

Synthesis of N-(3,4,10,10a-Tetrahydro-2H-1,9-dioxo-4a-azaphenanthrene-6-yl)alkyl and Aryl Sulfonamides

V. RAJACHANDRASEKHAR^{1,*}, B. GEORGE VINEEL¹, S. VENKATAIAHA and P.K. DUBEY²

¹CiVentiChem (India) Private Limited, Plot No 72/A, Part 2 Phase-1, IDA Jeedimetla, Hyderabad-500 055, India

²Department of Chemistry, Jawaharlal Nehru Technological University Hyderabad, Kukatpally, Hyderabad-500 085, India

*Corresponding author: E-mail: shekar.valamoni@gmail.com

Received: 10 January 2014;

Accepted: 24 April 2014;

Published online: 28 July 2014;

AJC-15674

Commercially available 2-amino-4-nitrophenol (**1**) was treated with chloroacetyl chloride to obtain 6-nitro-4H-benzo[1,4]oxazine-3,2-one (**2**). The latter was reacted with ethyl 3-bromopropionate to obtain 3-(6-nitro-3-oxo-2,3-dihydrobenzo[1,4]oxazine-4-yl)propionic acid ethyl ester (**3**), which on treatment with lithium aluminiumhydride gave 6-nitro-3,4,10,10a-tetrahydro-2H-1,9-dioxo-4a-azaphenanthrene (**4**) by reductive cyclization. Compound, **4** was treated with H₂/Pd-C containing di-*tert*-butyldicarbonate (Boc)₂O in THF to obtain the (3,4,10,10a-tetrahydro-2H-1,9-dioxo-4a-azaphenanthrene-6-yl)carbamic acid *tert*-butyl ester (**5**). The latter, on treatment with alkyl or arylsulfonyl chlorides in the presence of NaH gave N-(3,4,10,10a-tetrahydro-2H-1,9-dioxo-4a-azaphenanthrene-6-yl) alkyl or aryl sulfonamide-N¹-carbamic acid *tert*-butyl ester (**6**). N-Boc group of **6** was de-protected with Cs₂CO₃/imidazole in acetonitrile to give the title compounds N-(3,4,10,10a-tetrahydro-2H-1,9-dioxo-4a-azaphenanthrene-6-yl) alkyl or aryl sulfonamides (**7**) as potential anti-bacterial agents. All the new products obtained in the above sequences of reactions have been adequately characterized by spectral data.

Keywords: Synthesis, Substituted azaphenanthrenes, Reductive cyclization.

INTRODUCTION

1,4-Benzoxazin-3(4H)-one derivatives have shown various biological activities, such as antiinflammatory¹, antiulcer², antiplatelet³, antihypertensive⁴, antifungal⁵, antimicrobial⁶, neuropeptide Y (NPY) Y5 receptor antagonist⁷, serotonin reuptake inhibitors⁸, prostacyclin receptor agonist⁹, *etc.* Keeping in view the biological activities of various 1,4-benzoxazin-3-(4H)-one derivatives, it was considered worthwhile to prepare fused derivatives of benzoxazines as potentially biologically active compounds.

EXPERIMENTAL

All experiments were conducted under nitrogen atmosphere unless stated otherwise. All solvents and reagents were of reagent grade and used without further purification. All melting points were determined on Poloman MP-96 melting point apparatus. ¹H NMR spectra were recorded using a Bruker 300 MHz spectrometer with TMS as internal standard in DMSO-*d*₆ or CDCl₃. Mass spectra were recorded on an Agilent 6120 single quadrupole LCMS instrument giving M⁺ values either on [M + H]⁺ or [M – H][–] modes. IR spectra were obtained on a Perkin-Elmer 1720 FT-IR spectrometer as KBr Pellets. Analytical TLC was conducted on E-Merck- 60 GF-254

aluminium-packed silica gel plates (0.2 mm). Developed plates were visualized under UV light or iodine chamber.

Preparation of compound 2: A mixture of **1** (100 g, 0.649 mol), diisopropylethylamine (165 g, 1.298 mol), chloroacetyl chloride (73.3 g, 0.649 mol) and THF (700 mL) was stirred at room temperature for 4 h. To this solution was added K₂CO₃ (134 g, 0.974 mol) with continued stirring at 60 °C for 2 h. At the end of this period, the mixture was filtered and the filtrate rotary evaporated. The crude residue obtained was diluted with ice-cold water (2 L). The separated solid was filtered, washed with water (500 mL) and dried to obtain compound **2**. Yield: 103 g (80 %); m.p. 236-239 °C (Lit¹⁰, m.p. 235-237 °C), ¹H NMR (CDCl₃, 300 MHz): δ 4.75 (s, 2H -O-CH₂), 7.06-7.08 (d, *J* = 5.1 Hz, 1H, Ar-H), 7.72 (s, 1H, Ar-H), 7.19-7.94 (dd, *J* = 9 Hz, 1H, Ar-H), 8.01 (bs, 1H -NH-D₂O exchangeable). LC-MS (ESI) (M + H)⁺ *m/z* 194.

Preparation of compound 3: A mixture of **2** (30 g, 0.154 mol), K₂CO₃ (42.5 g, 0.308 mol), DMF (150 mL) and ethyl 3-bromo-propionate (30.7 g, 0.170 mol) was stirred at 80 °C for 10 h. At the end of this period, the reaction mass was diluted with water (700 mL). The separated solid was filtered, washed with water (100 mL) and the wet cake crystallized from methanol (150 mL) to obtain compound **3**. Yield: 35 g (77 %); m.p. 92-94 °C.

