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INSTRUMENTAL ANALYSIS AND THE MOLECULAR DOCKING STUDY FOR THE SYNTHESIZED INDOLE DERIVATIVES

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ABSTRACT

In the present work, the formation of 2-phenyl indole, 2 was carried out by the Fischer Indole Synthesis method through AcetoPhenyl hydrazine (1) and by cyclaization with Polyphosheric acid (PPA). 2-Phenyl Indole (2) was also synthesized by alternate method from direct Acetophenone through conc. H_2SO_4. The derivative 2-phenyl-1H-Indole-3-carbaldehyde (3a) was synthesized from Compd. (2) by the method of Vilsmeier reaction using Phosphorous oxy chloride in DMF. Phenyl (2-phenyl-1H-indol-3-yl) methanone (3b) and 1-(2-phenyl-1H-indol-3-yl) ethan-1-one (3c) was prepared by the Friedal Craft reaction method using benzoyl chloride and acetyl chloride respectively along with aluminum chloride and DCM. The synthesized derivatives (1), (2) and (3a-c) were screened for instrumental analysis and molecular docking studies.

Key words: Indole, Molecular docking, Fischer Indole, Friedel craft, Vilsemer.

INTRODUCTION

Indole chemistry began with the study of the dye indigo. Indole is an aromatic heterocyclic nucleus. It has a bicyclic structure, consisting of a six-member benzene ring fused to five member nitrogen containing pyrrole ring through the 2- and 3-positions of the pyrrole nucleus. Indole is called as benzopyrrole. Indole is a popular component of fragrances. Indoles are a pervasive class of compounds found in abundance in biologically active compounds such as pharmaceuticals, agrochemicals and alkaloids. Since the first synthesis of Indole in 1866, a number of synthetic methods for the construction of the Indole nucleus have been devised. Medicine and biochemistry are also interested in many aspects of the Indole chemistry. Hence, it is not surprising that indoles act as lead compounds and

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are key building blocks in numerous pharmaceuticals. Indole derivatives constitute an important class of therapeutic agents in medicinal chemistry including Anti-inflammatory activity[1], Analgesic activity[2], Antimicrobial activity[3], Antidepressant activity[4], antitumor activity[5], Antifungal activity[6], Antihypertensive activity[7], Antiviral activity[8], Antiproliferative activity[9], Anti-HIV activity[10], Anti-cancer activity[11-12], Antipsychotic[13], Antileukamic[14] etc. Although Indole moiety is very small but is fascinated by scientists because of the diverse biological activities by not only Indole but its various substituted derivatives as well. In this work, different Indole derivatives had been synthesized and screened by lab techniques (Table 1), studied by instrumental analysis (Table 2), and further studied for molecular docking studies (Table 3). The molecular docking study revealed that other derivatives along with 3- substituted Indoles such as Acetophenyl Hydrazone (1), 2-Phenyl Indole (2) and phenyl(2-phenyl-1H-indol-3-yl)methanone (3b) showed potent biological activity.

EXPERIMENTAL

Materials and methods

Melting points of the synthesized compounds were determined by open capillary and are uncorrected. The purity of the compounds was checked using TLC plates (glass) coated with silica gel. The developed chromatographic plates were visualized under iodine chamber. IR spectra were recorded using KBr on Shimadzu FTIR model 8400 spectrophotometer. ^{1}H NMR spectra and mass spectra was recorded through the software Chemdraw.

