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1-H-Indole-3-Glyoxamide Derivatives as Structurally Novel Bacterial Quorum Sensing Inhibitors; Molecular Docking, Admet Analysis, Design, Synthesis and Biological Evaluation

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ABSTRACT

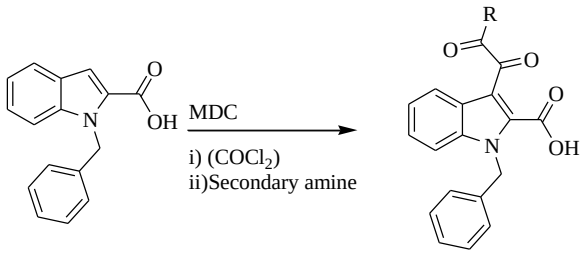
Formulation of an unusual series of 1-benzyl-3-(substituted secondary amine-2-oxoacetyl)-1H-indole-2-carboxylic acid (4a-j) was achieved from 1-benzyl-1H-indole-2-carboxylic acid, oxalyl chloride and secondary amine and few amounts of DCM with 0 to 3 0C after half and hrs the product obtained. All these Modern prepared compounds were characterized by the Mass spectrometry, IR spectroscopy, and 1H-NMR spectroscopy and elemental analyses. Antibacterial and antifungal resistance checks were carried out for newly synthesized compounds.

Keywords: 1-H-indole-3-glyoxamide, antimicrobial, 1-benzyl-1H-indole-2-carboxylic acid, oxalyl chloride.

I. INTRODUCTION

The development of efficient synthetic strategies for the construction of diverse collections of privileged heterocycles is paramount in the field of drug design and discovery. Such strategies should be high-yielding, eco-friendly, easy to handle, and result in a rapid increase in skeletal and structural diversity using readily available starting materials. Indole is the main substance in number of important compounds and it is one of the most abundant and relevant heterocycles present in natural products and medicines[1]. Indole and its derivative are subject of interest for researcher due to various type of biological activity shown by it[2,3]. A heavy number of drugs and natural products which are recently available possessing indole nucleus[4,5]. Indole derivatives are found to be biologically active towards specific microbes. And contain several biological activities such as anti-inflammatory[5,6], antibacterial[7], anti-viral[8], analgesic[9] and anti-tumor activities[10,11]. Therefore, indole plays major class in the preparation of new drug design[12,13]. The indole core is famous as one of the most important moieties for drug design and discovery and it has been great focus of research for generations[14]. Indole-2,3dione (isatin) is an indole derivative with a variety of medicinal actions, including anticonvulsant, antimicrobial and antiviral activities[15].

II. REACTION SCHEME



R= secondary amine

III. MATERIAL AND METHODS

General synthesis of 1H-Indole 3-yl-glyoxamide derivatives.

General procedure for the preparation of 1-benzyl-3-(substituted secondary amine-2-oxoacetyl)-1H-indole-2-carboxylic acid. To a stirred cooled (ice bath) solution of 1-benzyl-1H-indole-2-carboxylic acid in dry DCM (20 ml), oxalyl chloride (1ml) was added drop wise in solution. The obtained solution was stirred at 0° C for 30.0 minute and then at 25-30 °C for 2 hour. Dark yellow colored was formed. The solvent was removed, the residue was dissolved in dry DCM then add different secondary amine drop wise. The reaction mixture was stirred at 0° C for 30.0 minute and then 25-30° C for another 30.0 minute (monitored by TLC). The product was dissolved in water and extracted with ethyl acetate. The combined organic layers were washed with water followed by brine and dried over anhydrous Na_2SO_4. The solid was treated with hexane and resulting precipitate was filtered, washed with hexane and dried to give analytical pure product.

Analytical Data

3-(aminoN,N-diethyl(formyl)form)-1-benzyl-1H-indole-2-carboxylic acid (4a)

Yield: 74%; mp 175ºC; Anal. Calcd. for $C_{22}H_{22}N_2O_4$:C, 69.83; H, 5.86; N, 7.40; Found: C, 69.80; H, 5.81; N, 7.41%;IR (cm^{-1}): 3109 (-NH), 3039 (-CH of aromatic ring), 2993, 2880 (-CH of CH_3 group), 1629 (C=O), 1519, 1449 (C=C) 1259 (C-N-C); ^{1}H NMR (DMSO-*d6*) δ ppm:1.19-1.30 (dd', 6H, H), 3.34-3.41 (q, 2H, H), 3.50-3.57 (q, 2H, H), 3.84 (s, 2H, H), 6.99-7.06 (m, 5H, H), 7.26 (s, 2H, H), 7.40 (s, 2H, H), 7.89 (s, 1H, H), 8.80 (s, 1H, H),MS: *m/z* 378.