Preparation of compound 4: A solution of compound 3 (20 g, 0.0682 mol) in THF (150 mL) was cooled to 10 °C and lithium aluminium-hydride (4.77 g, 0.136 mol) was added in 5 min and the mixture stirred at room temperature for 3 h. At the end of this period, the mixture was quenched with saturated Na₂SO₄ solution (20 mL) at 5 °C and the precipitated cake was diluted with ethyl acetate (200 mL), filtered and washed with EtOAc (100 mL) and the organic filtrate dried over anhydrous Na₂SO₄. Then, the solvent was removed under reduced pressure on a rotary evaporator below 40 °C. The crude residue was stirred in methyl *tert*-butylether (50 mL) for 10 min and filtered to obtain pure compound 4 as insoluble solid. Yield: 11 g (69 %); m.p. 112-114 °C.

Preparation of compound 5: A mixture of compound 4 (8 g, 0.033 mol), (BoC)₂O (7.38 g, 0.033 mol) and Pd/C 10 % (0.8 g) in THF-MeOH (80-20 mL), was applied hydrogen gas pressure through balloons for 4 h. At the end of this period, the reaction mixture was filtered through celite pad and washed with THF (20 mL). The filtrate was rotary evaporated to obtain pure compound 5. Yield: 9 g (87 %); m.p. 121-123 °C.

Preparation of compound 6 (general procedure): A mixture of compound 5 (1.63 mmol), NaH (77 mg, 3.2 mmol) and DMF (2 mL) at 0 °C, was added alkyl or arylsulfonyl chloride (1.79 mmol). The reaction mixture was stirred at room temperature for 30-40 min. At the end of this period, the reaction mixture was diluted with ice cold water (10 mL). The separated solid was filtered, washed and dried to obtain compound 6.

Compound 6a: Yield: 0.25 g (66 %); m.p. 105-107 °C.

Compound 6b: Yield: 0.55 g (84 %); m.p. 121-123 °C; IR (KBr, $\nu_{\max}$, cm⁻¹): 1721 (carbamide stretching) and 1345 (sulfonamide stretching), 1142 (sulfonamide stretching); ¹H NMR (CDCl₃/TMS, 300 MHz); δ 1.43 (s, 9H, *tert*-butyl), 1.52 (m, 4H, -CH₂-CH₃ & one of the protons of 3-CH₂), 1.98-2.02 (m, 1H, one proton of 3-CH₂), 3.195-3.197 (t, *J* = 8 Hz, 1H, one proton of -N-CH₂), 3.62-3.66 (m, 2H, -CH₂-CH₃), 3.87-3.97 (t, 1H, *J* = 8 Hz, one proton of -N-CH₂), 3.98-4.01 (d, *J* = 9 Hz, 1H, one proton of 10-CH₂), 4.17-4.28 (m, 3H, one of the protons of 2-CH₂ & 10a-CH), 4.65 (s, 1H, one proton of 10-CH), 6.52-6.54 (d, *J* = 6 Hz, 1H, Ar-H), 6.71 (s, 1H, Ar-H), 6.79-6.82, (d, *J* = 6 Hz, 1H, Ar-H). LC-MS (ESI) (M + H)⁺ *m/z* 399.

Compound 6c: Yield: 0.46 g (69 %); m.p. 129-132 °C; IR (KBr, $\nu_{\max}$, cm⁻¹): 1719 (carbamide stretching) and at 1352 (sulfonamide stretching), 1147 (sulfonamide stretching); ¹H-NMR (CDCl₃/TMS, 300 MHz); δ 1.08-1.11 (t, *J* = 9 Hz, 3H, SO₂-CH₂-CH₂-CH₃), 1.39-1.39 (d, *J* = 9 Hz, 1H, one proton of 3-CH₂), 1.42 (s, 9H, *tert*-butyl), 1.90 (m, 2H, -CH₂-CH₂-CH₃), 1.98-2.1 (m, 1H, one proton of 3-CH₂), 3.18-3.20 (t, *J* = 6.2 Hz, 1H, one proton of -N-CH₂), 3.56-3.58 (m, 2H, -CH₂-CH₂-CH₃), 3.87-3.95 (t, *J* = 7.2 Hz, 1H, one proton of -N-CH₂), 3.98-4.01 (d, *J* = 9 Hz, 1H, one proton of 10-CH₂), 4.14-4.17 (m, 3H, one of the protons of 2-CH₂ & 10a-CH), 4.65 (s, 1H, one proton of 10-CH), 6.51-6.53 (d, *J* = 6 Hz, 1H, Ar-H), 6.78 (s, 1H, Ar-H), 6.79-6.80, (d, *J* = 3 Hz, 1H, Ar-H). LC-MS (ESI) (M + H)⁺ *m/z* 413.

Compound 6d: Yield: 0.45 g (67 %); m.p. 154-156 °C; IR (KBr, $\nu_{\max}$, cm⁻¹): 1720 (carbamide stretching) and 1347 (sulfonamide stretching), 1151 (sulfonamide stretching); ¹H-

NMR (CDCl₃/TMS, 300 MHz); δ 1.25-1.26 (d, *J* = 6.3 Hz, 1H, one proton of 3-CH₂), 1.42 (s, 9H, *tert*-butyl), 2.02 (m, 1H, one proton of 3-CH₂), 2.98 (s, 6H, -N(CH₃)₂), 3.96-3.3.98 (t, *J* = 6 Hz, 1H, one proton of -N-CH₂), 3.87-3.96 (t, *J* = 6.5 Hz, 1H, one proton of -N-CH₂), 3.99-4.02 (d, *J* = 9 Hz, 1H, one proton of 10-CH₂), 4.17 (m, 3H, one of the protons of 2-CH₂ & 10a-CH), 4.66 (s, 1H, one proton of 10-CH), 6.53-6.56 (d, *J* = 9 Hz, 1H, Ar-H), 6.72 (s, 1H, Ar-H), 6.98-7.00 (d, *J* = 6 Hz, 1H, Ar-H). LC-MS (ESI) (M + H)⁺ *m/z* 414.

