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Synthesis and biological evaluation of indoles

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ABSTRACT

Indole ring system is the most important heterocycle in nature have an important structural importance in many pharmaceutical agents. Indole nucleus has antimicrobial activities. Objective of this research is to synthesize and characterization of indole derivaties. Different kind of indole ring derivaties were synthesized such as 3-((E)-2-nitrovinyl)-1H-indole ***16;*** *2-(1H-indol-3-yl)ethanamine* ***17;*** *N-(2-(1H-indol-3-yl)ethyl)benzamide* ***18;*** *methyl 2-(3-(2-(benzamido)ethyl)-1H-indol-1-yl)acetate* ***19;*** *Synyhesis of 2-(3-(2-(benzamido)ethyl)-1H-indol-1-yl)acetic acid* ***20;*** *N-(2-(1-((2,3-dihydro-1H-inden-5-yl carbamoyl) methyl)-1H-indol-3-yl)ethyl)benzamide* ***21.***

Keywords: Indole dertiviaties, Organic synthesis, Anti-microbial activity and structural elucidation.

INTRODUCTION

The indole ring system is probably the most important heterocycle in nature. Owing to the great structural diversity of biologically active indoles, [1-3] it is not surprising that the indole ring system has become an important structural component in many pharmaceutical agents. This is exemplified by the amino acid tryptophan, hormones serotonin and melatonin, the psychotropic drug LSD, the antitumour agent vinblastine [4]. Chai et al. synthesized some new ethyl 6-bromo-5-hydroxy-1*H*-indole-3-carboxylates and disclosed their favorable anti-HBV[5] activities. Indomethacin,[6] Etodolac [7] and Tenidap [8] are NSAIDs, and have been shown to exert anti-inflammatory effects. Tenidap is an inhibitor of prostaglandin interleukin-1 [9] production in the body used for the treatment of rheumatoid arthritis and osteoarthritis. It also inhibits both enzymes cyclooxygenase and 5-lipoxygenase, [10] which convert arachidonic acid into prostaglandin and leukotrienes [11] and exhibit superior activity compared to indomethacin. The major mechanism of action by which non steroidal anti-inflammatory drugs (NSAIDs) exhibit anti-inflammatory activity involves the inhibition of cyclooxygenase (COX) derived prostaglandin (PG) synthesis.[12,13] PGs in addition to being undesirable effectors of inflammatory reactions, also exerts important physiological functions such as gastrointestinal cytoprotection and vascular homeostasis.[14, 25] Chronic use of NSAIDs is associated with alterations in gastrointestinal integrity and function,[26] which results in the development of gastric ulcers and bleeding. Synthetic approaches based on NSAIDs have been taken with the aim of improving their profile where the action of NSAID is in lowering the prostaglandin production through inhibition of cyclooxygenase (COX). Recently a number of selective inhibitors of COX-2 were shown to possess anti-inflammatory activity with little or no gastric side effects. [17,18] Several alkyl-substituted propanoic acids of indomethacin were prepared by Black et al.[19] It was found that the alkyl, aryl, aralkyl and heterocyclic esters **(Figure 1)** and amides **(Figure 2),** which are modified from indomethacin, exhibit high potency and selectivity[20].

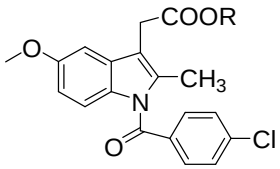


Figure-1

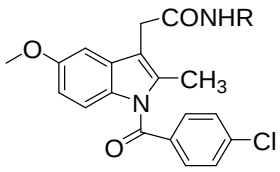
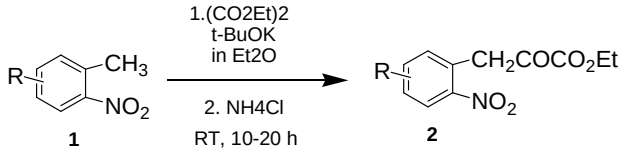


Figure-2

Chemistry and Literature Report:

The Reissert indole synthesis [27] has classically been known as a reliable synthetic method for the benzene-part substituted indole-2-carboxylates **3** from 2-nitro toluenes **1.** This reaction involves condensation of 2-nitro toluene **1** wiyh diethyl oxalate in the presence of base, followed by reduction of the resulting 2-nitrophenylpyruvate **2**. This Reissert indole synthesis is standardized in ‘’Organic synthesis” [28].



