IJPSR (2023), Volume 14, Issue 8 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 23 November 2022; received in revised form, 07 February 2023; accepted 27 May 2023; published 01 August 2023

SYNTHESIS, MOLECULAR DOCKING, SAR AND BIOLOGICAL ACTIVITIES OF NOVEL THIAZOLIDINE-4-ONE-PYRAZOLE HYBRIDS

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Keywords:

Pyrazole, Anthelmintic and Anticancer, MTT assay, MCF7, SKVO3, Doxorubicin

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ABSTRACT: A series of novel thiazolidine-4-one-pyrazole hybrids (4a-4j) had been synthesized by Claisen-Schmidt condensation, Schiff's base, and Cyclization mechanism. The newly synthesized target molecule structures were confirmed by IR, ^{1}H NMR and Mass spectral data. The synthesized hybrids were screened for *in-vitro* anticancer and anthelmintic activities. The anticancer activity was assessed using MTT assay against MCF7 and SKVO3 cell lines and Doxorubicin as the reference standard. Anthelmintic activity of compounds was studied by using Albendazole as standard. Most synthesized hybrids (4j, 4h, 4b) showed good anticancer and anthelmintic activities. The molecular docking studies were performed using the Ligprep tool of the Schrodinger suite. This study revealed that novel thiazolidne-4-one-pyrazole hybrids (4a-4j) had good interaction with the active site of EGFR receptor. The compound 4j reported the highest dock score of -4.229 with a Glide binding energy of -52.98 Kcal/mol. The pyrazole hybrids' dock score ranged from -4.229 to -2.19 Kcal/mol.

INTRODUCTION: The synthesis of fused heterocyclic moieties has always starved chemists' attention over the years because of their important biological properties. The fused heterocyclic moieties are one of the most attractive frameworks with a broad range of pharmacological activities [1]. This physiologically important nucleus is abundantly found in therapeutic agents and natural products. Many researchers have set out the synthesis of Thiazolidine-4-one pyrazole and its derivatives and its applications in literature [2].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.14(8).3942-51

This article can be accessed online on www.ijpsr.com

DOI link: http://doi.org/10.13040/IJPSR.0975-8232.14(8).3942-51

A lot of fused heterocyclic moieties containing the indole ring are accomplished with diverse pharmacological activities like Analgesic, Antiallergic, Antibacterial, Anticonvulsant, Antifungal, Antihistaminic, Anti-inflammatory, Anticancer, Anthelminthic, Anti-hypertensive, Cardiovascular, Antioxidant [3-]. Cancer disease is still a serious public health problem that afflicts humanity, making no distinction between social class, religious creed, or ethnicity.

Based on statistical data provided by WHO, the number of deaths from cancer worldwide in 2021 was 9.1 million people. The WHO also reports that 73 % of deaths from this disease occur in underdeveloped and developing countries and projects that 27 million people may be diagnosed with cancer in the next two decades. Such projection indicates that there will be a steady

increase in the number of deaths over the years [9]. From the last several years, hybrid drugs design has used as a prime method for developing novel anticancer and anthelmintic therapies that can solve many of the pharmacokinetic disadvantages of traditional anticancer drugs. Thus, several studies have indicated that thiazolidine-2-one-thiophen-indole hybrids have important anticancer activity. The present investigation was undertaken to develop an efficient method for synthesizing novel thiazolidine-4-one-pyrazole hybrids (4a-4j) derivatives having thiophene and thiazolidine-2-one moieties can be potent anthelmintic, anticancer agents.

MATERIAL AND METHODS: All the compounds' melting points were checked in open capillary tubes. TLC was checked for the synthesized compounds on silica gel-G plates of 0.5 mm thickness and spots were located by iodine chamber and UV cabinet. All compounds were purified by recrystallization with suitable organic solvents using n-Hexane: Ethyl acetate (8:2). IR spectra were recorded using Thermo Nicolet Nexus 670 in the range of 400-4000 cm^{-1} using KBr pellets. ^1H NMR spectra were recorded on Bruker DPX-200 MHz NMR spectrometer exploiting DMSO-d_6 and chemical shifts (δ) were prevalent in parts per million downfield from internal reference Tetramethylsilane (TMS). Mass spectra were catalogued on Mass spectrophotometer (model) by Shimadzu LCMS-8030 and the spectra were interpreted. The molecules docking studies had been carried out using the Ligprep device of the Schrodinger suite.

Chemistry: Step-I: Synthesis of Chalcones (1-(Substituted) Phenyl-3-thiophene Propenone (1a-1b): To a solution of substituted acetophenone (0.01 mol) in ethanol (20 ml), thiophene-2-carbalxyaldehyde (0.01 mol) was added and cooled to 5-10 ºC in an ice bath. To this cold solution, sodium hydroxide (30%) was added and stirred magnetically for 12 h and then left overnight or longer, monitored by TLC. The resultant solution was diluted with ice water and acidified with dilute HCl. The chalcone separated as a solid was collected by filtration after washing with water and recrystallized from ethanol [10].

