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Design, Synthesis, Characterization, Biological Activties and in Silico Docking Studies of Thizole Contain Novel Imidazoline Derivatives

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ABSTRACT

Imidazole and its derivatives contain different hetero moieties are considered Biologically most important active scaffoldthat possesses almost all types of pharmacological activities. The in the present study, we synthesized a new series of thiazole contain novel imidazole derivatives by conventional method via different mechanisms, such as cyclization between thiourea and Substituted Acetophenone to 2-Amino 4-Aryl Thiazole. The Benzoyl glycine derivatives reacts with substituted benzaldehyde to form Oxazole derivatives, then followed Schiff's with different aromatic amineto give imidazole derivatives. Finally, these are reacting with 2-Amino 4-Aryl Thiazole to gives the title of the products.All of these derivatives were purified through column chromatography and characterized by IR, ^{1}H NMR and mass spectral data. The newly synthesized (4a-4o) derivatives are screened for themin-vitro anthelmintic and anti-inflammatory activity by slandered procedure. The synthesized compound **4d, 4g**and **4n**are showed good Anti-inflammatory activities compare with Sodium diclofenac sodium as a standard drug. Whereas, the compounds **4c, 4g, 4i, 4k** and **4m** are has showed most potent anthelmintic activity compare with Albendazole as a standard drug.Among the docked ligands, dock scores of all the compounds ranged from -5.35 (compound TB-4g) to -1.509 (compound TB-4c). Compound TB-4g reported highest dock score of -5.35 with Glide binding energy of -39.159 Kcal/mol. Salt bridge was formed between nitro group of TB-4i and compound ASP 813.

Keywords: Thiazole, Imidazoline, substituted benzaldehyde, anthelmintic and anti-inflammatory and Albendazole, Sodium diclofenac sodium, Molecular docking.

I. INTRODUCTION:

Imidazolines are dihydro-Imidazole derivatives. They are also found to be equallypharmacologically interesting characteristic. Imidazolines displayed a broad spectrum of potentialpharmacological activities and are present in a number of pharmacologically active molecules.Some of major activities are listed as anti-inflammatory [1], anticancer [2,3], anti-inflammatory [4], antifungal [5], antiproliferative [6], anti-biofilm [7], and herbicidal activities [8]. Anti-inflammation is considered a worldwide health risk from 20 years onwards.In recent years, Schiff bases of carbonyl compounds are reported to exhibit broad–spectrumchemotherapeutic properties such as antiviral, anti-tubercular, antifungal and antibacterial activities. Several investigation of the structure activity relationshipsin Imidazoline derivatives revealed that halogenations are having the highest activity compare with other substituted imidazoline derivatives. The inflammation(Latin, inflammo, "I ignite, set alight") is part of the complex biologicalresponse of vascular tissues to harmful stimuli, such as pathogens,damaged cells, or irritants and the classical signs of acute inflammationare pain, heat, redness, swelling, and loss of functionantifungal [8-9]. Inflammation is aprotective attempt by the organism to remove the injurious stimuli andto initiate the healing process.In the present work is oriented towards synthesis of thiazole containing newly synthesised Imidazolines and its prepared derivatives by conventional method by using substituted benzaldehyde. The main aim of the present work is to find moleculessuch as these by synthesizing several Schiff bases from Imidazolines.

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II. MATERIALS AND METHODS:

All chemicals and Solvents are used in this study were of analytical reagentgrade and of the highest purity available. All the synthesized (4a-4o)werescreenedfor Anti-inflammatory and anthelmintic activities. Fourier Transform IR spectrometer (model Shimadzu 8700) inthe range of 400-4000 cm^{-1} Using KBr pellets and values are reported in cm^{-1}andthe spectra were interpreted. ^{1}H-NMR was scanned on Avance-400 MHz instrument. Chemical shifts are expressed in δ (ppm) relative to TMS as an internal standard using DMSO-d_6 as solvent. Massspectra were recorded on Mass spectrophotometer (model Shimadzu) by LC- MS and the spectra wereinterpreted.Precoated Silica Gel G plates were used to monitor the progress of reaction as well as to check the purity of the compounds**.** Ethyl acetate: n-Hexane (7:3) used as a mobile phase.

General procedures: [10-12]. **Step-1. Synthesis of 2-Amino 4-Aryl Thiazole (1a-1b):** A mixture of substituted acetophenone (0.1 mol), thiourea (0.2 mol) and Iodine (0.1 mol) was heated on a steam bath for 4 hrs. The hydroiodide, thus separated, was filtered, washed with ether and dried. It was dissolved in hot water, filtered while hot and the clear solution neutralized with a strong solution of ammonia. The solid separated was filtered, washed with water and recrystallized from Benzene. Yield: 96%, m.p. 145-150ºC.

Step: 2: Synthesis of Benzoyl glycine derivatives (2a-2b): In conical flask prepare 10% of sodium hydroxide solution and dissolve in it 0.03 mole of glycine. Add 0.03 mole of substituted benzoyl chloride in 5 portions to the solution. Stopper the vessel and shake vigorously after each addition until all the chloride has reacted. Transfer the solution to a beaker and rinse the conical flask with a little water. Place a few pieces of crushed ice to the solution and add slowly 5 mL of HCl with stirring until the mixture is acid to Congo red paper. Collect the resulting crystalline precipitate of benzoylglycine. Filter the product on Büchner funnel, and dry on air on Petri dish.

Step: 3: Synthesis of 2-phenyl-4-benzylidene oxazol-5(4H)-One derivative (3a-3b). The appropriate Terephthaldehyde (1 mmol), hippuric acid (2a-2b) (1 mmol), Ac_2O (1 ml) and $CaHPO_4$ as a catalyst (0.2 mmol) were mixed in a conical flask. Then, the reaction mixture was refluxed 2hr. After completion of the reaction as indicated by TLC, the reaction mixture was cooled to room temperature. 5 ml Cold ethanol/water (1:1) was added and the mixture was stirred for 15 min until a yellow solid precipitated. An aqueous solution of $NaHCO_3$ (10 ml, 20%) was added, the solid products and the catalyst were filtered. The solid materials were dissolved in hot ethanol to remove the catalyst. The solvent was allowed to cool in room temperature to obtain crude products.

Step: 4: Synthesis of 4-(-4-(-((4-substitutedphenyl) imino)substituted)benzylidene)-2-(p-tolyl)oxazol-5-one(3a-3h). Equimolar quantities (3a-3b) (0.01mol) of 2-phenyl-4-benzylidene oxazol-5(4H)-One derivative (3a-3b) and substituted aniline were dissolved in warm ethanol and glacial acetic acid (1:1%, 30ml). The reaction mixture was refluxed for 3hrs and then kept in refrigerator for overnight. The resultant solid was filtered, dried and recrystallized from suitable solvent to afford compounds.

