Original Article

Synthesis, Characterization, Antibacterial Activity And Molecular Docking Studies Of Novel Nitrogen Based Indole-2-One Schiff's Bases.

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Abstract

Series of some novel nitrogen based Indole-2-one Schiff's bases (4a-4j) were synthesized by a conventional method via Schiff's bases mechanism. The Istain Schiff's bases was made by combining substituted isatin with hydrazine hydrate in ethanol to generate a compounds 3a-3d, which was then reacted with terephthaldehyde and 5-amino pyrimidine to obtained final compounds. All the synthesized compounds gave a good yield between 76-88% and structure was confirmed by FT-IR, LC-MASS and ^{1}H-NMR spectral analysis. The novel nitrogen based Indole-2-one Schiff's bases are screened for antimicrobial activity using standard agar diffusion method and using four bacterial stains (*Staphylococcus aureus, Bacillus subtilis*, *Escherichia coli, Salmonella paratyphi*). The most of the compounds such as **4a, 4d, 4e, 4h** and **4j** shows good activity against gram positive and gram negative bacteria. Finally, molecular docking studies were carried out by using AUTODOCK suite of MGL Tools by using Fgb1 receptor with PDB ID (3K4P). Among the docked ligands, compound **4a, 4d** and **4h** reported highest docking score **(-9.8, -9.7** and **-9.7).**

Keywords: Isatin, 2-amino Pyrimidine, terephthaldehyde, Molecular Docking, Antimicrobial activity, Streptomycin.

INTRODUCTION:

In a generally, most of the bioactive organic compounds or molecules contains hard or soft donor sites of N/O/S atoms occur in nature. These bioactive organic molecules which contain heterocyclic nitrogen are predominantly present in biomolecules, vitamins and agrochemicals. Mostly heterocyclic nitrogen containing bases i.e. Indole, pyrimidine, Schiff bases are powerful antiviral and anticancer agents in pharmacological and physiological fields [1]. The discovery of novel potent anticancer agents and antimicrobial agents by laboratory preparation has been in progress for the improvement to design drugs based on the drug-receptor or drug-enzyme interactions. Therapeutically active and new drug constituents are needed for the treatment of different diseases and disorders due the increased resistance against the existing drugs, so organic compounds and pharmacists are endeavouring to contribute in this field for new compounds with great therapeutic potential.

Synthesis of indole Schiff's bases had been of increasing interest, since many of their derivatives exhibited useful applications such as antibacterial, anticonvulsant, anticancer and antiviral agents. The drugs with an Indole moiety include imine are an important class of heterocyclic compounds with potent antibacterial activity [2-5]. The Schiff Bases was initially synthesized by the Hugo Schiff in 1864, he is an Italian scientist. The dehydration/ Condensation reaction of aldehyde/ketones with aromatic amines leads to the discovery of compounds that were later called Schiff Bases. Schiff's are important organic compounds with a wide range of biological importance. The stability of imine bond makes the carbazone derivatives has a wide range of applications that are, the presence of unique electron donating and electron accepting moieties. Schiff bases possessed many potential biological activities like Antimicrobial, antidepressant, anthelmintic, anti-tubercular, anticonvulsant, anti-inflammatory, analgesic and anticancer activities [6-8].

In this current study, a series of novel nitrogen based Indole-2-one Schiff's bases (4a-4j) [6-(((E)-4-((E)-(((Z)-2-oxoindolin-3-ylidene) hydrazineylidene) methyl) benzylidene) amino) pyrimidine-2,4(1H,3H)-dione] were synthesized from Indole-2,3-dione with 2-amino pyrimidine/6-amino pyrimidine-2,3-dione with aim of finding bioactive compounds [9-11]. The structure of these synthesized compounds were confirmed by means of IR, Mass and ^{1}H NMR analysis. In addition, molecular docking studies and the preliminary antibacterial, antifungal activities was tested. The synthetic route of target compounds in showed in Schem-1.

MATERIALS AND METHOD:

All the chemicals and reagents are purchased from TCI, SD Fine and Hychem Laboratories. The synthesized derivatives are physical characterized by TLC methods by using silica gel plates. It is carried out by using mobile phase n-hexane: ethyl acetate (7:3). Then analytical techniques were performed by Spectral analysis like FTIR spectroscopy (Shimadzu), ^{1}HNMR spectroscopy (300MHZ) solvent DMSO-d6, Mass spectrometry (Shimadzu). Finally, Molecular docking studies were carried out by using Auto dock software.

General Procedures:

Step-I: Synthesis of 3-hydrazineylidene-5-substitutedindolin-2-one(2a-2e). Substituted Istain (Indole2,3-dione) was taken in a mixture of Hydrazine hydrate (0.01 mole), glacial acetic acid (2-5ml) and ethanol 30 ml in round bottom flask. Then the reaction mixture was refluxed for 2-3 hrs. The progress of the reaction was monitored by TLC (n-hexane: Ethyl acetate) (7:3). The reaction mixture was cooled to room temperature. A solid was obtained, which was filtered off, washed with hexane and recrystallized from methanol to give crystalline solid [12].

Step-II: Synthesis of 4-((E)-(((E)-5-substituted-2-oxoindolin-3-ylidene) hydrazine ylidene) Bmethyl) benzaldehyde (3a-3e). 3-hydrazineylidene-5-substitutedindolin-2-one(2a-2e) was taken in a mixture of terephthaldehyde (0.01 mole), glacial acetic acid (2-5ml) and ethanol 30 ml in round bottom flask. Then the reaction mixture was refluxed for 2-3 hrs. The progress of the reaction was monitored by TLC (n-hexane: Ethyl acetate) (7:3). The reaction mixture was cooled to room temperature. A solid was obtained, which was filtered off, washed with hexane and recrystallized from methanol to give crystalline solid [13].