Experimental protocol

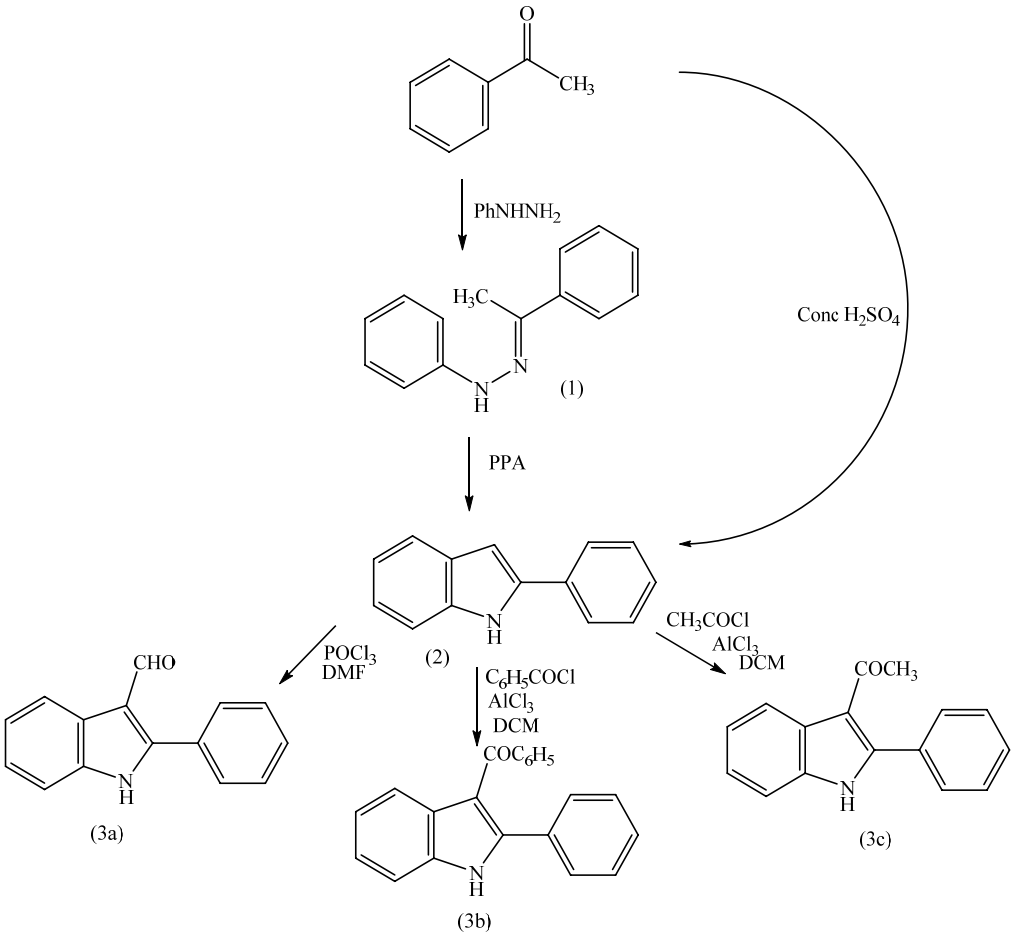
General procedure for the synthesis of acetophenyl hydrazone (1)

A mixture of 0.05 mol of Acetophenone and 0.05 mol of Phenyl hydrazine was taken in a round bottom flask, shaken well and added 30 mL of ethanol followed by few drops of glacial acetic acid. The resultant mixture was warmed for 15 min. The mixture was allowed to stir for 1 hr and then poured into ice cold water (10 mL). The crude compound got precipitated and then filtered by Buchner funnel. The filtrate was washed with water and dried to get compd. (1).

General procedure for the synthesis of 2-phenyl indole (2)

Method 1: In this method, 2-phenyl indole, 2 was prepared by by Fischer Indole synthesis method[15]. 20 g of polyphosphoric acid into a dry 50 mL beaker was warmed at 50^{o}C followed by addition of 0.05 mol of Compd. 1 with stirring. On completion of addition,

the mixture was heated for 15 min and poured the mixture into 30 mL of ice water followed by stirring until all the acid got dissolved in water. The mixture was filtered, washed with cold methanol and recrystallized with ethanol and water. Hot ethanol and 0.1 g charcoal was added into the reaction mixture, filtered and reheated the filtrate up to the boiling and then added the water, up to the cloudy point followed by adding 1-2 drops of ethanol to dissolve the finally cloudy precipitate. Now allowed the solution to cool, undisturbed and collected the crystals by Buchner funnel and allowed to cool at room temperature. The pure comp. underwent TLC, spectra analysis and melting point.



