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Improved Methods for the Synthesis of Irbesartan, an Antihypertensive Active Pharmaceutical Ingredient

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Improved Methods for the Synthesis of Irbesartan, an Antihypertensive Active Pharmaceutical Ingredient

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Abstract: New methods for the preparation of irbesartan **1** have been described. The dehydration and tetrazole formation in one step from substituted cyclopentane derivative **7** with tributyltin chloride and sodium azide is described. Selective hydrolysis of nitrile **3** with HCl has also been described in the preparation of N-acylaminocyclopentane-2-carboxylic acid **4**, which is the key intermediate for the preparation of irbesartan. The impurity profiling of irbesartan has also been discussed.

Keywords: antihypertensive drug, impurities, irbesartan, synthesis

INTRODUCTION

Irbesartan **1** is chemically known as 2-butyl-3-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl] methyl]-1,3-diazaspiro[4,4]non-1-en-4-one. It is one of the most important drugs in this class of tetrazole compounds. Tetrazole compounds have been used as anticancer[1] and antimicrobial[2] agents.

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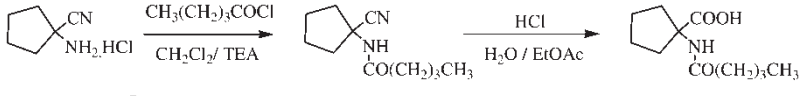
Recently, the substituted tetrazole compounds were found to be very useful drugs in the treatment of cardiovascular complaints. Irbesartan **1**, a tetrazole derivative, is an antihypertensive drug and highly selective nonpeptide compound that antagonizes angiotensin II.[3–5] It is a very useful drug in the treatment of cardiovascular complaints[6] such as hypertension, heart failure, glaucoma, diabetic retinopathy, renal insufficiency, and certain central nervous system complaints.

RESULTS AND DISCUSSION

Many synthetic approaches have been reported for the synthesis of irbesartan.[3–10] The most studied method developed by Bernhart et al.[3] starts with a biaryl intermediate 4-(2′-bromomethylphenyl) benzonitrile, which is condensed with 2-n-butyl-1,3-diazaspiro[4,4]-non-1-ene. The resulting nitrile was converted to irbesartan by a sequence of reactions. The major drawbacks of the reported methods are complex reactions, longer reaction times, lower yields, poor quality, and difficulty in use of sodium hydride. In another method,[10] 4-(2-aminomethylphenyl)benzonitrile (**6**) was coupled with N-pentanoylaminocyclopentane-1-carboxylic acid (**4**) in the presence of dicyclohexylcarbodiimide (DCC). The resulting diamide was cyclized to a spiro compound, which on treatment with 2 molar equivalents each of tributyltin chloride and sodium azide affords **1**. The major disadvantages of this method are very poor yield, believed to be a result of incomplete conversion and dimerization of free base of **6**, to the extent of 17–22%. Another major drawback of this route is insolubility of the coupling product in methylene chloride under the conditions. Therefore, it is crystallized out along with dicyclohexylurea, which is a by-product in this reaction. Hence, it is difficult to separate the desired product from the reaction mass. To circumvent difficulties, we have devised a short and high-yield process for the preparation of **1**.

In the present method, compound **3** was prepared from 1-aminocyclopentanecarbonitrile **2**, which on selective hydrolysis with hydrochloric acid gives acid **4** in about 90% yield with more than 99% of high performance liquid chromatographic (HPLC) purity (Scheme 1). We found that hydrolysis is a temperature-dependent reaction. Temperature should be maintained at 55–60°C for the preparation of compound **4**. At higher temperature, amide cleavage was observed. Compound **4** is one of the key intermediates in the preparation of compound **1**.