Step-III: Synthesis of 6-(((E)-4-((E)-(((Z)-5-nitro-2-oxoindolin-3-ylidene) hydraziney lidene) methyl) benzylidene) amino) pyrimidine-2,4(1H,3H)-dione. (4a-4j). 4-((E)-(((E)-5-substituted-2-oxoindolin-3-ylidene) hydrazine ylidene) Bmethyl)benzaldehyde (3a-3e) was taken in a mixture of Aromatic amines (0.01 mole), glacial acetic acid (2-5 ml) and ethanol 30 ml in round bottom flask. Then the reaction mixture was refluxed for 2-3 hrs. The progress of the reaction was monitored by TLC (n-hexane: Ethyl acetate) (8:2). The reaction mixture was cooled to room temperature. A solid was obtained, which was filtered off, washed with hexane and recrystallized from methanol to give crystalline solid [14].

Compound.4a:6-(((E)-4-((E)-(((Z)-2-oxoindolin-3-ylidene) hydrazineylidene) methyl) benzylidene) amino) pyrimidine-2,4(1H,3H)-dione. M.P. 187-189°C; Mol.Formula: $C_{21}H_{14}N_6O_3$; % Yield: 83%; IR(vcm^{-1}): 3391, 3310(-NH *Str*, Pyrimidine-2,3-dione); 3209(-NH *Str*, Indole); 3083(CH *Str*, Aromatic), 2909(-CH Str, Imine), 1707(-CO *Str*, Indole), 1700, 1688(-CO *Str*, Pyrimidine-2,3-dione), 1616(-C=N *Str*), 1528(-C=CH *Str*), 1460(-C=C *Str*), 1037(-C-N *Str*). ^{1}H-NMR(DMSO) δ ppm: 12.1548(1H, s, -NH proton in Indole), 12.1023(2H, s, -NH protons in Pyrimidine ring), 9.6875(1H, s, -CH=N), 9.2103(IH, s, -CH=N),8.1823(1H, s, pyrimidine proton), 7.7092-7.7007(2H, d, Ar-H), 7.6543-7.6342(2H, d, Ar-H), 7.5665-7.4818(2H, d, Ar-H), 7.8893-7.7998(2H, t, Ar-H). Mass (LC-MS): m/z 386.11(M), 387.21(M+1, 100%).

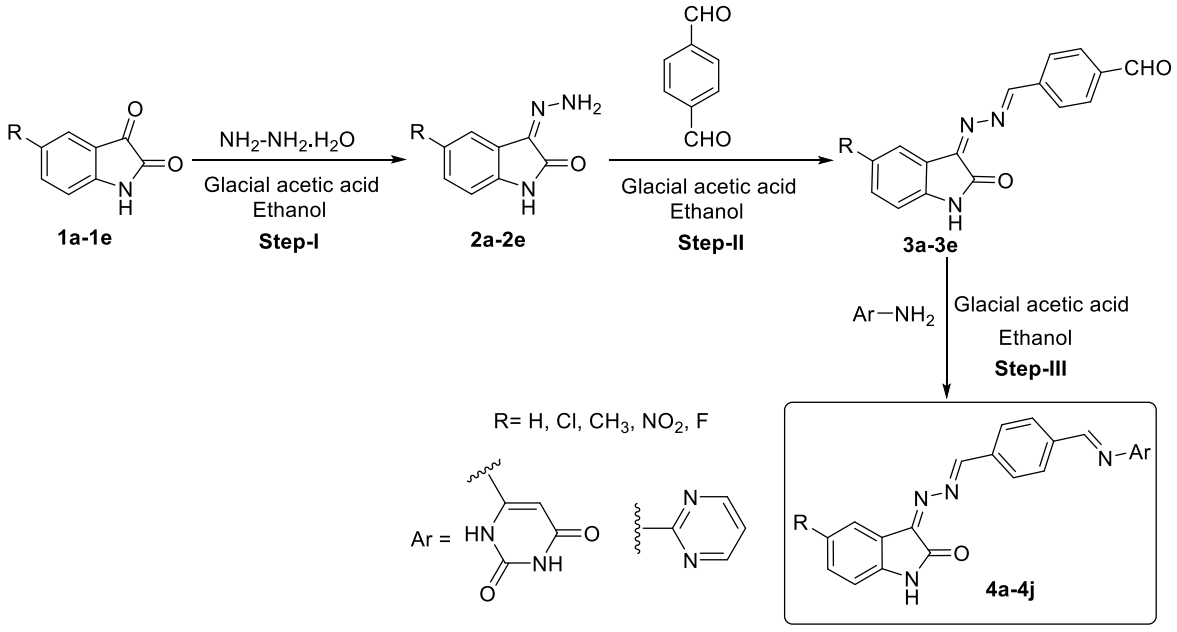


Fig.1. Scheme-I

Compound.4b:6-(((E)-4-((E)-(((Z)-5-nitro-2-oxoindolin-3-ylidene) hydrazineylidene) methyl) benzylidene) amino) pyrimidine-2,4(1H,3H)-dione. M.P. 213-215°C; Mol.Formula: $C_{20}H_{13}N_7O_5$; % Yield: 80%; IR(vcm^{-1}): 3318, 3308(-NH *Str*, Pyrimidine-2,3-dione); 3294(-NH *Str*, Indole); 3132(CH *Str*, Aromatic), 2931(-CH Str, Imine), 1715(-CO *Str*, Indole), 1701, 1692(-CO *Str*, Pyrimidine-2,3-dione), 1642(-NO_2 Str, Ar-NO_2), 1591(-C=N *Str*), 1511(-C=CH *Str*), 1453(-C=C *Str*), 1056(-C-N *Str*). ^{1}H-NMR(DMSO) δ ppm: 12.0980(2H, s, -NH proton in Pyrimidine ring), 11.5949(1H, s, -NH

