SYNTHESIS AND CHARACTERIZATION OF N-OXIDES AND METABOLITES OF ANTI-PSYCHOTIC DRUG, ARIPIPRAZOLE

Bollikonda Satyanarayana, Yasareni Sumalatha, Sythana Suresh Kumar, Sundaram Venkatraman, Ghanta Mahesh Reddy, Padi Pratap Reddy*
Research and Development Centre, Dr Reddy's Laboratories Limited, API, Unit IV, IDA, Jeedimetla, Hyderabad-506 055, A.P., India
E-Mail: reddyppou@yahoo.co.in

Abstract: Aripiprazole is a recently developed anti-psychotic drug used for the treatment of schizophrenia. Aripiprazole and its N-oxides exhibit a strong activity for influencing the neurotransmission of dopamine receptors and are devoid of side effects induced by the known drugs useful for the treatment of schizophrenia. Further, Aripiprazole is metabolized by different biotransformation pathways as dehydrogenation, hydroxylation and N-dealkylation giving rise to different metabolites. The present work details the development of a simple and novel process for the preparation of Aripiprazole N-oxides as Aripiprazole-4-N-oxide, Aripiprazole-1-N-oxide and Aripiprazole-1,4-di-N-oxide and Aripiprazole metabolites such as dehydro Aripiprazole and Aripiprazole hydroxy metabolite.

Introduction

Aripiprazole **1** is an anti-psychotic drug[1,2] used in the treatment of psychoses including schizophrenia[3]. Schizophrenia is a most common type of psychosis caused by an excessive neurotransmission activity of the dopaminergic nervous system in the CNS. Aripiprazole, a carbostyril derivative, functions as a partial agonist[4-7] at the dopamine D_2 and serotonin 5-HT_{1A} receptors and as an antagonist at serotonin 5-HT_{2A} receptor. Clinical studies have demonstrated that Aripiprazole and its N-oxides[8] are well tolerated and do not significantly induce extra pyramidal syndromes, which are the side effects, found in the case of drugs having a strong activity for blocking neurotransmission of dopaminergic receptor. The N-oxides of Aripiprazole include Aripiprazole-4-N-oxide, Aripiprazole-1-N-oxide and Aripiprazole-1,4-di-N-oxide.

Metabolism is often the major factor influencing the efficacy and side effect profile of drugs. An understanding of a drug's metabolism and recognition of potential drug-drug interactions is critical to successful drug development. Aripiprazole is metabolized primarily by three biotransformation pathways dehydrogenation, hydroxylation and N-dealkylation. 7-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl] butoxy]-3,4-dehydro-2-(1H) quinolinone[9] (Dehydro Aripiprazole, **9**), is a major active metabolite formed by the dehydrogenation of Aripiprazole. The other important metabolite is 7-(4-hydroxy butoxy)-3,4-dihydro-2-(1H)-quinolinone [9].

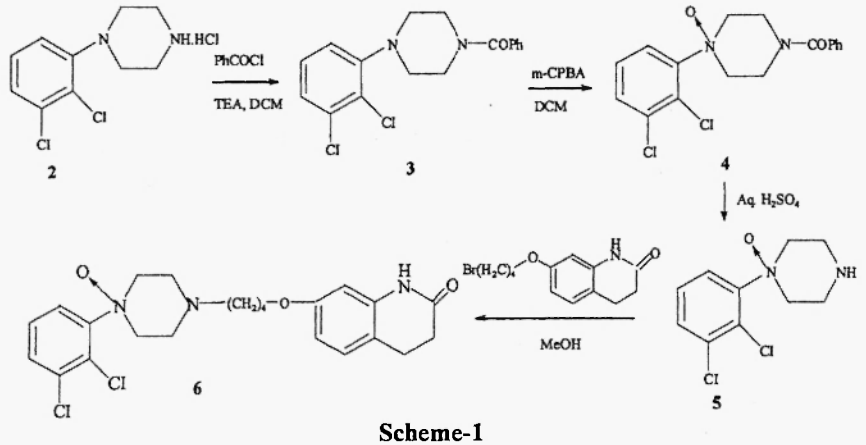
Discussions

In this present article, we herewith disclose our work regarding the synthesis and characterization of the various N-oxides and metabolites of Aripiprazole.