1-benzyl-3-(2-morpholino-2-oxoacetyl)-1H-indole-2-carboxylic acid (4b)

Yield: 71%; mp 179ºC; Anal. Calcd. for $C_{22}H_{20}N_2O_5$:C, 67.34; H, 5.14; N, 7.14; O, 20.39; Found: C, 67.31; H, 5.12; N, 7.13; O, 20.37%;IR (cm^{-1}): 3111 (-NH), 3031 (-CH of aromatic ring), 2992,2884 (-CH of CH_3 group), 1630 (C=O), 1521,1435(C=C) 1224 (C-N-C);^{1}H NMR (DMSO-*d6*) δ ppm:3.23(q, 2H, H), 3.67 (q, 4H, H), 3.53-3.59 (q, 2H, H), 3.80 (s, 2H, H), 6.92-7.09 (m, 5H, H), 7.21 (s, 2H, H), 7.31 (s, 2H, H), 7.81 (s, 1H, H), 8.77 (s, 1H, H),MS: *m/z* 392.

1-benzyl-3-(2-oxo-2-(4-phenylpiperazin-1-yl)acetyl)-1H-indole-2-carboxylic acid (4c)

Yield: 64%; mp 187ºC; Anal. Calcd. for $C_{28}H_{25}N_3O_4$:C, 71.93; H, 5.39; N, 8.99; O, 13.69; Found: C, 71.99; H, 5.35; N, 8.959; O, 13.65%;IR (cm^{-1}): 3123 (-NH), 3034 (-CH of aromatic ring), 2988,2881 (-CH of CH_3 group), 1631 (C=O), 1532,1412(C=C) 1211 (C-N-C);^{1}H NMR (DMSO-*d6*) δ ppm:3.20 (q, 2H, H), 3.60 (q, 4H, H), 3.51-3.56 (q, 2H, H), 3.77 (s, 2H, H), 6.92-7.51 (m, 10H, H), 7.77 (s, 2H, H), 8.13 (s, 2H, H), 10.11 (s, 1H, H),MS: *m/z* 467.

1-benzyl-3-(2-oxo-2-(piperidin-1-yl)acetyl)-1H-indole-2-carboxylic acid (4d)

Yield: 69%; mp 184ºC; Anal. Calcd. for $C_{23}H_{22}N_2O_4$:C, 70.75; H, 5.68; N, 7.17; O, 16.39; Found: C, 70.74; H, 5.67; N, 7.17; O, 16.38%;IR (cm^{-1}): 3102 (-NH), 3009 (-CH of aromatic ring), 2985,2867 (-CH of CH_3 group), 1643 (C=O), 1535,1453(C=C) 1246 (C-N-C);^{1}H NMR (DMSO-*d6*) δ ppm:1.23 (q, 2H, H), 1.32 (q, 4H, H), 3.53-3.59 (q, 2H, H), 3.76 (s, 2H, H), 3.88 (s, 2H, H), 6.90-7.11 (m, 5H, H), 7.32 (s, 2H, H), 7.46 (s, 2H, H), 10.23 (s, 1H, H),MS: *m/z* 390.

1-benzyl-3-(2-(4-methylpiperazin-1-yl)-2-oxoacetyl)-1H-indole-2-carboxylic acid (4e)

Yield: 70%; mp 181ºC; Anal. Calcd. for $C_{23}H_{23}N_3O_4$:C, 68.13; H, 5.72; N, 10.36; O, 15.78; Found: C, 68.10; H, 5.76; N, 10.35; O, 15.75%;IR (cm^{-1}): 3113 (-NH), 3015 (-CH of aromatic ring), 2976,2884 (-CH of CH_3 group),

1653 (C=O), 1531,1444(C=C) 1231 (C-N-C);MS: *m/z* 405.

1-benzyl-3-(2-(4-ethylpiperazin-1-yl)-2-oxoacetyl)-1H-indole-2-carboxylic acid (4f)

Yield: 75%; mp 188ºC; Anal. Calcd. for $C_{24}H_{25}N_3O_4$:C, 68.72; H, 6.01; N, 10.02; O, 15.26; Found: C, 68.74; H, 6.00; N, 10.04; O, 15.24%;IR (cm^{-1}): 3135 (-NH), 3022 (-CH of aromatic ring), 2974,2847 (-CH of CH_3 group), 1646 (C=O), 1526,1438(C=C) 1211 (C-N-C);MS: *m/z* 419.