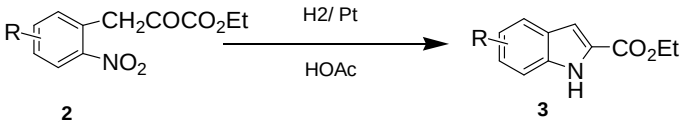


Figure-3: Reported synthetic routes-1

A large number of structural analogues of serotonin have been synthesized and their biological activities evaluated in recent years. In contribution of previous work [29] we report here the synthesis of various 2-(2-amino ethyl)-indoles and 2-(2-aminopropyl) indoles prepared for biological evaluation. While indole-3- carbaldehydes can be obtained in very high yields from corresponding indoles by the the method of smith, [30] indoles 2-carbaldehydes required as intermediates for the synthesis of the title compounds are not easily accessible. Indole -2-carbaldehyde was prepared in poor yield by Taylor [31] by the oxidation of 2-hydroxy methyl indole with potassium permanganate in acetone and by an improved method by Harley-Mason and Pavri [32] in which activated manganesedioxide was used to oxidize the alcohol. Dambal and Siddappa [33] reported the synthesis of some indole-2-carbaldehydes from 2-ethoxy carbonylindoles by the McFadyen and Stevens’s procedure. This method was now extended to the synthesis of other indoles-2-carbaldehydes. Ethyl 5-methoxy indole-2-carboxylate (4a) was converted almost quantitatively in to the carbohydrazide (5a); this was tosylated to obtain (6a) which upon reaction with anhydrous sodium carbonate in ethylene glycol yielded 5-methoxyindole-2-carbaldehyde (8a) (ca. 41%). Similarely, 5-methoxy-3-methyl indole-2-carbaldehydes (8b), 7-methoxy-3-methyl indole-2-carbaldehydes (8d), 5-methoxy indole-2-carbaldehydes (8f, and 3-methyl 5-ethoxyindole-2-carbaldehyde (5g) were prepared from the appropriate indole-2-carboxylates (4a, b, d, f and g). The aldehydes contained impurities which were removed by repeated chromatographic separation on alumina. Since the purification of the aldehydes obtained by this method was lengthy, we prepared the aldehydes by Harley- Mason’s procedure to compare the two routes. The appropriate indole-2-carboxylic ester (4) was reduced with lithium aluminium hydride to give the indole-2-methanol (7) which an oxidation with activated manganese dioxide yielded the indole-2-carbaldehyde (8).

The various aldehydes (8a-h) are described in Table-4. The indole-2-carbaldehydes condensed readily with nitro methane to give 2-(2-nitro vinyl) indoles (9a-d and f-h) in 70- 75% yields and on reduction with lithium aluminium hydride gave the required 2-(2-amino ethyl) indoles (10a-d and f-h) in 60-65% yields. Similarly, condensation of the aldehydes (10a, b, f, and g) with nitro methane gave 2-(2-nitropropenyl) indoles in 70- 75% yields and on subsequent reduction with lithium aluminium hydride gave the required 2-(2-amino propyl) indoles (12a, b, f and g) in 65 -70% yields.

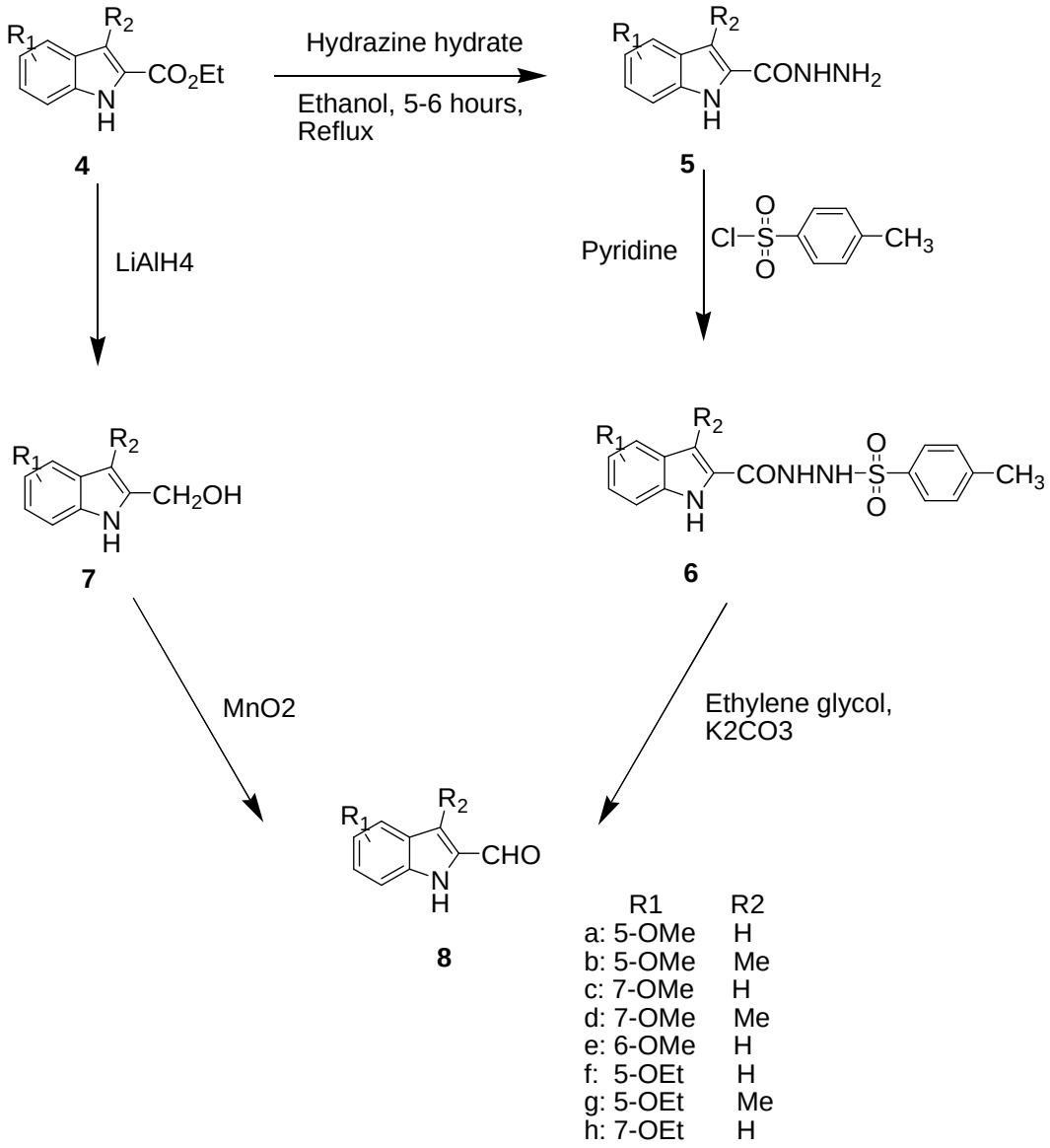


Figure-4: Reported synthetic routes-2

Preparation of Compound **4:**
The following substituted ethyl indole-2-carboxylates were prepared by literature methods, Viz., 5-methoxy-(4a),[34], 5-methoxy-3-methyl-(4b),[35], 7-methoxy- (4c),[35], 7-methoxy-3-methyl-(4d),[35], 6-methoxy-(4e),[36], 5-ethoxy-(4f),[34], and 5-ethoxy-3-methyl-(4g),[37]. Ethyl 7-ethoxy indole-2-nitrotoluene by Reissert method as described for (4a), [35].

