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Design, Synthesis and Characterization of Adducts of Nitrotetralins as Selective D_1 and D_2 Agonists

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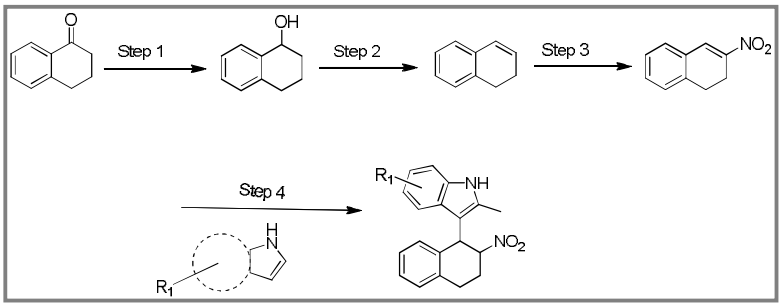
ABSTRACT

The present work emphasizes the synthesis, characterization of various adducts of nitrotetralins. Eight different nitrotetralins were synthesized and were purified by recrystallization or thin layer chromatographic techniques and were characterized by physical and spectral methods such as LC-MS, ^{1}H-NMR, and Mass data. Catalyst free aqueous mediated conjugative addition of various indoles at elevated temperature and other substrates to nitrotetralin was described. Most of indole derivatives were distributed widely in nature and possesses various pharmacological activities. In view of this, various indole moieties were used to synthesize nitrotetralin adducts was subject of interest. Biological activity studies to be carried out for the synthesized nitrotetrlins as selective D_1 and D_2 agonists.

Graphical Abstract



Synthetic scheme of nitrotetralins

Keywords: Characterization, Nitrotetralins, Spectral methods, and D_1 and D_2 agonists.

INTRODUCTION

Indole derivatives are considered as important heterocyclic compounds in the drug discovery studies. There has been an increasing interest in the use of indole derivatives as bioactive molecules against

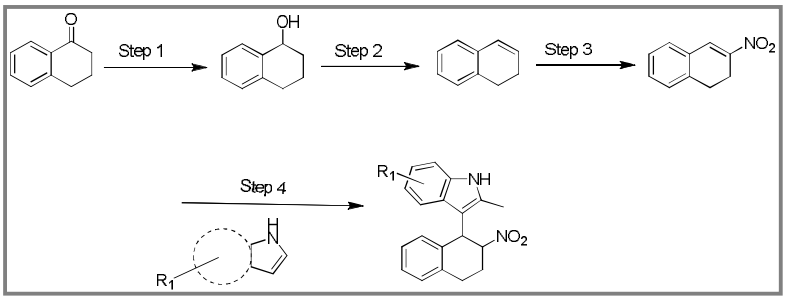
microbes, cancer cells, and various kinds of disorder in the human body. L-dopa remains the single most effective drug for the treatment of Parkinson's disease [**1-5**]. The drug is tolerated well and side effects. It has favorable response to L-dopa patients often develop disabling motor complications and dyskinesias [**6**]. The most commonly used alternative or adjunctive therapies for Parkinson's disease are directly acting dopamine D_2 receptor selective agonists [**7-8**]. Anti cancer activity of some nitroteralins was reported [**9**]. In view of biological activity of various reported nitrotetralins, the author in the present study synthesized eight nitrotetralins.

MATERIALS AND METHODS

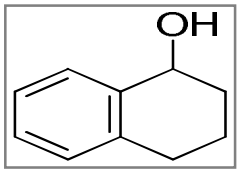
All the glassware was dried at120°C. All compounds were transferred using syringes wherever required and all moisture sensitive reactions were performed under nitrogen atmosphere. All solvents and reagents were purified by standard techniques (Sigma Aldrich and Merck). All evaporation of solvents was carried out under reduced pressure on rotary evaporator below 45°C.