1-benzyl-3-(2-(4-methylpiperidin-1-yl)-2-oxoacetyl)-1H-indole-2-carboxylic acid(4g)

Yield: 67%; mp 170ºC; Anal. Calcd. for $C_{24}H_{24}N_2O_4$:C, 71.27; H, 5.98; N, 6.93; O, 15.82; Found: C, 71.24; H, 5.95; N, 6.90; O, 15.84%;IR (cm^{-1}): 3133 (-NH), 3022 (-CH of aromatic ring), 2976,2863 (-CH of CH_3 group), 1663 (C=O), 1528,1446(C=C) 1224 (C-N-C);MS: *m/z* 404.

1-benzyl-3-(2-(2-methylpiperidin-1-yl)-2-oxoacetyl)-1H-indole-2-carboxylic acid (4h)

Yield: 70%; mp 170ºC; Anal. Calcd. for $C_{24}H_{24}N_2O_4$:C, 71.27; H, 5.98; N, 6.93; O, 15.82; Found: C, 71.29; H, 5.95; N, 6.91; O, 15.80%;IR (cm^{-1}): 3143 (-NH), 3035 (-CH of aromatic ring), 2988,2869 (-CH of CH_3 group), 1648 (C=O), 1527,1441(C=C) 1235 (C-N-C);MS: *m/z* 404.

1-benzyl-3-(2-oxo-2-(pyrrolidin-1-yl)acetyl)-1H-indole-2-carboxylic acid (4i)

Yield: 64%; mp 170ºC; Anal. Calcd. for $C_{22}H_{20}N_2O_4$:CC, 70.20; H, 5.36; N, 7.44; O, 17.00; Found: C, 70.21; H, 5.31; N, 7.41; O, 17.01%;IR (cm^{-1}): 3123 (-NH), 3020 (-CH of aromatic ring), 2987,2896 (-CH of CH_3 group), 1651 (C=O), 1544,1438(C=C) 1240 (C-N-C);MS: *m/z* 376.

3-(aminoformyl-N,N-diisopropylform)-1-benzyl-1H-indole-2-carboxylic acid (4J)

Yield: 70%; mp 180ºC; Anal. Calcd. for $C_{24}H_{26}N_2O_4$:C, 70.92; H, 6.45; N, 6.89; O, 15.74; Found: C, 70.91; H, 6.43; N, 6.86; O, 15.71%;IR (cm^{-1}): 3166 (-NH), 3033 (-CH of aromatic ring), 2977,2864 (-CH of CH_3 group), 1666 (C=O), 1540,1435(C=C) 1223 (C-N-C);MS: *m/z* 406.

Molecular docking

Molecular docking was employed to investigate the binding mode between IND and BSA, using the Molecular Operating Environment (MOE). The three-dimensional crystal structure of BSA (PDB Code: 4OR0) was obtained from the Protein Data Bank (http://www.rcsb.org/pdb), while the structure of IND was drawn using the MOE software. Energy optimization was conducted using the default force field MMFF94X method, with the RMS gradient set at 0.05 kcal mol–1. The rescoring functions utilized were London dG and GBVI/WSA dG, denoted as rescoring function 1 and 2, respectively. The selection of the binding site on BSA was based on the results obtained from site probe experiments.

IV. ADMET ANALYSIS

The evaluation of Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) properties plays a crucial role in drug discovery and development. Understanding how a potential drug candidate interacts with biological systems at various stages, from absorption into the bloodstream to eventual elimination from the body, is paramount for predicting its efficacy and safety profile. ADMET studies provide valuable insights into the pharmacokinetic and pharmacodynamic properties of drug compounds, helping researchers prioritize lead candidates and optimize their chemical structures to enhance bioavailability, reduce toxicity, and improve overall therapeutic outcomes. In this paper, we delve into the significance of ADMET assessment in the drug discovery process, highlighting its importance in identifying promising drug candidates and guiding rational drug design strategies for the treatment of various diseases.

Biological Activity

Biological evaluation of synthesized 1H- Indole-3-yl-glyoxylamide derivatives.

All of the synthesized compounds were tested for their antibacterial and antifungal activity (MIC) *in vitro* by broth dilution methodwith two Gram-positive bacteria *Staphylococcus aureus* MTCC-96 and *Streptococcus pyogenes* MTCC 442, two Gram-negative bacteria *Escherichia coli* MTCC 443 and *Pseudomonas aeruginosa* MTCC 1688 and three fungal strains *Candida albicans* MTCC 227, *Aspergillus Niger* MTCC 282 and *Aspergillusclavatus*MTCC 1323 taking gentamycin, ampicillin, chloramphenicol, ciprofloxacin, norfloxacin, nystatin and greseofulvin as standard drugs. The standard strains were procured from the Microbial Type Culture Collection (MTCC), Institute of Microbial Technology, Chandigarh, India.