Step: 5: Synthesis of thiazole contain novel imidazole derivatives (4a-4o). A mixture of equimolar quantities of4-(-4-(-((4-substitutedphenyl) imino)substituted)benzylidene)-2-(p-tolyl)oxazol-5-one(3a-3h) (0.01mol) and 2-Amino 4-Aryl Thiazole (1a-1b) (1a-1b) (0.01mol) was refluxed in pyridine for 7-8 h. One KOH pellet was added to this mixture. The progress of the reaction was monitored by TLC. After completion of the reaction resulting mass was poured into crushed ice and neutralised with dil. HCl. Precipitate was filtered, dried and the product was recrystallized form methanol.

Table.No.1. Physical characterization of compounds [4a-4o].

S.Code	**R**	**R_1**	**R_2**	**Mol. For**	**Mol.Wt gm/mol**	**M.P(°C)**	**%Yield**	**Rf.V**
4a	-H	-H	H	$C_{32}H_{22}N_4OS$	510.25	178-180	76	0.67
4b	$-CH_3$	-H	H	$C_{33}H_{24}N_4OS$	524.74	154-156	69	0.83
4c	$-CH_3$	$-CH_3$	H	$C_{34}H_{26}N_4O_2S$	538.03	130-132	81	0.76
4d	$-CH_3$	$-OCH_3$	H	$C_{34}H_{26}N_4O_2S$	554.17	121-123	73	0.58

International Journal of Pharmaceutical Research and Applications
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4e	-H	- OCH_3	H	$C_{32}H_{24}N_4O_2$	540.32	191-193	66	0.66
4f	-H	- CH_3	-H	$C_{33}H_{24}N_4OS$	524.01	177-179	82	0.60
4g	- CH_3	-CH_3	- CH_3	$C_{35}H_{28}N_4OS$	552.03	143-145	78	0.59
4h	-H	- CH_3	- CH_3	$C_{34}H_{26}N_4OS$	538.07	201-203	72	0.77
4i	-H	-CH_3	-NO_2	$C_{33}H_{23}N_5O_3S$	569.41	155-157	70	0.93
4j	-H	-CH_3	-Cl	$C_{33}H_{23}N_4OSCl$	558.17	189-191	69	0.68
4k	-H	- CH_3	-F	$C_{33}H_{23}N_4OSF$	542.05	133-135	78	0.54
4l	-H	-H	- CH_3	$C_{33}H_{24}N_4OS$	524.31	196-198	84	0.77
4m	-CH_3	-CH_3	-F	$C_{34}H_{25}N_4OSF$	556.02	211-213	71	0.80
4n	- CH_3	- OCH_3	-F	$C_{34}H_{25}N_4O_2SF$	572.32	163-165	66	0.68
4o	-H	-H	-NO_2	$C_{32}H_{21}N_5O_3S$	555.06	143-145	78	0.76

Compound.4a:2-phenyl-5-(-4-(-(phenylimino)methyl)benzylidene)-3-(4-phenyl thiazol-2-yl)-3,5-dihydro-4H-imidazol-4-one. IR, Cm-1 (KBr): 3034(-CH Str, aromatic), 2938, 2897, 2730 (-CH Str, aliphatic), 2342(-CSC-, Str n thiazole), 1715(C=O Str in Imidazole), 1534(C=N Str), 1484(C=C, Str), 1019(C-N, Str). ^{1}HNMR (DMSO, δppm): 8.923(1H, Benzyl proton), 8.447-8.143(2H, d, Ar-H), 8.062-8.059(2H, d, Ar-H), 7.964(1H, s, Ar-H), 7.716-7.699(2H, d, Ar-H), 7.574-7.534(3H, t, Ar-H), 7.524-7.504(2H, d, Ar-H), 7498-7.475(2H, d, Ar-H), 7.448(2H, t, Ar-H), 7.405(3H, t, Ar-H), 7.392(1H, s, Ar-H), 4.482(1H, t, -CH-), 2.788(2H, -CH_2- in acetyl proton). Mass (EI-MS): 510(M), 5111(M + 1).

Compound.4b:2-phenyl-5-(-4-(-(phenylimino) methyl)benzylidene)-3-(4-(p-tolyl) thiazol -2-yl)-3,5-dihydro-4H-imidazol-4-one. IR, Cm-1 (KBr): 3034(-CH Str, aromatic), 2992, 2830, 2750(-CH Str, aliphatic), 2391(-CSC-, Str in thiazole), 1712(C=O Str in Imidazole), 1512(C=N Str), 1438(C=C, Str), 1025(C-N, Str). ^{1}HNMR (DMSO, δppm): 9.4748(1H, Imine proton), 9.4339(1H, Benzylidine proton), 8.1621-8.0593(2H, d, Ar-H), 7.9751-7.9650(2H, d, Ar-H), 7.7187-7.6961(2H, d, Ar-H), 7.5924-7.5305(2H, d, Ar-H), 7.5295-7.5187(2H, d, Ar-H), 7.5060-7.5040(2H, d, Ar-H), 7.4971-7.4795(3H, t, Ar-H), 7.4766-7.4052(3H, t, Ar-H), 7.3952(1H, s, Ar-H), 2.0781(3H, s, Ar-CH_3). Mass (EI-MS): 524(M), 525(M + 1), 467(M + 2).

Compound.4c: 5-(-4-(-(phenylimino)methyl)benzylidene)-2-(p-tolyl)-3-(4-(p-tolyl) thiazol-2-yl)-3,5-dihydro-4H-imidazol-4-one. IR, Cm-1 (KBr): 3097(-CH Str, aromatic), 2987, 2933,2798(-CH Str, aliphatic), 2355(-CSC-, Str in thiazole), 1719(C=O Str in Imidazole), 1544(C=N Str), 1444(C=C, Str), 1103(C-N, Str).). ^{1}HNMR (DMSO, δppm): 9.2135(1H, Imine proton), 9.1091(1H, Benzylidine proton), 8.4960(2H, d, Ar-H), 8.3133(2H, d, Ar-H), 7.9311(2H, d, Ar-H), 7.8918-7.8413(2H, d, Ar-H), 7.7931-7.7863(2H, d, Ar-H), 7.6906-7.6828(2H, d, Ar-H), 7.5483-7.5110(2H, d, Ar-H), 7.4963-7.4870(3H, t, Ar-H), 7.1475(1H, s, Ar-H), 2.0802(6H, s, Ar-CH_3). Mass (EI-MS): 538(M), 539(M + 1).