Preparation of Compound **5:**
To ethyl 5-methoxyindole-2-carboxylate (5 g) dissolved in absolute Ethanol (50 mL) was added hydrazine hydrate (100%, 10 mL).

The reaction mixture was then heated under reflux for 5-6 hours. The colourless crystalline hydrazide that separated from the cool solution was filtered off washed with Ethanol, and crystallized from absolute ethanol. The various indole-2-carbohydrazides similarly prepared.

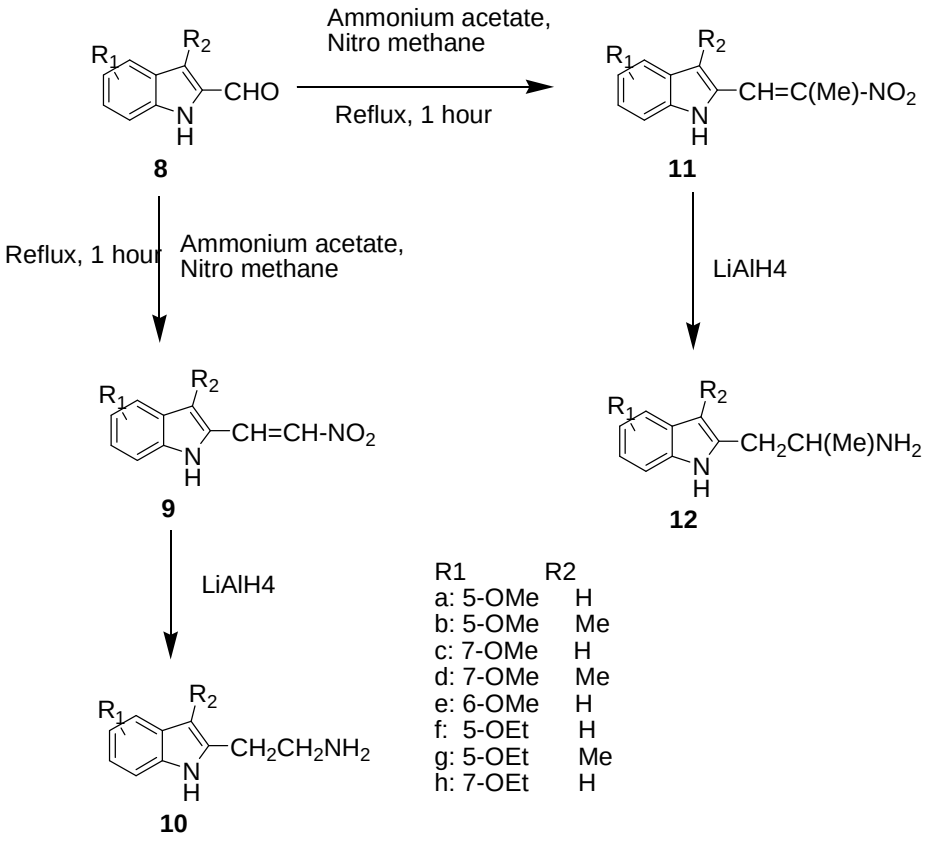


Figure-5: Reported synthetic routes-3

Preparation of Compound **6:**
Toluene-p-sulfonyl chloride (2.4 g) wsa added in small portions with constant shaking to an ice-cold solution of 5-methoxyindole-2-carbohydrazide (2.5 g), dissolved in freshly distilled pyridine (40 mL). The reaction mixture was set aside in an ice-bath for 1 hour, and then for 1 hour at room temperature. It was then then poured on crushed ice containing Conc.Hydrochloric acid (35 mL). The solid that separated was filtered off, washed with diluted hydrochloric acid and water, and crystallized from ethanol or dioxane. The 2-Toluene-p- sulphonhydrazidocarbonyl indoles were synthesized**.**

Preparation of Compound **7:**
A solution of the appropriate ethyl indole-2-carboxylate to (5 g) in dry ether (80 mL) was added drop wise to a stirred suspension of lithium aluminium hydride (1.5 g) in dry ether (50 ml). After complete addition it was stirred for a further hour. Excess of $LiAlH_4$ was decomposed by addition of water (1.5 mL), Sodium hydroxide solution (1.5 ml, 15%) and finally water (1.5 ml). The white precipitate was filtered off and washed several times with a little ether; the combined filtrates were washed with water. Taken organic layer and dried with anhydrous Na_2SO_4 filtered and evoparated to dryness; the residue was crystallized from the appropriate solvent. The 2-hydroxy methylindoles were synthesized and reported.