Instruments used: Analytical thin layer chromatography (TLC) was performed on MERCK pre coated silica gel. Visualization of the Spots on TLC plates was achieved either by exposure to iodine vapor or UV light or by dipping the plates into methanolic sulphuric acid, ninhydrin or methanolic anisaldehyde solution and heating the plates to 120°C.Column chromatography was performed using silica gel (60-120mesh) and was usually eluted with ethyl acetate-hexane. Mass spectra were obtained on Agilent Q-TOF-Mass Spectrometer 6540-UHD LC/HRMS operating at 70eV using direct inlet. ^{1}H-NMR spectra were recorded on Bruker Advance 500 MHz and recorded in $CDCl_3$ or DMSO-*d*6 solvents. Chemical shift were reported in parts per million (ppm) with respect to internal standard tetramethylsilane (TMS). Coupling constant are quoted in hertz (Hz) were used in the present work.

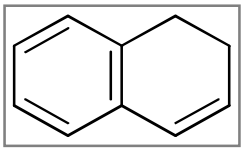
Proposed Synthetic scheme:



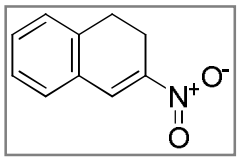
Step 1: Synthesis of 1, 2, 3, 4-Tetrahydronaphthalen-1-ol: Sodium borohydride (1.2 g, 31.12 mmol, 0.5 equiv.) was added in small portions to a stirred solution of 3, 4-Dihydronaphthalen-1(*2H*)-one (10g, 62.24 mmol, 1 equiv.) in absolute ethanol (155 mL, 2.5 mL mmol^{-1}) under inert atmosphere. After complete addition, the reaction mixture was refluxed at 80°C for 2.5 h and then it was cooled to RT. Crushed ice was added to the reaction mixture followed by removal of ethanol under reduced pressure. An aqueous saturated solution of ammonium chloride (50 mL) was added to it followed by extraction with ethyl acetate (125 mL×2). Combined organic extract was dried over sodium sulphate, filtered and concentrated under vacuum (11.6 g, 92.2 %).The product was confirmed by ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.41-7.44 (m, 1H), 7.18-7.22 (m, 2H), 7.09-7.11 (m, 1H), 4.78 (s, 1H), 2.79-2.85 (m, 1H), 2.70-2.76 (m, H), 1.88-2.00 (m, 3H), 1.75-1.81 (m, 1H), 1.67 (s, 1H).



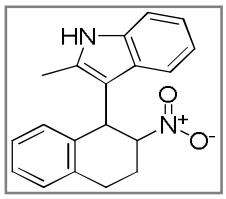
Step 2: Synthesis of 1, 2-Dihydronaphthalene: p-Toluene sulphonic acid (0.150 g, Cat.) was added to a benzene solution (370 mL, 5 mL $mmol^{-1}$) of 1, 2, 3, 4,-tetrahydronaphthalen-1-ol (11.5 g, 74.3 mmol) and the solution was heated under refluxed with azeotropic removal of water using a Dean-Stark apparatus until TLC analysis showed complete consumption of the starting material into the olefinic product. The reaction mixture was washed with 5% aq. sodium hydrogen carbonate solution (150 mL×2), dried over sodium sulphate, filtered and evaporated under reduced pressure. Finally, the product was purified by column chromatography using 100 % hexane as an eluant. (9.9 g, 98 %).The resultant product was confirmed by ^{1}H-NMR ($CDCl_3$, 400MHz):δ 7.09-7.17(m, 3H), 7.02 (d, *J*=6.72, 1H), 6.46 (d, *J*=9.6 Hz, 1H), 6.00-6.05 (m, 1H), 2.80 (t, 8.28, 2H), 2.30-2.34 (m, 2H).