Compound.4d:2-(4-methoxyphenyl)-5-(-4-(-(phenylimino)methyl)benzylidene)-3-(4-(p-tolyl)thiazol-2-yl)-3,5-dihydro-4H-imidazol-4-one. IR, Cm-1 (KBr): 3103(-CH Str, aromatic), 2995, 2868, 2755(-CH Str, aliphatic), 2355(-CSC-, Str n thiazole), 1702(C=O Str in Imidazole), 1522(C=N Str), 1381(C=C, Str), 1022(C-N, Str). ^{1}HNMR (DMSO, δppm): 9.4041(1H, Imine proton), 9.4050(1H, Benzylidine proton), 8.4600-8.3087(2H, d, Ar-H), 8.2738(2H, d, Ar-H), 8.0951-8.0432(2H, d, Ar-H), 7.9570-7.9121(2H, d, Ar-H), 7.9089-7.8580(2H, d, Ar-H), 7.6690-7.6499(2H, d, Ar-H), 7.5036-7.4930(2H, d, Ar-H), 7.7949-7.7487(3H, t, Ar-H), 7.0041(1H, s, Ar-H), 3.6410(3H, s, Ar-OCH_3). 2.0064(3H, s, Ar-CH_3). Mass (EI-MS): 554(M), 555(M + 1).

Compound.4e:2-(4-methoxyphenyl)-5-(-4-(-(phenylimino) methyl)benzylidene)-3-(4-phenyl thiazol-2-yl)-3,5-dihydro-4H-imidazol-4-one. IR, Cm-1 (KBr): 3076(-CH Str, aromatic), 2987, 2887, 2787(-CH Str, aliphatic), 2354(-CSC-, Str in thiazole), 1702(C=O Str in Imidazole), 1524(C=N Str), 1423(C=C, Str), 1065(C-N, Str). ^{1}HNMR (DMSO, δppm): 9.3722(1H, Imine proton), 9.2812(1H, Benzylidine proton), 8.3642-8.2833(2H, d, Ar-H), 8.120-8.0432(2H, d, Ar-H), 7.9843-7.8543(2H, d, Ar-H), 7.7643-7.6774(2H, d, Ar-H), 7.5643-7.3843(2H, d, Ar-H), 7.2983-7.0212(2H, d, Ar-H), 6.9733-7.8943(3H, t, Ar-H), 7.6654-7.5884(3H, t, Ar-H), 7.4534(1H, s, Ar-H), 3.5463(3H, s, Ar-OCH_3). Mass (EI-MS): 540(M), 541(M + 1).

Compound.4f:5-(-4-(-(phenylimino)methyl)benzylidene)-3-(4-phenylthiazol-2-yl)-2-(p-tolyl)-3,5-dihydro-4H-imidazol-4-one: IR, Cm-1 (KBr): 3054(-CH Str, aromatic), 2987, 2898, 2765(-CH Str, aliphatic),

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 1693-1704 www.ijprajournal.com ISSN: 2456-4494

2367(-CSC-, Str in thiazole), 1709(C=O Str in Imidazole), 1509(C=N Str), 1454(C=C, Str), 1044(C-N, Str). ^{1}HNMR (DMSO, δppm): 9.4092(1H, Imine proton), 9.3922(1H, Benzylidine proton), 8.1093-8.0023(2H, d, Ar-H), 7.9093-7.9002(2H, d, Ar-H), 7.7782-7.6932(2H, d, Ar-H), 7.5002-7.4093(2H, d, Ar-H), 7.3892-7.2143(2H, d, Ar-H), 7.1190-7.1023(2H, d, Ar-H), 7.0093-7.0005(3H, t, Ar-H), 6.9773-9.8932(3H, t, Ar-H), 6.8792(1H, s, Ar-H), 2.0023(3H, s, Ar-CH_3). Mass (EI-MS): 525(M), 526(M + 1), 467(M + 2).

Compound.4g:2-(p-tolyl)-3-(4-(p-tolyl)thiazol-2-yl)-5-(-4-((E)-(p-tolylimino)methyl) benzylidene)-3,5-dihydro-4H-imidazol-4-one. IR, Cm-1 (KBr): 3103(-CH Str, aromatic), 2995, 2868, 2755(-CH Str, aliphatic), 2355(-CSC-, Str n thiazole), 1702(C=O Str in Imidazole), 1522(C=N Str), 1381(C=C, Str), 1022(C-N, Str). ^{1}HNMR (DMSO, δppm): 9.4041(1H, Imine proton), 9.4050(1H, Benzylidine proton), 8.4600-8.3087(2H, d, Ar-H), 8.2738(2H, d, Ar-H), 8.0951-8.0432(2H, d, Ar-H), 7.9570-7.9121(2H, d, Ar-H), 7.9089-7.8580(2H, d, Ar-H), 7.6690-7.6499(2H, d, Ar-H), 7.5036-7.4930(2H, d, Ar-H), 7.7949-7.7487(3H, t, Ar-H), 7.0041(1H, s, Ar-H), 3.6410(3H, s, Ar-OCH_3). 2.0064(3H, s, Ar-CH_3). Mass (EI-MS): 552(M), 553(M + 1).

Compound.4h:3-(4-phenylthiazol-2-yl)-2-(p-tolyl)-5-(-4-((E)-(p-tolylimino)methyl) benzyli dene) -3,5-dihydro-4H-imidazol-4-one. IR, Cm-1 (KBr): 3043(-CH Str, aromatic), 2956, 2848, 2765(-CH Str, aliphatic), 2365(-CSC-, Str in thiazole), 1714(C=O Str in Imidazole), 1523(C=N Str), 1417(C=C, Str), 1054(C-N, Str). ^{1}HNMR (DMSO, δppm): 9.2983(1H, Imine proton), 9.1002(1H, Benzylidine proton), 8.3029-8.2810(2H, d, Ar-H), 8.1083(2H, d, Ar-H), 8.0432-8.0003(2H, d, Ar-H), 7.9043-7.0032(2H, d, Ar-H), 7.8732-7.7843(2H, d, Ar-H), 7.5643-7.4521(2H, d, Ar-H), 7.3872-7.2983(2H, d, Ar-H), 7.1033-7.0937(3H, t, Ar-H), 6.9043(1H, s, Ar-H), 3.5453(3H, s, Ar-OCH_3). 2.1922(3H, s, Ar-CH_3). Mass (EI-MS): 538(M), 539(M + 1). MS): 450(M), 451(M + 1).

