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SYNTHESIS, CHARACTERIZATION, MOLECULAR DOCKING STUDIES AND ANTHELMINTIC AND ANTI-CANCER ACTIVITY OF PYRAZOLE CONTAIN NOVEL INDOLIN-2-ONE DERIVATIVES

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Keywords:

Isatin, Pyrazole, Anthelmintic, Anticancer activities, Molecular Docking

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ABSTRACT: Background: Imidazole-5-one scaffold has been predicted in the important synthetic drug analogs, which gave valuable information for treatment and high binding affinity to the multiple receptors helpful drug development. **Objective:** To synthesize and evaluate the anthelmintic, anticancer, and Insilco docking studies of pyrazole contain novel Indole derivatives (4a-4h). **Methods:** In the present work, we intended to synthesize pyrazole containing novel Indole derivatives (4a-4h) by a conventional method. **Results:** All the newly synthesized molecules (4a-4h) were characterized by FTIR, ^{1}HNMR, and Mass spectral analysis. The compounds 4c and 4f showed high anthelmintic activity compared with Albendazole as a standard and the compounds 4b, 4e, 4f, and 4g exhibited good anticancer activity against MCF-7 cell line. In molecular docking research, dock rankings of all the synthesized derivatives ranged from -5.972 (compound 4h) to -3.127 (compound 4d). **Conclusion:** The literature reveals that Imidazole-5-one derivatives have diverse biological activities and a cytotoxic potential to be explored for newer therapeutic possibilities.

INTRODUCTION: Medicinal chemistry is a chemistry- grounded discipline involving aspects of birth, medical and knowledge. It's concerned with the invention, discovery, design, identification, and physic of biologically active amalgams, the interpretation of their mode of action at the molecular place, and the construction of the relationship between chemical structure and pharmacological exercise.

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Indole and its by-products, a class of well- known nitrogen and Sulphur containing heterocyclic admixtures, absorb an important position in medicinal and Acaridae chemistry with a wide range of bioactivities. Pyrazole spin-offs have a long history of use in agrochemicals as manures and manures and in pharmaceutical sedulousness as antipyretic and anti-inflammatory [1].

Antipyrine is one of the virgin synthetic specifics and is named after its antipyretic tracts. Benzo pyrrole heterocyclic combinations represent important edifice blocks in organic and medicinal chemistry. Multiple significant inquest exercise was carried out towards this structure. The heterocyclic Indole and its derivations show

remarkable consanguineous and pharmacological exercise as anti-viral exercise, Anthelmintic exercise, antibacterial, antifungal, anti-inflammatory, anti-oxidant, antidepressant & anticonvulsant, analgesic, antihistaminic. Molecular docking provides useful information about physic receptor intercourses. It analyzes the ribbon frontage of small scrap physic hopefuls to their protein targets to prophesy the small scrap's affinity and exertion. Docking is considered to be a puissant simulation of the molecular recognition process. It's used to illustrate the probable molecular intercourse of a designed ligand with the protein of interest, prophesy the affinity and exertion of the ligand and identify the energy of the intercourse between the ligand and protein [2-4].

MATERIALS AND METHODS: In this Investigation, all chemicals were purchased from a local dealer with S.D fine make use. The synthesized compounds were screened for anthelmintic, anti-cancer activities. Melting points (MP) were determined in an open capillary and are uncorrected [5-8]. The Fourier-transform infrared spectroscopy (FT-IR) was recorded on Shimadzu FTIR-8400S. The Proton Nuclear magnetic resonance (^{1}H-NMR) spectra were recorded in DMSO-d_6 and chemical shifts (δ) on Bruker DRX-300 MHz. Spectrometer using TMS as an internal reference with their values expressed in δ ppm [9-12]. The purity of all the synthesized compounds was routinely checked by Thin Layer Chromatography (TLC) on silica gel G in the solvent system (n-Hexane: Ethyl acetate (8:2).

Chemistry: The present work is constructed on substituted isatin compounds with hydrazine hydrate to hand 3-hydrazineylideneindolin-2-one (1a-d). Then the pyrazole derivatives (2a-d) go through acetylation reaction with acetic anhydrite to produce 1-(3-phenyl-5-(thiophen-2-yl)-4,5-dihydro-1H-pyrazol-1-yl) ethan-1-one (3a-3b) [13]. In final step, the compound (3-phenyl-5-(thiophen-2-yl)-4,5-dihydro-1H-pyrazol-1-yl) ethan-1-one derivatives (3a-3d, 0.01 mol) was taken in a round bottom flax, it contains mixture of 3-hydrazineylideneindolin-2-one (1a-b, 0.01 mol) and glacial acetic acid (5 mL) and Ethanol 30ml. Then the reaction mixture was refluxed for 1-2hrs and the progress of the reaction was observed by TLC (Hexane: EtoAc 7:3) method. Then the reaction mixture was cooled to room temperature, it will give the solid final product, which was filtered off and washed with hexane solvent and recrystallized from methanol to get a crystalline product. The obtained compounds were subjected to analytical characterization **Fig. 1.**