Step 3: Synthesis of 3-Nitro-1, 2- dihydronaphthalene: To a solution of sodium nitrite (10.6 g, 154 mmol, 4 equiv.) and ethylene glycol (6.4 mL, 115 mmol, 3 equiv.) in water (4 mL, 0.104 mL $mmol^{-1}$), a solution of 1, 2-Dihydronaphthalene (5 g, 38.4 mmol) in ethyl acetate (120 mL) was added followed by addition of iodine (14.6 g, 1.5 equiv.) at 0°C. The reaction mixture was stirred at RT for 6 h under inert atmosphere and then was poured into a separating funnel together with ethyl acetate and partitioned. The reaction mixture was successively washed with water, aq.10% sodium thiosulphate solution, and brine. After drying over anhydrous magnesium sulphate, the reaction mixture evaporated under reduced pressure and further purification was accomplished by column chromatography using EA: Hex as an eluant. (3.1 g, 47.1 %).The so obtained product was confirmed by ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.84 (s, 1H), 7.30-7.36 (m, 2H), 7.27 (d, *J*=7.36 Hz, 1H), 7.22 (d, *J*=7.36 Hz, 1H), 3.03-3.07 (m, 2H), 2.96-2.99 (m, 2H).

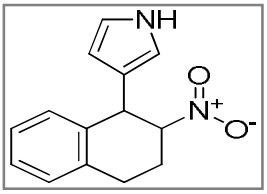


Step 4: Synthesis of Substituted 2-Methyl-3-(2-nitro-1, 2, 3, 4-tetrahydronaphthalen-1-yl)-1H-indole: A mixture of substituted 2-Methyl indole (15.9 mmol, 1.2 equiv.) and 3-Nitro-1, 2-dihydronaphthalene (13 mmol) was suspended in water (26 mL, 2 mL $mmol^{-1}$) and reaction mixture was heated at 100 ºC for 6 h. The progress of reaction was monitored by TLC (UV). After completion of reaction, the reaction was extracted with ethyl acetate (70 mL×3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated. Further purification was achieved by column chromatography using EA/Hex as eluant. (Yield: 2.2 g, 75 %).The resultant product was confirmed by ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.83 (s,1H), 7.27 (s, 1H), 7.12-7.19 (m, 2H), 6.97-7.07 (m, 2H), 6.85-6.90 (m, 2H), 6.79 (d, *J*=7.76 Hz, 1H), 5.15-5.21 (m, 1H), 4.97 (d, *J*=10.12 Hz, 1H), 3.10-3.25 (m, 2H), 2.50-2.57 (m, 2H), 2.36 (s, 3H) and LC-MS: UV: 260 nm, T_R: 3.67, % Area: 100 %, $(M+H)^+$307.

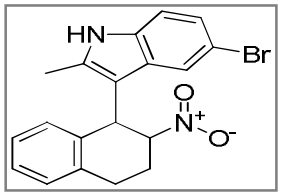


Synthesis of 3-(2-Nitro-1, 2, 3, 4-tetrahydronaphthalen-1-yl)-1H-pyrrole: A mixture of Pyrrole (0.09 mL, 1.38 mmol, and 1.2 equiv.) and 3-Nitro-1, 2-dihydronaphthalene (0.200 g, 1.15 mmol) was suspended in water (2.3 mL, 2 mL $mmol^{-1}$) and reaction mixture was heated at 100^0C for 6 h. The

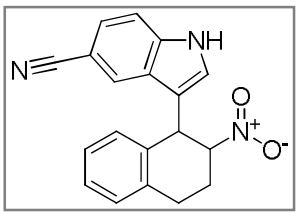
progress of reaction was monitored by TLC (UV). After completion of reaction, the reaction was extracted with ethyl acetate (30 mL×3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated. Further purification was achieved by column chromatography using EA/Hex as eluant. (Yield: 179 mg, 64 %).The product was confirmed by ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.81 (s, 1H), 6.99-7.22 (m, 4H), 6.65 (d, *J*=17.8 Hz, 1H),6.07-6.15 (m, 1H), 6.01 (s, 1H), 5.01 (d, *J*=4.96 Hz, 1H), 4.85-4.90 (m, 1H), 2.91-3.14 (m, 2H), 2.25-2.48 (m, 2H)and D_2O exchange.LC-MS**:** UV: 260 nm, T_R: 3.55, % Area: 73 %, (M+H)243;GC-MS**:** m/z = 242.