Preparation of Compound **8: Method A:**
5- Methoxy-2-Toluene-p- sulphonhydrazidocarbonylindole (2.5 g) in Ethylene glycol (25 mL) was heated to 160°C in an oil bath and at the boiling solution anhydrous potassium carbonate (2.5 g) was added. After 5 min at this temperature the reaction mixture was poured on crushed ice (500 g) and then set aside for 1 hr. The solid that separated was filtered off, dried and chromatographed repeatedely on a neutral alumina column with benzene as eluant.

Preparation of Compound **8: Method B:**
The 2-Hydroxymethyl indole (4 g) was dissolved in dichloromethane (250 mL). Activated manganese dioxide (10 g) was then added and the reaction mixture was stirred at room temperature for 20-30 hours. The reaction was followed by TLC, the end point being marked by the disappearance of the spot due to the 2-hydroxymethylindole. When ever necessary, fresh quantity of manganese dioxide (2-3 g) was added. The reaction mixture was filtered and the residual manganese dioxide was washed repeatedely with a little fresh dichloromethane. The combined filtrate was

evoparated to dryness to give the crude indole-2-carbaldehyde as a pale yellow solid; this was crystallized. The indole-2-carbaldehydes were synthesized and characterized.

Preparation of Compound **9:**
The Indole-2-carbaldehyde (5 g), nitromethane (8 ml), and ammonium acetate (1 g). The reaction mixture was heated under reflux for 30 minutes. The reaction mixture was cooled and the dark red crystals that separated were collected, washed thoroughly with water, dried and crystallized from ethanol. The nitro vinylindoles were prepared.
Preparation of Compound **10:**

A solution of the nitro vinyl indole (1 g) in tetrahydrofuran (25 ml) was added drop wise to stirred slurry of $LiAlH_4$ (1.5 g) in dry ether (100 ml). The reaction mixture was gently heated under reflux for 10 hours.

Excess of $LiAlH_4$ was decomposed by addition of water (1.5 mL), Sodium hydroxide solution (1.5 ml, 15%) and finally water (1.5 ml). The white precipitate was filtered off and washed several times with a little ether; the combined filtrates were washed with water. Taken organic layer and dried with anhydrous Na_2SO_4 filtered and evoparated to dryness; the residue was crystallized from the appropriate solvent. The aminoethylindoles were prepared.

Preparation of Compound **11:**
The Indole-2-carbaldehyde (1 g), nitroethane (0.5 ml), was added four drops of benzylamine). The reaction mixture was heated under reflux for 1hour. The reaction mixture was cooled and the dark red crystals that separated were collected, washed thoroughly with water, dried and crystallized from ethanol. The nitropropenylindoles were prepared.

Preparation of Compound **12:**
A solution of the 2-(2-Nitropropenyl) indole (1 g) in tetrahydrofuran (25 ml) was added drop wise to stirred slurry of $LiAlH_4$ (1.5 g) in dry ether (100 ml). The reaction mixture was gently heated under reflux for 10 hours. Excess of $LiAlH_4$ was decomposed by addition of water (1.5 mL), Sodium hydroxide solution (1.5 ml, 15%) and finally water (1.5 ml). The white precipitate was filtered off and washed several times with a little ether; the combined filtrates were washed with water. Taken organic layer and dried with anhydrous Na_2SO_4 filtered and evoparated to dryness; the residue was crystallized from the appropriate solvent. The aminopropylindoles were prepared.

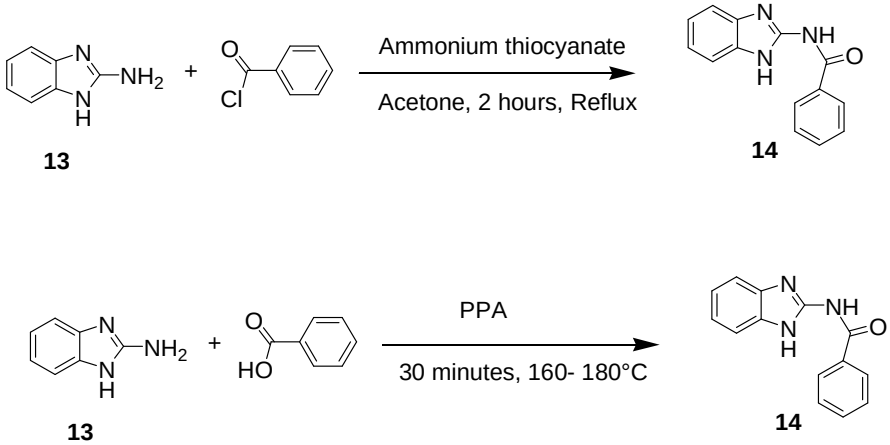


Figure-6: Reported synthetic routes-4

Preparation of Compound **14:** Method A:
To a solution of compound **13** (0.2 g) in acetone, was added Benzoyl chloride (0.15 g) and Ammonium thio cyanate (0.1 g). The reaction mixture was refluxed for 2 hours, cooled to the room temperature and distilled out under vacuum to get crude; the crude was diluated with Ethyl acetate (100 ml) and saturated $NaHCO_3$ soution (20 ml) separate the layers, taken organic layer and dried with anhydrous Na_2SO_4, filtered and evoparated to get Compound **14** (0.15 g) [38, 39].

Objective:
The indole nucleus has antimicrobial activities and useful chemical moiety. New indoles have been synthesized and investigated for medical applications. As resistance to antimicrobial drugs is wide spread, numerous attempts have been made to develop new structural proto types to search for more effective antimicrobials. Our objective is to synthesize and characterization of indole derivaties. Following chemical molecules are synthesized and characterized.