(E) – 3 - (((E) - 1 -(3-phenyl-5-(thiophen-2-yl) - 4, 5 – dihydro - 1H-pyrazol – 1 - yl) ethylidene) hydraziney lidene) indolin-2-one (4a): m.p. 232–234°C Mol. formula: $C_{23}H_{19}N_3OS$, Microwave irradiation yield 74%, IR (*ν* cm−1): 3414(N-H, *Str*, Indole), 3062 (C-H *Str*, Ar), 2992, 2842 (C–H *Str*, Aliphatic), 2349(-C-S-C, *Str*, Thiophene ring), 1700(C=O *Str*, Indole), 1636(-C=N, *Str*,), 1548 (CH=CH *Str*), 1432 (C=C, *Str*). ^{1}H-NMR (DMSO) *δδ* ppm: 12.090(s, 1H, Indole), 8.450-8.387(d, 2H, Ar-H),8.066-8.043 (d, 2H, Ar-H), 7.947-7.921(t, 1H, Ar-H), 7.821-7.757 (t, 3H, Ar-H), 7.171-7.140 (d, 2H, Ar-H), 6.812-6.201(t, 3H, Ar-H), 4.731(dd, 1H, -CH- pyrazole), 4.138-4.116(dd, 1H, -CH_2- pyrazole), 3.075-3.061(dd, 1H, -CH_2- pyrazole). Mass (ESI-MS): m/z 413(M), 414(M + 1, 100%).

(E)-5-methyl-3-(((E)-1-(3 – phenyl - 5-(thiophen-2-yl)-4, 5-dihydro-1H-pyrazol-1-yl) ethylidene) hydrazineylidene) indolin-2-one (4b): m.p. 219–221°C Mol. formula: $C_{24}H_{21}N_5OS$, Microwave irradiation yield 79%, IR (*ν* cm−1): 3414(N-H, *Str*, Indole), 3052 (C-H *Str*, Ar), 2972, 2840,2775(C–H *Str*, Aliphatic), 2342(-C-S-C, *Str*, Thiophene ring), 1700(C=O *Str*, Indole), 1657(-C=N, *Str*,), 1549 (CH=CH *Str*), 1485 (C=C, *Str*). ^{1}H-NMR (DMSO) *δδ* ppm: 11.763(s, 1H, Indole), 8.361(s, 1H, Ar-H),8.295-8.115(d, 2H, Ar-H), 7.885-7.884(d, 1H, Ar-H), 7.792-7.771 (d, 2H, Ar-H), 7.696-7.670 (t, 1H, Ar-H), 7.554-7.418(t, 3H, Ar-H), 4.893(dd, 1H, -CH- pyrazole), 4241-4.200(dd, 1H, -CH_2- pyrazole), 3.955-3.919(dd, 1H, -CH_2- pyrazole),-2.306(s, 3H, CH_3). Mass (ESI-MS): m/z 427(M), 428(M + 1, 100%).

(E) – 5 – chloro – 3 - (((E) - 1-(5-(thiophen-2-yl)-3-(phenyl - 4, 5-dihydro-1H - pyrazol - 1 - yl) ethyl idene) hydra zineylidene)indolin-2-one(4c): m.p. 199–201°C Mol. formula: $C_{23}H_{18}N_5OS$, Microwave irradiation yield 79%, IR (*ν* cm−1): 3427(N-H, *Str*, Indole), 3048(C-H *Str*, Ar), 2959, 2853,2754(C–H *Str*, Aliphatic), 2318(-C-S-C, *Str*, Thiophene ring), 1703(C=O *Str*, Indole), 1631(-C=N, *Str*,), 1591(CH=CH *Str*), 1536 (C=C, *Str*),

1236(-C=N, *Str*),790(-Ar-Cl, *Str*). ^{1}H-NMR (DMSO) *δδ* ppm: 12.031(s, 1H, Indole NH), 8.373(s, 1H, Ar-H), 8.313-8.103(d, 2H, Ar-H), 7.886-7.848(t, 1H, Ar-H), 7.688-7.638 (d, 3H, Ar-H), 7.586-7.579 (d, 2H, Ar-H), 7.513(d, 2H, Ar-H), 4.810(dd, 1H, -CH- pyrazole), 4.256-4.233(dd, 1H, -CH_2- pyrazole), 3.805-3.801(dd, 1H, -CH_2- pyrazole), 2.021(s, 3H, CH_3). Mass (ESI-MS): m/z 447(M), 448(M + 1, 100%), 449(M + 2, 30%).