Compound.5i:5-(-4-(-((4-nitrophenyl)imino)methyl)benzylidene)-3-(4-phenyl thiazol-2-yl)-2-(p-tolyl)-3,5-dihydro-4H-imidazol-4-one. IR, Cm-1 (KBr): 3054(-CH Str, aromatic), 2956, 2865, 2784(-CH Str, aliphatic), 2364(-CSC-, Str in thiazole), 1709(C=O Str in Imidazole),1645(NO_2, Str in Ar-NO_2), 1529(C=N Str), 1423(C=C, Str), 1123(C-N, Str). ^{1}HNMR (DMSO, δppm): 8.9463(1H, Imine proton), 8.7832(1H, Benzylidine proton), 8.3732-8.3452(2H, d, Ar-H), 8.18932-8.10032(2H, d, Ar-H), 8.1003-8.0032(2H, d, Ar-H), 7.9983-7.8427(2H, d, Ar-H), 7.6843-7.5632(2H, d, Ar-H), 7.3922-7.3093(2H, d, Ar-H), 7.2901-7.1092(2H, d, Ar-H), 6.9543-6.8943(2H, d, Ar-H), 6.7892(1H, s, Ar-H), 1.9833(3H, s, Ar-CH_3). Mass (EI-MS): 569(M), 570(M + 1).

Compound.4j:5-(-4-(-((4-chlorophenyl)imino)methyl)benzylidene)-3-(4-phenyl thiazol-2-yl)-2-(p-tolyl)-3,5-dihydro-4H-imidazol-4-one. IR, Cm-1 (KBr): 3074(-CH Str, aromatic), 2988, 2898, 2732(-CH Str, aliphatic), 2302(-CSC-, Str in thiazole), 1712(C=O Str in Imidazole), 1521(C=N Str), 1434(C=C, Str), 1132(C-N, Str), 798(Cl, Str in Ar-Cl). ^{1}HNMR (DMSO, δppm): 9.0432(1H, Imine proton), 8.9823(1H, Benzylidine proton), 8.2983-8.1032(2H, d, Ar-H), 8.1903-8.0331(2H, d, Ar-H), 7.9832-7.8322(2H, d, Ar-H), 7.78932-7.6903(2H, d, Ar-H), 7.5642-7.5093(2H, d, Ar-H), 7.4932-7.4021(2H, d, Ar-H), 7.3021-7.3002(2H, d, Ar-H), 7.0321-7.0021(2H, d, Ar-H), 6.9054(1H, s, Ar-H), 2.0321(3H, s, Ar-CH_3). Mass (EI-MS): 558(M), 559(M + 1), 560(M + 2).

Compound.4k:5-(-4-(-((4-fluorophenyl)imino)methyl)benzylidene)-3-(4-phenylthiazol -2-yl)-2-(p-tolyl)-3,5-dihydro-4H-imidazol-4-one. IR, Cm-1 (KBr): 3093(-CH Str, aromatic), 2932, 2865, 2774(-CH Str, aliphatic), 2389(-CSC-, Str in thiazole), 1719(C=O Str in Imidazole), 1533(C=N Str), 1429(C=C, Str), 1117(C-N, Str), 847(F, Str in Ar-F). ^{1}HNMR (DMSO, δppm): 9.4523(1H, Imine proton), 9.0323(1H, Benzylidine proton), 8.4238-8.4092(2H, d, Ar-H), 8.2832-8.1902(2H, d, Ar-H), 8.0032-8.0002(2H, d, Ar-H), 7.9864-7.8543(2H, d, Ar-H), 7.6543-7.4893(2H, d, Ar-H), 7.3674-7.2932(2H, d, Ar-H), 7.1032-7.0032(2H, d, Ar-H), 6.9943-6.8943(2H, d, Ar-H), 6.7832(1H, s, Ar-H), 2.1093(3H, s, Ar-CH_3). Mass (EI-MS): 542(M), 543(M + 1), 544(M + 2).

Compound.4l:2-phenyl-3-(4-phenylthiazol-2-yl)-5-(-4-(-(p-tolylimino) methyl) benzyli dene)-3,5-dihydro-4H-imidazol-4-one. IR, Cm-1 (KBr): 3065(-CH Str, aromatic), 2956, 2876, 2799(-CH Str, aliphatic), 2321(-CSC-, Str in thiazole), 1709(C=O Str in Imidazole), 1527(C=N Str), 1421(C=C, Str), 1046(C-N, Str). ^{1}HNMR (DMSO, δppm): 9.4032(1H, Imine proton), 9.2312(1H, Benzylidine proton), 8.3843-8.2387(2H, d, Ar-H), 8.1093-8.0212(2H, d, Ar-H), 7.9034-7.8322(2H, d, Ar-H), 7.6732-7.4895(2H, d, Ar-H), 7.3421-7.2984(2H, d, Ar-H), 7.2893-7.2002(2H, d, Ar-H), 7.1092-7.0032(3H, t, Ar-H), 6.9045-6.8932(3H, t,

International Journal of Pharmaceutical Research and Applications
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Ar-H), 6.8891(1H, s, Ar-H), 1.9892(3H, s, Ar-CH_3). Mass (EI-MS): 524(M), 525(M + 1).

Compound.4m:5-(-4-(-((4-fluorophenyl)imino)methyl)benzylidene)-2-(p-tolyl)-3-(4-(p-tolyl) thiazol-2-yl)-3,5-dihydro-4H-imidazol-4-one: IR, Cm-1 (KBr): 3032(-CH Str, aromatic), 2976, 2898, 2769(-CH Str, aliphatic), 2326(-CSC-, Str n thiazole), 1716(C=O Str in Imidazole), 1542(C=N Str), 1402(C=C, Str), 1065(C-N, Str), 825(F, Str in Ar-F). ^{1}HNMR (DMSO, δppm): 9.5212(1H, Imine proton), 9.2012(1H, Benzylidine proton), 8.3920-8.2931(2H, d, Ar-H), 8.1903(2H, d, Ar-H), 8.0032-8.00012(2H, d, Ar-H), 7.9893-7.8932(2H, d, Ar-H), 7.7682(2H, d, Ar-H), 7.4532(2H, d, Ar-H), 7.3982-7.2902(2H, d, Ar-H), 7.1092-7.0322(3H, t, Ar-H), 6.9883(1H, s, Ar-H), 2.3023(3H, s, Ar-CH_3). 1.9893(3H, s, Ar-CH_3). Mass (EI-MS): 556(M), 557(M + 1), 558(M + 2).