1. Synyhesis of 3-((E)-2-nitrovinyl)-1H-indole **16:**
2. Synyhesis of 2-(1H-indol-3-yl)ethanamine **17:**
3. Synyhesis of N-(2-(1H-indol-3-yl)ethyl)benzamide **18:**
4. Synyhesis of methyl 2-(3-(2-(benzamido)ethyl)-1H-indol-1-yl)acetate **19:**
5. Synyhesis of 2-(3-(2-(benzamido)ethyl)-1H-indol-1-yl)acetic acid **20:**
6. Synyhesis of N-(2-(1-((2,3-dihydro-1H-inden-5-yl carbamoyl) methyl)-1H-indol-3-yl)ethyl)benzamide **21:**

MATERIALS AND METHODS

1. Synyhesis of 3-((E)-2-nitrovinyl)-1H-indole 16:

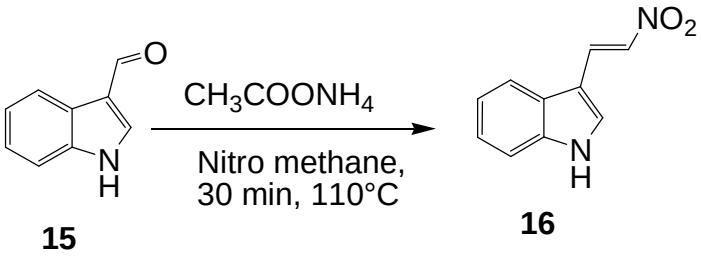


Figure-7: Reported synthesis

To a solution of 1H-indole-3-carbaldehyde **15** (5.0 g, 34.48 mmoles) in nitromethane (20 mL), was added ammonium acetate (5.31 g, 68.96 mmoles) The reaction mixture was stirred at 110°C for 30 minutes under nitrogen atmosphere; the reaction mixture was monitored by TLC, after complection of reaction the reaction mixture was cooled to the room temperature and diluated with ethyl acetate (200 mL) and water (100 mL) separate the layers, taken aqueous layer and extracted with ethyl acetate (100 mL). Taken total organic layer and dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum to get crude product (8.5 g).

Purification:
The crude product was purified by silica gel (100-200 mesh) column chromatography. The product was eluated with 10% Ethyl acetate in Hexane, collected fractions and concentrated under vacuum to give 3-((E)-2-nitrovinyl)-1H-indole **16** as a yellow solid.

2. Synyhesis of 2-(1H-indol-3-yl) ethanamine 17:

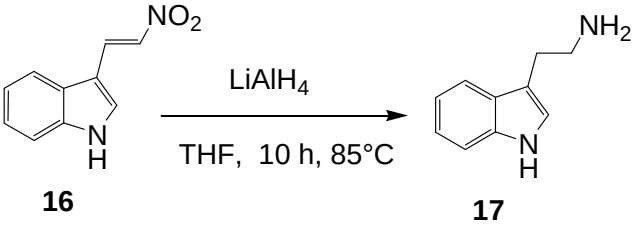
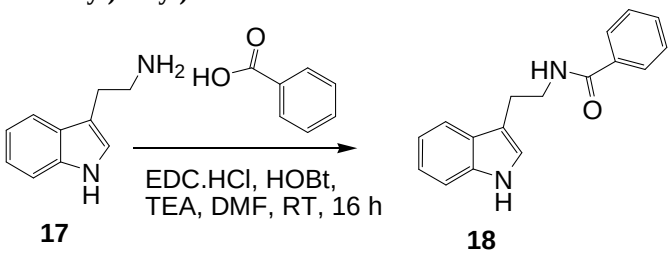


Figure-8: Reported synthesis

To a solution of 3-((E)-2-nitrovinyl)-1H-indole **16** (3.0 g, 15.87 mmoles) in THF (50 mL), was added $LiAlH_4$ (3.01 g, 79.365 mmoles) The reaction mixture was stirred at 85°C for 10 hours under nitrogen atmosphere; the reaction mixture was monitored by TLC, after complection of reaction the reaction mixture was cooled to the room temperature. Excess of $LiAlH_4$ was decomposed by addition of water (3.1 mL), Sodium hydroxide solution (3.1 ml, 15%) and finally water (3.1 ml). The white precipitate was filtered off and washed several times with a little Ethyl acetate (200 ml); the combined filtrates were washed with water. Taken organic layer and dried with anhydrous Na_2SO_4 filtered and evoparated under vacuum to get crude product (4.1 g).

Purification:
The crude product was purified by silica gel (100-200 mesh) column chromatography. The product was eluated with 70% Ethyl acetate in Hexane, collected fractions and concentrated under vacuum to give 2-(1H-indol-3-yl) ethanamine **17** as a colourless liquid.

3. Synyhesis of N-(2-(1H-indol-3-yl) ethyl) benzamide 18:



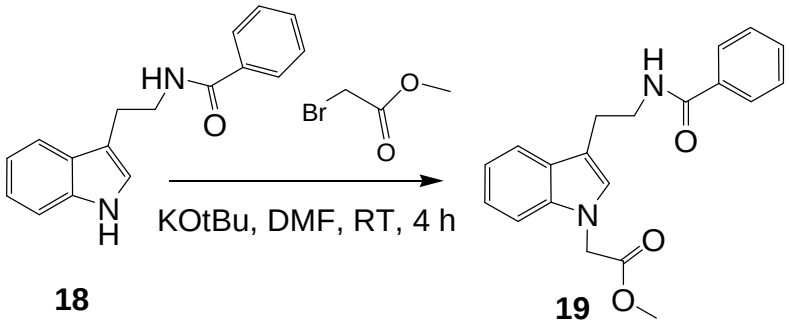
17 **18**

Figure-9: Reported synthesis

To a solution of 2-(1H-indol-3-yl) ethanamine **17** (3.0 g, 18.75 mmoles) in Dimethyl formamide (30 mL), was added Benzoic acid (2.74 g, 22.5 mmoles), EDC.HCl (4.92 g, 28.125 mmoles), HOBt (3.79 g, 28.125 mmoles) and Triethyl amine (7.846 mL, 56.336 mmoles), the reaction mixture was stirred at room temperature for 16 hours, the reaction mixture was monitored by TLC, after complection of reaction the reaction mixture was diluated with Ethyl acetate (300 mL) and water (100 mL) separate the layers, taken organic layer and washed with Water (50 mL). Taken organic layer and dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum to get crude product (4.2 g).