Scheme 1

Method 2: In this method, 2-phenyl Indole, 2 was prepared by by Shaikh et. al. method[16]. A mixture of 0.05 mol of Acetophenone, 0.05 mol of phenyl hydrazine and 30 mL

ethanol was refluxed for 2-3 hours at room temperature. The product formed was poured into 15 mL of H_2SO_4 and the reaction mixture was stirred and heated for 20-30 min. The product formation was checked by TLC and the crude compound was added into 40 mL ice cold water. The solid product was filtered, dried and recrystallized with methanol to give compd. (2).

General procedure for the synthesis of 2-phenyl-1H-indole-3-carbaldehyde (3a)[17]

5 mL of N, N-dimethyl formaldehyde (DMF) was added into 0.01 mol of phosphorous oxychloride dropwise under cooling with ice bath. The reaction mixture was stirred for 1 hr at 0-5^oC temperature to get Vilsmeier reagent. A mixture of 0.01 mol of comp. (1) and DMF (5 mL) was added into already prepared Vilsmeier reagent. The resultant mixture kept on stirring for 2 hrs at 0-5^oC after that the reaction mixture was allowed to stirrer for 60 min at 35^oC. The product formation was checked by TLC and the reaction mixture was poured into 90 ml ice cold water. The mixture was boiled for 1-10 min and upon cooling the crystals got precipitated. The crude product was recrystallized with DMF. Yellow colored product of compd. (3a) was formed.

General procedure for the synthesis of phenyl (2-phenyl-1H-indol-3-yl) methanone (3b)[18]

Benzoyl chloride (0.02 mol) was added into a mixture of $AlCl_3$ (0.03 mol) and Dichloromethane (20 mL). The mixture was allowed to stirr at room temperature for 15 min followed by drop wise addition of Compd. (2) (0.01 mol). This mixture was allowed to stir for 3 hr. During the process, TLC was checked for the progress of reaction. The mixture was poured over ice. Then the aqueous layer was extracted 3 times with DCM followed by washing with 3 molar of HCl solution (3 times), with saturated aqueous $NaHCO_3$ (3 times) and brine solution (3 times). The crude product was dried over Sodium Sulphate and then recrystallized from methanol. Thus it gave Compd. 3b.

General procedure for the synthesis of 1-(2-phenyl-1H-indol-3-yl) ethan-1-one (3c)[18]

Acetyl chloride (0.02 mol) was added into a mixture of $AlCl_3$ (0.03 mol) and Dichloromethane (20 mL) and the mixture was allowed to stir at room temperature for 15 min followed by drop wise addition of Compd. 2 (0.01 mol). This mixture was allowed to stir for 3 hr. During the process, TLC was checked for the progress of reaction. The mixture was poured over ice. Then the aqueous layer was extracted 3 times with DCM followed by washing with 3 molar of HCl solution (3 times), with saturated aqueous $NaHCO_3$ (3 times)

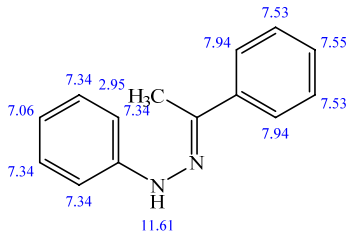
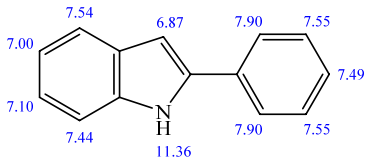
and brine solution (3 times). The crude product was dried over Sodium Sulphate and then recrystallised from methanol to give Compd. 3c.