Figure.No.1.Scheme

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 1693-1704 www.ijprajournal.com ISSN: 2456-4494

Compound.4n:5-(-4-(-((4-fluorophenyl)imino)methyl)benzylidene)-2-(4-methoxy phenyl) -3-(4-(p-tolyl)thiazol-2-yl)-3,5-dihydro-4H-imidazol-4-one. IR, Cm-1 (KBr): 3065(-CH Str, aromatic), 2987, 2867, 2739(-CH Str, aliphatic), 2328(-CSC-, Str n thiazole), 1702(C=O Str in Imidazole), 1563(C=N Str), 1416(C=C, Str), 1043(C-N, Str), 819(F, Str in Ar-F). ^{1}HNMR (DMSO, δppm): 9.1922(1H, Imine proton), 9.0032(1H, Benzylidine proton), 8.4630-8.3902(2H, d, Ar-H), 8.2093-8.0932(2H, d, Ar-H), 7.9803-7.9002(2H, d, Ar-H), 7.7832-7.6832(2H, d, Ar-H), 7.5893(2H, d, Ar-H), 7.4093-7.3894(2H, d, Ar-H), 7.2093-7.1232(3H, t, Ar-H), 7.0933-7.0023(3H, t, Ar-H), 6.9893(1H, s, Ar-H), 3.5643(3H, s, Ar-OCH_3). 2.0643(3H, s, Ar-CH_3). Mass (EI-MS): 572(M), 573(M + 1), 574(M + 2).

Compound.4o:5-(-4-(-((4-nitrophenyl)imino)methyl)benzylidene)-2-phenyl-3-(4-phenyl thiazol-2-yl)-3,5-dihydro-4H-imidazol-4-one. IR, Cm-1 (KBr): 3032(-CH Str, aromatic), 2967, 2898, 2745(-CH Str, aliphatic), 2356(-CSC-, Str n thiazole), 1715(C=O Str in Imidazole), 1623(NO_2 Str, Ar-NO_2), 1532(C=N Str), 1417(C=C, Str), 1043(C-N, Str). ^{1}HNMR (DMSO, δppm): 9.3423(1H, Imine proton), 9.2712(1H, Benzylidine proton), 8.2933-8.2376(2H, d, Ar-H), 8.1974-8.0421(2H, d, Ar-H), 7.8793-7.7843(2H, d, Ar-H), 7.6731-7.5632(2H, d, Ar-H), 7.4883(2H, d, Ar-H), 7.3894-7.3032(2H, d, Ar-H), 7.1093-7.0654(2H, d, Ar-H), 6.9883-6.8733(3H, t, Ar-H), 6.7832(1H, s, Ar-H). Mass (EI-MS): 555(M), 556(M+ 1).

Biological Evaluation:

Anti-Inflammatory: [13]Anti-inflammatory activity of the newly synthesized thiazole contain novel imidazoline derivatives (4a-4o) wasdeterminedbycarrageenan inducedpawedema assay method inrats. Two dose levels (10mg/kgand 20 mg/kg) of synthesized compoundsand Diclofenac sodium (10mg/kg and 20mg/kg) as standard wereadministered. The change in the pawvolumes were measured beforeand1h after carrageenan injection, usingthe mercurydisplacement technique withthehelpofplethysmograph. Thepercent inhibition of paw edemawascalculatedfrom percent inhibition formula.

%inhibition(I)=100[1-(a-x)/(b-y)]

Where,

x=meanpawvolumeof ratsbeforetheadministrationofcarrageenanandtestcompoundsor reference compound (testgroup)

a = meanpaw volume ofrats after the administration of carrageenan in the test group (drug treated)

b =is the mean paw volume of rats after the administration of carrageenan in the control group

y = mean paw volume of rats before the administration of carrageenan in the control group.

Anti-inflammatory activity of newly synthesized novel Imidazoline derivatives was evaluated by carrageenan induced paw edema bioassay in rats with Diclofenac sodium (10 and 20 mg/kg) as reference standard. Percentage inhibitions of the molecules are tabulated in Table 2 and Figure 2.

Table.2: Anti-Inflammatory activity of thiazole contain novel Imidazoline derivatives(4a-4o) (% inhibition of paw edema)

% Inhibition of Paw edema	Compounds															
	Diclofenac sodium	**4a**	**4b**	**4c**	**4d**	**4e**	**4f**	**4g**	**4h**	**4i**	**4j**	**4k**	**4l**	**4m**	**4n**	**4o**
10 mg/kg	**64.7**	30.4	32.5	43.8	**60.6**	47.7	26.6	**59.2**	35.7	29.1	39.1	33.2	35.8	50.5	**58.6**	47.6
20 mg/kg	**88.3**	43.9	38.7	64,2	**75.4**	60.3	33.8	**72.5**	43.2	49.2	53.8	49.3	45.5	67.9	**74.1**	60.5

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 1693-1704 www.ijprajournal.com ISSN: 2456-4494

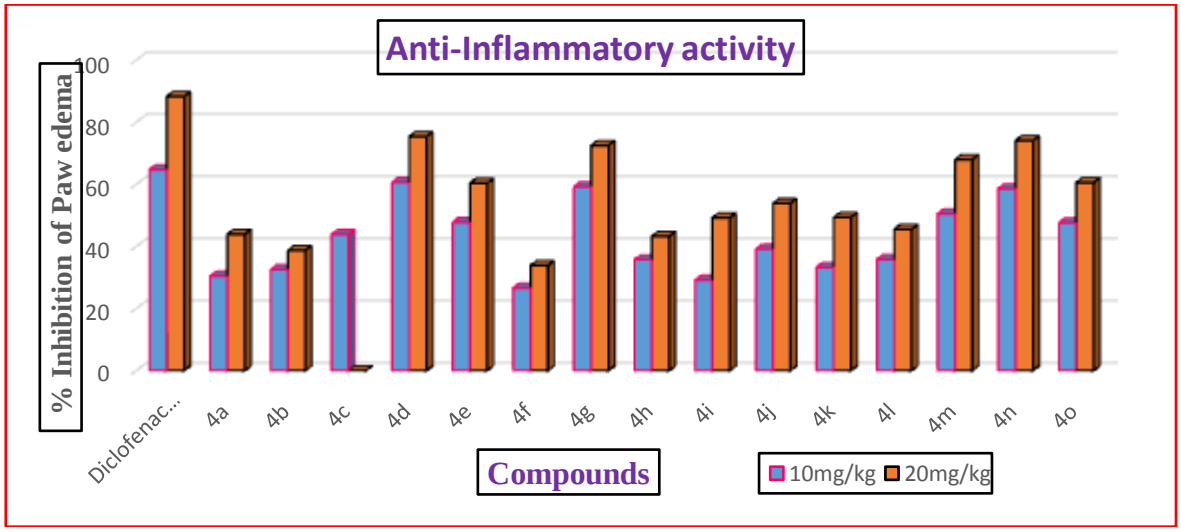


Figure.2: Anti-Inflammatory activity of thiazole contain novel Imidazoline derivatives (4a-4o) (% inhibition of paw edema)