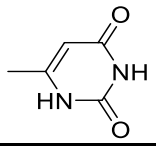
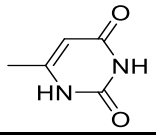
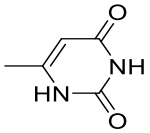
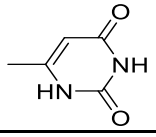
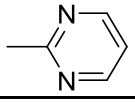
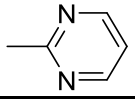
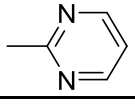
protons in Indole), 9.7983(1H, s, -CH=N), 9.3543(IH, s, -CH=N), 7.9828(1H, s, Ar-H), 7.8954-7.8786(2H, d, Ar-H), 7.7986-7.709(2H, d, Ar-H), 7.6887-7.5875(2H, d, Ar-H), 7.5765(1H, s, pyrimidine proton), Mass (LC-MS): m/z 431.10(M), 432.21(M+1, 100%).

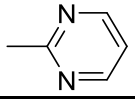
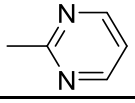
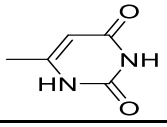
Compound.4c:6-(((E)-4-((E)-(((Z)-5-chloro-2-oxoindolin-3-ylidene)hydrazineylidene)methyl) benzylidene) amino) pyrimidine-2,4(1H,3H)-dione. M.P. 219-221ºC; Mol.Formula: $C_{20}H_{13}N_6ClO_3$; % Yield: 78%; IR(νcm^{-1}): 3385, 3359(-NH *Str*, Pyrimidine-2,3-dione); 3211(-NH *Str*, Indole); 3091(CH *Str*, Aromatic), 2985(-CH Str, Imine), 1723(-CO *Str*, Indole), 1710, 1697(-CO *Str*, Pyrimidine-2,3-dione), 1549(-C=N *Str*), 1486(-C=CH *Str*), 1359(-C=C *Str*), 1025(-C-N *Str*), 745(-Cl *Str*, Ar-Cl). ^{1}H-NMR(DMSO) δ ppm: 12.3350(2H, s, -NH proton in Pyrimidine ring), 11.8043(1H, s, -NH protons in Indole), 9.6564(1H, s, -CH=N), 9.5421(IH, s, -CH=N), 8.3012(1H, s, Ar-H), 7.9984(2H, d, Ar-H), 8.0273-8.0194(2H, d, Ar-H), 7.9983-7.9482(2H, d, Ar-H), 7.7997-7.7924(2H, d, Ar-H), 7.7875(1H, s, pyrimidine proton). Mass (LC-MS): m/z 420.07(M), 421.21(M+1, 100%), 422.31(M+2, 30%).

Compound.4d: 6-(((E)-4-((E)-(((Z)-5-methyl-2-oxoindolin-3-ylidene) hydrazineylidene) methyl) benzylidene) amino)pyrimidine-2,4(1H,3H)-dione. M.P. 237-249ºC; Mol.Formula: $C_{21}H_{16}N_6O_3$; % Yield: 85%; IR(νcm^{-1}): 3340, 3294(-NH *Str*, Pyrimidine-2,3-dione); 3240(-NH *Str*, Indole); 3084(CH *Str*, Aromatic), 2914(-CH Str, Imine), 1717(-CO *Str*, Indole), 1704, 1689(-CO *Str*, Pyrimidine-2,3-dione), 1614(-C=N *Str*), 1477(-C=CH *Str*), 1310(-C=C *Str*), 1039(-C-N *Str*). ^{1}H-NMR(DMSO) δ ppm: 12.1762(2H, s, -NH proton in Pyrimidine ring), 11.5643(1H, s, -NH protons in Indole), 9.8980(1H, s, -CH=N), 9.7028(IH, s, -CH=N), 8.4023(1H, s, Ar-H), 8.3674(1H, s, pyrimidine proton), 7.9984(2H, d, Ar-H), 7.8998-7.8784(2H, d, Ar-H), 7.7543(2H, d, Ar-H), 2.1947(1H, s, Ar-CH_3). Mass (LC-MS): m/z 400.13(M), 401.14(M+1, 100%).

Compound.4e:6-(((E)-4-((E)-(((Z)-5-chloro-2-oxoindolin-3-ylidene)hydrazineylidene)methyl) benzylidene) amino) pyrimidine-2,4(1H,3H)-dione. M.P. 197-199ºC; Mol.Formula: $C_{20}H_{13}N_6ClO_3$; % Yield: 86%; IR(νcm^{-1}): 3325, 3311(-NH *Str*, Pyrimidine-2,3-dione); 3259(-NH *Str*, Indole); 3098(CH *Str*, Aromatic), 2912(-CH Str, Imine), 1721(-CO *Str*, Indole), 1525(-C=N *Str*), 1395(-C=CH *Str*), 1337(-C=C *Str*), 1095(-C-N *Str*), 930(-Cl *Str*, Ar-Cl). ^{1}H-NMR(DMSO) δ ppm: 12.3728(2H, s, -NH proton in Indole ring), 9.5213(1H, s, -CH=N), 9.3092(IH, s, -CH=N), 7.6004-7.6001(1H, s, Ar-H), 7.5987-7.5652(2H, d, Ar-H), 7.5346-7.5209(2H, d, Ar-H), 7.4998-7.4873(2H, d, Ar-H), 7.5135(1H, t, Ar-H). Mass (LC-MS): m/z 388.08(M), 389.21(M+1, 100%), 390.03(M+2, 30%)