Compound 6e: Yield: 0.43 g (74 %); m.p. 132-135 °C; IR (KBr, $\nu_{\max}$, cm⁻¹): 1725 (carbamide stretching) and 1355 (sulfonamide stretching), 1145 (sulfonamide stretching); ¹H-NMR (CDCl₃/TMS, 300 MHz); δ 1.34 (s, 9H, *tert*-butyl), 1.42-1.45 (d, *J* = 6 Hz, 1H, one proton of 3-CH₂), 2.10 (m, 1H, one proton of 3-CH₂), 3.28-3.30 (t, *J* = 6 Hz, 1H, one proton of -N-CH₂), 3.87-3.98 (m, 2H, one of the protons of -N-CH₂ & 10-CH₂), 4.20 (m, 3H, one of the protons of 2-CH₂ & 10a-CH), 4.67 (s, 1H, one proton of 10-CH), 6.51-6.51 (d, *J* = 6 Hz, 1H, Ar-H), 6.78 (s, 1H, Ar-H), 6.81-6.83 (d, *J* = 6 Hz, 1H, Ar-H), 7.52-7.64 (m, 3H, Ar-H), 7.98-8.00 (d, *J* = 6 Hz, 2H, Ar-H). LC-MS (ESI) (M + H)⁺ *m/z* 447.

Compound 6f: Yield: 0.412 g (77 %); m.p. 142-145 °C; IR (KBr, $\nu_{\max}$, cm⁻¹): 1729 (carbamide stretching) and 1360 (sulfonamide stretching), 1151 (sulfonamide stretching); ¹H-NMR (CDCl₃/TMS, 300 MHz); δ 1.34 (s, 9H, *tert*-butyl), 1.45 (d, *J* = 6 Hz, 1H, one proton of 3-CH₂), 2.16 (m, 1H, one proton of 3-CH₂), 2.44 (s, 3H, -Ph-CH₃), 3.18-3.21 (t, *J* = 9 Hz, 1H, one proton of -N-CH₂), 3.80-3.92 (m, 2H, one of the protons of -N-CH₂ & 10-CH), 4.18-4.19 (m, 3H, one of the protons of 2-CH₂ & 10a-CH), 4.61 (s, 1H, one proton of 10-CH), 6.42-6.46 (d, *J* = 12 Hz, 1H, Ar-H), 6.73 (s, 1H, Ar-H), 6.76-6.79 (d, *J* = 9 Hz, 1H, Ar-H), 7.30-7.32 (d, *J* = 6 Hz, 2H, Ar-H), 7.84-7.86 (d, *J* = 6 Hz, 2H, Ar-H). LC-MS (ESI) (M + H)⁺ *m/z* 461.

Compound 6g: Yield: 0.35 g (78 %); m.p. 152-154 °C; IR (KBr, $\nu_{\max}$, cm⁻¹): 1717 (carbamide stretching) and 1351 (sulfonamide stretching), 1149 (sulfonamide stretching); ¹H-NMR (CDCl₃/TMS, 300 MHz); δ 1.29 (s, 9H, *tert*-butyl), 1.36-1.38 (d, *J* = 6 Hz, 1H, one proton of 3-CH₂), 2.16 (m, 1H, one proton of 3-CH₂), 3.18-3.20 (t, *J* = 6 Hz, 1H, one proton of -N-CH₂), 3.88-3.90 (t, *J* = 6 Hz, 1H, one proton of N-CH₂), 3.96-3.99 (d, *J* = 6 Hz, 1H, one proton of 10-CH), 4.18-4.19 (m, 3H, one of the protons of 2-CH₂ & 10a-CH), 4.66 (s, 1H, one of the proton of 10-CH), 6.75-6.79 (d, *J* = 12 Hz, 1H, Ar-H), 6.84-6.86 (m, 2H, Ar-H), 7.24-7.30 (m, 2H, Ar-H), 7.62 (m, 1H, Ar-H), 8.19-8.20 (t, *J* = 3 Hz, 1H, Ar-H). LC-MS (ESI) (M + H)⁺ *m/z* 465.

Compound 6h: Yield: 0.56 g (72 %); m.p. 151-154 °C; IR (KBr, $\nu_{\max}$, cm⁻¹): 1726 (carbamide stretching) and 1349 (sulfonamide stretching) 1147 (sulfonamide stretching); ¹H-NMR (CDCl₃/TMS, 300 MHz); δ 1.32 (s, 9H, *tert*-butyl), 1.42-1.44 (d, *J* = 6 Hz, 1H, one proton of 3-CH₂), 2.12 (m, 1H, one proton of 3-CH₂), 3.19-3.19 (t, *J* = 6 Hz, 1H, one proton of -N-CH₂), 3.92 (m, 5H, -N-CH₂, 10-CH & -O-CH₃), 4.19-4.20 (m, 3H one of the protons of 2-CH₂ & 10a-CH), 4.67 (s, 1H, one proton of 10-CH), 6.48-6.49 (d, *J* = 12 Hz, 1H, Ar-H), 6.7(s 1H, Ar-H) 6.74-6.79 (t, *J* = 12 Hz, 1H Ar-H), 6.98-7.00 (d, *J* = 5.1 Hz, 2H, Ar-H), 7.91-7.93 (d, *J* = 5.1 Hz, 2H, Ar-H). LC-MS (ESI) (M + H)⁺ *m/z* 477.