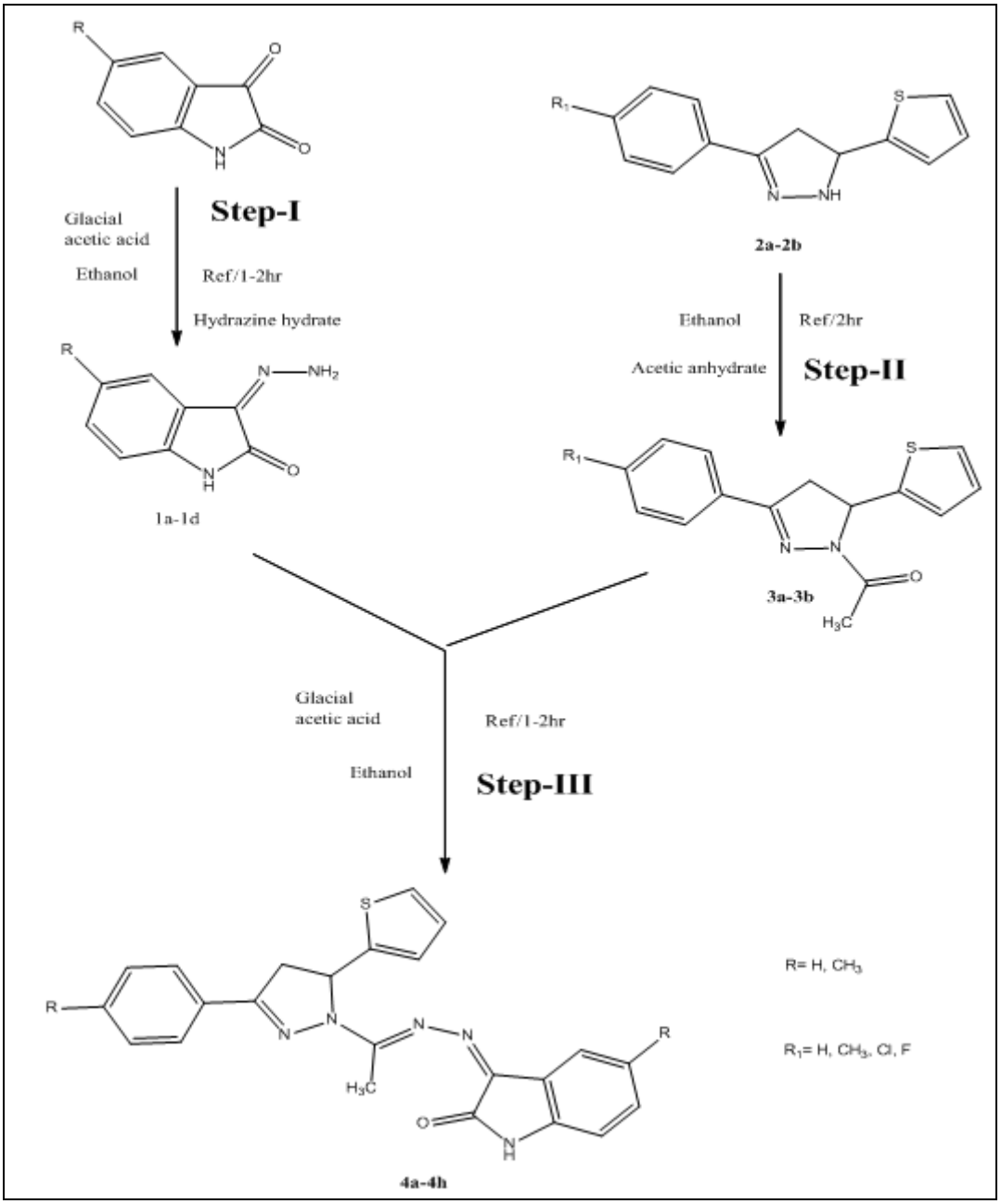


FIG. 1: SCHEME (PYRAZOLE CONTAINS NOVEL INDOLIN-2-ONE DERIVATIVES)

5-fluoro-3-(((E)-1-(3-phenyl-5-(thiophen-2-yl)-4, 5 – dihydro - 1H – pyrazol – 1 - yl) ethylidene) hydrazineylidene) indolin-2-one (4d): m.p. 209–211°C, Mol. formula: $C_{23}H_{18}N_5OSF$, Microwave irradiation yield 73%, IR (*ν* cm−1): 3417(N-H, *Str*, Indole), 3076(C-H *Str*, Ar), 2981, 2843, 2798(C–H *Str*, Aliphatic), 2327(-C-S-C, *Str*, Thiophene ring), 1715(C=O *Str*, Indole), 1642(-C=N, *Str*,), 1489(CH=CH *Str*), 1456 (C=C, *Str*), 1276(-C=N, *Str*), 765(-Ar-Cl, *Str*). ^{1}H-NMR (DMSO) *δδ* ppm: 11.984(s, 1H, Indole NH), 8.421(s, 1H, Ar-H), 8.423-8.374(d, 2H, Ar-H), 7.985-7.843(t, 1H, Ar-H), 7.732-7.698 (d, 3H, Ar-H), 7.467-7.321 (d, 2H, Ar-H), 7.214(d, 2H, Ar-H), 4.898(dd, 1H, -CH-pyrazole), 4.432-4.321(dd, 1H, -CH_2- pyrazole), 3.854-3.732(dd, 1H, -CH_2- pyrazole), 2.120(s, 3H,

CH_3). Mass (ESI-MS): m/z 437(M), 438(M + 1, 100%), 439(M + 2, 30%).

(E)-3-(((E)-1-(5 - (thiophen - 2 - yl) - 3 - (p-tolyl) - 4, 5-dihydro - 1H - pyrazol - 1 - yl) ethylidene) hydrazineylidene) indolin-2-one(4e): m.p. 237-239°C, Mol. formula: $C_{24}H_{21}N_5OS$, Microwave irradiation yield 80%, IR (ν cm−1): 3452(N-H, *Str*, Indole), 3092(C-H *Str*, Ar), 2976, 2864, 2784(C–H *Str*, Aliphatic), 2372(-C-S-C, *Str*, Thiophene ring), 1708(C=O *Str*, Indole), 1623(-C=N, *Str*,), 1476(CH=CH *Str*), 1441 (C=C, *Str*), 1283(-C=N, *Str*). ^{1}H-NMR (DMSO) $\delta\delta$ ppm: 11.672(s, 1H, Indole NH), 8.102-8.002(d, 2H, Ar-H), 7.832-7.653(d, 2H, Ar-H), 7.674-7.601 (d, 2H, Ar-H), 7.321-7.306 (d, 2H, Ar-H), 7.021-7.003(t, 1H, Ar-H), 6.983-6.821(t, 2H, Ar-H), 4.783(dd, 1H, -CH- pyrazole), 4.342-4.301(dd, 1H, -CH_2- pyrazole), 3.903-3.901(dd, 1H, -CH_2- pyrazole), 2.210-2.234(s, 3H, CH_3), 1.893-1.823(s, 3H, CH_3). Mass (ESI-MS): m/z 427(M), 428(M + 1, 100%).