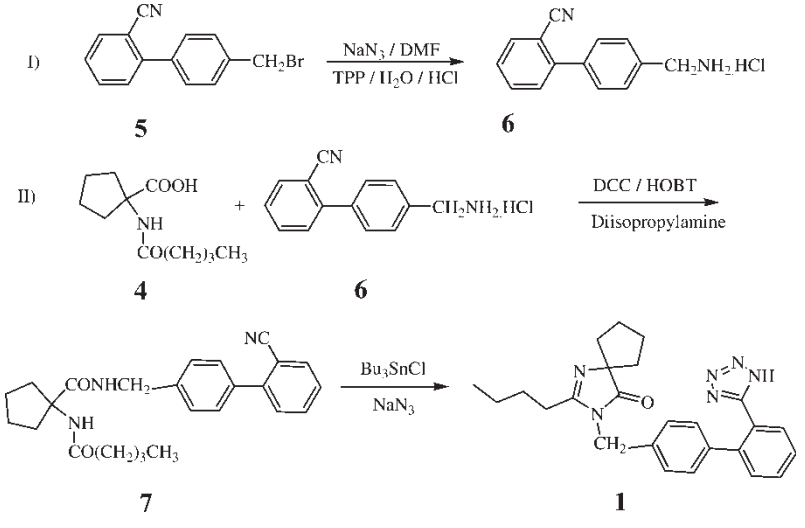
2 **3** **4**

Scheme 1.

Compound **6** was synthesized from bromomethyl compound (**5**) as shown in Scheme 2, which was coupled with acid **4** using dicyclohexylcarbodiimide, diisopropylethylamine (DIPEA) in the presence of 1-hydroxybenzotriazole (HOBT) to afford diamide **7**. Compound **7** was directly converted into irbesartan in one step. We observed that it was necessary to use compound **6** as its hydrochloride salt, and the coupling reaction of compound **6** with **4** must be done in the presence of an organic base, because under these conditions compound **7** remains in solution in methylene chloride and workup became very easy for the removal of by-product dicyclohexylurea (DCU) and the isolation of compound **7**. Treatment with tributyltin chloride and sodium azide in the presence of *N*,*N*-dimethylformamide (DMF) affords Irbesartan **1** in 70–75% yield. The irbesartan yield increased by 20% with the present method as compared to the literature methods,[8] and the purity obtained was 99.85% by HPLC analysis.

Irbesartan obtained with this method contains three potential impurities in a range of 0.05% to 0.1% by HPLC analysis. These impurities are identified as desbutyl irbesartan **8**, propyl irbesartan **9**, and acid **12**. The structures of these impurities are given in Fig 1. Impurity **9** was formed as a result of butyryl chloride present as an impurity in valeryl chloride, and other impurities are generated during the synthesis of irbesartan.

All these impurities are synthesized and characterized by ^{1}H NMR, ^{13}C NMR, mass, and IR analysis. The acid impurity **12** has been synthesized by the condensation of 4-(2′-bromomethylphenyl) benzoic acid (**10**)[11] with 2-butyl-2,3-diazaspiro[4.4]nonane-1,4-dione[3] (**11**) in a mixture of toluene



Scheme 2. DDC = dicyclohexylcarbodiimide; HOBT = 1-hydroxybenzotriazole.

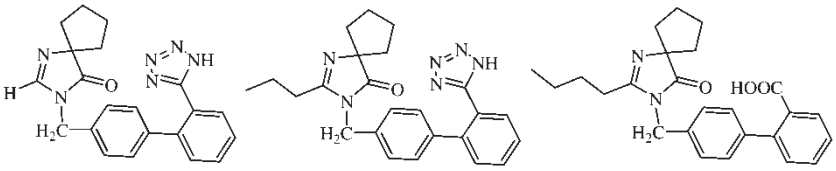


Figure 1. Chemical structures of Irbesartan impurities.

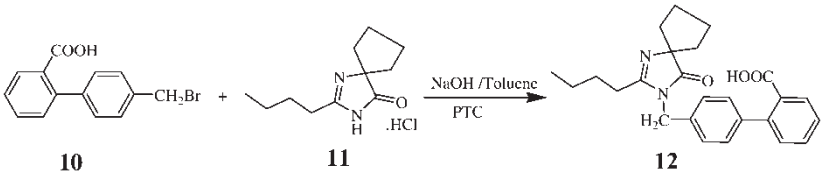
and water in the presence of sodium hydroxide and a phase-transfer catalyst (Scheme 3).

EXPERIMENTAL

Solvents and reagents were obtained from commercial sources and used without purification. Melting-points were determined on a Polmon melting-point apparatus. All melting points were uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker 300-MHz spectrometer. The chemical shifts are reported in δ Parts per million (ppm) relative to TMS. The IR spectra were recorded in solid state as KBr dispersion using a Perkin-Elmer FT-IR spectrometer. The mass spectra were recorded on an API 2000 Perkin-Elmer PE-SCIEX mass spectrometer.