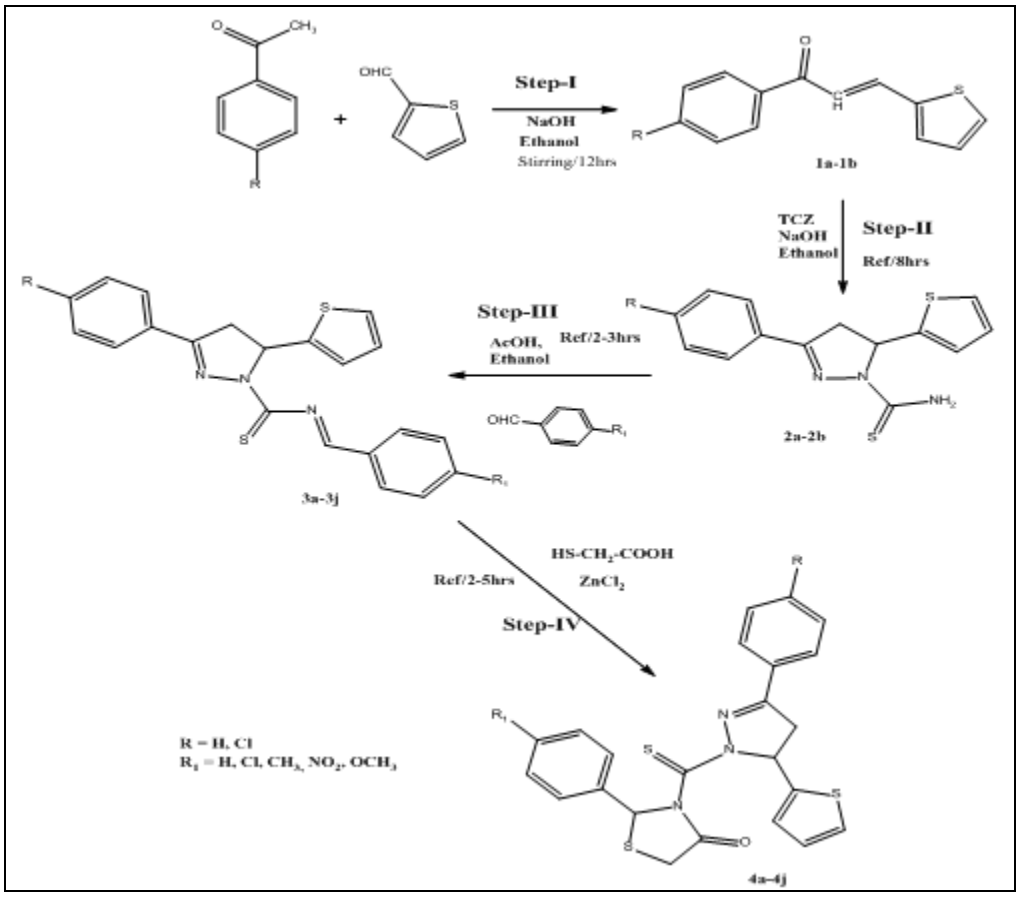

FIG. 1: SCHEME

Step-II: Synthesis of Pyrazole Derivatives (2a-2b): The compound 1a-1b (1-(substituted) phenyl-3-thiophene propenone) (0.01M) dissolved in ethanol (25 ml) were added to Thiosemicarbazide (0.01M). To this aq. Potassium hydroxide (KOH) solution (0.02M) was added (prepared by dissolving 0.12gm of potassium hydroxide in 100ml of distilled water). The reaction mixture was refluxed for 8 hours, cooled, diluted with water and acidified with conc. HCl. The product was filtered, dried and crystallized from ethanol [11].

Step-III: Synthesis of Pyrazolines Derivatives (3a-3j): A mixture of (0.01mol) substituted benzaldehyde and compounds 2a-2b (0.01mol) were dissolved in 40 ml of ethanol and 2 ml of glacial acetic acid (GAA) (as a catalyst) in a round bottom flask and then whole of the substance was refluxed for about 2-3 hours and then checked for completion by Thin Layer Chromatography (TLC). After refluxing, the whole of the content was poured into cold water. At last, the precipitated product was recrystallized [12].

Step-IV: Synthesis of Novel Pyrazole Derivatives (4a-4j): A mixture of compound 3(a–j) and thioglycolic acid (1:1mol) dissolved in methanol was allowed to react in the presence of a catalytic amount of Zinc chloride ($ZnCl_2$). The reaction mixture was first continuously stirred on a magnetic stirrer for about 2.10–2.30 h then kept on steam bath for about 1.45–4.15h at 80–90°C. The products were cooled and filtered at room temperature. The filtered products were purified over column chromatography using chloroform: ethanol (7:3 v/v) and recrystallized from ethanol at room temperature to yield compounds 4(a–j) [13].

TABLE 1: PHYSICAL DATA OF COMPOUNDS 4A-4J

Compound	Molecular Formula	R	R_1	Molecular Weight (gms)	M.P (°C)	%Yield
4a	$C_{23}H_{19}N_3OS_3$	H	H	449.07	133-135	78
4b	$C_{23}H_{18}N_3OClS_3$	Cl	H	483.03	127-129	75
4c	$C_{24}H_{21}N_3OS_3$	H	CH_3	463.08	166-168	68
4d	$C_{24}H_{20}N_3OClS_3$	Cl	CH_3	497.05	154-156	79
4e	$C_{24}H_{21}N_3O_2S_3$	H	OCH_3	479.08	179-181	71
4f	$C_{24}H_{20}N_3O_2ClS_3$	Cl	OCH_3	513.04	185-187	80
4g	$C_{23}H_{18}N_4O_3S_3$	H	NO_2	494.05	183-185	67
4h	$C_{23}H_{17}N_4O_3ClS_3$	Cl	NO_2	528.03	123-125	68
4i	$C_{23}H_{18}N_3OClS_3$	H	Cl	483.03	169-171	74
4j	$C_{23}H_{17}N_3OCl_2S_3$	Cl	Cl	516.99	151-153	72

Compound 4a: 2 - phenyl - 3 -(3 – phenyl – 5 - (thiophen-2-yl)-4,5-dihydro-1H-pyrazole-1-carbonothioyl) thiazolidin-4-one: 3015(C-H *Str*, Ar), 2996, 2863, 2764(C–H *Str*, Aliphatic), 2327(C–S-C *Str*, Thiazol/thiophene), 1708(C=O *Str*, Thazole), 1614(C=N *Str*, Pyrazole), 1573(C=CH *Str*), 1434(C=C *Str*, Ar), 1062(C-N*Str*).^{1}H-NMR (DMSO) *δδ* ppm: 8.4999-8.377(t, 3H, Ar-H), 7.976-7.877(d, 2H, Ar-H), 7.848-7.780(t, 3H, Ar-H), 7.698-7.682(d, 2H, Ar-H), 7.449-7.491(d, 2H, Ar-H), 7.760-7.515(t, 1H, Ar-H), 5.213(s, 1H, -CH- in thiazole), 3.998-3.982(dd, 2H, -CH_2- inpyrazole), 3.781(s, 2H, -CH_2- in thiazole), 3.101(t, 1H, -CH- in pyrazole). Mass (LC-MS): m/z 449(M), 450(M + 1, 100%).