7-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl (4-N-oxo)] butoxy] 3, 4-dihydro-2-(1H) quinoiinone (Aripiprazole-4-N-oxide, 6)

In the preparation of Aripiprazole-4-N-oxide 6, 2, 3-dichloro phenyl piperazine hydrochloride 2 was chosen as the starting material. The secondary nitrogen of 2 is highly reactive when compared to the tertiary nitrogen, having a possibility for N-oxide formation at the secondary nitrogen. Hence, in order to get the N-oxide at the tertiary nitrogen, the cyclic secondary amine 2 was protected using benzoyl chloride in the presence of dichloromethane as the solvent and triethyl amine as the base, to yield benzoyl protected dichloro phenyl piperazine 3. The EI mass spectrum of 3 showed the molecular ion at m/z 336. The presence of carbonyl group (1630 cm^{-1}) was evident in the infrared spectrum. Reaction of piperazine derivative 3 with *m*-chloro per benzoic acid in dichloromethane solvent resulted in benzoyl protected dichloro phenyl piperazine-N-oxide 4. The EI mass spectrum displayed the molecular ion of 4 at m/z 351. Deprotection by hydrolysis of 4 in the presence of aqueous

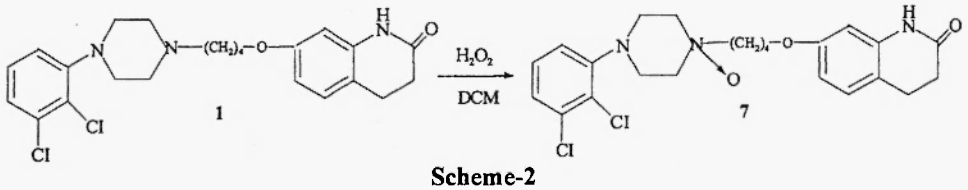
sulphuric acid yielded 4-N-oxide of dichloro phenyl piperazine 5. The EI mass spectrum of 5 displayed the molecular ion at m/z 247. Deprotection of secondary amine was evident from infrared spectral values showing NH at 3275 cm^{-1}. Finally, condensation of 4-N-oxide of dichlorophenyl piperazine 5 with 7-(4-bomobutoxy)-3,4-dihydro-2-(1H)-quinolinone furnished 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl (4-N-oxo)] butoxy]3,4-dihydro-2(1H) quinolinone 6 (Scheme-1). The molecular ion of 6 appeared as the base peak at m/z 465 in the EI mass spectrum. The presence of NH (3377 cm^{-1}), carbonyl (1679 cm^{-1}) aryl alkyl ether (1272, 1048 cm^{-1}) and aromatic C-Cl (1173 cm^{-1}) groups was evident in the infrared spectrum. In the ^1H NMR spectrum (δ ppm), the cyclic amide NH appeared as a singlet at 10.0, which disappeared on adding deuterium oxide. The O-CH_2 protons appeared as a triplet at 3.95. The methylene protons of the free nitrogen of piperazine moiety appeared at 3.05 whereas those methylene protons attached to the oxo nitrogen appeared as a triplet at 4.6.



Scheme-1

7-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl] (1N-oxo) butoxy]-3,4-dihydro-2-(1H) quinolinone (Aripiprazole-1-N-oxide, 7)

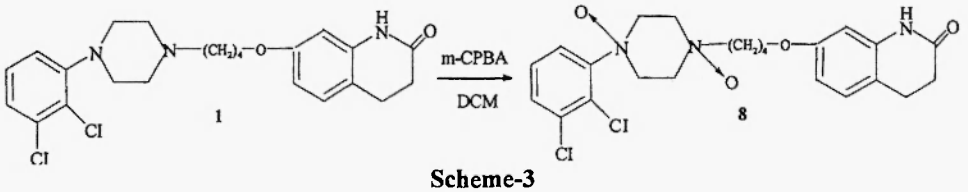
Aripiprazole **1** on treatment with H_2O_2 in dichloromethane smoothly afforded Aripiprazole-1-N-oxide **7** in quantitative yields. The reaction stopped with mono N-oxide **7** formation (Scheme-2). The molecular ion appeared as the base peak at m/z 465. IR spectrum showed the presence of NH (3428 cm^{-1}), carbonyl (1683 cm^{-1}) and aromatic C-Cl (1173 cm^{-1}) functions.