Physical properties (4a-4j)

Compounds	Molecular Formula	R	R_1	Molecular weight(gm)	M.P(^{0}C)	%Yield
4a	$C_{20}H_{14}N_6O_3$	H		386.11	187-189	83
4b	$C_{20}H_{13}N_5O_5$	NO_2		431.10	213-215	80
4c	$C_{20}H_{13}ClN_6O_3$	Cl		420.07	219-221	78
4d	$C_{21}H_{16}N_6O_3$	CH_3		400.13	237-239	85
4e	$C_{20}H_{13}ClFN_6O$	Cl		388.08	197-199	86
4f	$C_{21}H_{16}N_6O$	CH_3		386.14	167-169	81
4g	$C_{20}H_{14}N_6O$	H		354.12	183-185	86

4h	$C_{20}H_{13}N_7O_3$	NO_2		399.11	203-205	82
4i	$C_{20}H_{13}FN_6O$	F		372.11	144-143	81
4j	$C_{20}H_{13}FN_6O_3$	F		404.10	257-258	78

Compound.4f: (Z)-5-methyl-3-(((E)-4-((E)-(pyrimidin-2-ylimino)methyl) benzylidene) hydrazineylidene) indolin-2-one. M.P. 167-169ºC; Mol.Formula: $C_{21}H_{16}N_6O$; % Yield: 81%; IR(νcm^{-1}): 3243(-NH *Str*, Indole); 3102(CH *Str*, Aromatic), 2964(-CH Str, Imine), 2894(-CH *Str*, Alkyl), 1713(-CO *Str*, Indole), 1534(-C=N *Str*), 1409(-C=CH *Str*), 1329(-C=C *Str*), 1087(-C-N *Str*). ^{1}H-NMR(DMSO) δ ppm: 12.4021(1H, s, -NH proton in Indole ring), 9.6543(1H, s, -CH=N), 9.4834(IH, s, -CH=N), 7.9845(1H, s, Ar-H), 7.4895-7.3984(2H, d, Ar-H), 7.3982-7.2983(2H, d, Ar-H), 7.1982-7.1002(2H, d, Ar-H), 6.9833-6.8732(1H, t, Ar-H), 1.9982(3H, s, Ar-CH_3). Mass (LC-MS): m/z 368.23(M), 369.32(M+1, 100%).

Compound.4g:(Z)-3-(((E)-4-((E)-(pyrimidin-2-ylimino)methyl) benzylidene) hydrazineyl idene)indolin-2-one. M.P. 183-185ºC; Mol.Formula: $C_{20}H_{14}N_6O$; % Yield: 86%; IR(νcm^{-1}): 3264(-NH *Str*, Indole); 3091(CH *Str*, Aromatic), 2988(-CH *Str*, Imine), 1709(-CO *Str*, Indole), 1602(-C=N *Str*), 1486(-C=CH *Str*), 1365(-C=C *Str*), 1032(-C-N *Str*). ^{1}H-NMR(DMSO) δ ppm: 12.5632(1H, s, -NH proton in Indole ring), 9.6872(1H, s, -CH=N), 9.3872(IH, s, -CH=N), 7.982-7.9002(2H, d, Ar-H), 7.7643-7.6908(2H, d, Ar-H), 7.5633-7.5129(2H, d, Ar-H), 7.3982-7.2903(2H, d, Ar-H), 7.1902-7.1002(2H, t, Ar-H), 6.9832-6.8743(3H, s, Ar-H). Mass (LC-MS): m/z 354.12(M), 355.32(M+1, 100%).

Compound.4h: (Z)-5-nitro-3-(((E)-4-((E)-(pyrimidin-2-ylimino) methyl) benzylidene) hydrazineylidene) indolin-2-one. M.P. 203-205ºC; Mol.Formula: $C_{20}H_{13}N_7O_3$; % Yield: 82%; IR(νcm^{-1}): 3265(-NH *Str*, Indole); 3034(CH *Str*, Aromatic), 2965(-CH *Str*, Imine), 1712(-CO *Str*, Indole), 1632(-NO_2 *Str*, Ar-NO_2),1603(-C=N *Str*), 1498(-C=CH *Str*), 14023(-C=C *Str*), 1043(-C-N *Str*). ^{1}H-NMR(DMSO) δ ppm: 12.4352(1H, s, -NH proton in Indole ring), 9.4012(1H, s, -CH=N), 9.2983(1H, s, -CH=N), 8.2713(1H, s, Ar-H), 7.9902-7.8764(2H, d, Ar-H), 7.7832-7.7003(2H, d, Ar-H), 7.6543-7.5632(2H, d, Ar-H), 7.3012-7.2983(2H, d, Ar-H), 7.1354(1H, t, Ar-H). Mass (LC-MS): m/z 399.11(M), 340.22(M+1, 100%).

Compound.4i: (Z)-5-fluoro-3-(((E)-4-((E)-(pyrimidin-2-ylimino) methyl) benzylidene) hydrazineylidene) indolin-2-one. M.P. 141-143ºC; Mol.Formula: $C_{20}H_{13}FN_6O$; % Yield: 81%; IR(νcm^{-1}): 3246(-NH *Str*, Indole); 3087(CH *Str*, Aromatic), 2988(-CH *Str*, Imine), 1709(-CO *Str*, Indole),1612(-C=N *Str*), 1502(-C=CH *Str*), 1398(-C=C *Str*), 1082(-C-N *Str*), 812(-F *Str*, Ar-F). ^{1}H-NMR(DMSO) δ ppm: 12.2093(1H, s, -NH proton in Indole ring), 9.5764(1H, s, -CH=N), 9.1982(1H, s, -CH=N), 8.3092(1H, s, Ar-H), 8.1022-8.0098(2H, d, Ar-H), 7.9832-7.8732(2H, d, Ar-H), 7.5674-7.5021(2H, d, Ar-H), 7.2983-7.2032(2H, d, Ar-H), 7.0923(1H, t, Ar-H). Mass (LC-MS): m/z 372.11(M), 373.12(M+1, 100%), 374.32(M+2, 30%).