N-Pentanoylaminocyclopentane-1-carboxylic Acid (4)

Triethylamine (379.18 g, 3.75 mol) was added to a stirred suspension of 1-aminocyclopenta-necarbonitrile hydrochloride (**2**) (500 g, 3.41 mol) in methylene chloride (3.5 L) at 0–5°C in 15 min. Thereafter valerylchloride (412 g, 3.58 mol) was added slowly at 0–5°C in 40 min and stirred at the same temperature for 2 h. Water (1000 ml) was added and stirred for 10 min. The organic layer was separated and washed with water (1000 ml). The organic layer obtained was concentrated under reduced pressure at below 60°C. The residue obtained was added to hydrochloric acid (2130 ml,



Scheme 3.

30% w/w) slowly in 45 min at 25–55°C, and the temperature during the addition rose to 50–60°C. Thereafter, the reaction contents were stirred at 55–60°C for 2 h and poured into a mixture of water (13.2 L) and ethyl acetate (1500 ml) at 25–35°C. The solid obtained was filtered and washed with water (10 L) followed by ethyl acetate (2 L). The wet material was dried at 50–55°C to afford N-pentanoylaminocyclopentane-1-carboxylic acid **4** as an off-white crystalline powder (654 g, 90%).

Mp: 178–179°C; IR (KBr, cm^{-1}): 3330 (NH), 1704, 1621 (CO); ^1H NMR (DMSO, δ ppm): 0.83–0.88 (t, 3H, CH_3), 1.24–1.26 (quintet, 2H, CH_2), 1.42–1.45 (sextet, 2H, CH_2), 1.59 (m, 4H, cyclopentyl), 1.84–2.07 (m, 4H, cyclopentyl), 2.50–2.51 (t, 2H, CH_2), 8.02 (s, 1H, NH), 12.01 (brs, 1H, OH); mass: 212.1(M^-). Anal. calcd. for $C_{11}H_{19}NO_3$: C, 61.97; H, 8.92; N, 6.57. Found: C, 61.85; H, 8.90; 6.54.

4-(2′-Aminomethylphenyl)benzonitrile Hydrochloride (6)

Sodium azide (126 g, 1.938 mol) was added to a stirred solution of 4-(2′-bromomethylphenyl)benzonitrile (**5**[11] (500 g, 1.838 mol) in DMF (1500) at 25–30°C. After 10 min of the addition, the temperature rose to 35–40°C. The reaction mass was stirred at 30–40°C for 30 min. DM water (10 L) was added, followed by ethyl acetate (5 L), and stirred for 15 min. The organic layer was separated and washed with saturated sodium chloride solution (2 × 5 L) and dried over sodium sulfate (1 kg). Triphenylphosphine (810 g, 3.09 mol) was added to the ethyl acetate solution and stirred for 2 h at 25–35°C. DM water (181 g, 10.05 mol) was added in one lot and stirred for 24 h at 25–30°C. The reaction mass was diluted with ethyl acetate (5 L) and cooled to 0–5°C. Hydrochloric acid (210 g, 35% w/w) was added in 30–45 min at the same temperature, while this addition solid precipitated out. The resulting slurry was stirred at 0–5°C for 1 h. The solid was filtered, and washed with precooled ethyl acetate (2 L). The wet solid was dried at 50–55°C under reduced pressure to afford the title compound as a white crystalline powder (385 g, 92%).

Mp 239–240°C; IR (KBr, cm^{-1}): 3338 (NH), 1702, 1627 (CO); ^1H NMR (DMSO, δ ppm): 4.08–4.12 (d, 2H, CH_2), 7.58–7.98 (m, 8H, bi-phenyl), 8.73 (brs, 3H, $NH_2 \cdot HCl$); ^{13}C NMR: 42.6, 111.0, 119.4, 129.3, 129.7, 130.2, 131.0, 134.5, 134.8, 135.6, 138.7, 144.8. Mass: 209.1(M^+); Anal. calcd. for $C_{14}H_{13}N_2Cl$: C, 68.71; H, 5.31; N, 11.45. Found: C, 68.47; H, 5.30; 11.39.