Scheme-2

7-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl] (1-N, 4-N-oxo) butoxy]-3,4-dihydro- 2-(1H) quinolinone (Aripiprazole 1,4-di-N-oxide, 8)

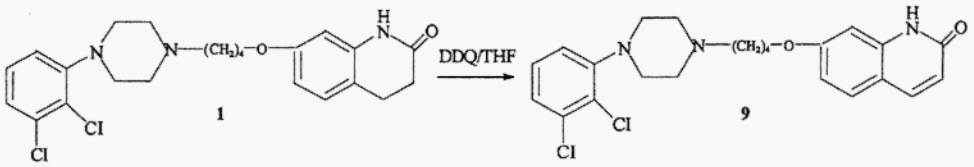
Oxidation of Aripiprazole **1** with meta chloro perbenzoic acid in dichloromethane yielded Aripiprazole 1,4-Di-N-oxide **8** (Scheme-3). The molecular ion appeared as the base peak at m/z 480. IR spectrum is characterized by the presence of NH (3428 cm^{-1}), carbonyl (1663 cm^{-1}) and aromatic C-Cl (1171 cm^{-1}) absorptions.



Scheme-3

7-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl] butoxy]-3,4-dehydro-2-(1H) quinolinone (Dehydro Aripiprazole, 9)

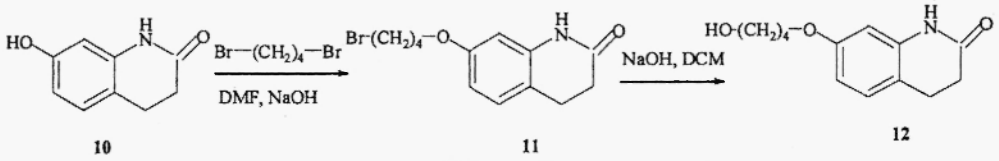
Aripiprazole **1** is converted into dehydro Aripiprazole **9** by treatment with dichloro dicyano quinone (DDQ) in tetrahydrofuran (Scheme-4). The molecular ion appeared as the base peak at m/z 447. In the IR spectrum, carbonyl absorption appeared at a lower frequency (1658 cm^{-1}), when compared to that of Aripiprazole (1678 cm^{-1}).



Scheme-4

7-(4-Hydroxy butoxy)-3,4-dihydro-2-(1H)-quinolinone 12

Condensation of 7-hydroxy 3,4 dihydro-2-(1H)-quinolinone with 1,4-dibromo butane followed by treatment with sodium hydroxide yielded 7-(4-Hydroxy butoxy)-3,4-dihydro-2-(1H)-quinolinone **12** (Scheme-5). The molecular ion appeared as the base peak at m/z 298. The IR spectrum showed OH group absorption at (3393 cm^{-1}) besides NH (3210 cm^{-1}) and carbonyl (1657 cm^{-1}) absorption.



Scheme-5

Conclusions

Knowledge of the different possible metabolites and their synthetic routes is prerequisite for a through understanding of the metabolistic pathway of the antipsychotic drug, Aripiprazole in the human system. Keeping in view the biological importance of Aripiprazole N-oxides and the significance of various metabolites, our efforts to synthesize and characterize them effectively, prove to be valuable.

Experimental Section

The ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 50 M Hz respectively on a Gemini 200 MHz FT NMR Spectrometer, the chemical shifts were reported on δ ppm relative to TMS. The IR spectra were recorded in the solid state as KBr dispersion using Perkin Elmer FT-IR Spectrophotometer. The mass spectra were recorded on Shimadzu LCMS-QP 8000 LC-MS and AB-4000 Q-trap LC-MS/MS.