Purification:
The crude product was purified by silica gel (100-200 mesh) column chromatography. The product was eluated with 50% Ethyl acetate in Hexane, collected fractions and concentrated under vacuum to give N-(2-(1H-indol-3-yl)ethyl) benzamide **18** as a white solid.

4. Synyhesis of methyl 2-(3-(2-(benzamido) ethyl)-1H-indol-1-yl) acetate 19:



18 **19**

Figure-10: Reported synthesis

To a solution of N-(2-(1H-indol-3-yl) ethyl) benzamide **18** (2.5 g, 9.469 mmoles) in Dimethyl formamide (30 mL), was added methyl 2-bromoacetate (2.17 g, 14.204 mmoles) and Potassium tertiary butoxide (3.18 g, 28.459 mmoles). The reaction mixture was stirred at room temperature for 4 hours under nitrogen atmosphere; the reaction mixture was monitored by TLC, after complection of reaction the reaction mixture was diluated with Ethyl acetate (300 mL) and water (100 mL) separate the layers, taken organic layer and washed with Water (50 mL). Taken organic layer and dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum to get crude product (3.5 g).

Purification:
The crude product was purified by silica gel (100-200 mesh) column chromatography. The product was eluated with 30% Ethyl acetate in Hexane, collected fractions and concentrated under vacuum to give methyl 2-(3-(2-(benzamido) ethyl)-1H-indol-1-yl) acetate **19** as a colourless liquid.

5. Synyhesis of 2-(3-(2-(benzamido) ethyl)-1H-indol-1-yl) acetic acid 20:
To a solution of methyl 2-(3-(2-(benzamido) ethyl)-1H-indol-1-yl) acetate **19** (1.5 g, 4.464 mmoles) in THF (10 mL), Methanol (10 mL) and Water (10 mL) was added LiOH (0.321 g, 13.329 mmoles). The reaction mixture was stirred at room temperature for 4 hours under nitrogen atmosphere; the reaction mixture was monitored by TLC, after complection of reaction the reaction mixture was dictilled out under vacuum and diluated with water (30 mL) cooled to the 0°C and slowly pH adjusted 3.0-3.5 with 2 N HCl (5 mL), white precipitate formed, filtered and dried under vacuum to give 2-(3-(2-(benzamido) ethyl)-1H-indol-1-yl) acetic acid **20** as a white solid.