4-(α-Pentanoylamino)cyclopetamidomethyl]-2′-cyanobiphenyl (7)

Compound **3** (300 g, 1.408 mol) was added to a stirred suspension of compound (**6**) (288.5 g, 1.099 mol) in methylene chloride (6 L) at 25°C. To the resulting suspension, dicyclohexylcarbodiimide (300.9 g, 1.461 mol), 1-hydroxybenzotriazole (35.75 g, 0.265 mol), and diisopropylethylamine

(160 g, 1.231 mol) were added at 25–30°C. Thereafter, the reaction mass was heated to reflux at 38–41°C and stirred for 7 h. The reaction mass was cooled to 25°C. The salts were filtered and washed with methylene chloride (600 ml). The filtrate was washed with water (2 × 1500 ml). The organic layer was concentrated to 2100 ml at temperatures less than 45°C. The slurry obtained was cooled to 0–5°C and stirred for 1 h. The solid was filtered, washed with precooled methtylene chloride (600 ml), and dried to afford 4-(α-pentanoylamino)cyclopetamidomethyl]-2′-cyanobiphenyl **7** as a white amorphous powder (525.80 g, 93%).

Mp 135–137°C; IR (KBr, cm^{-1}): 3313 (NH), 3256, 2221 (CN), 1650, 1598 (CO); ^{1}H NMR (DMSO, δ ppm): 0.82–0.87 (t, 3H, CH_3), 1.24–1.1.27 (quintet, 2H, CH_2), 1.45–1.50 (sextet, 2H, CH_2), 1.63 (m, 4H, cyclopentyl), 1.88–2.08 (m, 4H, cyclopentyl), 2.11–2.16 (t, 2H, CH_2), 4.34–4.35 (d, 2H, CH_2), 7.32–7.95 (m, 9H, biphenyl + NH), 8.07–8.10 (t, 1H, NH); ^{13}C NMR: 14.6, 22.7, 24.8, 28.1, 36.0, 37.1, 42.9, 67.0, 111.0, 119.5, 127.9, 128.9, 129.3, 130.9, 134.4, 134.7, 136.8, 141.7, 145.3, 173.3, 174.7; mass: 402.2 (M^-). Anal. calcd. for $C_{25}H_{29}N_3O_2$: C, 74.44; H, 7.20; N, 10.42. Found: C, 74.50; H, 7.22; 10.44.

2-Butyl-3-[[2′-(1H-tetrazol-5-yl)[[1,1′-biphenyl]-4-yl]methyl-1,3-diazaspiro[4,4]non-1-en-4-one, Irbesartan (1)

Sodium azide (60.50 g, 0.93 mol) was added to tributyltin chloride (302.60 g, 0.93 mol) under nitrogen atmosphere and stirred for 30 min at 20–25°C. DMF (45.28 g, 0.62 mol) was added to the stirred suspension, and stirring continued for 30 min. Thereafter, o-xylene (250 ml) was added followed by 4-(α-pentanoylamino)cyclopetamidomethyl]-2′-cyanobiphenyl (**7**) (250 g, 0.62 mol). The reaction mixture was heated to 150–155°C, and stirring continued at the same temperature for 20 h. Thereafter, temperature was brought down to 20–25°C. Methylene chloride (1500 ml), o-xylene (500 ml), and water (500 ml) were added followed by hydrochloric acid (64.75 g, 35% w/w, 0.62 mol). The reaction mass was stirred for 2 h at 20–25°C. The resulting slurry was stirred for 1 h at 20–25°C. The solid was filtered and washed with 500 ml of 1:3 v/v mixture of o-xylene and methylene chloride. The wet material was dried at 75–80°C under reduced pressure to afford (**1**), irbesartan, as an off-white powder. The crude product (250 g) was suspended in absolute alcohol (5 L) and heated to reflux for 30 min to get a hazy solution. The resulting solution was cooled to 50°C, and carbon (12.5 g) and hyflo (25 g) were added, heated to reflux for 15 min cooled to 60°C, and filtered through hyflo. The residue was washed with 500 ml of hot absolute alcohol. The filtrate was concentrated to distill the alcohol (2800 ml). The resulting suspension was cooled to 5–10°C and stirred for 60 min to complete the crystallization. The solid was filtered and washed with precooled absolute alcohol (250 ml, 5–10°C). The wet material was

dried at 50–60°C to obtain 2-butyl-3-[[2′-(1H-tetrazol-5-yl)[[1,1′-biphenyl]-4-yl]methyl-1,3-diazaspiro[4,4]non-1-en-4-one, irbesartan (**1**), as a white amorphous powder (160 g, 71%).