Compound 6i: Yield: 1 g (86 %); m.p. 164-168 °C; IR (KBr, $\nu_{\max}$, cm^{-1}): 1730 (carbamide stretching) and 1355 (sulfonamide stretching), 1156 (sulfonamide stretching); ^1H NMR (CDCl_3/TMS , 300 MHz); δ 1.38 (s, 9H, *tert*-butyl), 1.44-1.47 (d, $J = 7.8$ Hz, 1H, one proton of 3- CH_2), 2.15 (m, 1H, one proton of 3- CH_2), 3.19-3.22 (t, $J = 9$ Hz, 1H, one proton of -N- CH_2), 3.90 (m, 2H, one of the protons of -N- CH_2 & 10- CH), 4.19-4.21 (m, 3H, one of the protons of 2- CH_2 & 10a- CH), 4.69 (s, 1H, one proton of 10- CH), 6.47-6.48 (d, $J = 3$ Hz, 1H, Ar- H), 6.74 (s, 1H, Ar- H), 6.83-6.85 (d, $J = 6$ Hz, 1H, Ar- H), 7.77-7.80 (t, $J = 9$ Hz, 1H, Ar- H), 8.32-8.34 (d, $J = 6$ Hz, 1H, Ar- H), 8.49-8.51 (d, $J = 6$ Hz, 1H, Ar- H). LC-MS (ESI) ($\text{M} + \text{H}$) $^+$ m/z 492.

Preparation of 7 (general procedure): A mixture of compound 6 (0.7 mmol), Cs_2CO_3 (0.5 g, 1.51 mmol) and imidazole (0.1 g, 1.51 mmol) in acetonitrile (10 mL), was stirred at reflux temperature for 6 h. At the end of this period, the reaction mass was filtered and washed with acetonitrile (5 mL). The acetonitrile was rotary evaporated to obtain the title compounds compound 7 as solids.

Compound 7a: Yield: 0.13 g (88 %); m.p. 77-82 °C.

Compound 7b: Yield: 0.195 g (86 %); m.p. 145-147 °C; IR (KBr, $\nu_{\max}$, cm^{-1}): 3224 (sulfonamide N-H stretching), 1324 (sulfonamide stretching), 1143 (sulfonamide stretching); ^1H NMR (CDCl_3/TMS , 300 MHz); δ 1.35-1.36 (t, $J = 3.5$ Hz, 3H, $\text{CH}_2\text{-CH}_3$), 1.42-1.45 (d, $J = 6.2$ Hz, 1H, one proton of 3- CH_2), 1.97-2.05 (m, 1H, one proton of 3- CH_2), 3.195-3.197 (m, 2H, - $\text{CH}_2\text{-CH}_3$), 3.17-3.20 (t, $J = 5.1$ Hz, 1H, one proton of -N- CH_2), 3.88-3.90 (t, $J = 6$ Hz, 1H, one proton of 10- CH_2), 3.96-4.00 (d, $J = 9$ Hz, 1H, one proton of 10- CH_2), 4.13-4.16 (m, 3H, one of the protons of 2- CH_2 & 10a- CH), 4.65 (s, 1H, one proton of 10- CH), 6.37 (br s, 1H, NH, D_2O exchangeable proton), 6.48-6.49 (dd, $J = 1.2$ Hz, 1H, Ar- H), 6.75-6.77 (d, $J = 2.1$ Hz, 1H, Ar- H), 6.84 (s, 1H, Ar- H). LC-MS (ESI) ($\text{M} + \text{H}$) $^+$ m/z 299, Purity (HPLC) = 99.45 %.

Compound 7c: Yield: 0.3 g (79 %); m.p. 112-114 °C; IR (KBr, $\nu_{\max}$, cm^{-1}): 3242 (sulfonamide N-H stretching) 1340 (sulfonamide stretching), 1147 (sulfonamide stretching); ^1H NMR (CDCl_3/TMS , 300 MHz); δ 1.01-1.04 (t, $J = 4.5$ Hz, 3H, - $\text{CH}_2\text{-CH}_2\text{-CH}_3$), 1.40-1.42 (d, $J = 9$ Hz, 1H, one proton of 3- CH_2), 1.83-1.85 (m, 2H, - $\text{CH}_2\text{-CH}_2\text{-CH}_3$), 1.98-2.20 (m, 1H, one proton of 3- CH_2), 2.99-3.02 (t, $J = 4.5$ Hz, 1H, - $\text{CH}_2\text{-CH}_2\text{-CH}_3$), 3.18-3.10 (t, $J = 6$ Hz, 1H, one proton of -N- CH_2), 3.88-3.91 (t, $J = 9$ Hz, 1H, one proton of N- CH_2), 3.96-4.00 (d, $J = 12$ Hz, 1H, one proton of 10- CH), 4.12-4.21 (m, 3H, one of the protons of 2- CH_2 & 10a- CH), 4.66 (s, 1H, one proton of 10- CH), 6.28 (br s, 1H, NH, D_2O exchangeable proton), 6.49-6.50 (dd, J_1 & $J_2 = 1.2$ Hz, 1H, Ar- H), 6.76-6.84, (d, $J = 5.1$ Hz, 1H, Ar- H), 6.84 (s, 1H, Ar- H). LC-MS (ESI) ($\text{M} + \text{H}$) $^+$ m/z 313; Purity (HPLC) = 99.79 %.