Compound.4j: 6-(((E)-4-((E)-(((Z)-5-fluoro-2-oxoindolin-3-ylidene) hydrazineylidene) methyl) benzylidene) amino) pyrimidine-2,4(1H,3H)-dione. M.P. 257-259ºC; Mol.Formula: $C_{20}H_{13}N_6FO_3$; % Yield: 784%; IR(νcm^{-1}): 3354, 3321(-NH *Str*, Pyrimidine-2,3-dione); 3254(-NH *Str*, Indole); 3082(CH *Str*, Aromatic), 2977(-CH Str, Imine), 1712(-CO *Str*, Indole), 1708, 1699(-CO *Str*, Pyrimidine-2,3-dione), 1531(-C=N *Str*), 1490(-C=CH *Str*), 1328(-C=C *Str*), 1045(-C-N *Str*), 814(-F *Str*, Ar-F). ^{1}H-NMR(DMSO) δ ppm: 12.4982(2H, s, -NH proton in Pyrimidine ring), 11.6542(1H, s, -NH protons in Indole), 9.5674(1H, s, -CH=N), 9.2394(IH, s, -CH=N), 8.3123(1H, s, Ar-H), 8.1023-8.1002(2H, d, Ar-H), 7.8943-7.7843(2H, d, Ar-H), 7.6743-7.5886(2H, d, Ar-H), 7.4785-7.4002(2H, d, Ar-H), 7.2983(1H, s, pyrimidine proton). Mass (LC-MS): m/z 404.10(M), 405.34(M+1, 100%), 406.21(M+2, 30%).

Pharmacological activity

Antibacterial activity: Agar diffusion (Disk Plate) method was employed to test the antibacterial activity of the synthesised novel Schiff's bases of Indole derivatives(4a4j). This antibacterial activity was carried out against the *Staphylococcus aureus, Bacillus subtilis* (Gram positive) and *Escherichia coli, Salmonella paratyphi* (Gram negative) as test organisms. In this method the petridishes were filed with inoculated liquefied agar medium to uniform thickness the bores were made using core borer which filled with test drug and a Standard drug(Streptomycin) and inoculated at 37± 1ºC hrs[15]. The drug will diffuse in to the agar medium are prevents the growth of microbes and produce a clear zone of inhibition **Table.2.**

Molecular Docking Studies. The molecular docking studies is the most crucial step in drug discovery and development process to predict the lead molecules. The molecular docking models was applied to investigate the binding mode of target molecules via selected proteins with PDB ID (3K4P) for the protein active pocket of the modelled Fgb1. I have

docked 10 ligands like novel nitrogen based Indole-2-one Schiff's bases (4a-4j) in to active site of the Fgb1 protein using AUTODOCK suite of MGL Tools. The protein-ligand interactions of the dataset ligands were observed by using structurally optimized protein shape with Glide Xp docking protocol. Primarily, a 3D grid used to be set up to the binding active site of the Fgb1 protein into all the dataset ligands had been docked. Finally, the binding interactions and it was was calculated in phrases of Glide score [16]. It is a combination of hydrophilic, hydrophobic, metal binding groups, Van der Waals energy, Freezing rotatable bonds and polar interactions with receptor. Highest docked pose with lowest glide score was recorded for each ligand and extra precision was performed by using Auto dock suite.

RESULTS AND DISCUSION.

Chemistry: The synthetic route for the novel Schiff's bases of Indole derivatives(4a4j) is outline in the scheme-1. In the first step, 3-hydrazineylidene-5-substitutedindolin-2-one(2a-2e) were synthesized by Schiff's base reaction between substituted Isatin (1a-1e) and Hydazine hydrate in the presence of glacial acetic acid. It can be reacting via Schiff' base mechanism with teraphthadehyde to give 4-((E)-(((E)-5-substituted-2-oxoindolin-3-ylidene) hydrazine ylidene) Bimethyl) benzaldehyde (3a-3e). Finally, the 3a-3e compounds reacts with substituted Aromatic amine to give the title compounds (4a-4j). All the synthesized compounds were characterized by the physical**(Table.1)** and Spectral analysis.

In the IR (ν cm^{-1}) spectra appearance of novel Schiff's bases of Indole derivatives(4a4j) at 3210-3380cm^{-1} shows that –NH stretching bands. All the compounds having carbonyl stretching(>C=O) were observed at between 1690-1725 and compounds contain aromatic and aliphatic C-H stretching were observed around observed at around 3000-3150cm^{-1} and 2912-2898cm^{-1}. Some of the derivatives containing Ar-Cl/F group showed strong absorption peak around in the region of 750-830cm^{-1}. In the ^{1}HNMR spectrum of all the derivatives showed that singlet protons at δ 11.203-12.765 due to -NH protons of indole, Pyrimidine rings and at δ 9.203-9.897 due to imine protons(-CH=N-). All the synthesized compounds were showed singlets, doublets and triplets at δ 6.801-8.493 due to aromatic protons. In the ^{13}C NMR of novel novel Schiff's bases of Indole derivatives showed that peak appeared around at δ 170-178 ppm were confirmed by carbonyl carbon (C=O) and imine carbons(C=N) were conformed at δ 156-140ppm. Most of compounds were showed signal at δ 22-32 ppm were confirmed by methyl carbon(-CH_3). The Mass spectrum of all derivatives(4a-4j) are confirmed by their molecular ion peak and molecular weight given in the spectrum.

