is a two step process, which involves the imidoyl chloride formation by the reaction of amide compound **7** with $PCl_5$ in dichloromethane followed by the reaction with $NaN_3$ in DMF to afford the tetrazole product. The yield of the product obtained as low in this method and it was also observed that the dehydration of the amide was taking place concurrently to form the compound **4** as an impurity. Later, we used triphenylphosphine/diethyl azodicaroxylate (DEAD)/ trimethylsilylazide ($(CH_3)_3SiN_3$) for the construction of tetrazole ring from compound **7**. The transformation was clean and product obtained in high yield (91%) under these mild conditions.

After successful optimization of the tetrazole ring formation, the compound **8** is subjected to benzylic bromination using 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) in ethylacetate medium and 2,2'-azobis(2-methylpropionitrile) (AIBN) as free radical initiator to furnish the key intermediate **9** in 89% yield (Scheme 2). DBDMH was observed to be suitable brominating reagent among other reagents tried for this transformation.

The compound **9** is reacted with the spiro compound **3** in the presence of potassium hydroxide in acetone medium to afford the benzyl protected Irbesartan as a residue which is directly proceeded to debenzylation without isolation. The debenzylation was performed using 5% palladium over carbon and ammonium formate in isopropanol and water mixture to afford Irbesartan in 90% yield. Before we arrived at the final conditions of the debenzylation, other methods were attempted like hydrogenation using Pd/C under $H_2$ pressure, Pd/C with formic acid. These methods were observed to be low yielding.

In summary, an improved and efficient approach to the preparation of Irbesartan has been developed by employing the condensation of the key intermediate 1-benzyl-5-(4'-bromomethyl-biphenyl-2-yl)-1*H*-tetrazole (**9**) with 2-butyl-1,3-diaza-spiro[4.4]non-1-en-4-one hydrochloride (**3**) followed by the debenzylation.

Our process has the advantages like (a) toxic metal compounds such as tri-n-butyl tin azide are not used in the formation of tetrazole ring (b) hazardous reagents like sodium hydride are avoided for the condensation reaction (c) column chromatographic purifications are not required in any stage (d) the use of protecting groups which will give to the byproducts that can arise as impurities in the finished product are avoided (e) the overall yield of the process is high (66%) when compared to the reported synthesis (38%).

## 3.Conclusion

In conclusion, we have developed a new improved, inexpensive and industrially scalable process for the synthesis of the anti hypertensive drug Irbesartan, which can provide high throughputs and high quality product in each stage.

## 4. Experimental

### *4.1. General Procedures*

All solvents and reagents were purchased from the commercial suppliers and used without further purification. All non-aqueous reactions were performed in dry glassware under an atmosphere of dry nitrogen. Organic solutions were concentrated under reduced pressure. Thin layer chromatography (TLC) was performed on Merck precoated Silica-gel 60F254 plates. The NMR spectra were recorded in DMSO at 400 MHz on a Varian Gemini 200 MHz FT-NMR spectrometer. The chemical shifts were reported in δ ppm relative to TMS. The FT-IR spectra were recorded in the solid state as KBr dispersion using a Perkin-Elmer 1650 FT-IR spectrophotometer. The mass spectrum (70 eV) was recorded on an Agilent-6310 LC-MS spectrometer. The elemental analysis was carried out using Elementar Vario Micro analyzer.