7-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl (4-N-oxo)] butoxy] 3,4-dihydro-2-(1H) quinolinone (6)

Stage-1

To a mixture of 2,3-dichloro phenyl piperazine hydrochloride (100.0 g, 0.374 mol, **2**) and dichloromethane (600.0 mL), triethylamine (113.0 g, 1.119 mol) was added slowly and stirred for 30 min. Benzoyl chloride (52.5 g, 0.374 mol) in dichloromethane (100.0 mL) was added slowly to the reaction mass and stirred for 2 h for reaction completion. To the reaction mass, water (1000.0 mL) was added and stirred for 30 min. The organic and aqueous layers were separated. The organic layer was washed with water (1000.0 mL) and concentrated under reduced pressure below 40 ^{0}C to get the residue. To the residue pet ether (400.0 mL) was added and stirred for 30 min. The isolated solid was filtered, washed with pet ether (100.0 mL) and dried to a constant weight at 70-80 ^{0}C to yield benzoyl protected dichloro phenyl piperazine (**3**, Yield 116.0 g, 92.6 %).

IR (cm^{-1}): 3055 (Ar-H), 2847 (Ali-H), 1630 (C=O), 1285 (C-N), 1432 (C=C).

Mass: 336 (M^{+}).

Stage-2

A mixture of benzoyl protected dichlorophenyl piperazine (**3**, 40.0 g, 0.12 mol), dichloromethane (1600.0 mL) and m-chloro perbenzoic acid (80.0 g, 0.30 mol) was stirred for3-4 h for reaction completion. A solution of sodium hydroxide (40.0 mL, 0.60 mol) in water (1200.0 mL) was added slowly to the reaction mass and stirred for 30 min. The organic and aqueous layers were separated. The organic layer was concentrated under reduced pressure below 40 ^{0}C to get the residue. To the residue ethyl acetate (100.0 mL) was added and stirred for 30-60 min. The isolated solid was filtered, washed with ethyl acetate (20.0 mL) and dried to a constant weight at 25-35 ^{0}C to yield 4-N-oxide of benzoyl protected dichlorophenyl piperazine (**4**, Yield 27.6 g, 65.9 %).

IR (cm^{-1}): 3070 (Ar-H), 2955 (Ali-H), 1621.7 (C=O), 1295 (C-N), 1428 (C=C).

Mass: 351 (M^+).

Stage-3

To chilled water (250.0 mL) sulphuric acid (140.0 mL) was added slowly. N-oxide of benzoyl protected dichlorophenyl piperazine (**4**, 25.0 g, 0.071 mol) was added to aqueous H_2SO_4 and heated to 50-60 ^{0}C, and maintained for 30 h for reaction completion. The reaction mass was cooled to 25-35 ^{0}C and filtered to recover benzoic acid. The aqueous layer was washed with chloroform (150.0 mL). The organic and aqueous layers were separated. The pH of aqueous layer was adjusted to 8-9 using aqueous ammonia. The product was extracted into chloroform and the organic layer was concentrated under reduced pressure to get a residue. To the residue, ethyl acetate (50.0 mL) was added and stirred for 30 min. The isolated solid was filtered, washed with ethyl acetate (15.0 mL) and dried to a constant weight at 25-35 ^{0}C to yield N-oxide of dichloro phenyl piperazine (**5**, Yield 13 g, 73.8 %).

IR (cm^{-1}): 3275 (N-H), 3079 (Ar-H), 2958, 2929 (C-H), 1402 (C=C), 1321 (C-N), 1173 (Ar-Cl).

Mass: 247 (M^+).

Stage-4

To a mixture of methanol (65.0 mL), N-oxide of dichlorophenyl piperazine (**5**, 11.9 g, 0.048 mol) and 7-(4-bromobutoxy)-3,4-dihydro-2-(1H)-quinolinone (13.0g, 0.043 mol) triethyl amine (13.2 g, 0.131 mol) was added and the reaction mixture was refluxed for 30 h. The reaction mass was concentrated under reduced pressure below 40 ^{0}C and to the residue water (130.0 mL) and chloroform (130.0 mL) were added and stirred for 30 min. The organic and aqueous layers were separated. The organic layer was washed with water (265.0 mL) and concentrated under reduced pressure below 40 ^{0}C. To the residue, ethyl acetate (130.0 mL) was added and stirred for 30-60 min. The isolated solid was filtered, washed with ethyl acetate (25.0 mL) and dried at 25-35 ^{0}C to yield 7-[4-[-(2,3-dichlorophenyl)-1-piperazinyl (4-N-oxo] butoxy] 3,4 dihydro-2 (1H) quinolinone (**6**, Yield 13.0 g, 58.3 %).