Compound 7d: Yield: 0.06 g (80 %); m.p. 123-125 °C; IR (KBr, $\nu_{\max}$, cm^{-1}): 3220 (sulfonamide N-H stretching), 1350 (sulfonamide stretching), 1152 (sulfonamide stretching); ^1H NMR (CDCl_3/TMS , 300 MHz); δ 1.42-1.44 (d, $J = 6$ Hz, 1H, one proton of 3- CH_2), 1.98 (m, 1H, one proton of 3- CH_2), 2.84-2.85 (s, 6H, $\text{N}(\text{CH}_3)_2$), 3.19-3.3.20 (t, $J = 3.2$ Hz, 1H, one proton of -N- CH_2), 3.89-4.00 (m, 2H, one of the protons of -N- CH_2 & 10- CH), 4.19-4.22 (m, 3H, one of the protons of 2- CH_2 & 10a- CH), 4.35-4.38 (t, $J = 2.1$ Hz, 1H, one proton of

10- CH), 6.12 (br s, 1H, NH, D_2O exchangeable proton), 6.49-6.51 (dd, J_1 & $J_2 = 1.5$ & 2.7 Hz, 1H, Ar- H), 6.72 (s, 1H, Ar- H), 6.74-6.79 (d, $J = 6$ Hz, 1H, Ar- H), 6.82 (s, 1H, Ar- H), LC-MS (ESI) ($\text{M} + \text{H}$) $^+$ m/z 314.

Compound 7e: Yield: 0.23 g (85 %); m.p. 160-162 °C; IR (KBr, $\nu_{\max}$, cm^{-1}): 3215 (sulfonamide N-H stretching), 1342 (sulfonamide stretching), 1150 (sulfonamide stretching); ^1H NMR (CDCl_3/TMS , 300 MHz); δ 1.35-1.37 (d, $J = 6.3$ Hz, 1H, one proton of 3- CH_2), 1.92 (m, 1H, one proton of 3- CH_2), 3.15-3.19 (t, $J = 11$ Hz, 1H, one proton of -N- CH_2), 3.89 (m, 2H, one of the protons of -N- CH_2 & 10- CH), 4.15 (m, 3H, one of the protons of 2- CH_2 & 10a- CH), 4.63 (s, 1H, one proton of 10- CH), 6.21-6.21 (dd, $J = 2.1$ Hz, 1H, Ar- H), 6.40 (br s, 1H, NH, D_2O exchangeable proton), 6.62-6.63 (d, $J = 5.1$ Hz, 1H, Ar- H), 6.68-6.69 (s, 1H, Ar- H), 7.41-7.53 (m, 3H, Ar- H), 7.71-7.72 (m, 2H, Ar- H). LC-MS (ESI) ($\text{M} + \text{H}$) $^+$ m/z 347; Purity (HPLC) = 99.88 %.

Compound 7f: Yield: 0.25 g (92 %); m.p. 138-140 °C; IR (KBr, $\nu_{\max}$, cm^{-1}): 3244 (sulfonamide N-H stretching), 1348 (sulfonamide stretching), 1158 (sulfonamide stretching); ^1H NMR (CDCl_3/TMS , 300 MHz); δ 1.36-1.38 (d, $J = 6.3$ Hz, 1H, one proton of 3- CH_2), 1.8-1.9 (m, 1H, one proton of 3- CH_2), 2.38 (s, 3H, - Ph-CH_3), 3.15-3.19 (t, $J = 11$ Hz, 1H, one proton of -N- CH_2), 3.89 (m, 2H, one of the protons of -N- CH_2 & 10- CH), 4.12 (m, 3H, one of the protons of 2- CH_2 & 10a- CH), 4.62 (s, 1H, one proton of 10- CH), 6.19-6.20 (dd, $J = 2.5$ Hz, 1H, Ar- H), 6.35 (br s, 1H, NH, D_2O exchangeable proton), 6.60-6.61 (d, $J = 4.8$ Hz, 1H, Ar- H), 6.69 (s, 1H, Ar- H), 7.19-7.20 (m, 2H, Ar- H), 7.57-7.58 (d, $J = 4.7$ Hz, 2H, Ar- H). LC-MS (ESI) ($\text{M} + \text{H}$) $^+$ m/z 361; Purity (HPLC) = 96.29 %.

Compound 7g: Yield: 0.35 g (78 %); m.p. 143-145 °C; IR (KBr, $\nu_{\max}$, cm^{-1}) 3254 (sulfonamide N-H stretching), 1341 (sulfonamide stretching), 1152 (sulfonamide stretching); ^1H NMR (CDCl_3/TMS , 300 MHz); δ 1.36-1.39 (d, $J = 9$ Hz, 1H, one proton of 3- CH_2), 1.82-1.91 (m, 1H, one proton of 3- CH_2), 3.13-3.16 (t, $J = 6$ Hz, 1H, one proton of -N- CH_2), 3.85 (m, 2H, one of the protons of -N- CH_2 & 10- CH), 4.13 (m, 3H, one of the protons of 2- CH_2 & 10a- CH), 4.62 (s, 1H, one proton of 10- CH), 6.32-6.33 (dd, $J = 3.0$ Hz, 1H, Ar- H), 6.58 (br s, 1H, NH, D_2O exchangeable proton), 6.59-6.62 (d, $J = 9$ Hz, 1H, Ar- H), 6.72 (s, 1H, Ar- H), 7.16-7.19 (m, 2H, Ar- H), 7.58 (m, 1H, Ar- H), 7.74 (m, 1H, Ar- H). LC-MS (ESI) ($\text{M} + \text{H}$) $^+$ m/z 365; Purity (HPLC) = 96.90 %.