### *4.2. Preparation of 4'-Methyl-biphenyl-2-carboxylic acid benzylamide (7)*

To a stirred solution of 4'-Methyl-biphenyl-2-carboxylic acid (**6)** (100g, 0.471 moles) in toluene (500 mL) was added triethylamine (3.0 mL) and cooled the contents to 0-5$^{o}$C. Thionyl chloride (58.8 g, 0.494 moles) was added slowly drop-wise during 10-15 minutes by maintaining the internal temperature 0-5$^{o}$C. The reaction mixture was slowly allowed to reach 20-25$^{o}$C and stirred for 2 hours at same temperature. The contents were cooled to 0-5$^{o}$C and added benzylamine (55.7 g, 0.52 moles) slowly drop-wise during 20-25 minutes. The reaction mixture was allowed to reach 20-25$^{o}$C and maintained for 4 hours. Once the completion of the reaction is confirmed by TLC, the reaction mass was further diluted with toluene (300 mL) and added water (500mL) slowly to the reaction mass by keeping the temperature below 30$^{o}$C. The contents were stirred for 10-15 minutes at 25-30$^{o}$C and the organic phase is separated. The aqueous phase is further extracted with toluene (200 mL) and the combined organic layer was washed with saturated $NaHCO_3$ solution (50 mL) followed by water (50 mL). The organic phase was separated, dried over $Na_2SO_4$ (5.0g) and the solvent was distilled off completely under reduced pressure. To the residue, diisopropylether (100 mL) was added and again distilled completely to remove the traces of ethylacetate. Finally diisopropylether (200 mL) was added and stirred the contents for 30-45 minutes at 20-25$^{o}$C followed by maintenance for 30-45 minutes at 0-5$^{o}$C. The compound was filtered and washed with precooled diisopropylether (50 mL). The wet cake was dried under vacuum at 45-50$^{o}$C for 8 hours to obtain compound **7** as off-white solid. Yield: 135.3 g (95.3%). Purity by HPLC: 99.2%, m.p: 145$^{o}$C, IR (KBr, cm$^{-1}$) 3293 (-NH), 1648 (C=O); $^{1}$H NMR (DMSO-$d_6$): δ 7.75-7.72 (dd, 1H, *J*=7.6 Hz, *J*=1.2 Hz),7.48-7.26 (m, 5H), 7.24-7.15(m, 5H), 6.90-6.87(m, 2H), 5.45(s, 1H, exchanged with $D_2O$), 4.34(d, 2H, *J*=6.0 Hz), 2.39(s, 3H); $^{13}$C-NMR (DMSO-$d_6$):168.4, 142.1, 137.1, 135.9, 133.0, 132.5, 129.5, 128.1, 127.4, 127.9, 127.1,126.8, 126.1, 51.2, 23.2; MS (m/z): 302.3[$M^{+}$+1]; Anal. Calcd for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65. Found: C, 83.67; H, 6.30; N, 4.64.

### *4.3. Preparation of 1-Benzyl-5-(4'-methyl-biphenyl-2-yl)-1H-tetrazole (8)*

To a stirred solution of compound **7** (125g, 0.415 moles) in tetrahydrofuran (625 mL) was added Triphenylphosphine (161.8 g, 0.617 moles) under Nitrogen atmosphere. Diethylazo-dicarboxylate (98.8 g, 0.617 moles) was added slowly drop wise at below 20$^{o}$C and stirred the contents at 20-25$^{o}$C for 45 minutes. Trimethylsilylazide (71.1g, 0.617 moles) was added slowly drop wise and the reaction mixture was maintained at 20-25$^{o}$C for 24 hours. The completion of the reaction was assessed by TLC and the reaction mass was diluted with ethyl acetate (1500mL)) and washed with saturated sodium bicarbonate solution followed by water wash. The ethyl acetate layer was separated and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was crystallized from ethyl acetate and n-hexane mixture to afford compound **8** as off-white crystalline solid. Yield: 123.5 g (91.2%), Purity by HPLC: 98.6%, m.p: 137$^{o}$C, $^{1}$H NMR

(DMSO-$d_6$): δ 7.74-7.70 (dd, 1H, *J*=7.6 Hz, *J*=1.6 Hz), 7.59-7.50 (m, 3H), 7.27-7.19 (m, 3H), 7.09-7.08 (d, 2H, *J*=7.6 Hz), 6.89-6.87 (d, 2H, *J*=8.0 Hz), 6.80-6.79 (d, 2H, *J*=6.4 Hz), 5.08 (2H, s), 2.28 (3H, s); $^{13}$C-NMR (DMSO-$d_6$): δ 152.5, 137.5, 136.4, 135.6, 135.2, 133.7, 129.4, 129.3, 128.1,127.7, 127.4, 127.5, 125.2, 49.2, 21.7; MS (m/z): 327.2 [$M^+$+1]; Anal. Calcd for $C_{21}H_{18}N_4$: C, 77.28; H, 5.56; N, 17.17. Found: C, 77.23; H, 5.51; N, 17.14.