Mp 181–182°C; IR (KBr, cm^{-1}): NH 3447, CO 1733, ^1H NMR (DMSO, δ ppm): 0.7–0.9 (t, 3H, CH_3), 1.20–1.40 (sextet, 2H, CH_2), 1.45–1.60 (quintet, 2H, CH_2) 1.60–2.00 (m, 8H, cyclopentyl), 2.2–2.4 (t, 2H, CH_2), 3–3.6 (br, 1H, NH), 4.60–4.80 (s, 2H, Ar-CH_2), 7.32–7.95 (m, 8H, biphenyl); ^{13}C NMR: 14.5, 22.4, 26.3, 27.4, 28.3, 37.7, 43.1, 76.7, 124.3, 127.1, 128.7, 130.1, 131.4, 131.9, 137.2, 139.2, 141.9, 155.9, 162.0, 186.5; mass: 429 (M^+). Anal. calcd. for $C_{25}H_{28}N_6O$: 70.07, 6.59, 19.61. Found: 70.35, 6.61, 19.61.

3-[[2′-(1H-Tetrazol-5-yl)[[1,1′-biphenyl]-4-yl]methyl-1,3-diazaspiro [4,4]non-1-en-4-one, Desbutyl Irbesartan (8)

Formic acid (85.6 g, 1.86 mol) was added to acetic anhydride (158.14 g, 1.55 mol) under stirring at 20–45°C over 30–40 min. The reaction mixture was stirred for 90 min at 40–45°C and cooled to 15–20°C. 1-Amino-1-cyano-cyclopentane carboxylic acid[9] (20 g, 0.155 mol) was added in one lot at 15–25°C, and the reaction mixture was stirred for 90 min. Thereafter, the resulting slurry was cooled to 0–5°C and stirred for 2 h at the same temperature. The solid was filtered and washed with ethyl acetate (100 ml). The wet solid was dried at 40–45°C under reduced pressure to afford the corresponding formyl derivative (14 g). This formyl compound (9.63 g, 0.0613 mol) was added to a stirred suspension of 4–(2′-aminomethylphenyl) benzonitrile (**6**) (15 g, 0.0613 mol) in methylene chloride (300) at 25°C. To the resulting suspension, dicyclohexylcarbodiimide (13.90 g, 0.067 mol), and 1-hydroxybenzotriazole (1.65 g, 0.012 mol) were added, followed by diisopropylethylamine (8.77 g, 0.067 mol) at 25–30°C. Thereafter, the reaction mass was heated to reflux at 38–41°C and stirred for 4 h. The reaction mass was cooled to 25°C. The salts were filtered and washed with methylene chloride (38 ml). The filtrate was washed with water (2 × 38 ml). The organic layer was concentrated to distill 160 ml of methylene chloride at atmospheric pressure. The slurry obtained was cooled to 0–5°C and stirred for 1 h. The solid was filtered, washed with precooled methtylene chloride (38 ml, 2°C), and dried. The dried compound (16.5 g) was added to a stirred suspension of tributyltin chloride (23.20 g, 0.071 mol), sodium azide (4.65 g, 0.071 mol), DMF (3.47 g, 0.047 mol), and o-xylene (16.5 ml). The reaction mixture was heated to 150–155°C and stirred for 5 h at the same temperature. The reaction mass was cooled to 25°C, and methylene chloride (100 ml), o-xylene (35 ml), and water (35 ml) were added. Thereafter, hydrochloric acid (5 g, 35% w/w, 0.048 mol) was added over 15 min and stirred for 15 h. The slurry obtained was diluted with xylene (50 ml) and stirred for 30 min. The solid was filtered, washed with xylene, and dried to afford the crude compound as a

pale yellow powder (10 g), which was crystallized from ethanol to afford the title compound as white amorphous powder.