The data for the yield analysis and instrumental analysis of the synthesized derivatives is given in the Table 1 and Table 2, respectively.

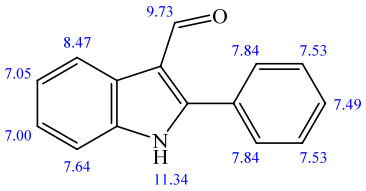
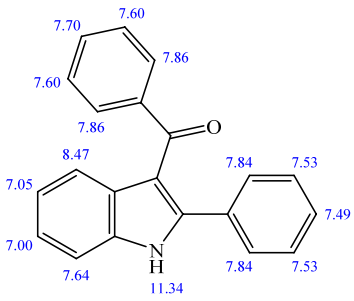
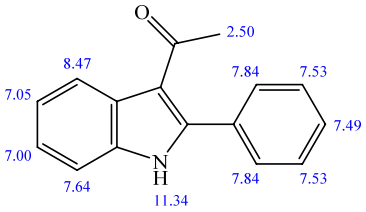
Table 1: Yield analysis for the synthesized derivatives

Comp. No.	Molecular Formula	Mol. wt. (g)	Yield (%)	M.P. (^oC)	Recrystalization Solvent	R_f.
1	$C_{14}H_{14}N_2$	210	92%	52^oC	EtOH	0.52 cm
2	$C_{14}H_{11}N$	193	93% (Method 1) 95% (Method 2)	110^oC	EtOH MeOH	0.88 cm
3a	$C_{15}H_{11}NO$	221	60%	210^oC	DMF	0.30 cm
3b	$C_{21}H_{15}NO$	297	25.5%	205 ^0C	MeOH	0.44 cm
3c	$C_{16}H_{13}NO$	235	33.46%	185 ^0C	MeOH	0.52 cm

Table 2: Instrumental analysis of synthesized derivatives

Compd.	Molecular formula	NMR analysis	IR analysis	Mass analysis
1	$C_{14}H_{14}N_2$		**FT-IR (KBr υ_{max} cm^{-1}):** - NH=N- (N-H stretch) 3439 cm^{-1}, Ar (overtones) 2607 cm^{-1}, 2488 cm^{-1}, 2360 cm^{-1}, Ar (C-H stretch) 2889 cm^{-1}, Ar (C=C) 1604 cm^{-1}, Ar (C-H bending) 688 cm^{-1}, 742 cm^{-1}	**MS:** m/z: 210.12 (100.0%), 211.12 (15.1%), 212.12 (1.1%)
2	$C_{14}H_{11}N$		**FT-IR (KBr υ_{max} cm^{-1}):** Indole (N-H stretch) 3439 cm^{-1}, Ar (overtones) 2607 cm^{-1}, 2488 cm^{-1}, 2360 cm^{-1}, Ar (C-H stretch) 2889 cm^{-1}, Ar (C=C) 1604 cm^{-1}, Ar (C-H bending) 688 cm^{-1}, 742 cm^{-1}	**MS: m/z:** 193.09 (100.0%), 194.09 (15.1%), 195.10 (1.1%)