(E) – 5 – methyl - 3-(((E)-1-(5-(thiophen-2-yl)-3-(p-tolyl)-4, 5-dihydro-1H-pyrazol-1-yl) ethyli dene) hydrazineylidene) indolin-2-one(4f): m.p. 253-255°C, Mol. formula: $C_{25}H_{23}N_5OS$, Microwave irradiation yield 77%, IR (ν cm−1): 3402(N-H, *Str*, Indole),3075(C-H *Str*, Ar), 2964, 2851, 2792(C–H *Str*, Aliphatic), 2303(-C-S-C, *Str*, Thiophene ring), 1721(C=O *Str*, Indole), 1627(-C=N, *Str*,), 1502(CH=CH *Str*), 1454 (C=C, *Str*), 1293(-C=N, *Str*). ^{1}H-NMR (DMSO) $\delta\delta$ ppm: 12.032(s, 1H, Indole NH), 8.320-8.302 (s, 1H, Ar-H), 7.993-7.901(d, 2H, Ar-H), 7.783-7.721 (d, 2H, Ar-H), 7.543-7.421 (d, 2H, Ar-H), 7.329-7.301(d, 2H, Ar-H), 7.209-7.193(t, 1H, Ar-H), 4.835(dd, 1H, -CH- pyrazole), 4.541-4.498(dd, 1H, -CH_2- pyrazole), 3.852-3.742(dd, 1H, -CH_2- pyrazole), 2.203-2.200(s, 3H, CH_3), 1.980-1.921(s, 3H, CH_3). Mass (ESI-MS): m/z 441(M), 442(M + 1, 100%).

(E) – 5 – chloro - 3-(((E) – 1 -(5 - (thiophen-2-yl)-3-(p - tolyl) - 4, 5 – dihydro - 1H-pyrazol – 1 - yl) ethylidene) hydrazineylidene) indolin-2-one(4g): m.p. 189-191°C, Mol. formula: $C_{24}H_{20}N_5OSCl$, Microwave irradiation yield 60%, IR (ν cm−1): 3432(N-H, *Str*, Indole), 3093(C-H *Str*, Ar), 2998, 2842, 2782(C–H *Str*, Aliphatic), 2312(-C-S-C, *Str*, Thiophene ring), 1707(C=O *Str*, Indole), 1632(-C=N, *Str*,), 1529(CH=CH *Str*), 1462(C=C, *Str*), 1289(-C=N, *Str*). ^{1}H-NMR (DMSO) $\delta\delta$ ppm: 12.210(s, 1H, Indole NH), 8.287-8.209(s, 1H, Ar-H), 8.093-8.834(d, 2H, Ar-H), 7.892-7.823 (d, 2H, Ar-H), 7.632-7.601 (d, 2H, Ar-H), 7.262-7.201(d, 2H, Ar-H), 7.103-7.100(t, 1H, Ar-H), 4.932(dd, 1H, -CH- pyrazole), 4.823-4.4802(dd, 1H, -CH_2- pyrazole), 3.629-3.601(dd, 1H, -CH_2- pyrazole), 2.109-2.101(s, 3H, CH_3), 1.834-1.802(s, 3H, CH_3). Mass (ESI-MS): m/z 461(M), 462(M + 1, 100%), 463(M + 2, 30%).

(E) – 5 – fluoro - 3-(((E) - 1-(5-(thiophen-2-yl)-3-(p-tolyl)-4, 5-dihydro - 1H – pyrazol - 1-yl) ethyli dene) hydrazineylidene) indolin-2-one(4h): m.p. 218-220°C, Mol. formula: $C_{24}H_{20}N_5OSF$, Microwave irradiation yield 82%, IR (ν cm−1): 3432(N-H, *Str*, Indole), 3093(C-H *Str*, Ar), 2998, 2842, 2782(C–H *Str*, Aliphatic), 2312(-C-S-C, *Str*, Thiophene ring), 1707(C=O *Str*, Indole), 1632(-C=N, *Str*,), 1529(CH=CH *Str*), 1462(C=C, *Str*), 1289(-C=N, *Str*). ^{1}H-NMR (DMSO) $\delta\delta$ ppm: 11.093(s, 1H, Indole NH), 8.301-8.281(s, 1H, Ar-H), 7.990-7.904(d, 2H, Ar-H), 7.812-7.800 (d, 2H, Ar-H), 7.56-7.523 (d, 2H, Ar-H), 7.420-7.401(d, 2H, Ar-H), 7.083-7.032(t, 1H, Ar-H), 4.903(dd, 1H, -CH- pyrazole), 4.798-4.703(dd, 1H, -CH_2- pyrazole), 3.789-3.732(dd, 1H, -CH_2- pyrazole), 2.320-2.301(s, 3H, CH_3). Mass (ESI-MS): m/z 445(M), 446(M+1, 100%), 447(M + 2, 30%)z.

Pharmacological Activity: Anticancer activity [14-15] Cell viability was evaluated by the MTT Assay with three independent experiments with six concentrations of compounds in triplicates. Cells were trypsinized, and the trypan blue assay was performed to know viable cells in cell suspension. Cells were counted by hemocytometer, seeded at a density of 5.0 X 10 3 cells / well in 100 µl media in 96 well plate culture medium, and incubated overnight at 37 °C. After incubation, take off the old media and add fresh media 100µl with different concentrations of the test compound in labelled wells in 96 plates. After 48 h, Discard the drug solution and add the fresh medic with MTT solution (0.5 mg/ mL-1) was added to each well and plates were incubated at 37 °C for 3 hrs.