Compound 4b: 3 - (3 - (4 - chlorophenyl) – 5 - (thiophen-2-yl)-4,5-dihydro-1H-pyrazole-1-carbonothioyl)-2-phenylthiazolidin-4-one: 3093(C-H *Str*, Ar), 2915, 2794(C–H *Str*, Aliphatic), 2237(C–S-C *Str*, Thiazol/thiophene), 1706(C=O *Str*, Thazole), 1614(C=N *Str*, Pyrazole), 1582(C=CH *Str*), 1456(C=C *Str*, Ar), 1073(C-N *Str*), 794(C-Cl *Str*, Ar-Cl).^{1}H-NMR (DMSO) *δδ* ppm: 8.371-8.297(d, 2H, Ar-H), 8.115-7.858(d, 2H, Ar-H), 7.802-7.793(d, 2H, Ar-H), 7.787-7.764(d, 2H, Ar-H), 7.695-7.667(t, 1H, Ar-H), 7.643-7.567(t, 3H, Ar-H), 5.239(s, 1H, -CH- in thiazole), 4.095-4.074(dd, 2H, -CH_2- in pyrazole), 3.733(s, 2H, -CH_2- in thiazole), 3.034(t, 1H, -CH- in pyrazole). Mass (LC-MS): m/z 483(M), 484(M + 1, 100%), 485(M + 2, 30%).

Compound 4c: 3 - (3 – phenyl - 5-(thiophen-2-yl)-4,5-dihydro-1H-pyrazole-1-carbonothioyl) - 2-(p-tolyl) thiazolidin-4-one: 3057(C-H *Str*, Ar), 2922, 2857, 2797(C–H *Str*, Aliphatic), 2257(C–S-C *Str*, Thiazol/thiophene), 1716(C=O *Str*, Thazole), 1656(C=N *Str*, Pyrazole), 1548(C=CH *Str*), 1467(C=C *Str*, Ar), 1126(C-N *Str*).^{1}H-NMR

(DMSO) *δδ* ppm: 7.972-7.809(d, 2H, Ar-H), 7.685-7.631(d, 2H, Ar-H), 7.534-7.473(t, 3H, Ar-H), 7.441-7.384(t, 1H, Ar-H), 6.763-6.581(d, 2H, Ar-H), 6.203-6.108(d, 2H, Ar-H), 5.391(s, 1H, -CH- in thiazole), 3.984(dd, 2H, $-CH_2-$ in pyrazole), 3.840(s, 2H, $-CH_2-$ in thiazole), 3.104(t, 1H, -CH- in pyrazole, 2.214(s, 3H, $-CH_3$, Ar-CH_3). Mass (LC-MS): m/z 463(M), 464(M + 1, 100%).

Compound 4d: 3 - (3 - (4 - chlorophenyl) - 5 - (thiophen-2-yl)-4,5-dihydro-1H-pyrazole-1-carbonothioyl) – 2 - (p - tolyl) thiazolidin -4-one: 3037(C-H *Str*, Ar), 2939, 2832, 2799(C–H *Str*, Aliphatic), 2392(C–S-C *Str*, Thiazol/thiophene), 1703(C=O *Str*, Thazole), 1624(C=N *Str*, Pyrazole), 1582(C=CH *Str*), 1470(C=C *Str*, Ar), 1046(C-N *Str*), 760(C-Cl *Str*, Ar-Cl). ^{1}H-NMR (DMSO) *δδ* ppm: 8.545-8.378(t, 1H, Ar-H), 8.318-8.195(d, 2H, Ar-H), 8.099-8.010(d, 2H, Ar-H), 7.949-7.853(d, 2H, Ar-H), 7.813-7.664(d, 2H, Ar-H), 7.260-7.128(d, 2H, Ar-H), 5.684(s, 1H, -CH- in thiazole), 4.249(dd, 2H, $-CH_2-$ in pyrazole), 3.863(s, 2H, $-CH_2-$ in thiazole), 3.290(t, 1H, -CH- in pyrazole), 2.045(s,3H, $-CH_3$, Ar-CH_3). Mass (LC-MS): m/z 497(M), 498(M + 1, 100%), 499 (M + 2, 30%).

Compound.4e:2-(4-methoxyphenyl)-3-(3-phenyl-5-(thiophen-2-yl)-4,5-dihydro-1H-pyrazole-1-carbonothioyl)thiazolidin-4-one: 3022(C-H *Str*, Ar), 2931, 2843, 2790(C–H *Str*, Aliphatic), 2309(C–S-C *Str*, Thiazol/thiophene), 1703(C=O *Str*, Thazole), 1649(NO_2*Str*, Ar-NO_2), 1522(C=CH *Str*), 1381(C=C *Str*, Ar), 1023(C-N *Str*).^{1}H-NMR (DMSO) *δδ* ppm: 8.495(t, 1H, Ar-H), 8.212-8.244(d, 2H, Ar-H), 8.141-8.120(d, 2H, Ar-H), 8.051-8.032(d, 2H, Ar-H), 7.853-7.785(t, 3H, Ar-H), 7.770-7.737(d, 2H, Ar-H), 5.582(s, 1H, -CH- in thiazole), 4.317-4.310(dd, 2H, $-CH_2-$ in pyrazole),3.827(s,3H, $-OCH_3$), 3.613(s, 2H, $-CH_2-$ in thiazole), 3.015(t, 1H, -CH- in pyrazole). Mass (LC-MS): m/z 479(M), 480(M + 1, 100%).

