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Research Article

Synthesis, Charectrisation of Novel Indole Based Derivatives Used as Medicinally Potent Agents

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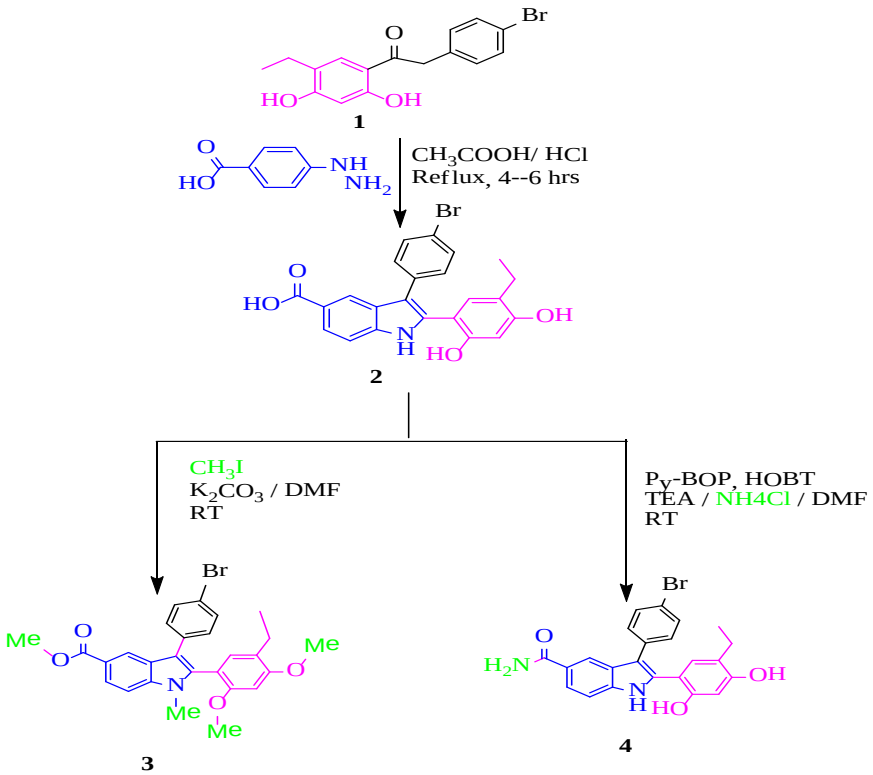
ABSTRACT

A large number of compounds containing indole nucleus have been patented, as chemotherapeutic agents, antimicrobial, cytotoxic, anti-inflammatory, antitumor, anti-convulsant, antitubercular and anti-HIV. A wide range of indole derivatives were investigated using different conditions. In the present work we synthesized various indole derivatives which are given below in **scheme-1** and summarized in after the scheme.

Keywords: Anti-Convulsant, Anti-HIV, Chemotherapeutic Agents, Antimicrobial, Antitumor.

INTRODUCTION:

Indole nucleus is present as a structural unit in many natural products. Indoles are a pervasive class of compounds found in abundance in biologically active compounds such as pharmaceuticals, agrochemicals and alkaloids. Indole derivatives have, therefore, captured the attention of organic synthetic chemists. Medicine and biochemistry are also interested in many aspects of indole chemistry. A number of indole derivatives are reported to exhibit antibacterial, antifungal, anti-tuberculosis, antithrombotic, anticancer, anti-inflammatory and CNS depressant activities. The indole alkaloids constitute the biggest single class of the alkaloids and account for about 20% of all known alkaloids.[1, 2]



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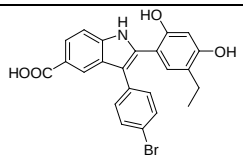
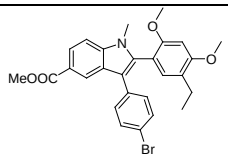
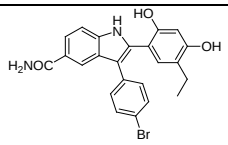
S. No	Structure of Compounds	Name of compounds	^{1}H NMR	LCMS Purity	MS Observed	RT (LCMS)
1.		3-(4-bromophenyl)-2-(5-ethyl-2,4-dihydroxyphenyl)-1H-indole-5-carboxylic acid	0.869-0.951(3H,t) 2.296-2.351(2h,q) 6.458(1H,s)6.772(1H,s) 7.268-7.289(2H,d) 7.440-7.462 (1H,d) 7.539-7.560 (2H,d) 7.718-7.739 (2H,d) 8.207 (1H,s) 9.404(1H,s)9.427 (1H,s)11.519 (1H,s) 12.383 (1H,s)	91.66%	452.02 454.02	3.11
2.		methyl 3-(4-bromophenyl)-2-(5-ethyl-2,4-dimethoxyphenyl)-1-methyl-1H-indole-5-carboxylate	0.932-0.969 (3H,t) 2.400-2.427 (2H,q) 3.555 (3H,s) 3.763 (3H,s) 3.845 (3H,s) 3.899 (3H,s) 6.781 (1H,s) 6.833 (1H,s) 7.154-7.175 (2H,d) 7.512-7.533 (2H,d) 7.630-7.652 (1H,d) 7.845-7.867 (1H,d) 8.255 (1H,s)	95.36%	508.10 510.10	4.15
3.		3-(4-bromophenyl)-2-(5-ethyl-2,4-dihydroxyphenyl)-1H-indole-5-carboxamide	0.834-0.955 (3H,t) 2.319-2.337 (2H,q) 6.455 (1H,s) 6.766 (1H,s) 7.084 (1H,s) 7.297-7.315 (2H,d) 7.385-7.406 (1H,d) 7.508-7.527 (2H,d) 7.655-6.676 (1H,d) 7.866 (1H,s) 8.151 (1H,s) 9.341(1H,s) 9.377 (1H,s) 11.353 (1H,s)	93.88%	450.82 452.82	3.39