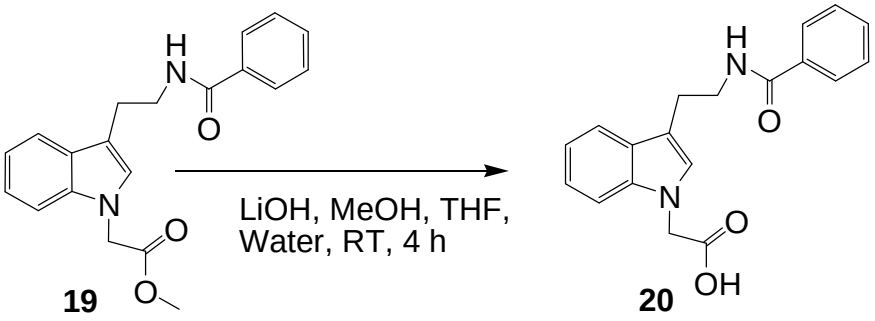


Figure-11: Reported synthesis

6. Synyhesis of N-(2-(1-((2,3-dihydro-1H-inden-5-yl carbamoyl) methyl)-1H-indol-3-yl) ethyl)benzamide 21a:

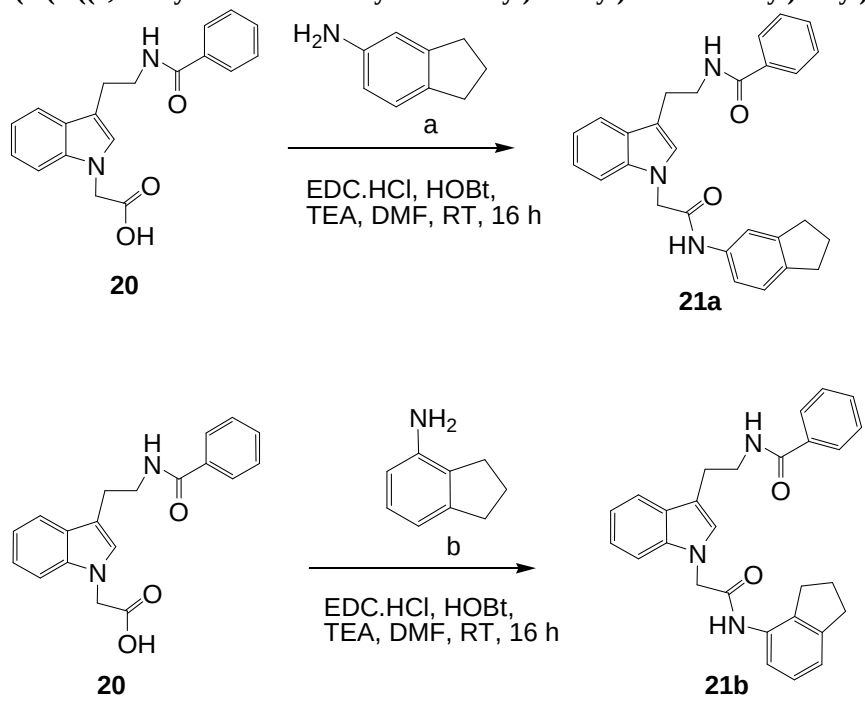


Figure-12: Reported synthesis

To a solution of 2-(3-(2-(benzamido) ethyl)-1H-indol-1-yl) acetic acid **20** (0.3 g, 0.936 mmoles) in Dimethyl formamide (6 mL), was added 2,3-dihydro-1H-inden-5-amine (0.14 g, 1.118 mmoles), EDC.HCl (0.244 g, 1.397 mmoles), HOBt (0.188 g, 1.397 mmoles) and Triethyl amine (0.389 mL, 2.786 mmoles), the reaction mixture was stirred at room temperature for 16 hours, the reaction mixture was monitored by TLC, after complection of reaction the reaction mixture was diluated with Ethyl acetate (100 mL) and water (50 mL) separate the layers, taken organic layer and washed with Water (20 mL). Taken organic layer and dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum to get crude product (0.5 g).

Purification:
The crude product was purified by silica gel (100-200 mesh) column chromatography. The product was eluated with 100% Ethyl acetate, collected fractions and concentrated under vacuum to give N-(2-(1-((2,3-dihydro-1H-inden-5-yl carbamoyl) methyl)-1H-indol-3-yl) ethyl)benzamide **21a** as a brown solid.

6.1 Synyhesis of N-(2-(1-((2,3-dihydro-1H-inden-4-ylcarbamoyl)methyl)-1H-indol-3-yl)ethyl)benzamide 21b:
To a solution of 2-(3-(2-(benzamido) ethyl)-1H-indol-1-yl) acetic acid **20** (0.3 g, 0.936 mmoles) in Dimethyl formamide (6 mL), was added 2,3-dihydro-1H-inden-4-amine (0.14 g, 1.118 mmoles), EDC.HCl (0.244 g, 1.397 mmoles), HOBt (0.188 g, 1.397 mmoles) and Triethyl amine (0.389 mL, 2.786 mmoles), the reaction mixture was stirred at room temperature for 16 hours, the reaction mixture was monitored by TLC, after complection of reaction the reaction mixture was diluated with Ethyl acetate (100 mL) and water (50 mL) separate the layers, taken organic layer and washed with Water (20 mL). Taken organic layer and dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum to get crude product (0.45 g).

Purification:
The crude product was purified by silica gel (100-200 mesh) column chromatography. The product was eluated with 100% Ethyl acetate, collected fractions and concentrated under vacuum to give N-(2-(1-((2,3-dihydro-1H-inden-4-ylcarbamoyl)methyl)-1H-indol-3-yl)ethyl)benzamide **21b** as a brown solid.

RESULTS AND DISCUSSION

All synthesized chemical molecules were produced with best yields. Chemical structures were evaluated with LC-MS, 1H NMR, Mass and FT-IR spectrophotmetries. The results are tabulated in below table-1.

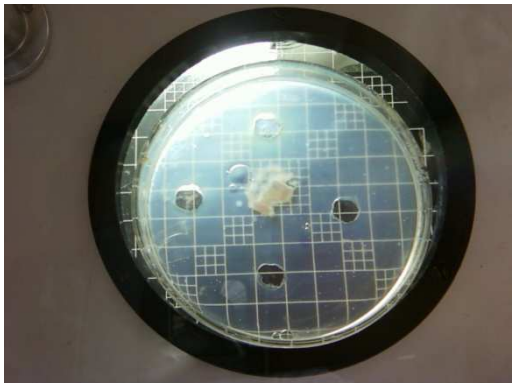
Table-1: Chemical molecules 16 to 21 results.