Compound 4f: 3 - (3 - (4 - chlorophenyl)-5-(thiophen-2-yl)-4,5-dihydro-1H-pyrazole-1-carbonothioyl)2-(4-methoxyphenyl)thiazolidin-4-one: 3020(C-H *Str*, Ar), 2985, 2881, 2748(C–H *Str*, Aliphatic), 2387(C–S-C *Str*, Thiazol/thiophene), 1708(C=O *Str*, Thazole), 1625(C=N *Str*, Pyrazole), 1588(C=CH *Str*), 1341(C=C *Str*, Ar), 1248 (C=S *Str*), 1081(C-N *Str*), 804(C-Cl *Str*, Ar-Cl).^{1}H-NMR (DMSO) *δδ* ppm: 8.501-8.362(d, 2H, Ar-H), 8.043-8.013(d, 2H, Ar-H), 7.945-7.926(d, 2H, Ar-H), 7.821-7.787(d, 2H, Ar-H), 7.179-7.146(t, 1H, Ar-H), 6.885-6.873(d, 2H, Ar-H), 5.472(s, 1H, -CH- in thiazole), 4.298(dd, 2H, $-CH_2-$ in pyrazole), 3.648(s, 3H, OCH_3), 3.347(s, 2H, $-CH_2-$ in thiazole), 3.185(t, 1H, -CH- in pyrazole). Mass (LC-MS): m/z 513(M), 514(M + 1, 100%), 515 (M + 2, 30%).

Compound 4g: 2-(4-nitrophenyl)-3-(3-phenyl-5-(thiophen-2-yl)-4, 5-dihydro-1H-pyrazole -1-carbonothioyl) thiazolidin-4-one: 3020(C-H *Str*, Ar), 2975, 2855, 2720(C–H *Str*, Aliphatic), 2370(C–S-C *Str*, Thiazol/thiophene), 1720(C=O *Str*, Thazole), 1623(C=N *Str*, Pyrazole), 1507(C=CH *Str*), 1420(C=C *Str*, Ar), 1268 (C=S *Str*), 1183 (C-N *Str*). ^{1}H-NMR (DMSO) *δδ* ppm: 8.545-8.465-8.279(d, 2H, Ar-H), 8.096-8.045(d, 2H, Ar-H), 7.959-7.858(d, 2H, Ar-H), 7.791-7.738(d, 2H, Ar-H), 7.665-7.497(t, 3H, Ar-H), 7.350-7.231(t, 1H, Ar-H), 5.417(s, 1H, -CH- in thiazole), 4.350(dd, 2H, $-CH_2-$ in pyrazole), 3.643(s, 2H, $-CH_2-$ in thiazole), 3.104(t, 1H, -CH- in pyrazole). Mass (LC-MS): m/z 494(M).495(M+1,100%).

Compound 4h: 3 - (3 - (4 - chlorophenyl) – 5 - (thiophen-2-yl)-4,5-dihydro-1H-pyrazole-1-carbonothioyl)-2-(4-nitrophenyl)thiazolidin-4-one: 3050(C-H *Str*, Ar), 2976, 2878, 2750(C–H *Str*, Aliphatic), 2353(C–S-C *Str*, Thiazol/thiophene), 1753(C=O *Str*, Thazole), 1605(C=N *Str*, Pyrazole), 1484(C=CH *Str*), 1453(C=C *Str*, Ar), 1306 (C=S *Str*), 1094(C-N *Str*), 755(C-Cl *Str*, Ar-Cl).^{1}H-NMR (DMSO) *δδ* ppm: 8.373-8.286(d, 2H, Ar-H), 8.103(d, 2H, Ar-H), 7.886-7.848(d, 2H, Ar-H), 7.688-7.638(d, 2H, Ar-H), 7.586-7.513(t, 1H, Ar-H), 7.145-7.110(d, 2H, Ar-H), 5.457(s, 1H, -CH- in thiazole), 4.540(dd, 2H, $-CH_2-$ in pyrazole), 3.705(s, 2H, $-CH_2-$ in thiazole), 3.015(t, 1H, -CH- in pyrazole). Mass (LC-MS): m/z 528(M), 529(M + 1, 100%), 530 (M + 2, 30%).

Compound 4i: 2-(4-chlorophenyl)-3-(3-phenyl-5-(thiophen-2-yl)-4,5-dihydro-1H-pyrazole-1-carbonothioyl)thiazolidin-4-one: 3023(C-H *Str*, Ar), 2927, 2891, 2723(C–H *Str*, Aliphatic), 2259(C–S-C *Str*, Thiazol/thiophene), 1713(C=O *Str*, Thazole), 1616(C=N *Str*, Pyrazole), 1553(C=CH *Str*), 1422(C=C *Str*, Ar), 1275 (C=S

Str), 1043(C-N *Str*), 791(C-Cl *Str*, Ar-Cl).^{1}H-NMR (DMSO) *δδ* ppm: 8.749-8.401(d, 2H, Ar-H), 7.993-7.788(d, 2H, Ar-H), 7.697-7.686(d, 2H, Ar-H), 7.592-7.406(t, 3H, Ar-H), 7.813-7.603-6.518(d, 2H, Ar-H), 7.182(d, 1H, Ar-H), 5.680(s, 1H, -CH- in thiazole), 4.540(dd, 2H, -CH_2- in pyrazole), 3.949(s, 2H, -CH_2- in thiazole), 3.058(t, 1H, -CH- in pyrazole). Mass (LC-MS): m/z m/z 483(M), 484(M+1,100%).

Compound 4j: 2-(4-chlorophenyl)-3-(3-(4-chlorophenyl)-5-(thiophen-2-yl)-4,5-dihydro-1H-pyrazole-1-carbonothioyl)thiazolidin-4-one:
3010(C-H *Str*, Ar), 2984, 2776(C–H *Str*, Aliphatic), 2370(C–S-C *Str*, Thiazol/thiophene), 1704(C=O *Str*, Thazole), 1642(C=N *Str*, Pyrazole), 1573(C=CH *Str*), 1470(C=C *Str*, Ar), 1325(C=S, *Str)*, 1114(C-N *Str*), 785(C-Cl *Str*, Ar-Cl). ^{1}H-NMR (DMSO) *δδ* ppm: 8.449(d, 2H, Ar-H), 8.160-8.057(d, 2H, Ar-H), 7.976-7.576(d, 2H, Ar-H), 7.534-7.515(d, 2H, Ar-H), 7.505-7.503(d, 2H, Ar-H), 7.497-7.473(t, 1H, Ar-H), 5.154(s, 1H, -CH- in thiazole), 4.144-4.134(dd, 2H, -CH_2- in pyrazole), 3.784(s, 2H, -CH_2- in thiazole), 3.093(t, 1H, -CH- in pyrazole). Mass (LC-MS): m/z 516(M), 517(M + 1, 100%), 518 (M + 2, 30%).