Anthelmintic activity [14]: Thiazole contain novel Imidazoline compounds were screened for anthelmintic activity by using Indian earth worms. One earthworm is placed in standard drug solution and test compound's solutions at room temperature and normal saline used as control. The standard drug and test compounds were dissolved in minimum quantity of dimethyl sulfoxide (DMSO) and adjusted the volume up to 10 ml with normal saline solution to get the concentration of 0.1% w/v, 0.2 % w/v and 0.5% w/v. Albendazole was used as a standard drug. 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. The time taken by worms to become motionless was noted as paralysis time. To certain the death of the motionless worms was frequently applied with external stimuli, which stimulate and induce movement in the worms, if alive. The mean lethal time and paralysis time of the earthworms for different test compounds and standard drug are tabulated in Table.3, Fig.3,4.

Table.3: Anthelmintic activity of thiazole contain novel Imidazoline derivatives (4a-4o) (Paralysis and Death time)

S.No.	Compound	Time in minutes					
		For paralysis % Concentration			For death % Concentration		
	Concentration	0.1	0.2	0.5	0.1	0.2	0.5
	Control	-	-	-	-	-	-
	Albendazole	16	14	9	42	31	27
1	4a	30	24	18	50	46	39
2	4b	29	25	22	59	45	40
3	4c	**19**	**16**	**13**	**44**	**36**	**33**
4	4d	22	20	19	52	45	35
5	4e	34	27	25	69	57	32

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 1693-1704 www.ijprajournal.com ISSN: 2456-4494

6	**4f**	30	22	20	57	46	42
7	**4g**	**20**	**18**	**11**	**45**	**36**	**30**
8	**4h**	30	26	21	58	49	40
9	**4i**	**18**	**14**	**12**	**44**	**36**	**30**
10	**4j**	35	29	23	20	54	37
11	**4k**	**21**	**17**	**13**	**47**	**34**	**31**
12	**4l**	34	28	22	68	54	47
13	**4m**	**22**	**17**	**11**	**43**	**36**	**33**
14	**4n**	29	26	20	66	55	41
15	**4o**	32	24	21	69	56	42

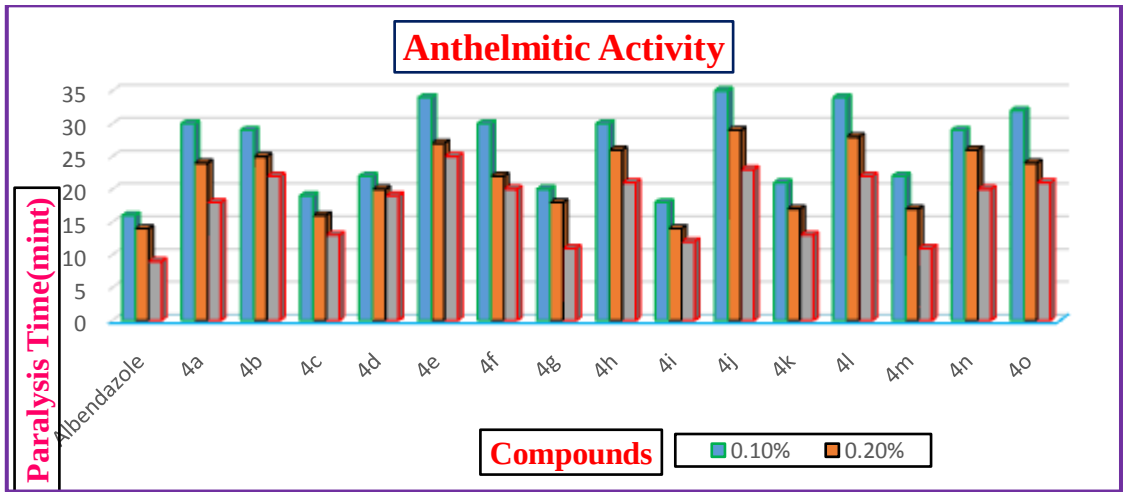


Fig.No. 3: Anthelmintic activity of thiazole contain novel Imidazoline derivatives(4a-4o) (Paralysis)(mint)

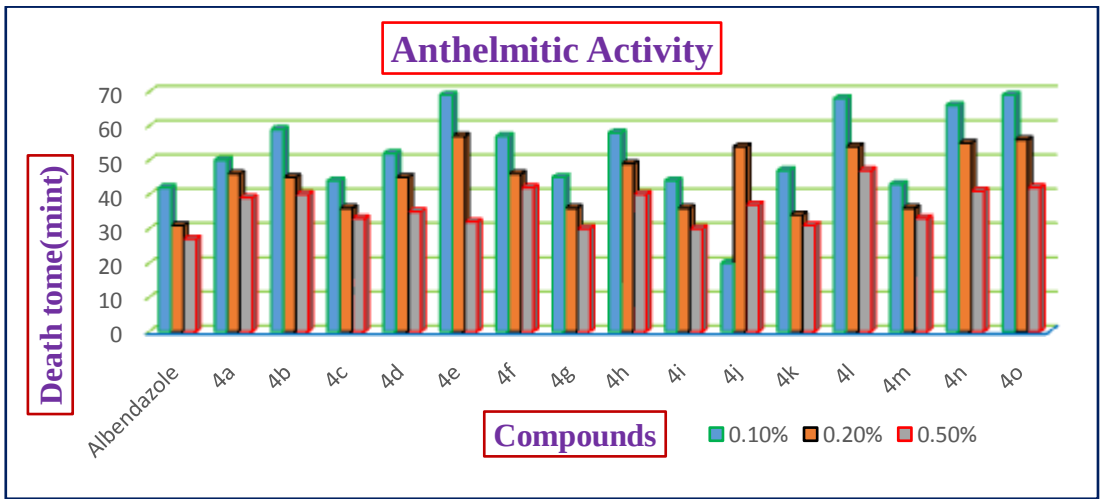


Fig.No. 4: Anthelmintic activity of thiazole contain novel Imidazoline derivatives (4a-4o) (Death time)

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 1693-1704 www.ijprajournal.com ISSN: 2456-4494

Molecular Docking Studies [15]. The molecular docking studies play an important role in mechanistically by placing a molecule into the binding site of the target moleculein drug design. I have docked the synthesized thiazole contain novel imidazoline compounds into active site of 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.