Compound	Synthetic Results	
3-((E)-2-nitrovinyl)-1H-indole **16**	**Yield**	3.1 gm, (47.69 %)
	LC-MS purity	93.72%
	^{1}H NMR ($CDCl_3$/TMS)	δ 7.1-7.2 (s, 1H), 7.20-7.3 (m, 1H), 7.3-7.45 (m, 2H), 7.5-7.6 (d, 1H), 7.6-7.7 (d, 1H), 8.10-8.15 (d, 1H), 8.2-8.4 (broad, 1H).
	Mass (m/z)	187.05 (M-H).
2-(1H-indol-3-yl)ethanamine **17**	**Yield**	2.0 gm, (78.0 %)
	LC-MS purity	68.54%
	Mass (m/z)	161.13 (M+H).
N-(2-(1H-indol-3-yl)ethyl)benzamide **18**	**Yield**	3.0 gm, (60.60%)
	LCMS purity	90.04%
	^{1}H NMR (DMSO-d6/TMS)	δ 2.95-3.1 (m, 2H), 3.6-3.65 (m, 2H), 6.2-6.22 (s, 1H), 6.9-7.10 (m, 2H), 7.22-7.31 (m, 1H), 7.4-7.6 (m, 4H), 7.8-7.85 (m, 2H), 8.6-8.65 (s, 1H), 10.95-11.0 (s, 1H).
	Mass (m/z)	263.23 (M-H).
methyl 2-(3-(2-(benzamido)ethyl)-1H-indol-1-yl)acetate **19**	**Yield**	2.0 gm, (62.99%)
	LCMS purity	64.50%
	^{1}H NMR (DMSO-d6/TMS)	δ 2.95-3.1 (m, 2H), 3.6-3.65 (m, 2H), 3.65-3.70 (s, 3H), 5.1-5.20 (s, 2H), 6.3-6.4 (s, 1H), 6.9-7.10 (m, 2H), 7.3-7.4 (d, 1H), 7.4-7.6 (m, 4H), 7.8-7.9 (m, 2H), 8.6-8.7 (s, 1H).
	Mass (m/z)	337.17 (M+H).
2-(3-(2-(benzamido)ethyl)-1H-indol-1-yl)acetic acid **20**	**Yield**	1.0 gm, (68.89%)
	LCMS purity	86.66%
	^{1}H NMR (DMSO-d6/TMS)	δ 2.95-3.1 (m, 2H), 3.6-3.65 (m, 2H), 5.0-5.1 (s, 2H), 6.3-6.4 (s, 1H), 6.95-7.10 (m, 2H), 7.3-7.4 (d, 1H), 7.4-7.6 (m, 4H), 7.8-7.9 (m, 2H), 8.6-8.7 (s, 1H), 12.9-13.2 (broad, 1H).
	MASS (m/z)	323.07 (M+H).
N-(2-(1-((2,3-dihydro-1H-inden-5-yl carbamoyl) methyl)-1H-indol-3-yl) ethyl)benzamide **21a**	**Yield**	0.25 gm, (61.16%)
	LCMS purity	95.56%
	IR (In KBr)	3293, 3269, 3199, 3137, 3083, 3054, 2950, 2917, 2847, 1677, 1633, 1616, 1604, 1577, 1547, 1492, 1463, 1438, 1425, 1414, 1379, 1360, 1323, 1290, 1268, 11190, 1167, 1134, 1108, 1076, 1050, 1021, 1001, 954, 925, 896, 869, 847, 820, 802, 778, 740, 709, 689, 672 cm^{-1}
	^{1}H NMR (DMSO-d6/TMS)	δ 2.0-2.1 (m, 2H), 2.7-2.8 (m, 4H), 3.0-3.1 (m, 2H), 3.6-3.7 (m, 2H), 5.0-5.1 (s, 2H), 6.3-6.4 (s, 1H), 6.95-7.10 (m, 3H), 7.3-7.4 (m, 1H), 7.4-7.6 (m, 5H), 7.8-7.82 (m, 2H), 8.6-8.7 (broad, 1H), 10.3-10.4 (s, 1H).
	Mass (m/z)	438.53 (M+H).
N-(2-(1-((2,3-dihydro-1H-inden-4-ylcarbamoyl)methyl)-1H-indol-3-yl)ethyl)benzamide **21b**	**Yield**	0.25 gm, (61.16%)
	LCMS purity	95.56%
	IR (In KBr)	3293, 3269, 3199, 3137, 3083, 3054, 2950, 2917, 2847, 1677, 1633, 1616, 1604, 1577, 1547, 1492, 1463, 1438, 1425, 1414, 1379, 1360, 1323, 1290, 1268, 11190, 1167, 1134, 1108, 1076, 1050, 1021, 1001, 954, 925, 896, 869, 847, 820, 802, 778, 740, 709, 689, 672 cm^{-1}
	^{1}H NMR (DMSO-d6/TMS)	δ 2.0-2.1 (m, 2H), 2.7-2.8 (m, 4H), 3.0-3.1 (m, 2H), 3.6-3.7 (m, 2H), 5.0-5.1 (s, 2H), 6.3-6.4 (s, 1H), 6.95-7.10 (m, 3H), 7.3-7.4 (m, 1H), 7.4-7.6 (m, 5H), 7.8-7.82 (m, 2H), 8.6-8.7 (broad, 1H), 10.3-10.4 (s, 1H).
	Mass (m/z)	438.53 (M+H).

Table–2: Antifungal activity by disc diffusion method for N-(2-(1-((2,3-dihydro-1H-inden-5-yl carbamoyl) methyl)-1H-indol-3-yl)ethyl)benzamide 21a and 21b

S.No	Compd	Zone of inhibition (mm)		
		Aspergillus Niger		
		50µg	100µg	150µg
1	21a	NS	3mm	5mm
2	21b	NS	3mm	6mm

Zone of inhibition for standard samples *Aspergillus Niger (08mm);* ***Abbreviation:*** *NS= Not significant.*



21a and 21b Aspergillus
Figure-13: Microbial activity results

CONCLUSION

Indole derivaties were synthesized and investigated for medical applications. Following chemical molecules are synthesized and characterized.

i. Synyhesis of 3-((E)-2-nitrovinyl)-1H-indole **16:**
ii. Synyhesis of 2-(1H-indol-3-yl)ethanamine **17:**
iii. Synyhesis of N-(2-(1H-indol-3-yl)ethyl)benzamide **18:**
iv. Synyhesis of methyl 2-(3-(2-(benzamido)ethyl)-1H-indol-1-yl)acetate **19:**
v. Synyhesis of 2-(3-(2-(benzamido)ethyl)-1H-indol-1-yl)acetic acid **20:**
vi. Synyhesis of N-(2-(1-((2,3-dihydro-1H-inden-5-yl carbamoyl) methyl)-1H-indol-3-yl)ethyl)benzamide **21:**

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