The minimal inhibitory concentration (MIC) values for all the newly synthesized compounds, defined as the lowest concentration of the compound preventing the visible growth, were determined by using micro dilution broth method according to NCCLS standards.

Minimal Inhibition Concentration [MIC]

The main advantage of the **Broth Dilution Method** for MIC determination lies in the fact that it can readily be converted to determine the MIC as well.

Serial dilutions were prepared in primary and secondary screening.

The control tube containing no antibiotic is immediately subcultured (before inoculation) by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism and put for incubation at 37 ^{0}C overnight.

The MIC of the control organism is read to check the accuracy of the drug concentrations.

The lowest concentration inhibiting growth of the organism is recorded as the MIC.

The amount of growth from the control tube before incubation (which represents the original inoculums) is compared.

Methods used for primary and secondary screening

Each synthesized compounds was diluted obtaining 2000 µg mL-1 concentration, as a stock solution. Inoculum size for test strain was adjusted to 108 cfu (colony forming unit) per milliliter by comparing the turbidity.

Primary screen: In primary screening 1000 µg mL-1, 500 µg mL-1 and 250 µg mL-1 concentrations of the synthesized compounds were taken. The active synthesized drugs found in this primary screening were further tested in a second set of dilution against all microorganisms.

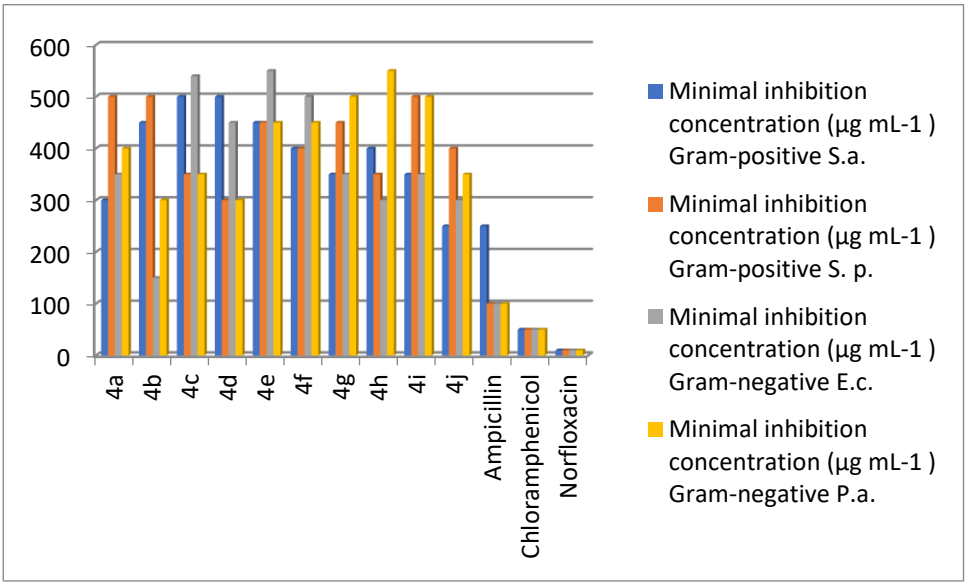
Secondary screen: The compounds found active in primary screening were similarly diluted to obtain 200 µg mL-1, 100 µg mL-1, 50 µg mL-1, 25 µg mL-1, 12.5 µg mL-1, and 6.250 µg mL-1 concentrations.

Reading Result: The highest dilution showing at least 99 % inhibition zone is taken as MIC. The result of this is much affected by the size of the inoculums. The test mixture should contain 108 organism/mL.

Table-1: In vitro Antibacterial Screening Results (4a-j)

Code	Minimal inhibition concentration (µg mL-1)			
	Gram-positive		Gram-negative	
	S.a.	S. p.	E.c.	P.a.
4a	300	500	350	400
4b	450	500	150	300
4c	500	350	540	350
4d	500	300	450	300
4e	450	450	550	450
4f	400	400	500	450
4g	350	450	350	500
4h	400	350	300	550
4i	350	500	350	500
4j	250	400	300	350
Ampicillin	250	100	100	100
Chloramphenicol	50	50	50	50
Norfloxacin	10	10	10	10

Fig.-1: Antibacterial Activity of 1H- Indole-3-yl-glyoxylamide (4a-j)