At the end of incubation time, precipitates are formed as a result of the reduction of the MTT salt to chromophore Formosan crystals by the cells with metabolically active mitochondria. The optical density of solubilized crystals in DMSO was

measured at 570 nm on a microplate reader. The percentage growth inhibition was calculated using the following formula and the concentration of test drug needed to inhibit cell growth by 50% values is generated from the dose-response curves for each cell line using with origin software **Table 1 Fig. 2.**

% Inhibition = 100 (Control – Treatment) / Control

The IC_{50} value was determined by using a linear regression equation i.e. y = mx+c. Here, y = 50, m and c values were derived from the viability graph.

TABLE 1: CYTOTOXIC ACTIVITY OF PYRAZOLE CONTAINS NOVEL INDOLIN-2-ONE DERIVATIVES ON MCF-7 CELLS

S. no.	Sample Name	IC_{50} (µg)
1	4a	37.19
2	4b	30.12
3	4c	43.32
4	4d	42.06
5	4e	27.35
6	4f	17.63
7	4g	22.78
8	4h	47.79
9	Cisplatin	15.32

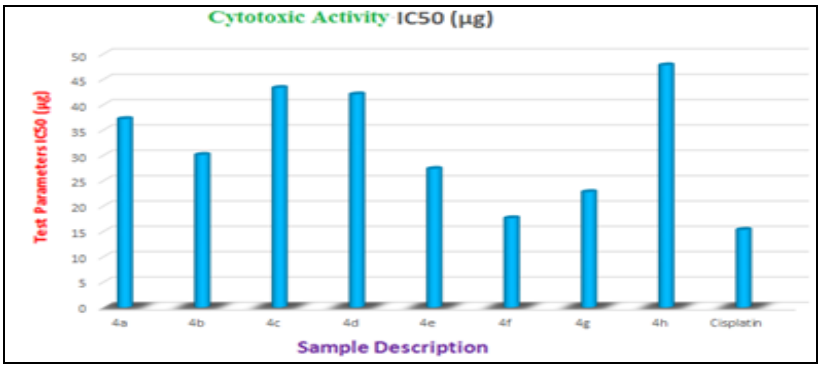


FIG. 2: GRAPHICAL REPRESENTATION OF CYTOTOXIC ACTIVITY OF PYRAZOLE CONTAINING NOVEL INDOLIN-2-ONE

Anthelmintic Activity: The synthesized compounds are screened for anthelminthic recreation by using the usage of Earthworms. Six earthworms of almost equal measurement had been positioned in preferred drug answer and take a look at compound's options at room temperature. Normal saline used as control [16-17]. The widespread drug and check compounds have been dissolved in minimal volume of dimethyl sulfoxide (DMSO) and adjusted the extent up to 10 ml with regular saline answer to get the attention of 0.1% w/v, 0.2 percent w/v and 0.5% w/v. Albendazole was once used as a widespread drug.

The compounds had been evaluated by way of the time taken for whole paralysis and earthworm loss of life (**Fig. 3)**. This implies deadly time for every check compound used to be recorded and in contrast with trendy drugs. The time taken via worms to turn out to be immobile was once cited as paralysis time. To verify the dying of the immobile worms had been regularly utilized with exterior stimuli, which stimulate and set off motion in the worms, if alive. This suggests the deadly time and paralysis time of the earthworms for specific check compounds and general drugs are tabulated in **Table 2.**

TABLE 2: ANTHELMINTIC ACTIVITY OF VARIOUS PYRAZOLES CONTAIN NOVEL INDOLIN-2-ONE DERIVATIVES

S. no.	Name	Time in minutes					
		For paralysis % Concentration			For death % Concentration		
		0.1	0.2	0.5	0.1	0.2	0.5
	Control	-	-	-	-	-	-
	Albendazole	15	12	8	44	34	26
1	4a	23	26	20	55	48	36
2	4b	22	18	14	49	40	33
3	4c	29	27	22	54	42	39
4	4d	24	21	19	53	49	38
5	4e	25	21	20	54	45	35
6	4f	18	16	11	46	36	30
7	4g	19	15	12	48	37	29
8	4h	18	18	16	54	42	30

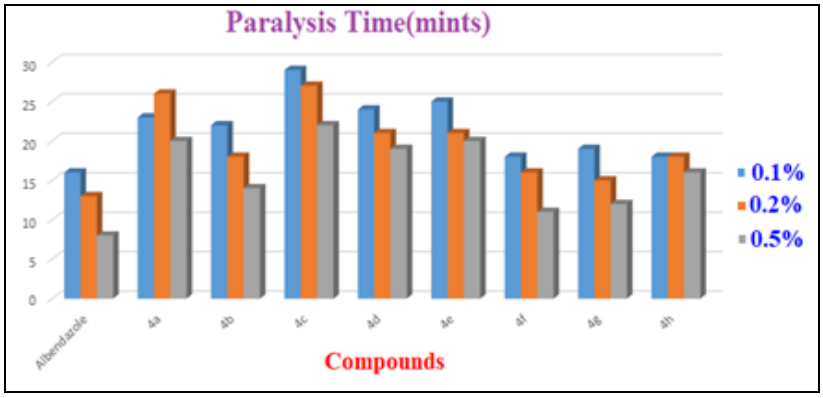


FIG. 3: GRAPHICAL REPRESENTATION OF ANTHELMINTIC ACTIVITY OF PYRAZOLE CONTAIN NOVEL INDOLIN-2-ONE DERIVATIVES (4A-4H) – PARALYSIS TIME (MIN)