III. RESULTS AND DISCUSSION:

Chemistry: Newly synthesized thiazole contain novel Imidazoline derivatives(4a-4o) gave fruitful results for the proposed structures, and confirmed by their physical and spectral analysis by FT-IR, LC-MASS and ^{1}H NMR data. In this conventional method involves via different mechanisms, such as cyclization between thiourea and Substituted Acetophenone to 2-Amino 4-Aryl Thiazole. The Benzoyl glycine derivatives reacts with substituted benzaldehyde to form Oxazole derivatives, then followed Schiff's with different aromatic amine to give imidazole derivatives. Finally, these are reacting with 2-Amino 4-Aryl Thiazole to gives the title of the products(4a-4o). All structure of the newly synthesized these compounds were characterized as **4a-4o** on the basis of satisfactory physical and spectral data including IR, LC-MASS and ^{1}H NMR data.

Anti-inflammatory: All the synthesizedthiazole contain novel imidazoline derivatives **(4a-4o**) was screened for their Anti-inflammatory activity by carrageenan induced paw edema assay in albino rats. The results indicated that all the compounds reported fruitful results at dose of 10 and 20mg/kg when compared to that of slandered diclofenac sodium as drug doses. However, the anti-inflammatory effect of compound **4d(60.6,75.4), 4g (59.2, 72.5)** and **4n (58.6, 74.1)** at 10 and 20mg/kg are showing more potent activity as compared to standard.

Anthelmintic activity: All the synthesizedthiazole contain novel imidazoline derivatives (4a-4o) were evaluated for anthelmintic activity by using Indian earthworms (Pheretima posthuma) as shown in table.No.6. Among the compounds tested all the compounds were showed significant paralysis time of earthworms, compared to standard drug Albendazole at 0.1%, 0.2% and 0.5% concentrations. A very closer inspiration of data from this table indicated that compound **4c, 4g**, **4i** and **4m** having more activity.

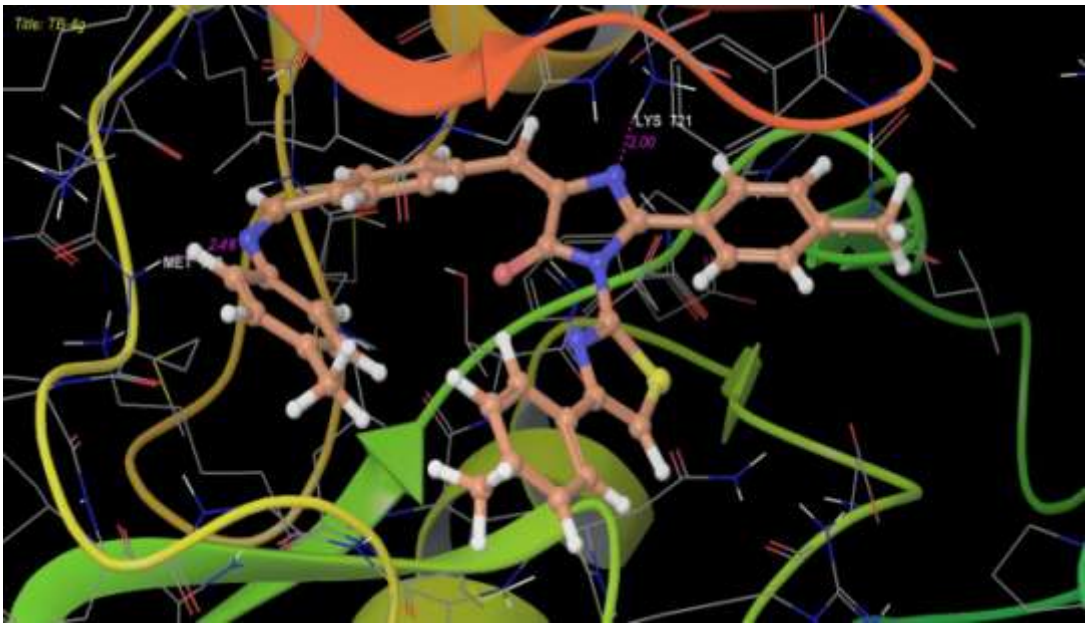
Molecular Docking Studies: Molecular docking studies were performed in order to find the possible protein ligand interactions of the dataset ligands. Additionally, these also assisted in identifying the conformational changes of the ligand in the protein environment. About 100 different protein-ligand complex conformations for each docked complex were generated through Glide XP module; the confirmation with highest EModel energy was only displayed in the result. Glide dock sores of the dataset ligands were shown in **Table 4** along with the interaction amino acids and number of amino acids.Among the docked ligands, dock scores of all the compounds ranged from -5.35 (compound TB-4g) to -1.509 (compound TB-4c). Compound TB-4g reported highest dock score of -5.35 with Glide binding energy of -39.159 Kcal/mol. Compounds TB-4g and TB-4j possessed two H-bonds with LYS 721 and MET 769, whereas, Hydrophobic interactions were observed between compound TB-4c and Arg 779. Pi-Cation interactions were observed with compounds TB-4i (ARG 817) and TB-4c (ARG 817). Salt bridge was formed between nitro group of TB-4i and compound ASP 813.

Table.4:Glide dock sores of the dataset ligands, along with the interaction amino acids.

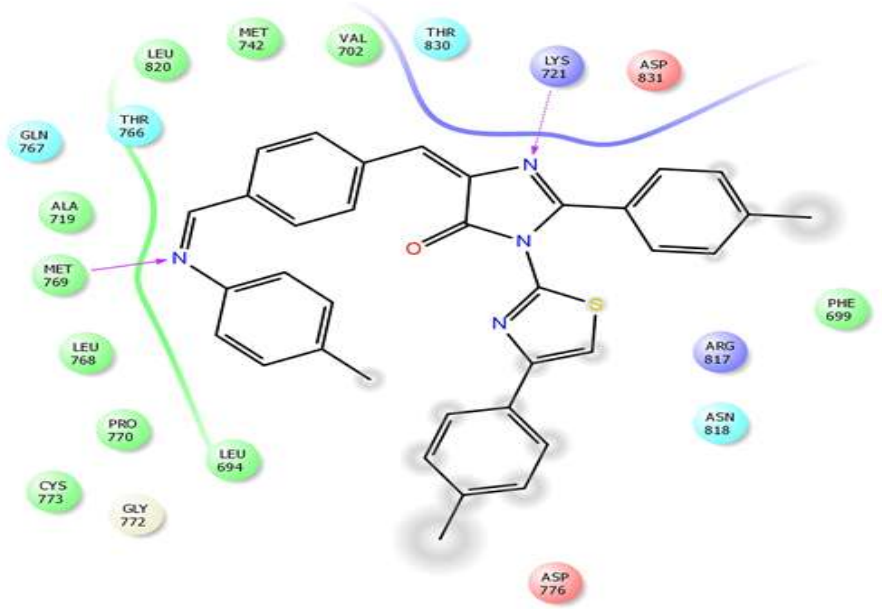
Compound No	Dock score XP GScore	No of H-bonds	Interacting amino acids	H-bond lengths (Å)	Emodel energy	Glide energy
TB-4g	-5.35	2	LYS 721 MET 769	2.00 2.16	-46.549	-39.159
TB-4j	-5.152	2	LYS 721 MET 769	2.61 1.97	-65.348	-38.522
TB-4b	-4.112	0	-	-	-58.078	-45.794