Compound 7h: Yield: 0.3 g (85 %); m.p. 123-125 °C; IR (KBr, $\nu_{\max}$, cm^{-1}): 3256 (sulfonamide N-H stretching) 1372 (sulfonamide stretching), 1161 (sulfonamide stretching); ^1H NMR (CDCl_3/TMS , 300 MHz); δ 1.38-1.44 (d, $J = 6.2$ Hz, 1H, one proton of 3- CH_2), 1.98 (m, 1H, one proton of 3- CH_2), 3.12-3.16 (t, $J = 9$ Hz, 1H, one proton of N- CH_2), 3.89 (m, 5H, one of the protons of -N- CH_2 , 10- CH & -O- CH_3), 4.13-4.15 (m, 3H, one of the protons of 2- CH_2 & 10a- CH), 4.62 (s, 1H, one proton of 10- CH), 6.20-6.22 (dd, $J = 3.50$ Hz, 1H, Ar- H), 6.34 (br s, 1H, NH, D_2O exchangeable proton), 6.14-6.21 (d, 1H, $J = 6.2$ Hz, Ar- H), 6.7 (s, 1H, Ar- H), 6.86-6.88 (t, $J = 5.1$ Hz, 2H, Ar- H), 7.62-7.64 (d, $J = 5.4$ Hz, 2H, Ar- H). LC-MS (ESI) ($\text{M} + \text{H}$) $^+$ m/z 377 Purity (HPLC) = 99.66 %.

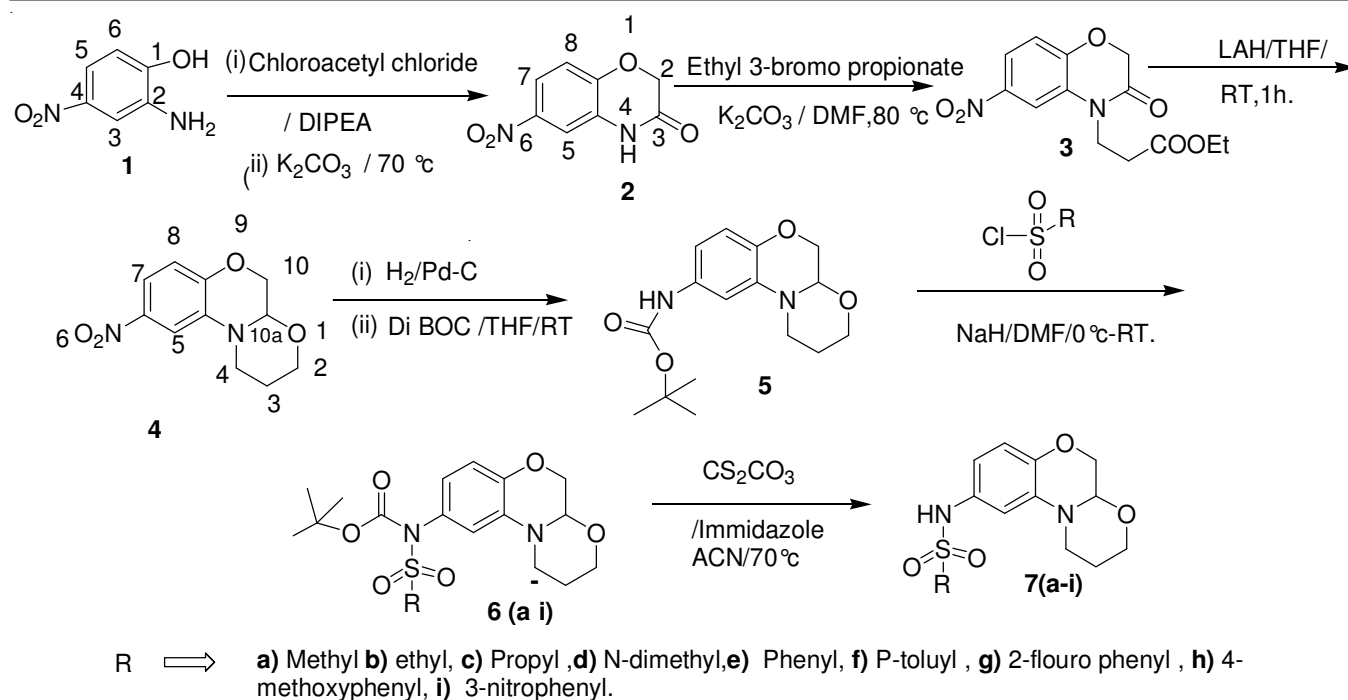
Compound 7i: Yield: 0.6 g (76 %); m.p. 173-176 °C; IR (KBr, $\nu_{\max}$, cm^{-1}): 3256 (sulfonamide N-H stretching) 1332 (sulfonamide stretching), 1167 (sulfonamide stretching), 1535

(Nitro group stretching), 1370 (Nitro group stretching); ^1H -NMR (CDCl_3/TMS , 300 MHz); δ 1.44-1.47 (d, $J = 7.8$ Hz, 1H, one proton of 3- CH_2), 1.98 (m, 1H, one proton of 3- CH_2), 3.195-3.21 (t, $J = 8.5$ Hz, 1H, one proton of -N- CH_2), 3.90 (m, 2H, one of the protons of -N- CH_2 & 10- CH_2), 4.19-4.21 (m, 3H, one of the protons of 2- CH_2 & 10a- CH), 4.62 (s, 1H, one proton of 10- CH), 6.26-6.29 (d, $J = 9$ Hz, 1H, Ar- H), 6.5 (br s, 1H, NH , D_2O exchangeable proton), 6.61-6.69 (d, $J = 6$ Hz, 1H, Ar- H), 6.79 (s, 1H, Ar- H), 7.63-7.68 (t, $J = 9$ Hz, 1H, Ar- H), 7.95-7.99 (d, $J = 6$ Hz, 1H, Ar- H), 8.39-8.40 (d, $J = 6$ Hz, 1H, Ar- H), 8.61 (s, 1H, Ar- H). LC-MS (ESI) ($\text{M} + \text{H}$) $^+$ m/z 392, Purity (HPLC) = 98.54 %.