Pharmacological Activity:

Anthelmintic Activity: The anthelmintic activity was screened for all the synthesized novel thiazolidine-4-one-pyrazole hybrids (4a-4j) on adult Indian earth worms (*Pheretima posthuma*) at concentrations of 0.1%, 0.2% and 0.5%. Albendazolewas used as the standard drug to compare anthelmintic activity. Observations were made for the time taken for paralysis and death of individual worms **Table 2** [15].

Anticancer Activity: Ten substituted novel thiazolidine-4-one-pyrazole hybrids (4a-4j) were screened for anticancer activity against MCF7 and SKVO3 cell lines by MTT (3,[dimethyl thiuazoli-2-yl]-2.5diphenyl tetrazoassaylium bromide) method. Doxorubicin was used as a standard drug. The MTT Cell Proliferation assay measures the cell proliferation rate and conversely, when metabolic events lead to apoptosis or necrosis, cell viability is reduced. The Cell lines were purchased from NCCS(National Centre for Cell Science) Pune and the cells were maintained in MEM (Minimum Essential Medium) supplemented with 10% FBS (Fetal Bovine Serum) and the antibiotic Doxorubicin (0.5 Ml^{-1}), in the atmosphere of 5% CO_2 /95% air at 37°C. Cytotoxic (IC_{50}) activity generated by the novel synthesized hybrids with three independent experiments with six concentrations (5, 10, 25, 50 and 100µg/ml). The percentage growth inhibition was calculated using standard formula and concentration of test drugs needed to inhibit cell growth by 50 % values (IC_{50}) generated from the dose-response curves for each cell line using with origin software **Table 3** [16].

Molecular Docking Studies: All the synthesized molecules 4a-4j were constructed by Chem Draw Pro 12.0and the molecular docking process was done by using Ligprep tool of Schrodinger suite. The 2D structures were converted into 3D structures using potential algorithms and applying highly efficient force fields. Various ionization states were generated using the Ligprep module with a special program EPIK and various possible conformers and tautomers. The digital structure of the epidermal growth factor receptor (EGFR) was retrieved from the Protein databank website with PDB Id: 1M17 and the structure was optimized by deleting unbound water molecules which are over 1 Å, adding hydrogen atoms to satisfy the valences, adding missing amino acids to stabilize side chains and energy of the whole structure was minimized using OPLS-2005 force field using Protein Preparation Wizard tool of Schrodinger Suite [17-18].

RESULTS AND DISCUSSION:

Synthesis: The conventional method prepared ten novelthiazolidine-4-one-pyrazole hybrids (4a-4j) via Claisen-Schmidt condensation, Schiff's base and Cyclization mechanism. IR, 1H NMR, and Mass spectral data Confirmed for all the molecule structures.

Anthelmintic Activity: The synthesized compounds (4a-4j) were screened for anthelmintic activity by using earthworms. The compounds were evaluated by the time taken for complete paralysis and death of earthworms. The mean lethal time for each test compound was recorded and compared with standard drug. A closer inspection of the resulting data indicates that compounds 4a, 4c, 4e, 4f and 4j showed very high activity (paralysis and death) than remaining synthesized compounds.

TABLE 2: ANTHELMINTIC ACTIVITY OF COMPOUNDS [4a-4j]

S. no.	Compound	Mean lethal Time of earthworms to get paralysed and the death timein minutes					
		Concentration of compound(%)to paralyse helminth			Concentration of compound(%)to cause death of helminth		
	Concentration	0.1	0.2	0.5	0.1	0.2	0.5
	Control	-	-	-	-	-	-
	Albendazole	18	13	9	42	31	25
1	4a	23	20	17	54	46	35
2	4b	30	25	20	58	49	38
3	4c	23	19	15	46	35	29
4	4d	29	24	21	48	38	27
5	4e	21	18	15	46	36	31
6	4f	20	17	13	44	35	30
7	4g	32	24	19	47	36	32
8	4h	34	24	21	54	47	35
9	4i	35	22	19	56	45	32
10	4j	22	19	16	47	35	32

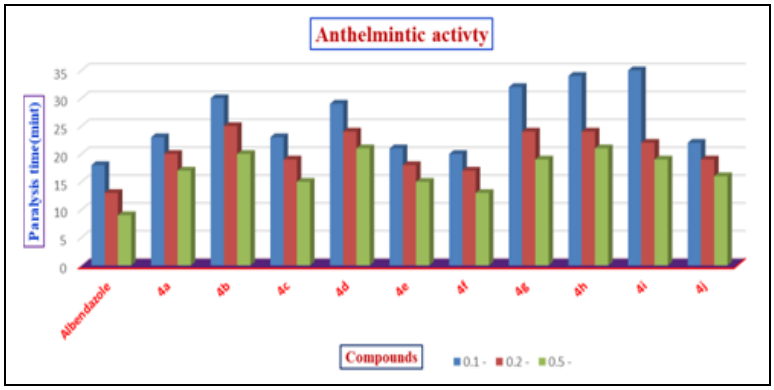

FIG. 2: GRAPHICAL REPRESENTATION OF ANTHELMINTIC ACTIVITY OF COMPOUNDS (4A-4J)-PARALYSIS TIME (MIN)