Figure 1:

Table 1: Spectral Analysis of Compound 2, 3 and 4

Procedure

(i) Synthesis of compound (4-bromophenyl)-2-(5-ethyl-2,4-dihydroxyphenyl)-1H-indole-5-carboxylic acid (2)

2-(4-bromophenyl)-1-(5-ethyl-2, 4-dihydroxyphenyl) ethanone (**1**) (10g,0.0298mol, 1eq) and 4-hydrazinylbenzoic acid(5.44g,0. 0358mol,1.2eq) were taken in CH_3COOH (200 ml) in 2N RBF attached with water condenser in oil bath. Then reaction mixture was heated at 500C for 30 min. then con. HCl (50ml) was added drop wise into the reaction mixture at 50^0C within 20 min. Then reflux the reaction mixture for 4 to 6 hrs. Reaction monitor by TLC. In work up procedure, poured reaction mixture into ice-water and extracted by ethyl acetate. Combine ethyl acetate layer dried over sodium sulfate and concentrated under vacuum to get crude mass. Compound purify by coloumn chromatography to get 5.2 g of desire product as a brown solid. (Yield-32.09%)

(Silica-230-400 mess, Solvent- 20% Ethyl acetate: Hexane)

TLC: 50% Ethyl acetate: Hexane

(ii) Synthesis of methyl 3-(4-bromophenyl)-2-(5-ethyl-2,4-dimethoxyphenyl)-1-methyl-1H-indole-5-carboxylate (3)

Dissolved4-bromophenyl)-2-(5-ethyl-2,4-dihydroxyphenyl)-1H-indole-5-carboxylicacid (**3**) (200 mg, 0.00044mol, 1eq) in DMF (10 ml) and K_2CO_3 (305mg, 0.0021 mol, 5eq) was added and cool the reaction mix down to 0^0C. Then CH_3I (0.137ml, 0.0021mol, 5eq) was added drop wise and stir for 30 min at RT. Then rise temperature up to RT and stir for 2 hrs. Reaction monitor by TLC. In work up procedure reaction mixture diluted with water (30 ml) and extracted by ethyl acetate (20x3ml). Combine ethyl acetate layer dried over sodium sulfate and concentrated under vacuum to get crude mass. Compound purifies by column chromatography .to get 190 mg of desire product as a light yellow solid. (Yield-85.20%)

(Silica-230-400 mess, Solvent- 10% Ethyl acetate: Hexane)

TLC: - 30% Ethyl acetate: Hexane

(iii) Synthesis of 3-(4-bromophenyl)-2-(5-ethyl-2,4-dihydroxyphenyl)-1H-indole-5-carboxamide (4)

Dissolved 4-bromophenyl)-2-(5-ethyl-2,4-dihydroxyphenyl)-1H-indole-5-carboxylic acid (**2**) (100mg, 0.00022mol, 1eq)was taken in DMF (5ml) in 2N RBF at RT. Then NH_4Cl (71mg, 0.00132mol, 6eq), Py-BOP (90mg, 0.000286, 1.3eq), HOBT (36mg, 0.00264mol, 1.2eq) and DIPEA (0.1ml, 0.00066mol, 3eq) was added at RT and stir the reaction mixture at RT for overnight. Reaction monitor by TLC. In work up procedure reaction mixture diluted with water (25 ml) and extracted by ethyl acetate (15x3 ml). Combine ethyl acetate layer dried over sodium sulfate and concentrated under vacuum to get crude mass. Compound purify by column chromatography to get 50 mg of desire product as off white solid. (Yield-50.50%)
(Silica-230-400 mess, Solvent- 20% Ethyl acetate: Hexane)
TLC: 50% Ethyl acetate: Hexane

Results and Discussion

A stepwise procedure for the synthesis of various indole derivatives. The intermediate **1** undergoes Fischer-indolization to give key intermediate **2.** The compound **2** undergo different reaction conditions *viz*. methylation, amidation, Suzuki coupling reaction and acid amine coupling reaction to get the final indole derivatives **3** and **4** respectively.

In the **scheme-1** the reaction of compound **2** with methyl iodide in presence of K_2CO_3 gave a compound **3** in the second reaction of compound **2** with NH_4Cl in presence of Py-BOP and HOBT in basic condition gave the compound **4**

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