IR (cm^{-1}): 3377 (N-H), 3096, 3059 (Ar-H), 2945, 2874 (Ali-H), 1679 (C=O), 1272,1048(-C-O-C-), 1184 (C-N), 1173 (Ar-Cl).

^{1}H- NMR (DMSO, δ ppm): 1.5-1.8 (m, 4H, CH_2), 2.3-2.6 (m, 4H, CH_2), 2.7-2.9 (m, 2H, CH_2), 2.7-2.9 (m, $4H_a$, CH), 3.05 (t, $2H_e$, CH_2), 3.95 (t, 2H, CH_2), 4.6 (t, $2H_e$, CH_2), 6.45 (s, 1H, Ar-H), 6.50 (d, 1H, Ar-H), 7.05 (d, 1H, Ar-H), 7.60 (t, 1H, Ar-H), 7.80 (d, 1H, Ar-H), 9.10 (d, 1H, Ar-H), 10.0 (s, N-H).

Mass: 464.6 (M^+).

7-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl](1N-oxo)butoxy]-3,4-dihydro-2-(1H)quinolinone (7)

A solution of Aripiprazole (**1**, 25.0 g, 0.055 mol), methylene chloride (250.0 mL) and 30% H_2O_2 (32.0 mL, 0.282 mol) was stirred at 25-35 ^{0}C for 24 h. 30% H_2O_2 (32.0 mL, 0.282 mol) and acetic acid (67.0 mL, 1.116 mol) was added to the reaction mass and maintained for 24 h. Water (250.0 mL) was added to the reaction mass and stirred for 30 min. The organic and aqueous layers were separated. To the organic layer water (100.0 mL) was added and pH was adjusted to 8.0 using aqueous ammonia. The organic and aqueous layers were separated. To the organic layer water (100.0 mL) was added and pH was adjusted to 4-5 using acetic acid (67.0 mL). The organic & aqueous layers were separated. To the organic layer water (100.0 mL) was added and stirred for 15-30 min. The organic layer was separated and concentrated under reduced pressure resulting in a thick residue of 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl](1N-oxo) butoxy]-3,4-dihydro-2-(1H) quinolinone (**7**, Yield 23.3 g, 90 %, Purity by HPLC 98.8 %).

IR (cm^{-1}): 3428 (N-H), 3080,3006 (Ar-CH), 1683 (C=O), 1272,1053 (C-O-C), 1190 (C-N), 1173 (C-Cl).
^{1}H NMR ($CDCl_3$, ∂ ppm): 1.96 (m, 2H, CH_2), 2.16 (m, 2H, CH_2), 2.54 (t, 2H, CH_2); 2.86 (t, 4H, CH_2), 3.0-3.9 (m, 8H, CH_2) 3.99 (t.2H, CH_2), 6.46 (d, 1H, Ar-H); 6.49 (s, 1H, Ar-H), 6.9-7.3 (m, 3H, Ar-H), 6.98 (d, 1H, Ar-H); 9.72 (br, NH).
Mass: 465 (M^+).

7-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl](1-N,4-N-oxo)butoxy]-3,4-dihydro-2-(1H) quinolinone (8)
To a solution of Aripiprazole (**1**, 10.0 g, 0.022mol) and dichloromethane (500.0 mL) a mixture of meta chloro perbenzoic acid (35.6 g, 0.2855 mol) in dichloromethane (500.0 mL) was added and stirred for 1 h. To the reaction mass water (500.0 mL) and caustic lye (22.0 mL) were added and stirred for 30-60 min. The isolated solid was filtered, washed with water (50.0 mL) and dried to a constant weight at 25-35 ^{0}C to yield 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl] butoxy]-3-4-dihydro-2-(1H)-quinolinone di-N-oxide (**8**, Yield 4.5 g, 42.0 %, Purity by HPLC 96.43 %).
IR (cm^{-1}): 3428 (N-H), 3100 (Ar-H), 1663 (C=O), 1268,1045 (C-O-C), 1197 (C-N), 1171 (C-Cl).
^{1}H NMR (DMSO + CD_3OD, ∂ ppm): 1.62-2.2 (m, 4H, CH_2), 2.4-2.6 (t, 4H, CH), 2.80 (t, 2H, CH_2), 3.1-4.1 (m, 8H, CH_2), 5.40 (t, 2H, CH_2), 6.50 (d, 1H, Ar-H), 6.50 (s, 1H, Ar-H), 7.10 (d, 1H, Ar-H), 7.60 (t, 1H, Ar-H), 7.90 (d, 1H, Ar-H); 8.90 (d, 1H, Ar-H),
Mass: 480.4 (M^+).