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 1693-1704 www.ijprajournal.com ISSN: 2456-4494

TB-4i	-3.091	0	-	-	-59.173	-50.3
TB-4c	-1.509	0	-	-	-68.108	-49.416

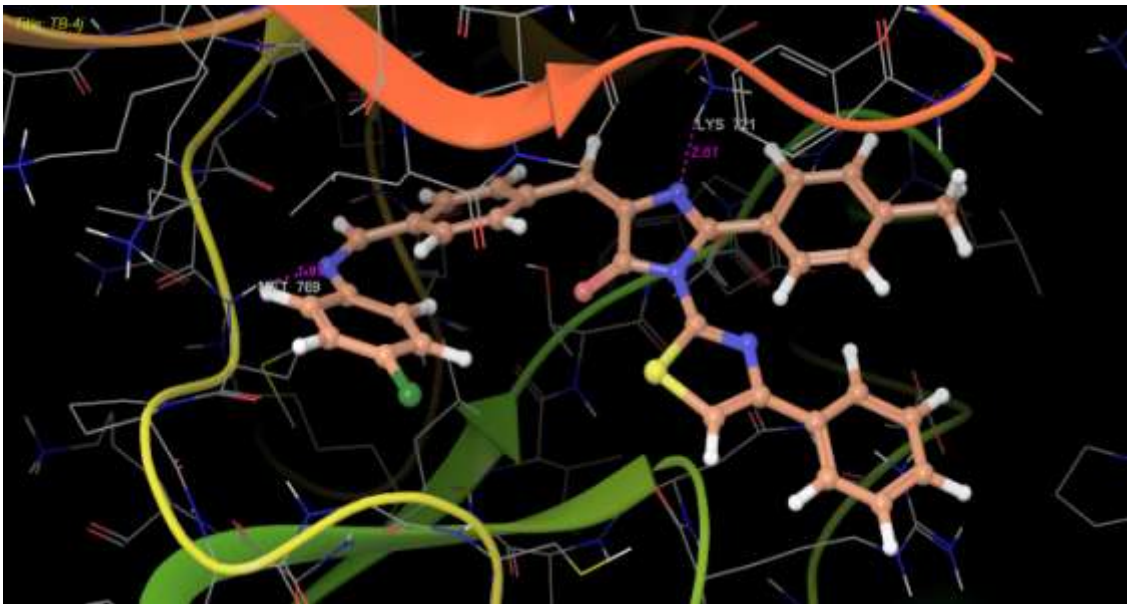


Compound-4g Dock-1

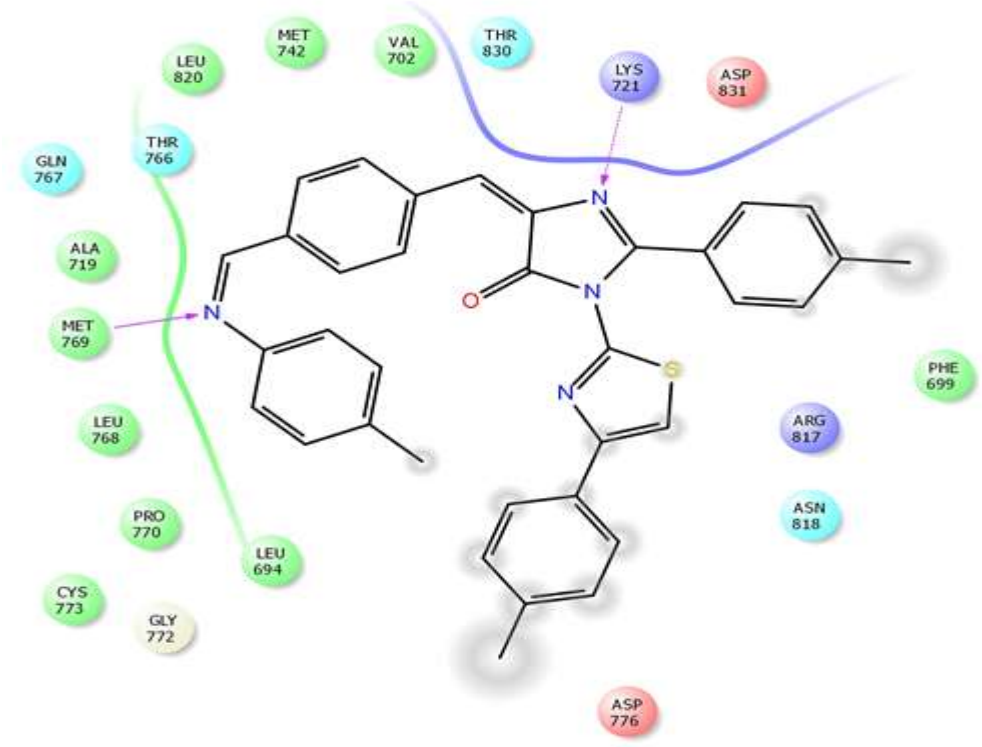


Compound-4g Dock-2

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 1693-1704 www.ijprajournal.com ISSN: 2456-4494



Compound-4j Dock-1



Compound-4j Dock-2

Figure.4. Docking Pose between the Ligand and the Protein (Dock1 and Dock-2)

IV. CONCLUSION:

A series of thiazole contain novel imidazoline derivatives were synthesized andevaluated for them in vitro anthelmintic and Anti-inflammatory activities. The newly designed Imidazoline derivatives were synthesized and characterized by analytical and spectral techniques. These compounds exhibited significant biological

activities like anti-inflammatory and anthelmintic activities.Among the docked ligands, dock scores of all the compounds ranged from -5.35 (compound TB-4g) to -1.509 (compound TB-4c).

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