RESULTS AND DISCUSSION

Commercially available 2-amino-4-nitrophenol (**1**) was treated with chloroacetyl chloride in the presence of K_2CO_3 in THF at 50 °C for 5 h, to obtain the previously reported¹⁰ 6-nitro-4*H*-benz[1,4]oxazin-3-one (**2**). Compound **2** was treated with ethyl 3-bromopropionate in the presence of K_2CO_3 in DMF at 80 °C for 10 h, to obtain a product that has been characterized as 3-(6-nitro-3-oxo-2,3-dihydrobenz[1,4]oxazin-4-yl)propionic acid ethyl ester (**3**), on the basis of its spectral data. Thus, its IR (KBr pellet) spectrum showed diagnostic peaks at 1717 cm^{-1} (due to ester carbonyl stretching) and at 1682 cm^{-1} (due to amide carbonyl stretching), 1520 cm^{-1} (due to nitro group stretching), 1344 cm^{-1} (due to nitro group stretching); Its ^1H NMR (CDCl_3 , 300 MHz) showed signals at δ 1.23-1.26 (t, $J = 9.1$ Hz, 3H, $\text{CH}_2\text{-CH}_3$), 2.70-2.73 (t, $J = 6$ Hz, 2H -N- CH_2), 4.12-4.16 (q, 2H, - $\text{CH}_2\text{-CH}_3$), 4.26-4.4.29 (t, $J = 6$ Hz, 2H, - $\text{CH}_2\text{-CH}_2\text{-CO-}$), 4.71 (s, 2H, -O- CH_2), 7.06-7.08 (d, $J = 5.1$ Hz, 1H, Ar-H), 7.92-7.95 (m, 2H, Ar-H). Its LCMS showed the molecular ion ($\text{M}^+ + 1$) peak at m/z 295 corresponding to a molecular mass of 294 when recorded in the Q+1 ion mode. Reduction of compound **3** with lithium aluminium-hydride in tetrahydrofuran afforded a product which has been characterized as 6-nitro-3,4,10,10a-tetrahydro-2*H*-1,9-dioxo-4a-azaphenanthrene (**4**) on the basis of its spectral data. Thus, its IR (KBr pellet) spectrum showed diagnostic peaks at 1514 cm^{-1} (due to Nitro group stretching), 1344 cm^{-1} (due to Nitro group stretching); Its ^1H -NMR (CDCl_3/TMS , 300 MHz) spectrum showed signals at δ 1.45-1.48 (d, $J = 9$ Hz, 1H, one proton of 3- CH_2), 2.01-2.03 (m, 1H, one proton of 3- CH_2), 3.26-3.26 (t, $J = 8$ Hz, 1H, one proton of -N- CH_2), 3.91-3.94 (t, $J = 9$ Hz, 1H, one proton of -N- CH_2 -), 4.05-4.26 (d, $J = 8.4$ Hz, 1H, one proton of 10- CH_2), 4.15-4.26 (m, 3H, one of the protons of 2- CH_2 & 10- CH_2), 4.69-4.70 (s, 1H, one proton of 10- CH), 6.85-6.87 (d, $J = 6.1$ Hz, 1H, Ar- H), 7.65-7.85 (dd, $J = 13$, Hz, 1H, Ar- H), 7.72 (s, 1H, Ar- H) and its LCMS showed the molecular ion ($\text{M}^+ + 1$) peak at m/z 237 corresponding to a molecular mass of 236 when recorded in the Q + 1 ion mode. Compound **4** was treated with H_2 in the presence of Pd/C as catalyst containing di-*tert*-butyl dicarbonate in THF-MeOH (8:2) at room temperature for 2 h, giving a pure product which has been characterized as (3,4,10,10a-tetrahydro-2*H*-1,9-dioxo-4a-azaphenanthrene-6-yl)carbamic acid *tert*-butyl ester (**5**) on the basis of its spectral data. Its IR (KBr pellet), spectrum showed diagnostic peaks at 3290 cm^{-1} (due to amide N-H