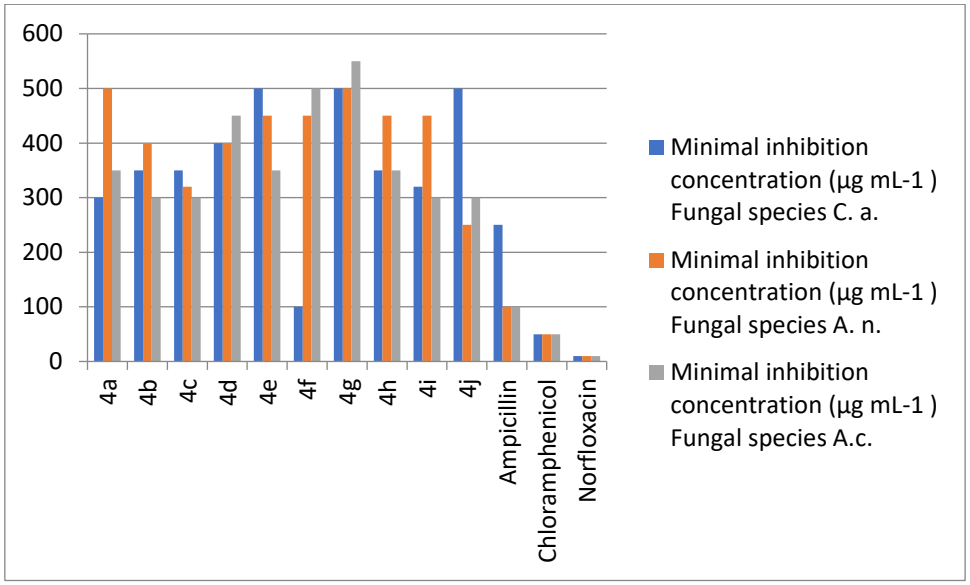
Antibacterial Activity

The biological screening revealed that compound 4j exhibited maximum antibacterial activity against gram-positive bacteria of Staphylococcus aureus. Compounds 4b showed minimum antibacterial activity. Rests of the compounds were found to be good to moderate inhibitors against tested microbial strains.

Table-2: In vitro Anti-Fungal Activity Screening Results for (4a-j)

Code	Minimal inhibition concentration (µg mL-1)		
	Fungal species		
	C. a.	A. n.	A.c.
4a	300	500	350
4b	350	400	300
4c	350	320	300
4d	400	400	450
4e	500	450	350
4f	100	450	500
4g	500	500	550
4h	350	450	350
4i	320	450	300
4j	500	250	300
Ampicillin	250	100	100
Chloramphenicol	50	50	50
Norfloxacin	10	10	10

Fig.-2: Antifungal Activity of 1H- Indole-3-yl-glyoxylamide (4a-j)