Cont…

Compd.	Molecular formula	NMR analysis	IR analysis	Mass analysis
3a	$C_{15}H_{11}NO$		**FT-IR (KBr υ_{max} cm^{-1}):** Indole (N-H stretch) 3439 cm^{-1}, C=O 3049 cm^{-1}, Ar (overtones) 2362 cm^{-1}, 1890 cm^{-1}, Ar (C-H stretch) 2827 cm^{-1}, Ar(C=C) 1599 cm^{-1}, Ar (C-H bending) 690 cm^{-1}, 742 cm^{-1}	**MS:** m/z: 221.08 (100.0%), 222.09 (16.2%), 223.09 (1.2%)
3b	$C_{21}H_{15}NO$		**FT-IR (KBr υmax cm^{-1}):** Indole (N-H stretch) 3441 cm^{-1}, Ar (C-H stretch) 3049 cm^{-1}, 3022 cm^{-1}, Ar (overtones) 2901 cm^{-1}, 2839 cm^{-1}, 2362 cm^{-1}, Ar (C=O stretch) 1680 cm^{-1}, Ar (C-O stretch) 1296 cm^{-1}, Ar (C=C) 1597 cm^{-1}, Ar (C-H bending) 690 cm^{-1}, 740 cm^{-1}	**MS:** m/z: 297.12 (100.0%), 298.12 (22.7%), 299.12 (2.5%)
3c	$C_{16}H_{13}NO$		Indole (N-H stretch) 3047 cm^{-1}, C=O 2926 cm^{-1}, 1707 cm^{-1} Ar (overtones) 1946 cm^{-1}, 1890 cm^{-1}, 1867 cm^{-1}, Ar (C-H stretch) 2852 cm^{-1}, Ar (C=C) 1604 cm^{-1}, Ar (C-H bending) 688 cm^{-1}, 742 cm^{-1}	**MS:** m/z: 235.10 (100.0%), 236.10 (17.3%), 237.11 (1.4%)

Molecular docking study

Molecular docking is one of the most frequently used methods in SBDD because of its ability to predict, with a substantial degree of accuracy, the conformation of small-molecule ligands within the appropriate target binding site[19]. Following the development of the first algorithms in the 1980s, molecular docking became an essential tool in drug discovery[20]. For example, investigations involving crucial molecular events, including ligand binding modes and the corresponding intermolecular interactions that stabilize the ligand-receptor complex, can be conveniently performed[21]. Furthermore, molecular docking algorithms execute quantitative predictions of binding energetic, providing rankings of docked compounds based on the binding affinity of ligand-receptor complexes[20-21]. The

identification of the most likely binding conformations requires two steps: (i) exploration of a large conformational space representing various potential binding modes; (ii) accurate prediction of the interaction energy associated with each of the predicted binding conformations[22]. Molecular docking programs perform these tasks through a cyclical process, in which the ligand conformation is evaluated by specific scoring functions. This process is carried out recursively until converging to a solution of minimum energy[21-23]. The current study of molecular docking calculations was carried out using ArgusLab software. The molecular docking studies revealed that ligands of comp. (1), (2) and (3b) has been docked successfully on the binding site (amino acids) of the enzymes PDB with H bonding. The best ligand pose energies have been quite remarkable such as listed in Table 3.

Table 3: Molecular docking studies

Compd.	Clustering the final poses	Best ligand pose; energy	Docking run: elapsed time	Binding amino acid	H-bonding	Figure
1	75 final unique configuration	-11.3066 kcal/mol	7 seconds	145 TYR: coil	2.613795 and 2.175935	1
2	81 final unique configuration	-10.6504 kcal/mol	6 seconds	145 TYR: coil	2.134796	2
3a	-	-	-	-	-	-
3b	64 final unique configuration	-14.2726 Kcal/mol	6 seconds	580 THR: alpha helix	2.367769	3
3c	-	-	-	-	-	-

The docking for ligand binding sites of synthesized compounds with amino acids has been displayed through the Fig. 1, 2 and 3.

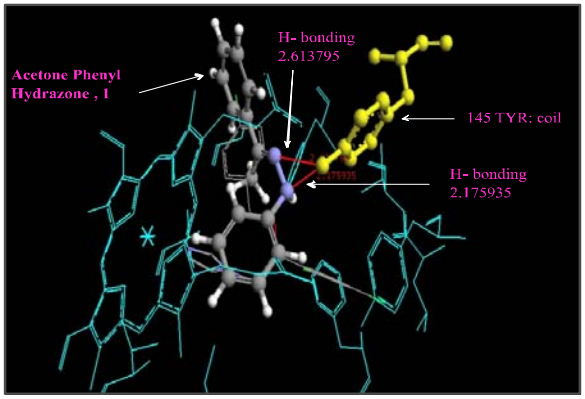


Fig. 1: Docking of acetone phenyl hydrazone (1)