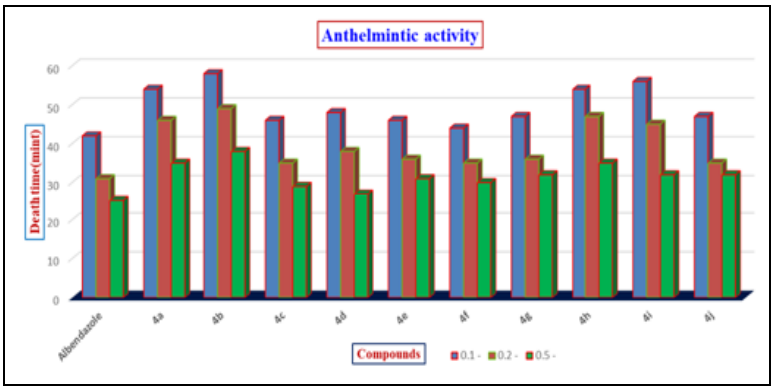

FIG. 3: GRAPHICAL REPRESENTATION OF ANTHEMINTIC ACTIVITY OF COMPOUNDS (4A-4J)-DEATH TIME IN MINUTES

FIG. 4: PHOTOGRAPHFORCOMPOUND4c-ANTHELMINTIC ACTIVITY

Anticancer Activity: Novel thiazolidine-4one pyrazole hybrids were screened for cytotoxic activity against two cancer cells like MCF7 (Human breast cancer cells) and SKVO3 (Ovarian cancer cells) by using MTT assay method. From the resulting data compounds showed IC_{50} values in the range of 20.18µg to 48.15µg against MCF7 cell line and 26.01 to 8µg against SKVO3 cell line. The compounds 4b (28.95µg), 4j (20.18µg) and 4h (27.47µg) showed good activity against both cell lines. The remaining molecules exhibited moderate anticancer activity compared to the standard.

TABLE 3: ANTICANCER ACTIVITY OF NOVEL THIAZOLIDINE-4-ONE-PYRAZOLE ON MCF7 AND SKVO3 CELL LINES

Sample Description	Test Parameters IC_{50} (µg)	
	MCF 7	SKVO3
4a	31.01	43.43
4b	28.95	29.12
4d	37.61	48.33
4h	27.47	30.91
4i	48.15	68.23
4j	20.18	26.01
Doxorubicin	12.04	15.42