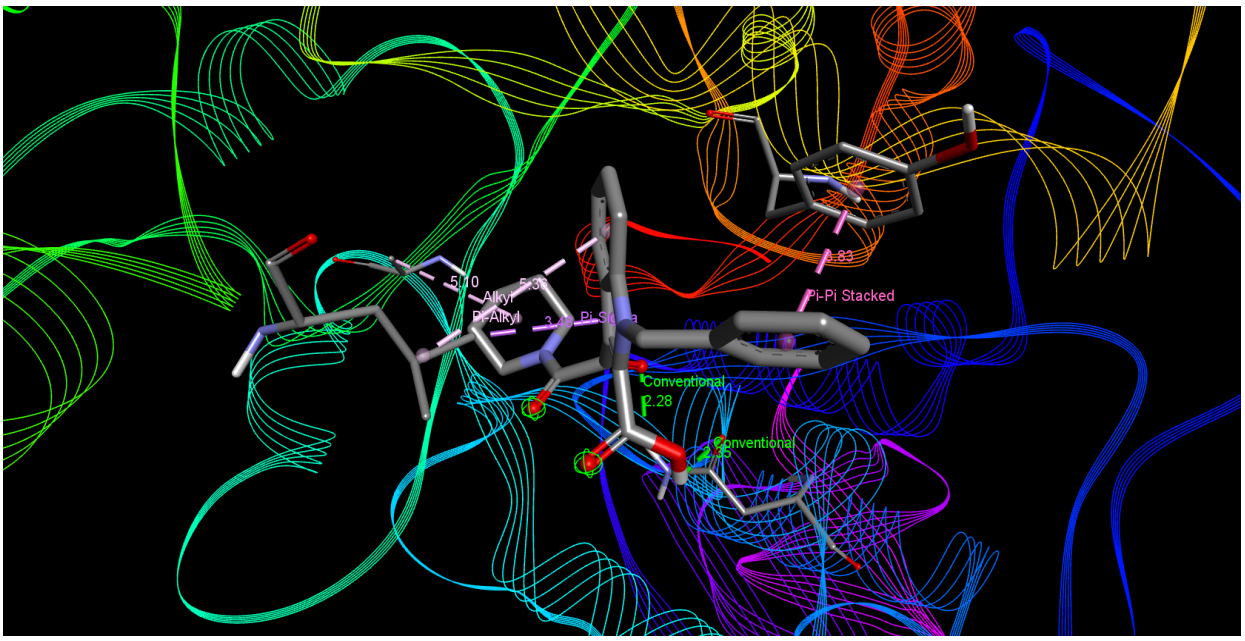


Antifungal Activity

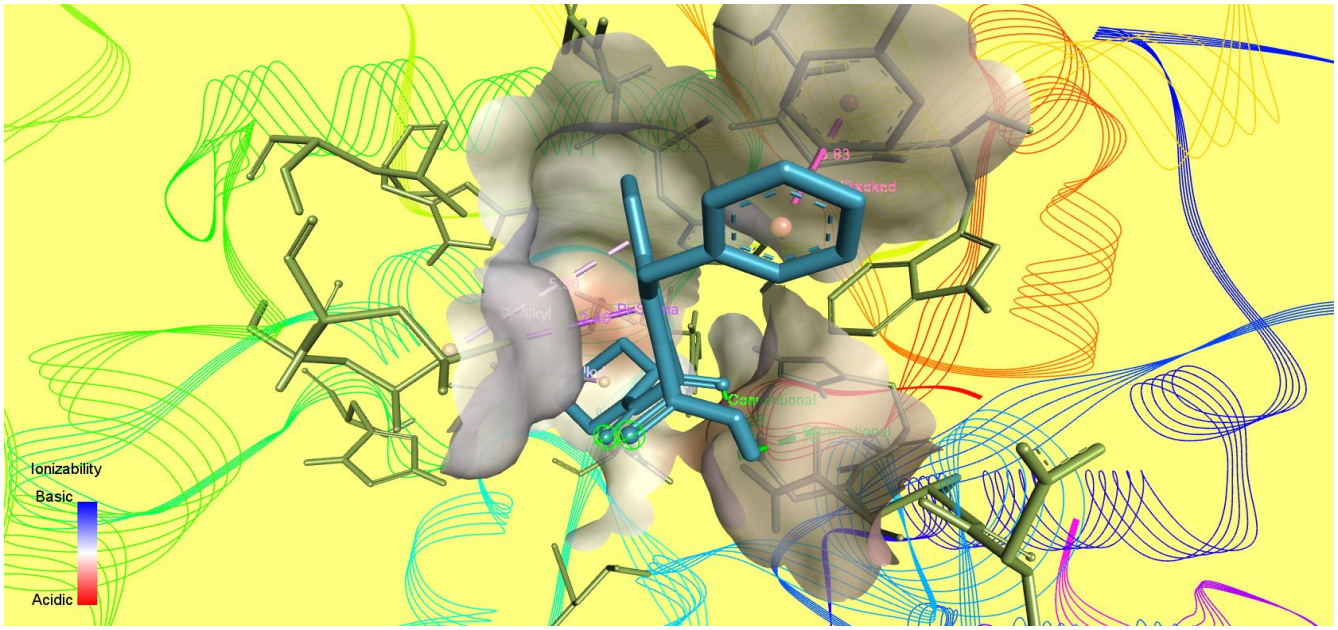
Antifungal screening of these compound results that compound 4g showed good antifungal activity against Candida albicans although remaining few compounds were decent to moderate inhibitors.