7-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl] butoxy]-3,4-dehydro-2-(1H) quinolinone (9)
A mixture of THF (660.0 mL), Aripiprazole (**1**, 20.0 g, 0.045 mol) and dichloro dicyano quinone (40.5 g, 0.1784 mol) was stirred at 25-35 ^{0}C for reaction completion. The reaction mass was concentrated under reduced pressure at 50-55 ^{0}C, to obtain the crude. To the crude, water (660.0 mL) was added and stirred at 25-35 ^{0}C for 15-30 min. The reaction mass pH was adjusted to 8-9 using caustic lye. The reaction mass was extracted with ethyl acetate and this layer was washed with (2x100 mL) water. The organic layer was concentrated under reduced pressure at 50-55 ^{0}C to get the residue. To the residue pet ether (200.0 mL) was added and stirred for 30-60 min at 25-35 ^{0}C. The isolated solid was filtered, washed with ether (20.0 mL) and dried to a constant weight at 25-35 ^{0}C to yield 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl] butoxy]-3,4-dehydro-2-(1H) quinolinone (9, Yield 8.5 g, 42.5 %, Purity by HPLC 98.12 %).
IR (cm^{-1}): 1658 (C=O), 1234,1034 (C-O-C), 1187 (C-N), 1149 (C-Cl).
^{1}H NMR ($CDCl_3$+CD_3CN, δ ppm): 1.60-2.02 (m, 4H, CH_2), 2.49 (t, 2H, CH_2), 2.64 (br, 4H, CH_2), 3.05 (br, 4H, CH_2), 4.09 (t, 2H, CH_2), 6.4-7.8 (2H), 6.4-7.8 (m, 3H, Ar-H), 6.45 (d, 1H, CH); 6.77 (s, 1H, Ar-H), 7.73 (d, 1H, CH), 11.2 (br, N-H).
Mass: 446 (M^+).

7-(4-Hydroxy butoxy)-3,4-dihydro-2-(1H)-quinolinone (12)
Stage 1
A mixture of DMF (400 mL), sodium hydroxide flakes (27.0 g, 0.67 mol), 1,4-dibromobutane (432.0 g, 1.22 mol), and 7-hydroxy 3,4 dihydro-2-(1H)-quinolinone (100.0 g, 0.61 mol) was stirred at 25-35 ^{0}C for reaction completion. To the reaction mass water (600.0 ml) and cyclohexane were added and stirred for 1-2 h. The isolated solid was filtered and washed with cyclohexane (100.0 mL). The wet product was treated with 0.2 % aqueous sodium hydroxide solution (600.0 mL), filtered, washed with water(100.0 mL), dried to a constant weight at 70-80 ^{0}C and purified by using a mixture of ethyl acetate(600.0 mL) and cyclohexane (1200.0 mL) to yield 7-(4-bromo butoxy)-3,4-dihydro-2-(1H) quinolinone (**11**, Yield 115.0 g, 63 %, Purity by HPLC 97.0%).
IR (cm^{-1}): 3196 (N-H), 1676 (C=O).
^{1}H-NMR ($CDCl_3$+CD_3CN, δ ppm):1.6-1.8 (m, 2H, CH_2), 1.8-2.0 (m, 2H, CH_2), 2.4-2.6 (t, 2H, CH_2), 2.7-2.9 (t, 2H, CH_2), 3.4-3.7 (t, 2H, CH_2), 3.8-4.0 (t, 2H, CH_2), 6.4-6.6 (d, 1H, CH), 6.4-6.6 (s, 1H, CH), 7.0-7.3 (d, 1H, CH), 9.9-10.1 (s, 1H, NH).
Mass: 298 (M^+).