Antibacterial activity: All the **s**ynthesized (4a-4j) were subjected to antibacterial activity by agar diffusion method. The novel nitrogen based Indole-2-one Schiff's bases are screened against by using four bacterial stains (*Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Salmonella paratyphi*). From the results, the compounds such **4b(**24*), **4d**(23*) against *E.Coli*; compounds **4d**(25*), **4f**(24*), **4h**(25*), **4j**(25*) against the *Staphylococcus aureus;***4h**(23*) and **4j**(23*) against the *Salmonella paratyphi* by comparison with standard drug.

Table.2. Antibacterial activity of novel nitrogen based Indole-2-one Schiff's bases **(4a-4j)**

	Zone of Inhibition (in mm)			
	Staphylococcus aureus	***Bacillus subtilis***	***E.Coli***	***Salmonella paratyphi***
4a	21	10	0	19
4b	12	23	**24***	21
4c	18	17	19	13
4d	25*	10	23*	20
4e	09	13	20	15
4f	24*	23*	0	0
4g	16	19	17	12
4h	25*	10	19	23*
4i	16	0	0	20
4j	25*	20	18	23*
Streptomycin	28	31	33	32

All values are expressed as % Inhibition; Bore size = 6mm; Concentration of test compounds is 100µg/mL

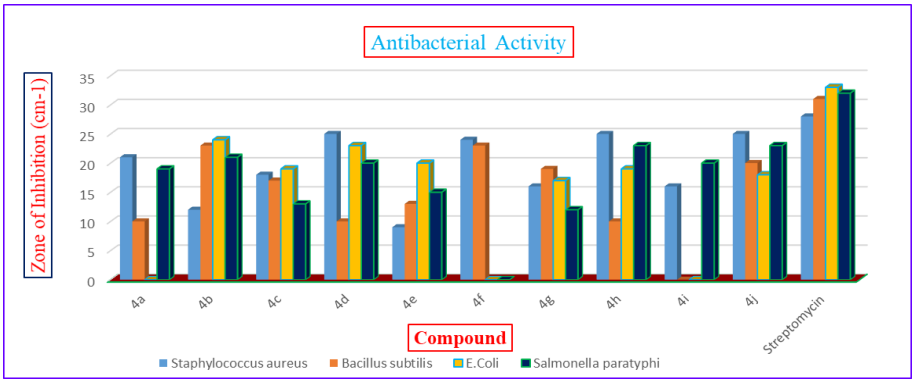


Fig.2. Graphical representation of novel nitrogen based Indole-2-one Schiff's bases (4a-4j)

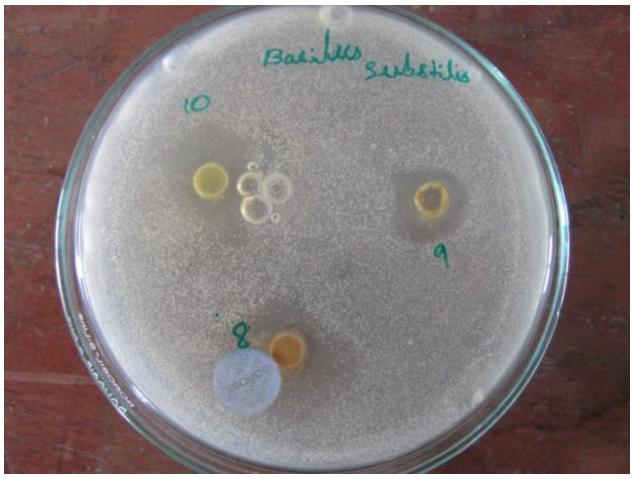
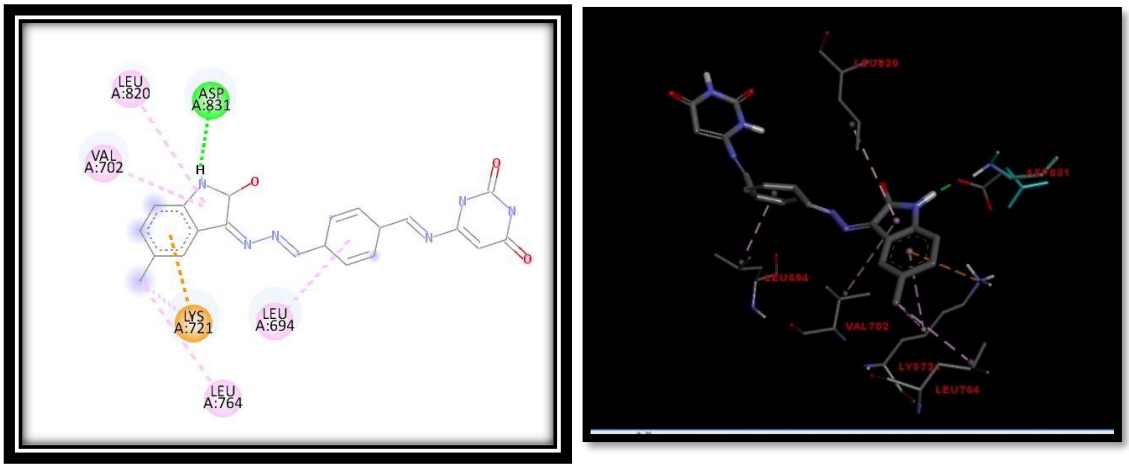


Fig.3: Photographs of Antibacterial activity- novel nitrogen based Indole-2-one Schiff's bases (4a-4j)

