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Synthesis Of Indole Novel Derivatives And Their Importance In Medicine

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Abstract:

The indoles occurring naturally and synthetic have a diverse range of biological activities. Among their natural derivatives, unusual and complicated molecular structures are found. The international chemical community continues to pay attention to this significant ring system as a result, and novel approaches to creating this heteroaromatic ring, which is constantly relevant, are currently being researched. This paper introduce novel derivative of indole. The synthesis pathway are scalable and obtained high yield and purity.

Keywords: Indole, Heterocyclic, Indole, Synthesis, Biological activity, Anti-inflammatory.

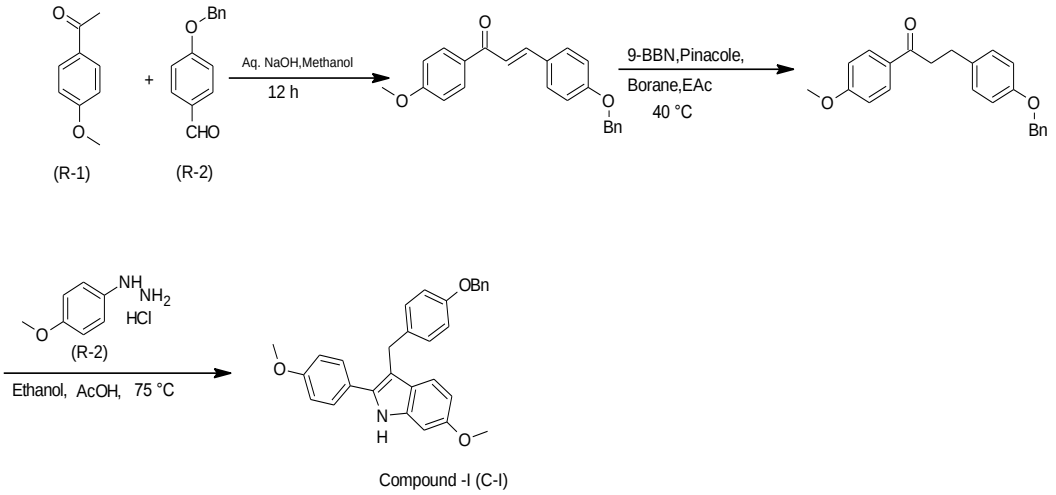
INTRODUCTION:

One of the most prevalent and significant heterocycles in nature is the indole ring system. The significance of indoles to biological chemistry cannot be overstated as they are present in a hugely diverse range of biologically significant natural compounds, from simple derivatives like the neurotransmitter serotonin to complex alkaloids like the clinically used anticancer drugs vinblastine and mitomycin C, and the Lurbinectedin for lung cancer. In addition, a number of significant synthetic pharmaceuticals with combined sales of $ 10 billion in 2022 include Almotriptan, Sumatriptan, Binedaline, Tadalafil, Rizatriptan, Fluvastatin, Carvedilol and Ondansetron etc. According to their significance, organic synthesis's main focus over the past century has been the continuing development of routes to indoles [1]. However, there are still restrictions on the readily accessible chemical space; this is clearly shown by contrasting naturally occurring indole medicines with their synthesized equivalents. Particularly, the pattern of substitution around the six-membered ring is noticeably less complex in synthetic indoles than in those that are produced naturally [2]. No synthetic indoles with substituents at more than one benzenoid ring position are currently being used in therapeutic settings, as far as we are aware. We relate this observation to their relative synthetic intractability rather than any alleged pharmacological drawbacks of substantially substituted indoles. Because of this, indole synthesis is still an area that needs development. [3-4]
In continuation of nitrogen containing heterocyclic compound development we have developed a new synthesis procedure of indole derivatives.

SUBJECTS AND METHODS

We report herein industrially scalable, efficient synthesis of novel derivative of indole by using safe reagents and experimental conditions.
All the key raw materials used for synthesis were obtained from, Sigma Aldrich and was used without further purification. All other solvents and reagents were used analytical or HPLC grade. Melting points were calculated by Spectra Lab device. Using a Shimadzu 8300 IR Spirit Fourier transform infrared spectrometer, infrared (KBr) spectra were examined. In DMSO and $CDCl_3$ solutions, ^1H and ^{13}C NMR were captured on Bruker spectra at 400 and 100 MHz, respectively. On a Waters TQD device with an ionisation potential of 110 V, ESI mass spectra were captured. Using a Thermofisher-chromeon 7, 2, HPLC analysis was carried out. On 0.25 mm silica gel plates, thin layer chromatography (TLC) experiments were carried out (60F254, Merck). UV light at a wavelength of 254 nm was used for visualisation.