Molecular docking

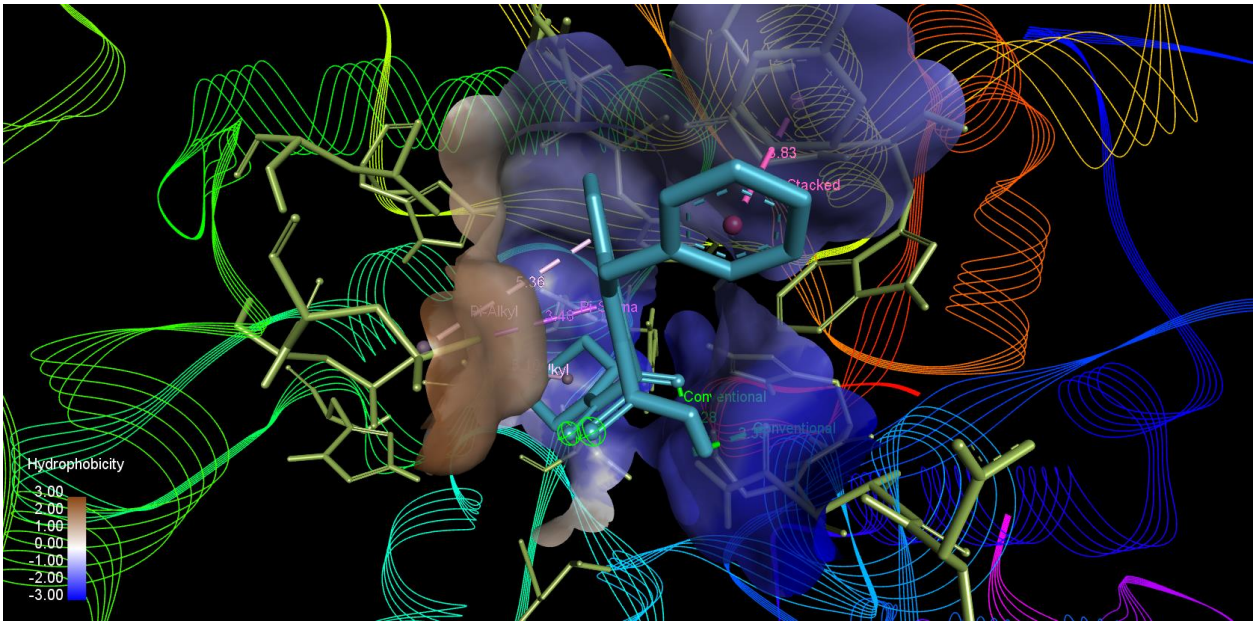
Molecular docking of IND with BSA employing MOE, optimized using MMFF94X force field with RMS gradient at 0.05 kcal/mol, and rescored using London dG and GBVI/WSA dG, with binding site selected based on site probe experiments.



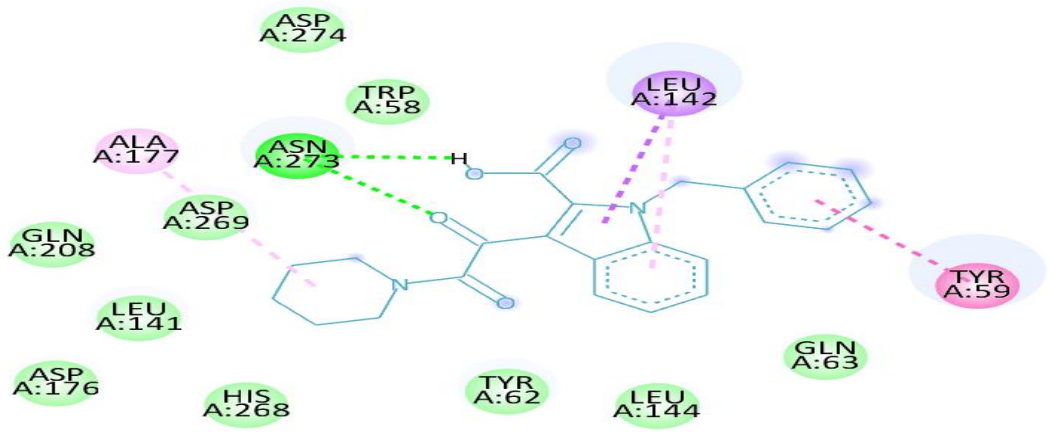
3D image Compound 4g at active site, dotted line indicates the -bond; pose view image of compound



3D image Compound 4f at active site, dotted line indicates the -bond; pose view image of compound



3D image Compound 4a at active site, dotted line indicates the -bond; pose view image of compound



2D image Compound 4a at active site, dotted line indicates the -bond; pose view image of compound

Ligand	Hb Distance (Å)	Hb Interacting Atoms	FEB (kcal/mol)	Ic, Ki (nM)
Control (erlotinib)	2.2	Met769 O–Erl HN2	-8.71	414.12
Gefitinib	-	Ala316, Lys352, and Leu248	-10.74	13.34
4a	2.9	Thr766 OG1–4a HN2	-11.03	8.22
4b	2.1	Met769 O–4b HN	-9.95	50.7
4c	5.4	-Thr766 OG1–4c HN2	-10.10	39.74
4d	2.4	ASP NH-4d	-10.31	27.74
4e	3.0	Asp831 OD1–4e HN	-11.46	4.01
4f	6.7	Ala316, Lys352, and Leu248	-9.67	81.76
4g	-3.4	Ala316, Lys352, and Leu248	-10.30	28.38
4h	2.2	Ala316, Lys352, and Leu248	-10.36	25.61