stretching) and at 1713 cm^{-1} (due to carbamide stretching); Its ^1H -NMR (CDCl_3/TMS , 300 MHz) spectrum showed signals at δ 1.37-1.40 (d, $J = 9$ Hz, 1H, one proton of 3- CH_2), 1.50 (s, 9H, *tert*-butyl), 2.06-2.15 (m, 1H, one proton of 3- CH_2), 3.17-3.19 (t, $J = 6$ Hz, 1H, one proton of -N- CH_2), 3.82-3.85 (t, $J = 9$ Hz, 1H, one proton of -N- CH_2 -), 3.98-4.02 (d, $J = 12$ Hz, 1H, one proton of 10- CH), 4.11-4.13 (m, 3H, one of the protons of 2- CH_2 & 10a- CH), 4.63-4.64 (s, 1H, one proton of 10- CH), 6.3 (s, 1H, Ar- H), 6.47-6.48 (d, $J = 3$ Hz, 1H, Ar- H), 6.71-6.73 (d, $J = 6$ Hz, 1H, Ar- H), 7.18 (br s, 1H, NH , D_2O exchangeable proton). Its LCMS showed the molecular ion ($\text{M}^+ + 1$) peak at m/z 307 corresponding to a molecular mass of 306 when recorded in the Q + 1 ion mode. Treatment of compound **5** with methanesulfonyl chloride in the presence of NaH in DMF at 0 °C to room temperature for 40 min, gave a product which has been characterized as N-(3,4,10,10a-terhydro-2*H*-1,9-dioxo-4a-azaphenanthrene-6-yl)methane sulfonamide-N¹-carbamic acid *tert*-butyl ester (**6a**), on the basis of its spectral data. Thus, its IR (KBr pellet), spectrum showed diagnostic peaks at 1717 cm^{-1} (due to carbamide stretching) and at 1342 cm^{-1} (due to sulfonamide stretching) 1167 cm^{-1} (due to sulfonamide stretching); ^1H -NMR (CDCl_3/TMS , 300 MHz) spectrum showed signals at δ 1.42 (s, 9H, *tert*-butyl), 1.25-1.27 (d, $J = 6$ Hz, 1H, one proton of 3- CH_2), 1.96-2.00 (m, 1H, one proton of 3- CH_2), 3.19-3.19 (t, $J = 6$ Hz, 1H, one proton of -N- CH_2), 3.4 (s, 3H, - $\text{SO}_2\text{-CH}_3$), 3.82-3.85 (t, $J = 8.2$ Hz, 1H, one proton of -N- CH_2 -), 3.92-4.02 (d, $J = 10$ Hz, 1H, one proton of 10- CH), 4.18-4.20 (m, 3H, one of the protons of 2- CH_2 & 10a- CH), 4.64 (s, 1H, one proton of 10- CH), 6.53-6.55 (d, $J = 6$ Hz, 1H, Ar- H), 6.71-6.73 (s, 1H, Ar- H), 6.79-6.81, (d, $J = 6$ Hz, 1H, Ar- H). Its LCMS showed the molecular ion ($\text{M}^+ + 1$) peak at m/z 385 corresponding to a molecular mass of 384 when recorded in the Q + 1 ion mode. **6a** was de-protected with Cs_2CO_3 and imidazole in acetonitrile at 70 °C to obtain a pure compound, which has been characterized as N-(3,4,10,10a-terhydro-2*H*-1,9-dioxo-4a-azaphenanthrene-6-yl)methylsul-fonamide (**7a**) on the basis of its spectral data. Thus, its IR (KBr pellet), spectrum showed a diagnostic peak at 3220 cm^{-1} (due to sulfonamide N-H stretching vibration), 1325 cm^{-1} (due to sulfonamide stretching), 1143 cm^{-1} (due to sulfonamide stretching); Its ^1H -NMR (CDCl_3/TMS , 300 MHz) spectrum showed signals at δ 1.40-1.43 (d, $J = 9$ Hz, 1H, one proton of 3- CH_2), 1.95-2.05 (m, 1H, one proton of 3- CH_2), 2.94-3.00 (s, 3H, - $\text{SO}_2\text{-CH}_3$), 3.19-3.19 (t, $J = 5.6$ Hz, 1H, one proton of -N- CH_2), 3.88-3.90 (t, $J = 5.6$ Hz, 1H, one proton of -N- CH_2), 3.97-4.00 (d, $J = 9$ Hz, 1H, one proton of 10- CH), 4.13-4.17 (m, 3H, one of the protons of 2- CH_2 & 10a- CH), 4.66 (s, 1H, one proton of 10- CH), 6.13 (br s, 1H, NH , D_2O exchangeable proton), 6.49-6.51 (dd, $J = 3$ Hz, 1H, Ar- H), 6.77-6.79 (d, $J = 5.1$ Hz, 1H, Ar- H), 6.83 (s, 1H, Ar- H). Its LCMS showed the molecular ion ($\text{M}^+ + 1$) peak at m/z 285 corresponding to a molecular mass of 284. The above reaction was found to be a general one and was extended to prepare other derivatives of compound **7** through the sequence **6(b-i)** $\rightarrow$ **7(b-i)**, respectively. All the above reactions are shown in the summarized form (Scheme-I).



Scheme-I

ACKNOWLEDGEMENTS

This work was supported by Civentichem (India) Private Limited. The authors thank Dr. Bhaskar Rao Venepalli and Dr. Vasu Cittineni, for their support. The authors also thank the authorities of Jawaharlal Nehru Technological University Hyderabad for encouragement.

REFERENCES

1. S. Wahindulla and J.J. Bhattacharjee, *J. Indian Inst. Sci.*, **4**, 485 (2001).
2. Y. Katsura, S. Nishino and H. Takasugi, *Chem. Pharm. Bull. (Tokyo)*, **1**, 2937 (1991).
3. A.R. Katritzky, M. Pacureanu, S. Slavov, D.A. Dobchev and M. Karelson, *Bioorg. Med. Chem.*, **14**, 7490 (2006).
4. M. Kajino, Y. Shibouta, K. Nishikawa and K. Meguro, *Chem. Pharm. Bull. (Tokyo)*, **39**, 2896 (1991).
5. R. Fringuelli, D. Pietrella, F. Schiaffella, A. Garraci, S. Perito, F. Bistoni and A. Vecchiarelli, *Bioorg. Med. Chem.*, **10**, 1681 (2002).
6. S. Alper-Hayta, E. Aki-Sener, B. Tekiner-Gulbas, I. Yildiz, O. Temiz-Arpaci, I. Yalcin and N. Altanlar, *Eur. J. Med. Chem.*, **41**, 1398 (2006).
7. S. Deswal and N. Roy, *Eur. J. Med. Chem.*, **41**, 552 (2006).
8. D. Zhou, B.L. Harrison, U. Shah, H. Andree, G.A. Hornby, R. Scerni, L.E. Schechter, D.L. Smith, K.M. Sullivan and R.E. Mewshaw, *Bioorg. Med. Chem. Lett.*, **16**, 1338 (2006).
9. M. Ohno, Y. Tanaka, M. Miyamoto, T. Takeda, K. Hoshi, N. Yamada and A. Ohtake, *Bioorg. Med. Chem.*, **14**, 2005 (2006).
10. Z.T. Pio, L.M. Zhao, H.R. Piao and Z.S. Quan, *Eur. J. Med. Chem.*, **43**, 1216 (2008).