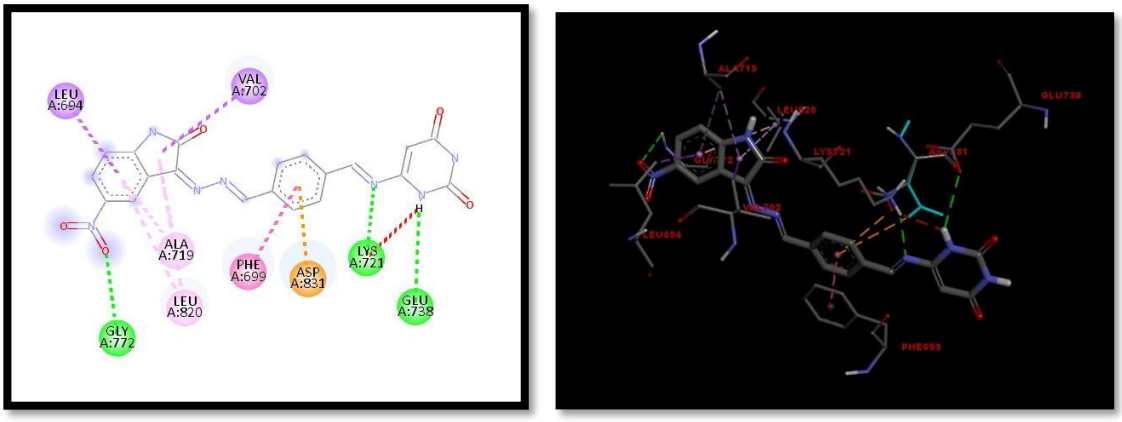
Molecular Docking Studies: The molecular docking models was applied to investigate the binding mode of target molecules via selected proteins with PDB ID (3K4P) for the protein active pocket of the modelled Fgb1. I have docked 10 ligands like novel nitrogen based Indole-2-one Schiff's bases (4a-4j) in to active site of the Fgb1 protein using AUTODOCK suite of MGL Tools. Glide dock score of the dataset ligand were showed in Table.3. along with the interaction amino acids like LEU:694, PHE:699, VAL:702, ALA:719, LYS:721, GLU:738, LEU:820, ASP:831, MAT:742, CYS:773, MET:769. From the results with Fgb1 protein, compound 4a, 4d, and 4h (-9.8, -9.7, -9.7). The docking score of the ligands ranged from -**9.8**(compound **4a**) to-**9.1**(Compound **4c**)**.** Except compound 4c, 4e, 4f, 4g and 4j all compound one hydrogen bond with most of the amino acids.

Table.3. Docking scores of novel nitrogen based Indole-2-one Schiff's bases (4a-4j)-Glide dock score of the dataset ligands.

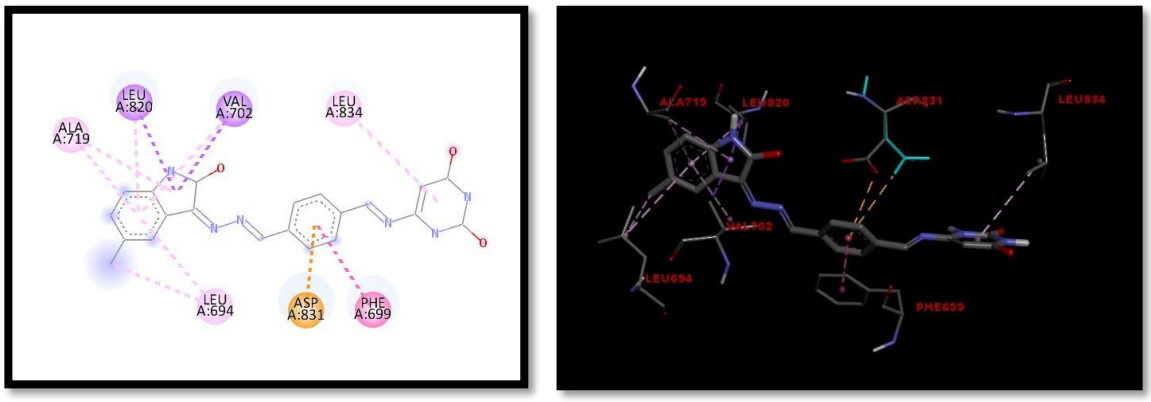
Compound No	Binding Energy (Kcal/mol)	No of H-bonds	Interacting amino acids	H-bond lengths (Å)
4a	-9.8	1	LEU:694, VAL:702, LYS:721, LEU:764, LEU:820, ASP:831	1.85
4b	-9.5	3	LEU:694, PHE:699, VAL:702, ALA:719, GLY:772, ASP:831, LEU:820, LYS:721, GLU:739	2.27, 2.89, 2.93
4c	-9.1	Nil	PHE:699, VAL:702, ALA:719, LEU:820,	Nil
4d	-9.7	0	LEU:694, PHE:699, VAL:702, ALA:719, LEU:820, LEU:834, ASP:831	-
4e	-9.2	Nil	PHE:699, VAL:702, ASP:831	Nil
4f	-9.3	Nil	VAL:702, ALA:719, LEU:820, ASP:831	Nil
4g	-9.1	Nil	PHE:699, VAL:702, ALA:719, LEU:820,	Nil
4h	-9.7	2	PHE:699, VAL:702, ALA:719, , LEU:820, ASP:831, LYS:721	1.82,2.43
4i	-9.5	2	PHE:699, VAL:702, ALA:719, LEU:820, CYS:773, ASP:831, LYS:721	2.12, 2.15
4j	-9.5	Nil	LEU:694, PHE:699, VAL:702, ALA:719, GLY:772, ASP:831, LEU:820, ASP:776, MET:769	-