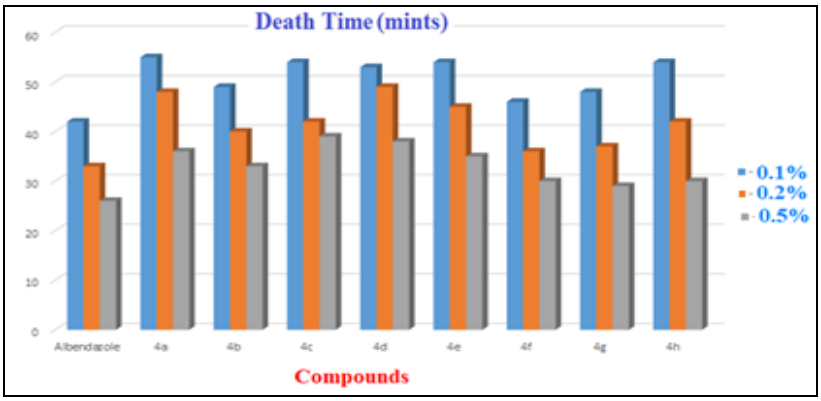


FIG. 4: GRAPHICAL REPRESENTATION OF ANTHELMINTIC ACTIVITY OF PYRAZOLE CONTAIN NOVEL INDOLIN-2-ONE DERIVATIVES (4A-4H) – DEATH TIME (MIN)

Molecular Descriptors, Bioactivity Prediction and ADMET Properties: All the newly synthesized compounds 4a-4h were subjected to molinspiration (https://www.molinspiration.com/), an online server was used to predict the drug likeness character and bioactivity parameters of all the selected ligand molecules. These descriptors are useful in the general understanding of the chemical interactions between the interested compound and its target and help ascertain the drug properties [18]. These are results are tabulated in **Table 3, 4, 5.**

Molecular Docking Studies: The digital structure of the Acetylcholine-binding protein (AChBP) used to be retrieved from the Protein databank website with PDB Id: 2ZJU and the structure was once optimized *via* deleting unbound water molecules which are over 1 Å, adding hydrogen atoms to satisfy the valences, adding lacking amino acids to stabilize aspect chains and power of the whole structure was minimized using OPLS-2005 force discipline the usage of Protein Preparation Wizard tool of Schrodinger Suite. Thus structurally optimized protein shape was used to look at protein ligand interactions of the dataset ligands using Glide Xp docking protocol. Initially, a 3D grid was hooked up to the protein's binding pocket (active site), into which all the dataset ligands were docked. Binding interactions and efficiency of the binding were calculated in phrases of Glide Score, which is a mixture of hydrophilic, hydrophobic, metal binding groups, Van der Waals energy, freezing rotatable bonds and polar interactions with receptor. G Score = 0.065 x Van der Waals energy + 0.130 x Coulomb energy + Lipophilic term (Hydrophobic interactions) + H bonding + Metal-binding + Bury P (Penalty for buried polar groups) + RotB (Penalty for freezing rotatable bonds) + Site (Polar interactions in the active site).

RESULTS AND DISCUSSION: The synthesis of pyrazole containing novel Indolin-2-one derivatives (4a-4h) was performed in 3 steps **Fig. 1**. The present work is constructed on substituted isatin compounds with hydrazine hydrate to hand 3-hydrazineylideneindolin-2-one (1a-d). Then the pyrazole derivatives (2a-d) go through acetylation reaction with acetic anhydrite to produce 1-(3-phenyl-5-(thiophen-2-yl)-4, 5-dihydro-1H-pyrazol-1-yl) ethan-1-one (3a-3b), were it was under go

Schiff base reaction with 3-hydrazineylideneindolin-2-one in the presence of glacial acetic acid to give the pyrazole contain novel Indolin-2-one derivatives (4a-4h). The synthesized novel indole derivatives and Molecular Docking studies were screened for them in-vitro anthelmintic and anticancer activities. The characterization data of all novel indole 4a-4h derivatives are given in the experimental section and all the synthesized compounds gave satisfactory analysis for the proposed structures, which were confirmed on the basis of their physical parameters and spectral analysis using IR, ^{1}H NMR and LC-MS.

The pyrazole contains novel Indolin-2-one derivatives (4a-4h) was characterized by primarily IR spectroscopy. Practically, all of the compounds have N-H stretching frequency in indole observed at 3410-3440 cm^{-1}, the C-H stretching frequency in aromatic and aliphatic, as expected, is observed at around 3002-3095 cm^{-1} and at 2990-2810 cm^{-1} correspondently.

Compounds containing the strong absorption peak observed at around 1690-1730 cm-1 are found to be the presence of C=O stretching frequency in indole and the C=N stretching in most of the compounds showing around at 1610-1635 cm^{-1} respectively. The C=C stretching is attributed to the strong absorption in the region 1500-1550 cm^{-1}.

The compounds containing -OCH_3 group shows peaks due to asymmetric and symmetric bending of –OCH_3 group is observed at around 1255 cm^{-1} and 1040 cm^{-1} and C-Cl stretching is attributed to the strong absorption in the region 782-813 cm^{-1}. Similarly, the ^{1}HNMR (DMSO-d6) spectra of novel Indole derivatives show a singlet at δ 12.80-10.00 for NH protons in Indole moiety. All the synthesized compounds show a triplet and singlet at around δ 6.78-8.320 for aromatic CH protons.