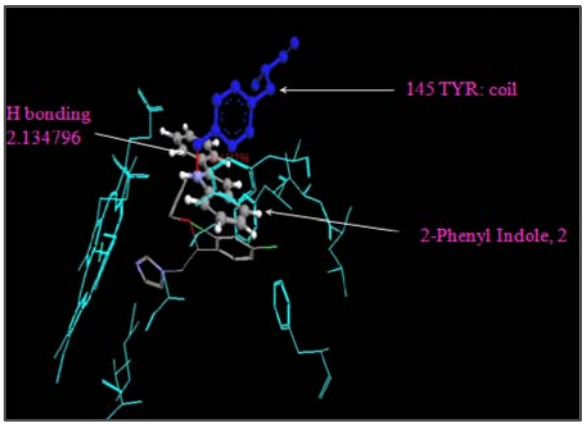


Fig. 2: Docking of 2-phenyl indole (2)

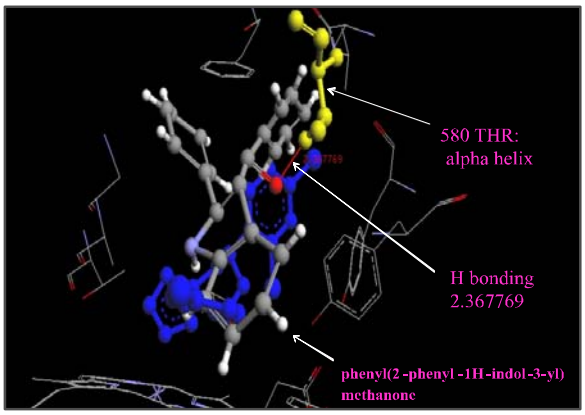


Fig. 3: Docking of phenyl(2-phenyl-1H-indol-3-yl) methanone (3b)

RESULTS AND DISCUSSION

The interesting outcome of the work was that Friedel-Crafts reaction could be successfully applied for the synthesis of 3-substituted Indole derivatives. Though the low yield had been a matter of concern. For better yield, $PhSO_2Cl$ could be used for the protection of NH of Indole.

As shown in the highlighted case studies, molecular docking had been able to identify promising compounds that might represent future solutions in critical areas of human health. Acetophenyl Hydrazone (1), 2-Phenyl Indole (2) and Phenyl (2-phenyl-1H-indol-3-yl) methanone (3b) showed promising activity of varying degree. Acetone Phenyl Hydrazone (1) had been docked with binding amino acid- 145 TYR: coil by H-bonding

(2.613795 and 2.175935), 2-Phenyl Indole (2) had been docked with binding amino acid- 145 TYR: coil by H- bonding (2.134796) and phenyl(2-phenyl-1H-indol-3-yl)methanone (3b) had been docked with binding amino acid- 580 THR: alpha helix by H- bonding (2.367769). The present work clearly stated about some synthesized Indole derivatives and their pharmacological profiles which might contribute in future to synthesize various analogs and to develop new pharmacologically less toxic medicines.

CONCLUSION

In the present study, our attention was focused on the synthesis and molecular docking evaluation of a series of 2-phenyl indole derivatives. Phenyl (2-phenyl-1H-indol-3-yl) methanone (3b) showed remarkable docked characteristic among 3-substituted Indole derivatives. 2-phenyl-1H-indole-3-carbaldehyde (3a) and 1-(2-phenyl-1H-indol-3-yl) ethan-1-one (3c) didn't show any docked characteristic. We can assume that compd. (3b) would definitely show remarkable biological activity while compd. (3a) and compd. (3c) might show mild to moderate biological potential among the entire synthesized compound.

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