Route of synthesis:



Synthesis of (2E)-3-[4-(benzyloxy) phenyl]-1-(4-methoxyphenyl)prop-2-en-1-one.
To the solution of compound 1-(4-methoxyphenyl) ethanone (0.1 meq) and 4-(benzyloxy) benzaldehyde (0.011 eq) in methanol, aqueous sodium hydroxide was added at 5-10°C. Reaction mixture was heated 35-40°C and stirred for 12.0 hrs. The reaction progress was monitored by TLC and after 2.0 hr stirring starting material was consumed completely. After reaction completion the reaction mass was cooled to 10 -15°C.and stir for 2-3 hrs at 10 -15°C. Solid suspension was observed then filtered the reaction mass and wash with methanol 50 ml. the compound was dried at 40-45°C. Yield (65.0%)

HPLC Purity 99.7%, MS (ES+) m/z 345.2 [M+1].
H NMR (400 MHz, DMSO-d6) : δ 3.85 (3H, s), 5.27 (2H, s), 6.67 (1H, d), 7.00-7.26 (6H, d), 7.15 -7.18 (2H, d), 7.20-7.23 (2H, d), 7.29 -7.3 1H, t), 7.7.41-7.44 (2H, d), 7.46-7.47 (2H. d), 7.51 (1H, d), 7.88-7.93(2H, d);.
^{13}C NMR (100 MHz, DMSO-*d*6): 56.0 (1C, s), 70.2 (1C, s), 114.3-114.3 (4C, 114.3 (s), 114.3 (s)), 121.2 (1C, s), 127.7-127.8 (3C, 127.7 (s), 127.8 (s)), 128.4 (2C, s), 128.7 (2C, s), 130.3 (1C, s), 130.7 (2C, s), 135.5 (1C, s), 136.5 (1C, s), 144.1 (1C, s), 158.5 (1C, s), 159.8 (1C, s), 188.9 (1C, s).

Synthesis of 3-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)propan-1-one
To the solution of (2E)-3-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)prop-2-en-1-one in ethyl acetate pinnacle was added followed by boron solution dropwise added at RT.reaction mass was heated to 40°C and stirred for 12.0 hrs The reaction progress was monitored by TLC and after 12.0 hr stirring starting material was consumed completely. After reaction completion the reaction mass was cooled to 20 -30°C.and filter through filter cloth solid suspension was observed then filtered. The filtrate was concentrated and added methanol. The solid suspension was observed. the reaction mass filter and wash with methanol 50 ml to get the solid compound and dried at 40-45°C. Yield (68.0%)

HPLC Purity 98.0%, MS (ES+) m/z 347.1 [M+1].

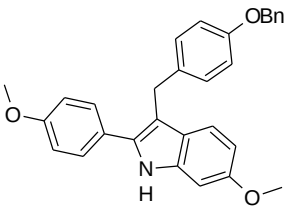
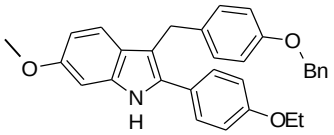
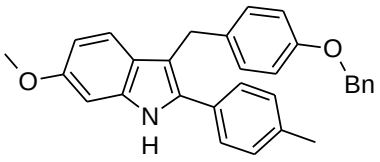
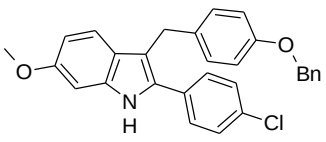
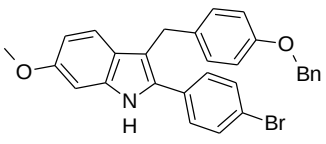
H NMR (400 MHz, DMSO-d6) : δ 2.42-2.44 (2H, t), 2.84-2.88 (2H, t), 3.80 (3H, s), 5.11-5.15 (2H, s), 7.00 (2H, d), 7.05 -7.08 (2H, d), 7.10-7.13 (2H, d), 7.29 -7.3 (1H, t), 7.4-7.42 (2H, d), 7.46-7.47 (2H. d), 7.90-7.97(2H, d);.