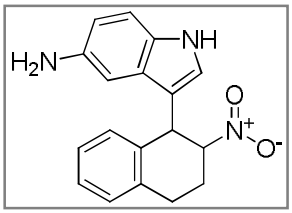
Synthesis of 5-Bromo-2-methyl-3-(2-nitro-1, 2, 3, 4-tetrahydronaphthalen-1-yl)-1H-indole: A mixture of 5-Bromo-2-methyl indole (0.146g, 0.694 mmol,1.2 equiv.) and 3-Nitro-1, 2-dihydro-naphthalene (0.100 g, 0.578 mmol) was suspended in water (1.16 mL 2 mL $mmol^{-1}$) and reaction mixture was heated at 100 °C for 16 h. The progress of reaction was monitored by TLC (UV). After completion of reaction, the reaction was extracted with ethyl acetate (25 mL×3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated. Further purification was achieved by column chromatography using EA/Hex as eluant. (Yield: 88 mg, 39.6 %).The obtained product was confirmed by ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.89 (s, 1H), 6.99-7.20 (m, 5H), 6.89 (s, 1H), 6.82 (d, *J*=7.76 Hz, 1H), 5.10-5.13 (m, 1H), 4.91 (d, *J*=10.32 Hz, 1H), 3.14-3.16 (m, 2H), 2.52-2.56 (m, 2H), 2.35 (s, 3H); and D_2O exchange; LC-MS: UV: 260 nm, Column: REPROSIL, T_R: 3.95, % Area: 99.5 %, $(M+H)^+$385.



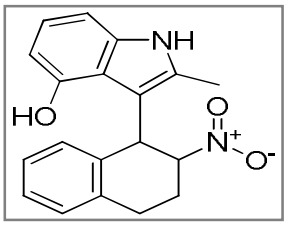
Synthesis of 3-(2-Nitro-1, 2, 3, 4-tetrahydronaphthalen-1-yl)-1H-indole-5-carbonitrile: A mixture of 5-Cyano indole (0.099 g, 0.694 mmol, 1.2 equiv.) and 3-Nitro-1, 2-dihydronaphthalene (0.100 g, 0.578 mmol) was suspended in water (1.16 mL, 2 mL $mmol^{-1}$) and reaction mixture was heated at 100^0C for 16 h. The progress of reaction was monitored by TLC (UV). After completion of reaction, the reaction was extracted with ethyl acetate (25 mL×3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated. Further purification was achieved by column chromatography using EA/Hex as eluant. (Yield: 36 mg, 19.6 %). The product was confirmed by ^{1}H-NMR ($CDCl_3$, 400MHz): δ 8.42 (s,1H), 7.03-7.44 (m,16H), 6.88-6.94 (m, 2H), 6.63 (s, 1H), 5.20 (d, *J*=5.48, 1H), 4.98-5.09 (m,3H), 3.06-3.26 (m,4H), 2.51-2.54 (m, 2H) and D_2O exchange; LC-MS**:** UV: 260 nm, T_R: 3.53, % Area: 81.2 %, $(M+H)^+$318.