Mp: 190–191°C; IR (KBr, cm^{-1}): 3436 (NH), 1734 (CO), ^1H NMR (DMSO, δ ppm): 1.65–1.86 (m, 8H, cyclopentyl), 4.65 (s, 2H, CH_2), 7.08–7.19 (m, 4H, phenylic), 7.54–7.71 (m, 4H, phenylic), 8.0 (s, 1H, CH), 16.37 (brs, 1H, NH); ^{13}C NMR: 26.2, 37.4, 44.1, 77.7, 124.3, 127.8, 128.7, 130.1, 131.5, 132, 137, 139.4, 141.9, 153.3, 155.9, 185.5; mass: 371.1 (M^-). Anal. calcd. for $C_{21}H_{20}N_6O$: 67.73, 5.41, 22.57. Found: 67.85, 5.42, 22.60.

2-Propyl-3-[[2′-(1H-tetrazol-5-yl)[[1,1′ -biphenyl]-4-yl]methyl-1,3-diazaspiro[4,4]non-1-en-4-one, Propyl Irbesartan (9)

This compound was prepared per the methods described for the preparation of irbesartan by changing valeryl chloride by butyryl chloride in the preparation of compound **3**.

Mp: 110–112°C; IR (KBr, cm^{-1}): 3338 (NH), 1702 (CO), ^1H NMR (DMSO, δ ppm): 0.83–0.89 (t, 3H, CH_3), 1.55–1.60 (quintet, 2H, CH_2), 1.85–2.02 (m, 8H, cyclopentyl), 2.72–2.77 (t, 2H, CH_2), 3.20–3.80 (br, 1H, NH), 7.10–7.20 (m, 4H, biphenyl), 7.50–7.70 (m, 4H, biphenyl); ^{13}C NMR: 14.0, 19.0, 26.1, 29.8, 37.6, 44.2, 72.7, 124.4, 127.7, 128.8, 130.2, 131.4, 131.5, 131.9, 134.9, 139.9, 141.8, 155.9, 172.5, 180.4; Mass: 413.2 (M^-). Anal. calcd. for $C_{24}H_{26}N_6O$: C, 69.56; H, 6.28; N, 20.28. Found: C, 69.63; H, 6.29; N, 20.30.

1[2′-Carboxybiphenyl-4-yl-methyl]-2-n-butyl-4-spirocyclopentane-2-imidazoline-5-one (12)

Sodium hydroxide (5.28 g, 0.132 mol) was dissolved in water (20 ml) at 20–25°C and cooled to 15°C. 2-Butyl-2,3-diazaspiro[4.4]nonane-1,4-dione[3] **11** (12 g, 0.055 mol), toluene (165 ml), and 75% w/w tetrabutylammoniumhydroxide solution (1 ml) were added to the sodium hydroxide solution followed by 2-(4-bromomethylphenyl) benzoic acid, **10**[11] (10 g, 0.0343 mol). The reaction mixture was warmed to 32–34°C and stirred for 24 h at the same temperature. Thereafter, the reaction mixture was diluted with toluene (165 ml) and water (50 ml). The organic layer was separated, and the aqueous layer was washed with ethyl acetate (60 ml). The aqueous layer was cooled to 5–10°C, and the pH was adjusted to 4 with 1:1 HCl solution. The sticky material obtained was washed with water (3 × 50 ml) at 50–55°C, dissolved in isopropyl alcohol (150 ml), and cooled to 2–5°C. The solid crystallized out was filtered washed with precooled IPA (15 ml). The wet material was dried at 50–55°C under reduced pressure to afford the title compound as a white crystalline powder (4.5 g, 24%).

Mp 149–150°C; IR (KBr, cm^{-1}): NH 3451; CO 1734; ^1H NMR (DMSO, δ ppm): 0.79–0.81 (t, 3H, CH_3), 1.26–1.29 (m, 2H, CH_2), 1.50 (brs, 2H, CH_2) 1.68–1.86 (m, 10H, cyclopentyl and CH_2), 2.35 (brs, 2H, CH_2), 4.73 (s, 2H, Ar-CH_2), 7.17–7.74 (m, 8H, Ar), 12.77 (brs, 1H, COOH); ^{13}C NMR: 14.5, 22.4, 26.3, 27.5, 28.4, 37.7, 43.2, 76.7, 127.0, 128.4, 129.6, 130.0, 131.3, 131.8, 133.0, 136.8, 140.9, 141.4, 162.0, 170.4, 186.5; mass: 405.3 (M^+). Anal. calcd. for $C_{25}H_{28}N_2O_3$ C, 74.23; H, 6.98; N, 6.93. Found: C, 74.43; H, 6.99; N, 6.94

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