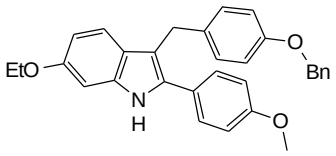
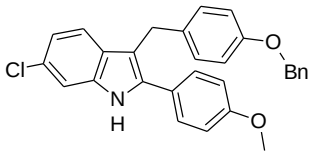
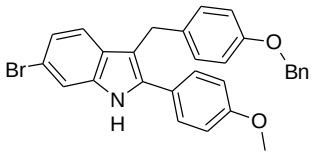
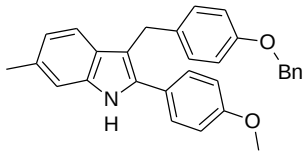
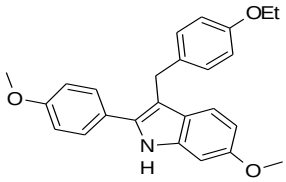
^{13}C NMR (100 MHz, DMSO-*d*6): 30.0 (1C, s), 45.3 (1C, s), 56.0 (1C, s), 70.2 (1C, s), 114.3 (4C, s), 127.8 (3C, s), 128.4 (2C, s), 130.0 (2C, s), 130.7 (2C, s), 135.2 (1C, s), 136.5 (1C, s), 140.6 (1C, s), 158.5 (1C, s), 159.8 (1C, s), 199.0 (1C, s).

Synthesis of 3-(4-(benzyloxy) benzyl)-6-methoxy-2-(4-methoxyphenyl)-1H-indole.
To the solution of (3-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)propan-1-one in acetic acid, (4-thoxyphenyl)hydrazine hydrochloride was added. Reaction mass was heated to 90°C and stirred for 6.0 hrs The reaction progress was monitored by TLC and after 6.0 hr stirring starting material was consumed completely. After reaction completion the compound was extracted from reaction by toluene. Then stirred 2 hrs at 20 -30°C.and filter through filter cloth solid suspension was observed then filtered. The solid suspension was observed. Reaction mass was filtered and washed with toluene to get the solid compound and dried at 50-55°C. Yield (85.0%)

HPLC Purity 99.3%, MS (ES+) m/z 347.1 [M+1].
^{1}H NMR: δ 3.71 (2H, s), 3.77 (3H, s), 3.78 (3H, s), 5.11 (2H, s), 6.25 (1H, d), 6.95-7.24 (5H, m), 7.27-7.52 (7H, m), 7.74 (2H, m), 8.09 (1H, m).
^{13}C NMR: δ 32.2 (1C, s), 56.0 (2C, s), 70.2 (1C, s), 94.8 (1C, s), 109.7 (1C, s), 114.3 (5C, s), , 120.2 (1C, s), 127.2 (1C, s), 127.7(3C, s), 128.4 (2C, s), 129.0 (2C, s), 129.5 (1C, s), 130.0 (2C, s), 135.7 (1C, s), 136.1 (1C, s), 136.5 (1C, s), 138.3 (1C, s), 158.1 (1C, s), 158.5 (1C, s), 159.8 (1C, s).
FT-IR (υ cm^{-1}): 3050, 1600, 1300, 1240,

Series of compound were synthesised using this method:

C.No	Reagent-1 (R-1)	Reagent-2 (R-2)	Reagent-3 (R-3)	Isolated Product (IP)
C-I	R-1	R-2	R-3	
C-II	R-OEt	R-2	R-3	
C-III	R-CH_3	R-2	R-3	
C-IV	R-Cl	R-2	R-3	
C-V	R-Br	R-2	R-3	

C-VI	R-1	R-2	R-OEt	
C-VII	R-1	R-2	R-Cl	
C-VIII	R-1	R-2	R-Br	
C-IX	R-1	R-2	R-CH_3	
C-X	R-1	R-OEt	R-3	

DETERMINATION OF THE COMPOUND'S ANTIBACTERIAL ACTIVITY (C-I):

The antibacterial activity of compound C-I was evaluated using disc diffusion.

Compound C-I was dissolved in water and diluted to the desired quantities (25, 50, 75, and 100 g/ml). Tetracyclin was a widely used antibacterial agent. A loopful of the strains was inoculated in the nutrient broth (30 ml) and cultured for 6 hours to maintain McFarland standard turbidity (106 cells/ml). Following that, 1 ml of bacterial strain inoculum was injected into molten Muller Hinton agar and dispersed uniformly into petri plates. Each test sample (40 l) was dried after being placed on the disc (6 mm). The disc was then impregnated on seeded agar plates. The plates were allowed to stand for an hour to allow the compound C-1 to pre-diffusion.

The antibacterial activity of the compound (C-1) was shown to be very active against Bacillus subtilis and less active against Escherichia coli, as shown in Table-01. As a result, the aforementioned chemical could be used as an effective antibacterial agent against bacteria-caused disorders.

The findings from the experiments are recorded in the Table-1.