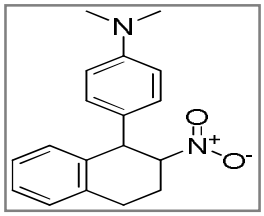
Synthesis of 3-(2-Nitro-1, 2, 3, 4-tetrahydronaphthalen-1-yl)-1H-indol-5-amine: A mixture of 5-Amino indole (0.092 g, 0.694 mmol, 1.2 equiv.) and 3-Nitro-1, 2-dihydronaphthalene (0.100 g, 0.578 mmol) was suspended in water (1.16 mL, 2 mL $mmol^{-1}$) and reaction mixture was heated at 100^0C for 18 h. The progress of reaction was monitored by TLC (UV). After completion of reaction, the reaction was extracted with ethyl acetate (25mL×3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated. Further purification was achieved by column chromatography using EA/Hex as eluant. (Yield: 28 mg, 16 %).The product was confirmed by ^{1}H-NMR ($CDCl_3$, 400MHz): δ 10.52 (s, 1H), 7.11-7.19 (m, 2H), 6.96-06 (m, 2H), 6.84 (d, *J*=7.24 Hz, 1H), 6.40-6.48 (m, 1H), 6.33 (s, 1H), 5.75 (s, 1H), 5.25-5.29 (m, 1H), 4.73 (d, *J*=9.12 Hz, 1H), 4.39 (s, 2H), 3.12-3.14 (m, 1H), 2.98-3.02 (m, 1H), 2.32-2.38 (m, 1H); LC-MS:UV: 260 nm, T_R: 3.19, % Area: 69.8 %, $(M+H)^+$308.



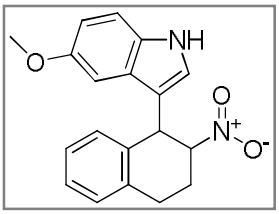
Synthesis of 2-Methyl-3-(2-nitro-1, 2, 3, 4-tetrahydronaphthalen-1-yl)-1H-indol-4-ol: A mixture of 4-Hydroxy-2- methyl indole (0.102 g, 0.694 mmol, 1.2 equiv.) and 3-Nitro-1,2-dihydronaphthalene (0.100 g, 0.578 mmol) was suspended in water (1.16 mL, 2 mL $mmol^{-1}$) and reaction mixture was heated at 100^0C for 24 h. The progress of reaction was monitored by TLC (UV). After completion of reaction, the reaction was extracted with ethyl acetate (25mL×3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated. Further purification was achieved by column chromatography using EA/Hex as eluant. (Yield: 66 mg, 35.9 %).The resultant product was confirmed by ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.84 (s, 1H), 7.12-7.16 (m, 2H), 6.87-7.05 (m, 4H), 6.48 (d, *J*=7.44, 1H), 6.24-6.29 (m, 1H), 5.51 (s, 1H), 4.83-4.93 (m, 1H), 4.10-4.18 (m, 1H), 3.06-3.18 (m, 2H), 2.48-2.55 (m, 2H), 2.42 (s, 3H); LC-MS: UV: 260 nm, T_R: 3.43, % Area: 66 %, $(M+H)^+$323.



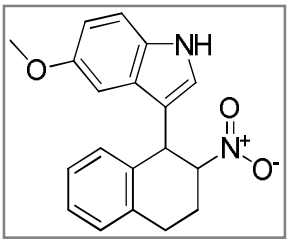
Synthesis of N, N-Dimethyl-4-(2-nitro-1, 2, 3, 4-tetrahydronaphthalen-1-yl) benzenamine: A mixture of N, N-Dimethyl aniline (0.18 ml, 1.387 mmol, 1.2 equiv.) and 3-Nitro-1, 2-dihydro-naphthalene (0.200 g, 1.156 mmol) was suspended in water (2.31 mL, 2 mL $mmol^{-1}$) and reaction mixture was heated at 100 ºC for 24 h. The progress of reaction was monitored by TLC (UV). After completion of reaction, the reaction was extracted with ethyl acetate (30mL×3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated. Further purification was achieved by column chromatography using EA/Hex as eluant. (Yield: 18 mg, 5.3 %).The product was confirmed by ^{1}H-NMR ($CDCl_3$, 400MHz): δ 6.54-7.25 (m, 8H), 4.88-4.98 (m, 1H), 4.63-4.82 (m, 1H), 2.96-3.13 (m, 4H), 2.83-2.92 (m, 6H); LC-MS: UV: 220 nm and 260 nm, T_R: 3.71, % Area: 47.2 %, $(M+H)^+$ 297.