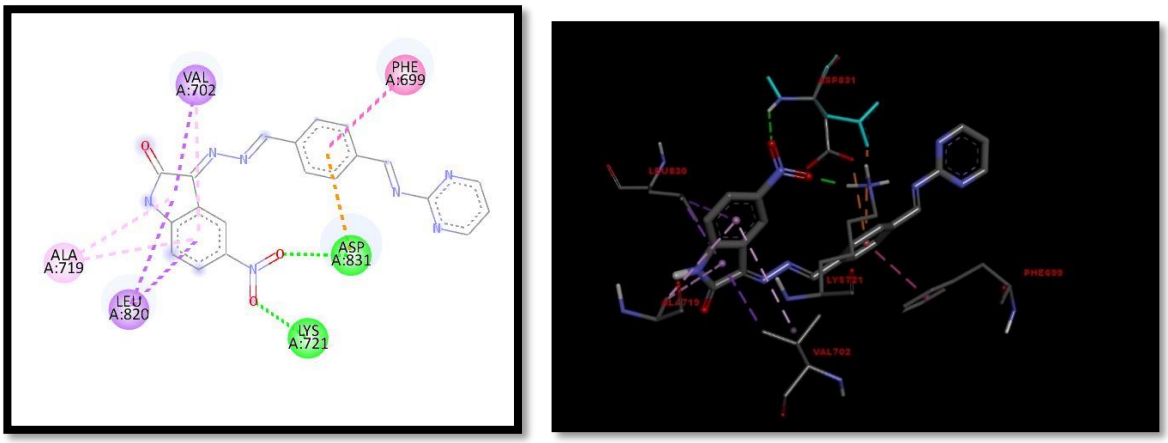
Compound4a.Dock1 and 3d structures



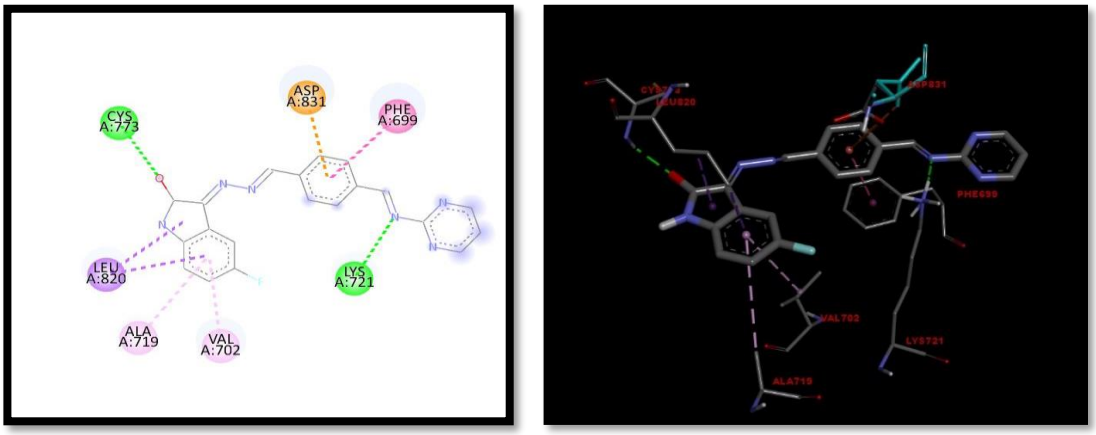
Compound4b.Dock1 and 3d structures



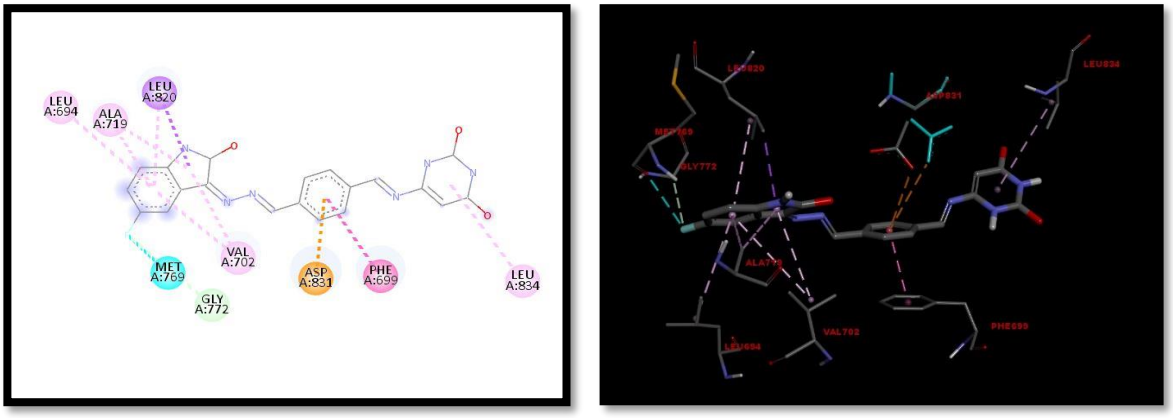
Compound4d.Dock1 and 3d structures



Compound4h.Dock1 and 3d structures



Compound4i.Dock1 and 3d structures



Compound4j.Dock1 and 3d structures

CONCLUSION:

In this study, ten new nitrogen based Indole-2-one Schiff's bases(4a-4j) were synthesized and all structures of the compounds were confirmed by IR, 1H-NMR and Mass spectrometry. The antibacterial activity was investigated for their inhibitory action on the growth of *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Salmonella paratyphi* bacteria, respectively. The results indicated, the compound 4b, 4d against *E. Coli*; compounds 4d, 4f, 4h, 4j against the *Staphylococcus aureus;* 4h and 4j against the Salmonella paratyphi are showing more activity by comparison with standard drug. The docking score of the ligands ranged from -9.8 (compound 4a) to-9.1 (Compound 4g).

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CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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