*4.3. Preparation of 1-Benzyl-5-(4'-bromomethyl-biphenyl-2-yl)-1H-tetrazole (9)*

To a stirred solution of compound **8** (120 g, 0.368 moles) in ethylacetate (480 mL) was added DBDMH (71.5 g, 0.250 moles) and stirred for 10-15 minutes at 20-25°C. Added AIBN (1.2 g, 0.007 moles) to the reaction mixture and the contents were refluxed for 6 hours. After the completion of the reaction, the contents were cooled to 20-25°C and added water (250 mL). The contents were stirred at same temperature for 20-30 minutes. The organic phase was separated and washed with saturated sodium bicarbonate solution (150 mL) followed by water (150 mL) and dried over anhydrous sodium sulphate (6.0 g). The solvent was evaporated completely under reduced pressure to afford compound **9** as a semi solid. Yield: 133.8g (89.7 %). Purity by HPLC: 98.1%; $^1$H NMR (DMSO-$d_6$): δ 7.76-7.72 (t, 1H, *J*=7.4 Hz), 7.76-7.48 (m, 3H), 7.44-733 (m, 2H), 7.25-7.18(m, 3H), 7.01-6.92 (m, 2H), 6.81 (d, 2H, *J*=6.82 Hz), 5.14(s, 2H), 4.68 (s, 2H); $^{13}$C-NMR(DMSO-$d_6$): δ 152.1, 139.7, 137.1, 136.5, 135.2, 134.4, 129.5, 129.1, 128.9, 128.1, 127.7, 127.5, 127.3, 124.1, 47.2, 36.4; MS (m/z): 405.3 [$M^+$]; Anal. Calcd for $C_{21}H_{17}BrN_4$: C, 62.23; H, 4.23; Br, 19.72; N, 13.82. Found: C, 62.18; H, 4.20; N, 13.78.

*4.4. Preparation of 2-Butyl-3-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1,3-diaza-spiro [4.4]non-1-en-4-one (1)*

To a stirred solution of 2-Butyl-1,3-diaza-spiro[4.4]non-1-en-4-one hydrochloride (**3**) (74.7 g, 0.324 moles) in acetone (625 mL) was added potassium hydroxide (69 g, 1.232 moles) at below 30°C. The contents were stirred for 30-45 minutes at 25-30°C was added 1-Benzyl-5-(4'-bromomethyl-biphenyl-2-yl)-1*H*-tetrazole (**9**) (125 g, 0.308 moles) portion wise and stirred for 2 hours at 25-30°C. The completion of the reaction can be monitored by TLC. The salts were filtered off, washed with acetone (50 mL) and the filtrate was completely distilled off under reduced pressure to obtain 3-[2'-(1-Benzyl-1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-2-butyl-1,3-diaza-spiro[4.4]non-1-en-4-one (**10**) as a residue. This compound was dissolved in mixture of methanol (435 mL) and water (275 mL). Added palladium carbon (15 g, 5% wet), ammonium formate (73.7 g, 1.17 moles), the resultant reaction mixture was heated to 50-55°C and stirred for 15 hours. The reaction completion is confirmed by TLC and the reaction mass was filtered through celite and washed with methanol (75 mL). The filtrate was distilled off completely under reduced pressure to obtain crude product, which was recrystallized from isopropanol to obtain Irbesartan **1** as a white solid. Yield: 112.7 g (85.3 %). Purity by HPLC: 99.6 %, m.p:181-182°C, IR (KBr, cm$^{-1}$) 1732 (C=O), 1616 (C=N); $^1$H NMR (DMSO-$d_6$): δ 7.95–7.32 (m, 8 H), 4.80 –4.60 (s, 2 H), 3.60– 3.00 (br s, 1 H), 2.40– 2.20 (t, 2 H , *J* = 6.04 Hz), 2.00– 1.60 (m, 8 H),1.60–1.45 (quint, 2 H), 1.40– 1.20 (sext, 2 H), 0.91–0.70 (t, 3H, *J* = 7.41 Hz); $^{13}$C-NMR (DMSO-$d_6$): δ 186.5, 162.0,155.9, 141.9, 139.2, 137.2. 131.9, 131.4, 130.1, 128.7, 127.1, 124.3, 76.7, 43.1, 37.7, 28.3, 27.4, 26.3, 22.4, 14.5; MS: m/z= 429 [M+1]; Anal. Calcd for $C_{25}H_{28}N_6O$ : C, 70.07; H, 6.59; N, 19.61. Found: C, 70.04; H, 6.57; N, 19.58.

**3-[2'-(1-Benzyl-1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-2-butyl-1,3-diaza-spiro[4.4]non-1-en-4-one (10).** $^1$H NMR (DMSO $d_6$): δ 7.74(d, 1H, *J*=7.2 Hz), 7.62(t, 1H, *J*=6.8 Hz), 7.54 (t, 1H, *J*=7.2 Hz), 7.46(d, 1H, *J*=7.6 Hz), 7.39-7.37(m, 3H), 7.18-7.16(m, 2H), 7.08-7.02(m, 4H), 5.82(s, 2H), 4.68(s, 2H), 2.28(t, 2H, *J*=7.6 Hz), 1.85-1.83(m, 6H), 1.68-1.66(m, 2H), 1.50-1.41(m, 2H), 1.27-1.21(m, 2H), 0.77(t, 3H, *J*=7.2 Hz); MS (m/z): 519.2 [$M^+$+1].

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