Synthesis of 5-Methoxy-3-(2-nitro-1, 2, 3, 4-tetrahydronaphthalen-1-yl)-1H-indole: A mixture of 5-Methoxy indole (0.102g, 0.694mmol, 1.2 equiv.) and 3-Nitro-1, 2-dihydronaphthalene (0.100 g, 0.578 mmol) was suspended in water (1.16 mL, 2 mL $mmol^{-1}$) and reaction mixture was heated at 100^0C for 18 h. The progress of reaction was monitored by TLC (UV). After completion of reaction, the reaction was extracted with ethyl acetate (25mL×3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated. Further purification was achieved by column chromatography using EA/Hex as eluant. (Yield: 167 mg, 89.7 %).The product was confirmed by ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.96 (s, 1H), 7.21-7.24 (m, 1H),7.17 (d, *J*=2.76 Hz, 1H), 7.12 (d, *J*=2.24 Hz, 1H), 7.03-7.07 (m, 2H), 6.91 (d, *J*=2.28 Hz, 1H), 6.82-6.85 (m, 1H), 6.53-6.55 (m, 1H), 5.06-5.10 (m, 1H), 5.01 (d, *J*=8.16 Hz, 1H), 3.68 (d, *J*=8.48 Hz, 3H), 3.05-3.10 (m, 2H), 2.45-2.51 (m, 2H) and D_2O exchange; LC-MS:UV: 260 nm, T_R: 3.58, % Area: 99.7 %, $(M+H)^+$323.



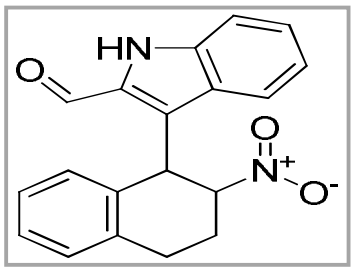
Step 5: Reduction of 5-Methoxy-3-(2-nitro-1, 2, 3, 4-tetrahydronaphthalen-1-yl)-1H-indole: To a solution of 5-Methoxy-3-(2-nitro-1, 2, 3, 4-tetrahydronaphthalen-1-yl)-1H-indole (0.050 g, 0.155 mmol) in THF (0.82 mL) and AcOH (1.2 mL), Zn (5.714 mmol, 36.8 eq.) was added. After stirred for 0.5 hrs at RT, the mixture was filtered, and the filtrate was concentrated and partitioned between aqueous $NaHCO_3$ and AcOEt. The combined organic layer was washed with brine and dried over sodium sulphate and concentrated. Further purification was achieved by column chromatography using AcOEt/MeOH as eluant. (Yield: 18 mg, 39.7 %). The product was confirmed by ^{1}H-NMR (DMSO, 400 MHz): δ 10.73 (s, 1H), 7.24 (d, *J*=8.76 Hz, 1H), 6.68-7.14 (m, 6H), 6.59 (d, *J*=2.2 Hz, 1H), 3.90 (d, *J*=8.08 Hz, 1H), 3.56-3.63 (m, 4H), 2.92-2.96 (m, 3H), 1.99 (m, 1H), 1.89 (s, 2H); LC-MS:UV: 220 nm and 260 nm, T_R: 2.79, % Area: 87.5 %, $(M+H)^+$293.