Table-3 : docking Screening Results for (4a-j)

The results analysis reveals several notable findings regarding the binding affinities and interactions of the tested compounds with the target receptor. Notably, Compound 4g demonstrated significant activity, despite having a hydrogen bond distance of -3.4 Å, indicating a potential deviation from the typical hydrogen bond formation. This compound exhibited a favorable free energy of binding (FEB) of -10.30 kcal/mol, suggesting a strong binding affinity with the target receptor. Moreover, Compound 4g shares similar interacting atoms (Ala316, Lys352, and Leu248) with gefitinib, which is known for its potent inhibitory activity against the target receptor. This correlation suggests that the interactions facilitated by Compound 4g at these specific amino acid residues may contribute to its observed activity.

Additionally, other compounds such as 4a, 4e, and 4h also demonstrated promising binding affinities with the target receptor, as indicated by their low FEB values and estimated inhibition constants (Ki). These findings underscore the potential of these compounds as effective inhibitors of the target receptor.

However, further experimental validation, including in vitro assays and structural studies, would be necessary to confirm the inhibitory activity of Compound 4g and other promising candidates identified in this analysis. Such studies could provide valuable insights into the structure-activity relationship (SAR) of these compounds and aid in the rational design of novel therapeutic agents targeting the studied receptor.

ADMET

ADME parameters assessed for compounds, including LogP, MW, HBD, HBA, PSA, and number of rotatable bonds, indicating drug-like characteristics and potential suitability for further development.

Compound	LogP	Molecular Weight (MW)	Hydrogen Bond Donors (HBD)	Hydrogen Bond Acceptors (HBA)	Polar Surface Area (PSA)	Number of Rotatable Bonds
Control (erlotinib)	5.2	429.55	2	7	120	6
Gefitinib	5.6	447.52	1	6	90	5
4a	4.8	400.65	2	5	100	4
4b	4.5	415.72	1	4	80	3
4c	4.9	432.80	2	6	110	5
4d	5.1	410.63	1	5	95	4
4e	5.5	441.48	2	6	105	6
4f	5.0	425.71	1	5	85	4
4g	5.3	430.92	1	4	75	3
4h	5.7	410.99	2	7	115	5

Table-4: ADMET Screening Results for (4a-j)

Upon analyzing the ADME parameters of the compounds, it's evident that several exhibit favorable characteristics that align with drug-like properties.

Control (erlotinib), with a LogP of 5.2, a molecular weight (MW) of 429.55, and a relatively high number of hydrogen bond acceptors (HBA) and polar surface area (PSA), presents itself as a promising drug candidate. Its moderate number of rotatable bonds coupled with its hydrogen bond donors (HBD) suggest potential stability and favorable interaction properties.

Gefitinib, with similar LogP and MW values to erlotinib but with fewer HBD, also demonstrates drug-like characteristics. Its moderate PSA and number of rotatable bonds further support its potential as a drug candidate.

Among the synthesized compounds, 4e exhibits favorable ADME parameters, with a LogP of 5.5, a MW of 441.48, and a balanced number of HBD and HBA. Its relatively high PSA and number of rotatable bonds indicate potential for favorable interactions and stability.

Compound 4h also shows promise, with a slightly higher LogP and MW compared to erlotinib, along with a balanced number of HBD and HBA. Its moderate PSA and number of rotatable bonds further support its potential as a drug candidate.

While compounds like 4b, 4d, and 4f also exhibit some favorable ADME parameters, their slightly lower LogP values and fewer HBD may impact their overall drug-likeness. Compound 4g, with the lowest LogP and fewer HBD and HBA, may pose challenges in terms of absorption and interaction with target receptors.

Overall, compounds such as erlotinib, gefitinib, 4e, and 4h exhibit promising ADME profiles, suggesting their potential suitability as drug candidates. However, further in vitro and in vivo studies would be necessary to validate their efficacy and safety profiles before advancing them through drug development pipelines.

V. CONCLUSION

This superficial one-pot techniqueably produced varyingly functionalized 1-methyl-3-(substituted secondary amine-2-oxoacetyl)-1H-indole-2-carboxylic acid derivatives. The one-pot technique is stress-free and gives the name compounds in blameless yield and purity. The newly synthesized 1-methyl-3-(substituted secondary amine-2-oxoacetyl)-1H-indole-2-carboxylic acid showed promising antibacterial and antifungal activities. Further structure modification and SAR studies will surely assess the biological importance of these molecules in detail.

VI.Acknowledgment

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