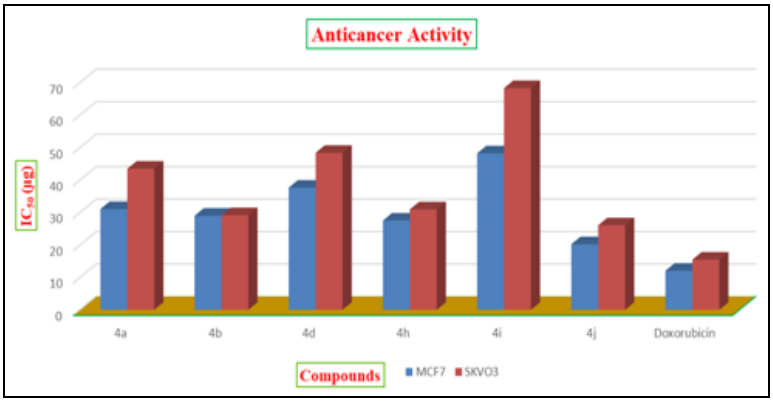

FIG. 5: GRAPHICAL REPRESENTATION OFNOVEL THIAZOLIDINE-4-ONE PYRAZOLE HYBRIDS ON MCF7 AND SKVO3 CELL LINES

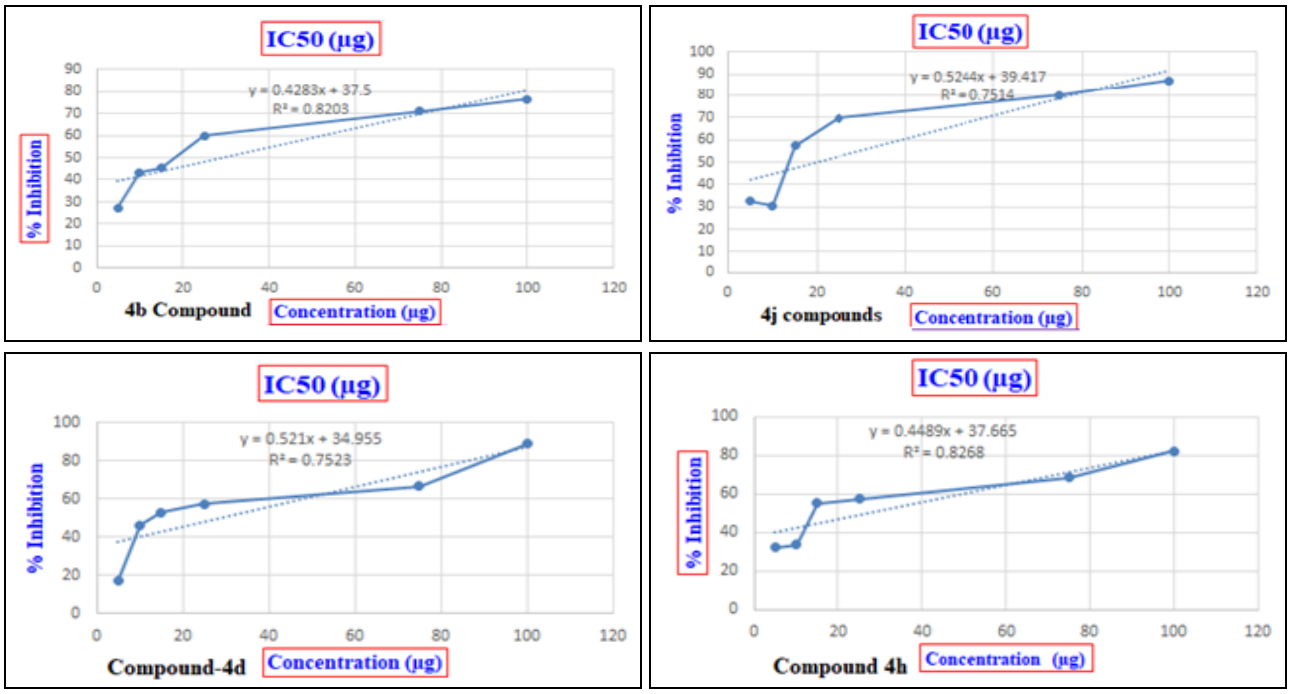

FIG. 6: GRAPHICAL REPRESENATION OF NOVELTHIAZOLIDINE -4-ONE PYRAZOLE HYBRIDS IC_{50}VALUES

SAR of Novel Thiazolidine-4-One-Pyrazole Hybrids: The structure-activity relationship for anthelmintic and anticancer activities of synthesized Novel thiazolidine-4-one pyrazole hybrids can be deduced as follows. The novel pyrazole molecule contains aromatic ring with electron withdrawing groups like –Cl, -NO_2 at ortho and para position of the substituted aromatic ring enhance biological activities like antimicrobial, anti-inflammatory and anticancer activities. Novel Pyrazole derivatives have electron-donating groups like methyl and methoxy at the aromatic ring's ortho or para position, enhancing the anti-inflammatory, anticancer and antimicrobial activities. Pyrazole analogues having electron releasing group (-CH_3, -OCH_3) at ortho position and electron-withdrawing groups (-X: -Cl, -Br, F and –NO_2) at para position enhance the anti-inflammatory, anticancer and antimicrobial activities.

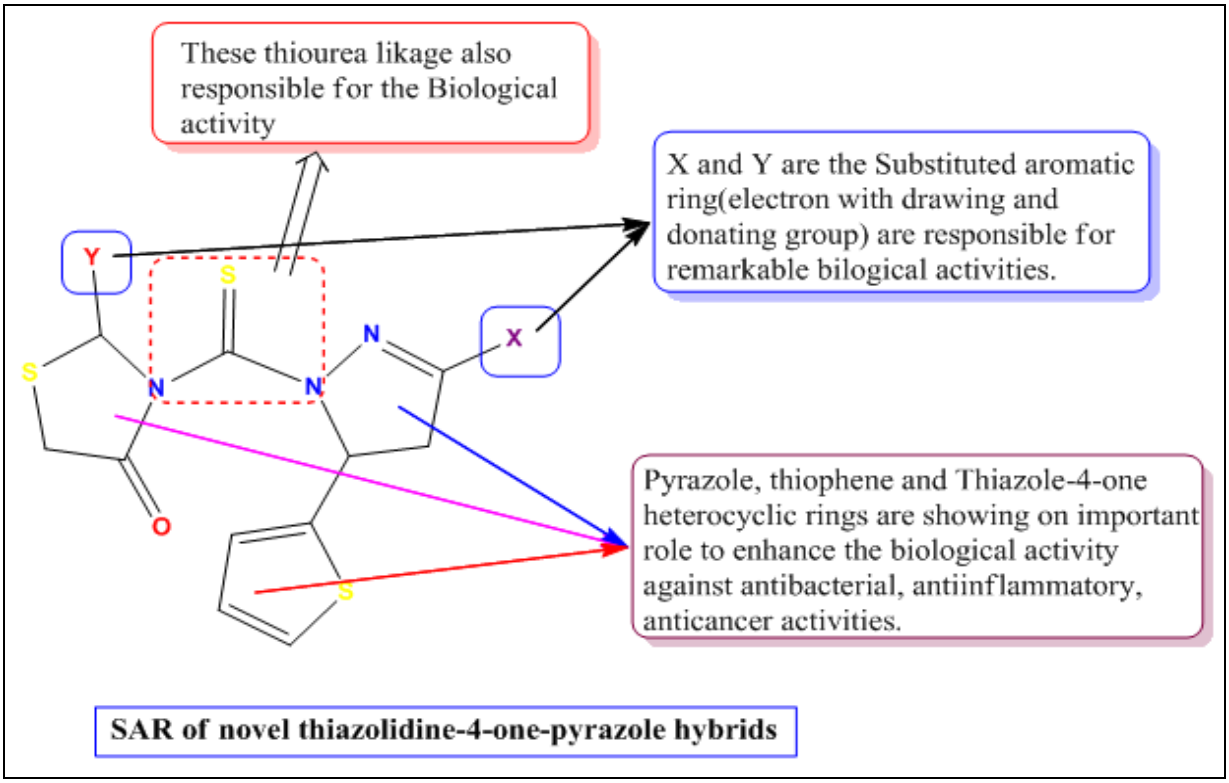

FIG. 7: GRAPHICAL REPRESENTATION OF SAR OF NOVEL-THIAZOLIDINE -4-ONE PYRAZOLE HYBRIDS

The SAR of novel pyrazole derivatives (4a-4j) revealed that the anticancer activity of synthesized compounds depends necessarily on the attached group like R & R_1 (-Cl, NO_2, OCH_3) at the 4^{th} position of the aromatic rings exhibited remarkable anticancer activity (4b, 4j and 4h). Most of the synthesised compounds with para methyl (4c and 4d) or methoxy group (4e, 4f) were more active (anticancer and anti-inflammatory) analogues compared with unsubstituted derivatives (4a). Generally, all the derived analogues bearing the para-substituted phenyl group(4a-4j) resulted in increasing cytotoxicity and anti-inflammatory activities, especially on the MCF-7 cell lines. The compounds having hydrophobic group on the phenyl ring at 4^{th} position such as Chlorine (4b and 4f) or methyl (4c) assume to be crucial leading to the remarkable increase in cytotoxicity and anti-inflammatory activity. Consequently, 4b analogue with Chloro group and 4c compound with methyl groups are more active analogues than remaining derivatives. The Structural activity relationship (SAR) of the synthesized novel pyrazole compounds indicated that the compounds bearing electron withdrawing and electron releasing groups at different positions (ortho, meta and para) of the substituted portion significantly enhance the anti-inflammatory, antimicrobial and anticancer activities.

Molecular Docking Studies: Molecular docking studies are one of the most basic and important strategies for drug design and discovery. In this end, the interaction and affinity of the newly

synthesized potent anticancer hybrids (4b, 4f and 4h) toward one protein: PDB Id: 1M17. Glide dock sores of the dataset ligands have been proven in **Table 4**. Among the docked ligands, compound 4j reported highest dock score of -4.229 with Glide binding energy of -44.032Kcal/mol. Dock scores of all the compounds ranged from –4.229 (compound 4j) to -2.196 (compound 4f). Hydrophobic interactions were observed with PHE 699 residue in compound 4f. Hydrophobic interactions were observed with PHE 699, LYS 721 and LYS 851 residue in compounds 4c and 4f.