Step 6: Synthesis of 3-(2-Nitro-1, 2, 3, 4-tetrahydronaphthalen-1-yl)-1H-indole-2-carbaldehyde: To a solution of oxalyl chloride (0.27 mL, 3.265 mmol) in dry DCM (5.6 mL), at -78 ºC under argon atmosphere, was added DMSO (0.32 mL, 4.57 mmol). The solution was stirred for 10 min, until effervescence ceased. A solution of 2-methyl-3-(2-nitro-1,2,3,4-tetrahydronaphthalen-1-yl)-1H-indole (200 mg, 0.653 mmol) in dry DCM (1.5 mL) was added drop wise, and the solution was stirred for 10 min at -78^0C. Triethylamine (0.916 mL, 6.57 mmol) was then added and the solution was left to warm to room temperature for 20 min, while stirred. The reaction mixture was diluted with DCM (20mL) and washed with saturated aqueous NH_4Cl (3×20 mL). The organic layer was dried (Na_2SO_4) and evaporated, and the residue was purified by column chromatography using EA/Hex as an eluant. (Yield: 4 %).The product was confirmed by ^{1}H-NMR ($CDCl_3$, 400MHz): δ 9.87 (s, 1H), 8.97 (s, 1H), 7.40 (d, *J*=8.24 Hz, 1H), 7.29-7.34 (m, 1H), 7.16-7.22 (m,2H), 6.96-7.04 (m, 3H), 6.88 (d, *J=7.68* Hz, 1H), 5.49-5.55 (m,1H), 5.18-5.24 (m,1H), 3.16-3.25 (m, 2H), 2.51-2.64 (m, 2H); LC-MS:UV: 220 nm and 260 nm, T_R: 4.04, % Area: 48.98 %, $(M+H)^+$321.

RESULTS AND DISCUSSION

Catalyst free aqueous mediated conjugative addition of various indole at elevated temperature and other substrates to Nitrotetralin was described in the present work. No catalyst, simple workup procedure, easy isolation and environmentally acceptable medium are the best features in this process. The use of water as a green media for organic synthesis has become an important research area. Thus, the development of organic reaction in water medium is necessitating in the present days.



Many materials like 2-Methyl indole, Pyrrole, Aniline, Furan, Thiaphene, N,N-Dimethyl aniline, 5-Bromo-2- methyl indole,5-cyano indole, 5-Methoxy indole, 4-Hydroxy-2- methyl indole and 5-Amino indole. Out of these, Pyrrole, 2-Methyl indole, N,N-Dimethyl aniline, 5-Bromo-2- methyl indole, 5-cyano indole, 5-Methoxy indole, 5-Amino indole were tried for the synthesis of tetrahydronaphthalene derivative, in which 4-Hydroxy-2- methyl indole became successful while rest got failed. The conjugated adduct of 5-Methoxy indole and 2-Methyl indole with Nitrotetralin was treated with sodium hydrogen carbonate to examine the diastereomer excess but results were not satisfactory. For both adducts, the de was found to be zero. The oxidation of 2-Methyl-3-(2-nitro-1, 2, 3, 4tetrahydronaphthalen-1-yl)-1H-indole, to convert the CH_3 into aldehydic group, tried with selenium oxide by Swern oxidation was successful but very less yield. Due to this, we tried for alternative pathway i.e. reduction of 5-Methoxy-3-(2-nitro-1, 2, 3, 4-tetrahydronaphthalen-1-yl)-1H-indole followed by oxidation step of conjugative adduct products of various indoles with Nitrotetralin. The formylation and cyclization may be carried out by using absolute ethanol, 37 % formaldehyde in water allowed to stir at room temperature for 15 min followed by conc. HCl under reflux for 4h.

Indole and many of its derivatives are widely distributed in the nature, which possesses biological and pharmacological activity. Several indole alkaloids such as Uleine and Tryptamine derivatives possess some important biological activity. Hence, the development of new strategies to synthesize indole derivatives has been the subject of interest in the present days.

CONCLUSIONS

Hetero cyclic compounds such as D_1 and D_2agonists were the subject of interest in the present work. Currently available pharmacological therapies are neither able to arrest, nor reverse the progression of this relentlessly progressive and severely debilitating condition. The many neuroprotective agents investigated offer exciting opportunity for the development of future treatments. We have synthesized eight nitrotetralin adducts using different indole moieties. We have tried few reactions to get our desired product and it requires further research. The synthetic pathway is being worked on various nitroteralins through economic and feasible means. This could promise enhanced selectivity, potency and efficacy. Moreover, this can explore the therapeutic scenario in a better way.

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