All the pyrazole protons were found doublet of doublet protons (-CH_2, -CH) around at δ 4.00-4.890 ppm. The carbon atoms of compounds 4a-4o are most affected by substitution. All the compounds obey Lipinski rule of 5, which indicates these molecules have good pharmacodynamics and pharmacokinetic properties with better permeability. All the compounds show good pharmacokinetic properties and better permeability with less toxicity.

All the newly synthesized compounds (4a-4h) were evaluated for anthelmintic activity on Indian earthworms *(Pheretima posthuma) a*s shown in the table. Among the compounds tested, all showed a significant paralytic time of earthworms, compared to standard drug albendazole at 0.1%, 0.2%, and 0.5% concentrations of compounds.

A closer inspiration of data from this table indicated that compounds 4c and 4f have more activity. Then further evaluation of vitro anticancer activity was carried out by against MCF cell line using MTT Assay method and comparison with Cisplatin as a standard.

From the results **Table 1**, the IC_{50} values of all test compounds were between 17.63 -47.79 mM and the 4b, 4e, 4f and 4g exhibited good anticancer activity against breast (MCF-7) cancer cell lines at a concentration of 0.5mg / mL^{-1}.

TABLE 3: CHEMOINFORMATICS OF SYNTHESIZED COMPOUNDS

Comp	MW	logP	HBD	HBA	NROTB	Viol
Rule						
Lipinski	<500	<5	<5	<10		0
Veber					<10	0
4a	417.53g	3.43	2	5	4	0
4b	431.565g	3.82	2	5	4	0
4c	451.983g	3.62	2	5	4	0
4d	435.528g	3.72	2	5	4	0
4e	431.565g	3.73	2	5	4	0
4f	445.592g	4.12	2	5	4	0
4g	466.01g	4.30	2	5	4	0
4h	449.555g	4.03	2	5	4	0

MW - Molecular weight, HBD – No. of hydrogen bond donors, HBA – No. of hydrogen bond acceptors, NROTB – No. of rotatable bonds, Viol.- No of violations.

TABLE 4: BIOACTIVITY OF PYRAZOLE CONTAIN NOVEL INDOLIN-2-ONE DERIVATIVES

Comp	GPCRL	ICM	KI	NRL	PI	EI
4a	-0.20	-0.71	-0.54	-0.60	-0.31	-0.25
4b	-0.22	-0.63	-0.60	-0.49	-0.40	-0.14
4c	-0.33	-0.88	-0.73	-0.76	-0.48	-0.42
4d	-0.15	-0.64	-0.60	-0.52	-0.19	-0.20
4e	-0.23	-0.74	-0.56	-0.61	-0.34	-0.29
4f	-0.25	-0.67	-0.62	-0.50	-0.43	-0.18
4g	-0.35	-0.91	-0.74	-0.76	-0.52	-0.45
4h	-0.18	-0.68	-0.61	-0.53	-0.23	-0.23

GPCRL – G-Protein coupled receptor ligand, KI-Kinase inhibitor, NRL- Nuclear receptor ligand, ICM- Ion channel modulator, PI-Protease inhibitor, EI- Enzyme inhibitor.

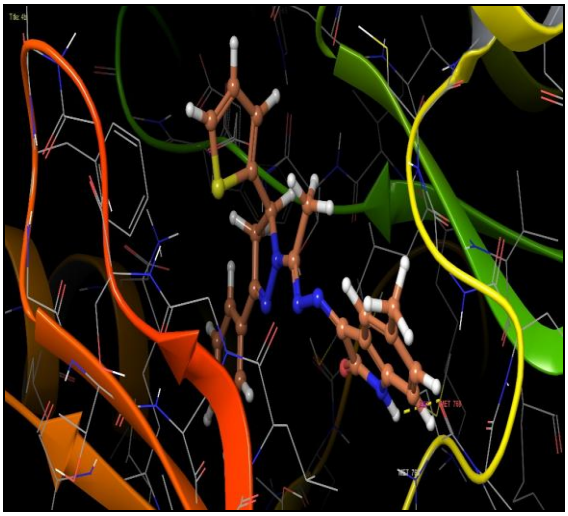
TABLE 5: ADMET PROPERTIES OF PYRAZOLE CONTAIN NOVEL INDOLIN-2-ONE DERIVATIVES

Comp	Absorption			Distribution		Metabolism			Excretion		Toxicity	
	IS	SP	PGPI	CNS	BBB	CYP 2D6 inhibitor	CYP 3A4 inhibitor	TC	RS	MTD(mg)	ORAT (LD50)	HT
4a	90.944	-2.91	Yes	-2.055	-0.01	N0	Yes	0.241	yes	-0.698	2.81	yes
4b	90.876	-2.8	Yes	-1.9	0.03	NO	Yes	0.19	yes	-0.66	2.81	yes
4c	89.72	-2.7		-1.9	-0.1	NO	Yes	0.096	yes	-0.65	2.87	yes
4d	89.76	-2.9		-2.0	-0.1	NO	Yes	0.011	yes	-0.722	2.75	yes
4e	91.15	-2.9		-1.9	-0.01	NO	Yes	0.18	yes	-0.72	2.84	yes
4f	91.01	-2.8		-1.8	0.03	N O	Yes	0.13	yes	-0.68	2.843	yes
4g	89.93	-2.7		-1.8	-0.1	NO	Yes	0.03		-0.686	2.88	yes
4h	89.97	-2.9		-1.9	-0.1	NO	Yes	0.05		-0.75	2.79	yes