Stage 2

A mixture of 7-(4-bromo butoxy)-3,4-dihydro-2-(1H) quinolinone (50.0 g, 0.168 mol), methylene chloride (500.0 mL), sodium hydroxide (67.1 g, 0.168 mol) in water (200 mL) was stirred at 25-35 ^{0}C for 30-45 min. To it methanol (400.0 mL) was added to get a homogeneous solution and was maintained at 50-60 ^{0}C till reaction completion. The reaction mass was extracted into methylene chloride (2 X 1000.0 mL) and was washed with water (2 X 250 mL). The organic layer was dried and concentrated atmospherically to obtain the residue. To the residue cyclohexane (200.0 mL) was added and stirred for solid separation. The isolated solid was filtered, washed with cyclohexane (50.0 mL) and dried to a constant weight at 50-60 ^{0}C to yield 7-(4-hydroxy butoxy)-3,4-dihydro-2-(1H)-quinolinone (**12**, Yield 35.4 g, 90 %, Purity by HPLC 97.5 %)

IR (cm^{-1}): 3210 (N-H), 3393 (O-H), 1657 (C=O).

^{1}**H-NMR** ($CDCl_3$+CD_3CN, δ ppm): 1.5-1.7 (m, 2H, CH_2), 1.8-2.0 (pentet, 2H, CH_2), 2.4-2.6 (m, 2H, CH_2), 2.8-3.0 (t, 2H, CH_2), 3.4-3.6 (quartet, 2H, CH_2), 3.8-4.0 (t, 2H, CH_2), 4.2-4.4 (s, 1H, OH), 6.4-6.6 (m, 2H, CH_2), 6.9-7.1 (m, 1H, CH), 9.8-10.0 (s, 1H, NH).

Mass: 236 (M^+).

Acknowledgements

The authors wish to thank the management of Dr. Reddy's Laboratories Ltd., Bulk Actives, Unit-IV for supporting this work.

References

1. U.S. Patent 5,006,528, (1991).
2. C.P. Lawler; C. Prioleau; M.M. Lewis; C. Mak; D. Jiang; J.A. Schetz; A.M. Gonzalez; D.R. Sibley; R.B. Mailman, *Neuropsychopharmacology* **20** (6), 612 (1999).
3. a) M. Rowley; L.J. Bristow; P.H. Hutson, *J. Med. Chem.* **44**, 477 (2001). b) B. Capuno; I.T. Crosby; E.J. Lloyd., *Curr. Med. Chem.* **9**, 521 (2002). c) S. Kapur, G. Remington, *Annu. Rev. Med.*, **52**, 503 (2001). d) J.P. Kelleher, F. Centorrino, M.J. Albert, R.J. Baldessarini, *CNS Drugs*, **16**, 249 (2002).
4. S. Jordan; V. Koprivica; R. Chen; K. Tottori; T. Kikuchu; C.A. Altar, *European Journal Pharmacol.* **441** (3), 137 (2002).
5. Y. Oshiro; S. Sato; N. Kurahashi; T. Tanaka; T. Kikuchi; K. Tottori; Y. Uwahodo; T. Nishi, *J. Med. Chem.*, **41** (5), 658 (1998).
6. a) S.M. Stahl, *J. Clin. Psychiatry*, **62**, 841 & 923 (2001). b) C.A. Tamminga; A. Carlsson, *Current Drug Targets-CNS and Neurological Disorders*, **1**, 141 (2002).
7. a) P.J. Goodnick; J.M. Jerry, *Expert Opin Pharmacother*, **3**, 1773 (2002). b) V. Ozdemir; J. Fourie; F. Ozdoner, *Curr. Opin. Invest. Drugs*, **3**, 113 (2002). c) J.K. McGavin; K.L. Goa, *CNS Drugs*, **16**, 779 (2002). d) D.M. Taylor, *Int. J. Clin. Pract*, **57**, 49 (2003).
8. PCT Appl. WO 03/064393 A1, (2003).
9. NDA 21-436, Otsuka Pharmaceuticals Company Ltd.

Received on July 15, 2005