TABLE 4: *IN-SILICO* EGFR INHIBITION OF NOVEL THIAZOLIDINE-4-ONE-PYRAZOLE HYBRIDS-GLIDE DOCK SORES OF THE DATASET LIGANDS

Compound No	Dock score XP G Score	No of H-bonds	Interacting amino acids	H-bond lengths (Å)	E model energy	Glide energy
4j	-4.229	0	-	-	-52.988	-44.032
4c	-4.086	1	LYS 721	-	-36.932	-30.591
4d	-3.787	0	-	-	-46.244	-35.179
4h	-3.279	0	-	-	-28.384	-41.172
4a	-3.06	0	-	-	-30.485	-40.908
4f	-2.196	3	LYS 721, PHE 699, LYS 851	2.07	-43.759	-36.444

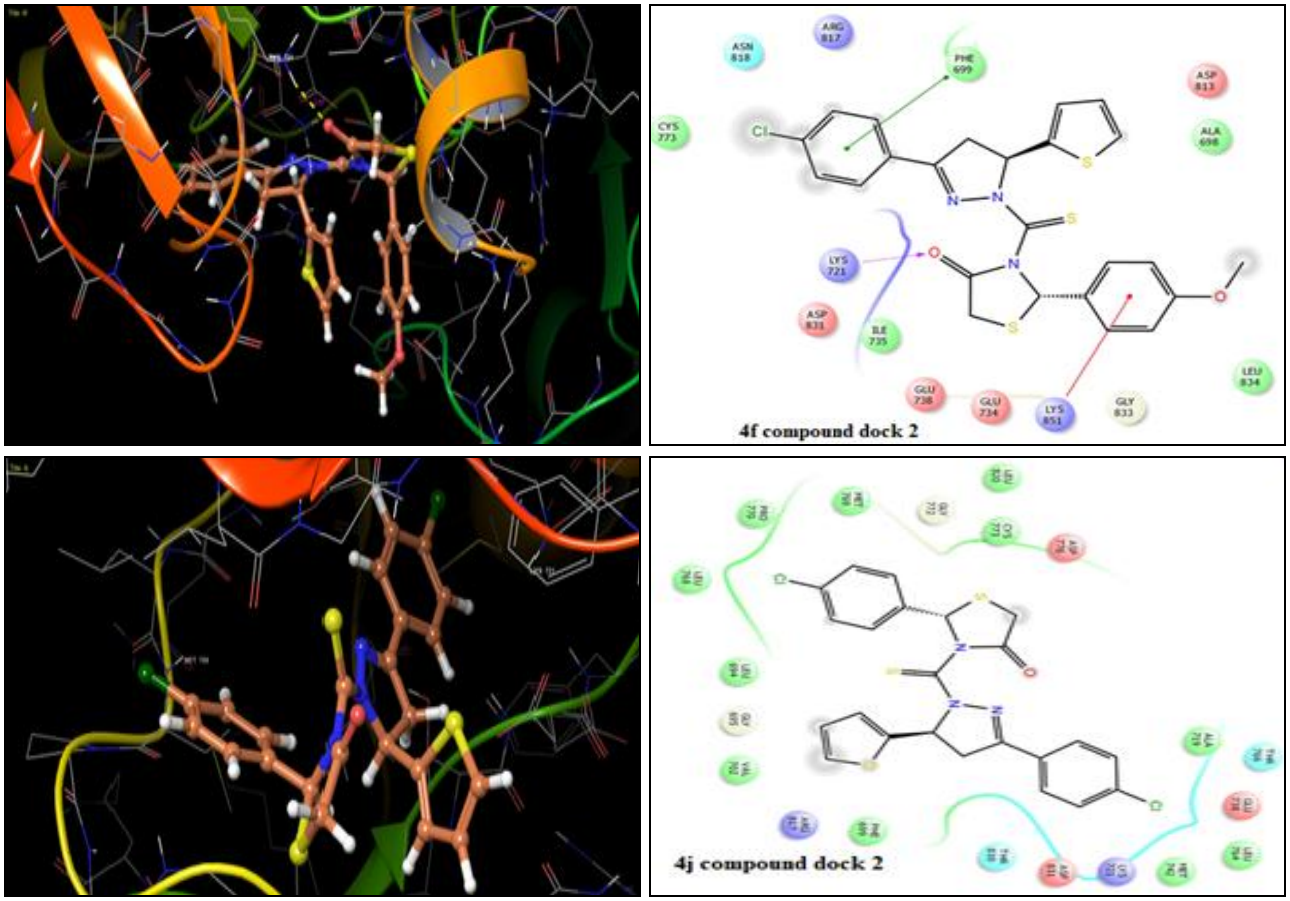

FIG. 8: DOCKING POSE BETWEEN THE LIGAND A (4F AND 4J DOCK1 AND DOCK-2)

CONCLUSION: In this research novel thiazolidne-4-one-pyrazole hybrids (4a-4j) were synthesized successfully by conventional method. These structures are confirmed by FT-IR, 1H NMR and MASS spectral data. All the hybrids were evaluated for anthelmintic and anticancer activities. Most of the synthesized hybrids were found to have good activity; among all the active compounds of thiazolidne-4-one-pyrazole hybrids, 4-5 compounds showed good anthelmintic activity. Anticancer activity results revealed promising activities for compound 4b, 4h and 4j compared to standard drugs.

ACKNOWLEDGMENT: The authors are grateful to the Department of Chemistry, Sri Venkateshwara College of Pharmacy, and JNTU,

Hyderabad, Telangana, India for providing the laboratory facilities.

CONFLICTS OF INTEREST: The authors declare no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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How to cite this article:
Prasanna NL, Ajitha M: Synthesis, molecular docking, SAR and biological activities of novel thiazolidine-4-one-pyrazole hybrids. Int J Pharm Sci & Res 2023; 14(8): 3942-51. doi: 10.13040/IJPSR.0975-8232.14(8).3942-51.