Table -1

S.NO	Bacteria	Diameters of zone of inhibition (mm)* Concentration of compound I (µg/ml)				Std**
		25	50	75	100	
1	Bacillus subtilis (gram positive)	10.1	15.9	17.9	20.2	23.8
2	Staphylococcus aureus (gram positive)	10.4	12.1	14.3	16.5	20.5
3	Escherichia coli (gram negative)	6.8	9.2	10.5	13.7	20.1
4	Pseudomonus aueruginosa (gram negative)	10.5	12.3	15.01	17.1	24.5

EVALUATION OF IN VITRO ANTI-INFLAMMATORY ACTIVITY OF COMPOUND C-I

Human red blood cell membrane stabilization technique was used to test compound C-I's anti-inflammatory efficacy in vitro [5-6]. Blood was drawn from healthy participants and combined with an equal volume of sterilized Alsevers solution (2% dextrose, 0.8% sodium citrate, 0.5% citric acid, and 0.42% sodium chloride). This blood solution was centrifuged at 3000 rpm to separate the packed cells. This HRBC suspension was used to calculate anti-inflammatory activity. Separately, 1.0 mL of compound C-1 and reference drug (Diclofenac sodium) doses were combined with 1 mL of phosphate buffer, 2 mL of hyposaline, and 0.5 mL of HRBC suspension. 1 mL of phosphate buffer, 2 mL of distilled water, and 0.5 mL of HRBC suspension were used to make the control solution. All reaction mixtures were incubated for 25 minutes at 35C before being centrifuged at 3000 rpm. The supernatant liquid was decanted, and the hemoglobin concentration was measured at 560 nm using a UV/VIS Double Beam spectrophotometer. The absorbance of the control was 0.611.The percentages of hemolysis and membrane stability were estimated using the equations below.

% Haemolysis = (Optical density of Test sample / Optical density of Control)
X 100

% membrane stabilisation = [1- (OD sample/ OD control)] X 100%

The Table -02 and Table -03 include the outcomes of experimental studies.

TABLE-02 Effect of Compound C-1 on HRBC Membrane Hemolysis and Membrane Stabilization

Concentration of compound GS in reaction mixture (µg/ml)	%Membrane stabilization of Compound C-1	%Hemolysis of compound C-I
100	33.698	46.301
250	55.302	34.897
500	71.669	17.330
1000	91.289	7.7103

TABLE-03 Effect of Diclofenac Sodium on HRBC Membrane Hemolysis and Membrane Stabilization

Concentration of Diclofenac sodium In reaction mixture (µg/ml)	%Membrane stabilization of Diclofenac sodium	% Hemolysis of Diclofenac sodium
100	33.535	46.464
250	51.702	37.297
500	78.869	21.130
1000	91.653	7.3469

Above Table-02 and Table-03 showed that % of membrane stabilization of compound C-I is greater than % of membrane stabilization of reference drug (Diclofenac sodium) and % Hemolysis of compound C-1 is less than % Hemolysis of reference drug (Diclofenac sodium). Therefore from above findings it was concluded that compound C-I shows good anti-inflammatory activity. [7-8]

MIC of Indole derivatives against different fungal strains

Compound ID	MIC (µg/mL)		
	C. albicans MTCC227	*A. niger* MTCC282	*A. clavatus* MTCC1323
C1	500	1000	1000
C2	500	500	1000
C3	**250**	1000	500
C4	500	1000	1000
C5	500	1000	1000
C6	500	500	1000
C7	**250**	500	1000
C8	500	1000	500
C9	500	1000	1000
C10	500	500	1000
Nystatin	100	100	100

Griseofulvin	500	100	100

In the present study, we have synthesized several novel Indole scaffolds and analysed their antibacterial and antifungal effects against a variety of bacteria and fungi properties. The antibacterial profiling of the Indole derivatives showedgood antibacterial property. Among these derivatives, C4, C5,and C8were the most effective against E. coli and compound C5 was the most effective against P. aeruginosa as shown in table 5.1.Two compounds C3 and C7manifested good antifungal potency against C. albicans with MIC values lower than griseofulvin. [9-11]

RESULTS & DISCUSSION:

The indole ring system is present in complex alkaloids like vinblastine, a commonly used chemotherapeutic drug, as well as neurotransmitters like serotonin. Additionally, an indole ring can be found in a number of significant synthetic pharmaceuticals, which is why chemists all over the world are still fascinated by this significant ring system.A series of indole novel derivative were synthesised.
This new molecule may have potential as an aspirant, to be designed as a novel therapeutic against challenging diseases like Antibacterial, Anti-inflammatory, antifungal, anticancer, and diabetes,

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