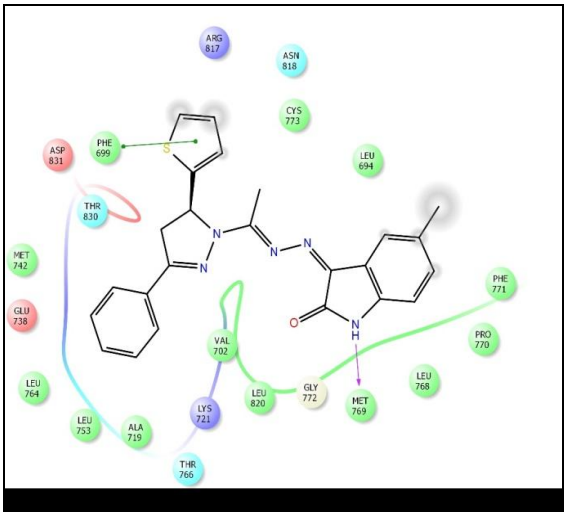
IS –Intestinal absorption (% absorbed), SP –Skin permeability (log Kp), PGP- I inhibitor P-glycoprotein –I inhibitor, BBBP – Blood brain barrier permeability (log BB), CNSP –ORAT – Oral rat acute toxicity(mol/kg), MTD – Maximum tolerated dose(log mg/kg/day), ORCT – Oral rat chronic toxicity(log mol/kg_bw/day), HT – Hepatotoxicity.

TABLE 6: MOLECULAR DOCKING SCORES OF VARIOUS PYRAZOLES CONTAIN NOVEL INDOLIN-2-ONE DERIVATIVES 4A-4H

Compound no	Dock score XP G Score	No of H-bonds	Interacting amino acids	H-bond lengths (Å)	Emodel energy	Glide energy
4e	-5.972	1	MET 769	2.14	-53.608	-44.18
4d	-5.348	1	MET 769	2.07	-62.998	-50.477
4c	-4.331	1	ARG 817	2.30	-61.805	-39.261
4g	-3.916	1	MET 769	2.31	-64.028	-43.466
4h	-3.127	1	ASP 831	1.85	-67.924	-45.559
4a	-5.972	1	MET 769	2.14	-53.608	-44.18
4b	-5.348	1	MET 769	2.07	-62.998	-50.477
4f	-4.331	1	ARG 817	2.30	-61.805	-39.261



4B-DOCK-1



4B-DOCK-2

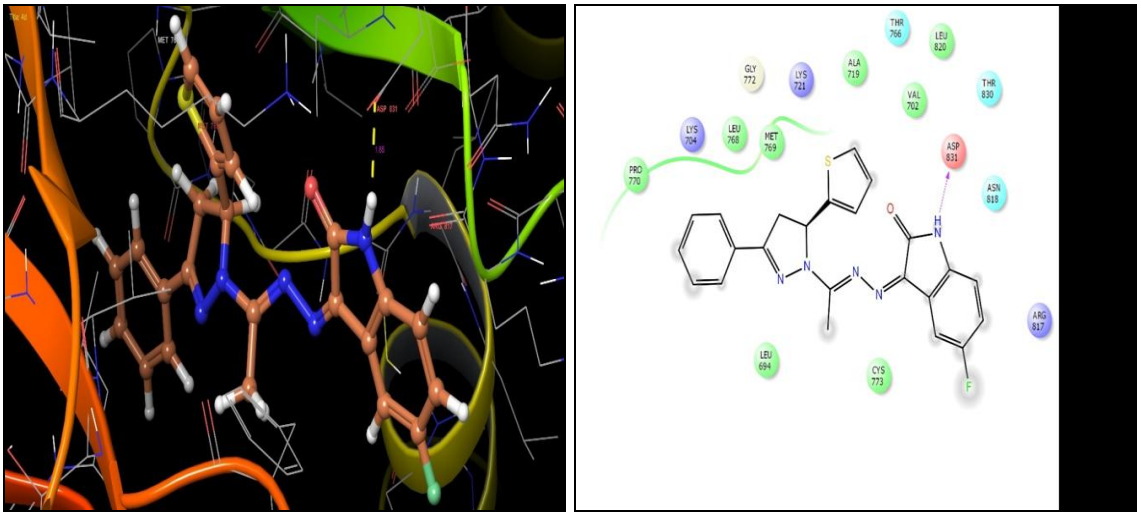


FIG. 5: MOLECULAR DOCKING IMAGES OF VARIOUS PYRAZOLES CONTAIN NOVEL INDOLIN-2-ONE DERIVATIVES

Gray colour indicates the active site, yellow reed colour indicates the ligand, and yellow dotted lines indicates the hydrogen bond interactions

CONCLUSION: The novel Indolin-2-one derivatives (4a-4h) derivatives were synthesized and characterized by Physical characterization and

spectral techniques and the % yield was to be between 72-86%. All these compounds revealed significant biological activities like anticancer and anthelmintic activities. All the Docking scores of the synthesized novel Indolin-2-one derivatives were ranged between -5.972 (compound 4h) to -3.127 (compound 4d). MET 769 is the most many times interacted amino acid and compound 4f interacted with ARG 817 and 4d with ASP 831. Hydrophobic interactions were discovered with PHE 699 (4b) and LYS721 (4h), however, compounds 4b and 4c possessed an insignificant H-bond.

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