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DESIGN, SYNTHESIS, DOCKING STUDY AND PHARMACOLOGICAL EVALUATION OF NOVEL -2- (5-(1H-INDOL-3-YL)- 1, 3, 4-THIADIAZOL -2 -YLIMINO) -5 -(SUBSTITUTED BENZYLIDENE) THIAZOLIDIN-4-ONE ANALOGUES

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Anti-inflammatory, Antimicrobial, *In-silico* docking, Thiadiazole

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ABSTRACT: A series of novel analogues of 2-(5-(1H-indol-3-yl)-1, 3, 4-thiadiazol-2-ylimino)- 5- (substituted benzylidene)thiazolidine-4-one have been synthesized. The structures of newly synthesized compounds were confirmed by FT-IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectroscopy. The synthesized compounds showed significant antibacterial activity against gram-positive bacteria: *Staphylococcus aureus* (MTCC 3160), *Bacillus subtilis* (MTCC 2061), gram-negative *Escherichia coli* (MTCC 1652), *Pseudomonas aeruginosa* (MTCC 741) and antifungal activity against fungal strains: *Candida albicans* (MTCC 183) and *Aspergillus niger* (MTCC 2110). Also, their anti-inflammatory activity was evaluated by using carrageenan-induced rat paw edema method. Compounds 7d and 7h with the methoxy substitution on phenyl ring were found as active derivatives of the series, exhibited 49.86% and 49.88% inhibition respectively as compared with Diclofenac sodium. *In-silico* molecular docking studies of the synthesized compounds was done on crystal structures of proteins of microbes *Aspergillus niger*, *Bacillus subtilis*, *Candida albicans*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and cyclooxygenase-2 using GRIP batch docking method of V-life MDS 3.0 software to study their observed activity which revealed a significant correlation between the binding score and biological activity for these compounds.

INTRODUCTION: Thiadiazole is a five-membered heterocyclic compound with isomers such as 1, 2, 3- thiadiazole, 1, 2, 5-thiadiazole, 1, 2, 4-thiadiazole, and 1, 3, 4-thiadiazole. 1, 3, 4-thiadiazole is the most widely studied isomer, and it exhibits a broad spectrum of biological activities such as antimicrobial, anti-inflammatory, anticancer, antituberculosis, antiparasitic, anticonvulsants, anti-oxidant, herbicidal and insecticidal properties [1, 2].

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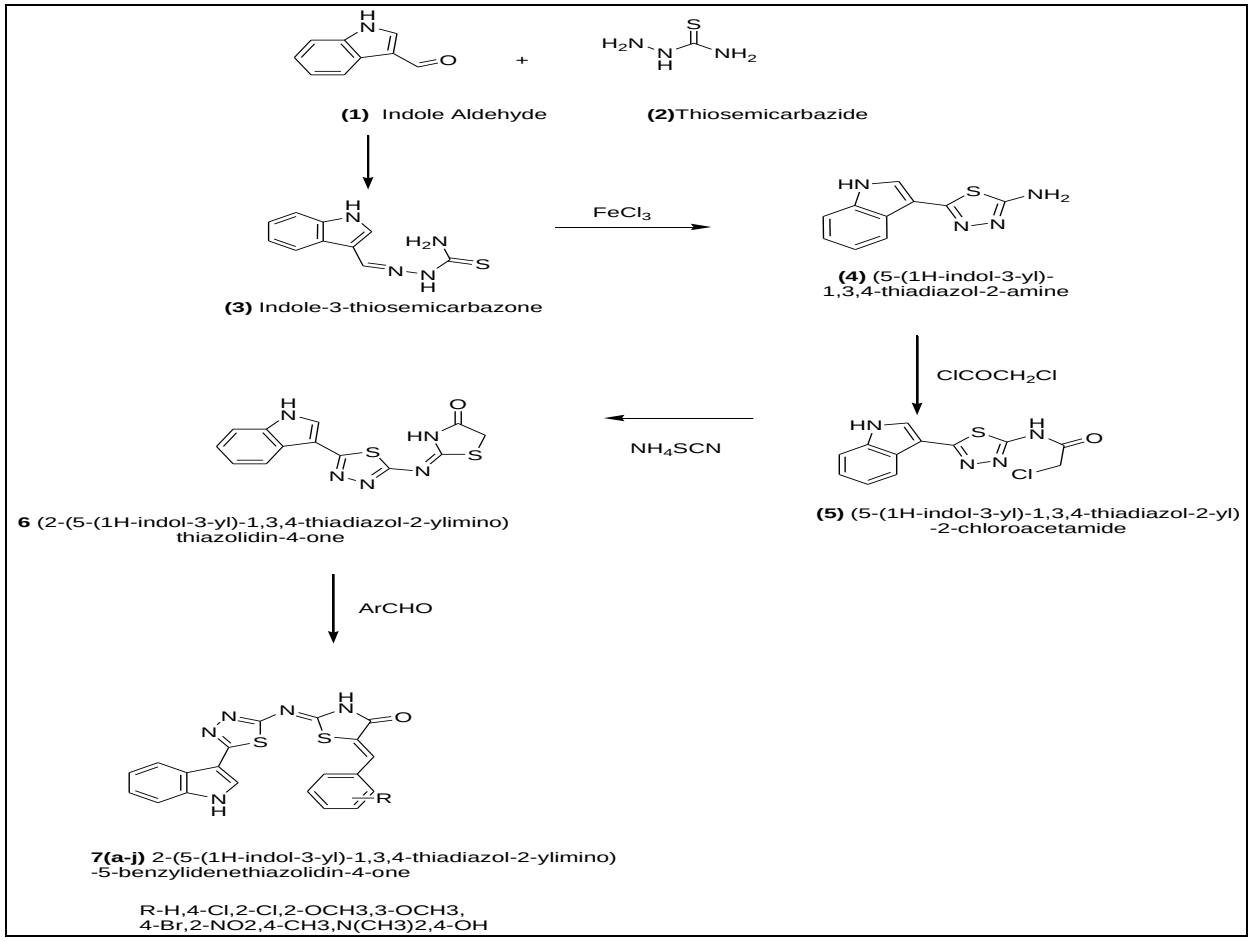
1,3,4-thiadiazole core is found in several marketed drugs such as Acetazolamide (I) and Methazolamide (II) (which are carbonic anhydrase inhibitors for the treatment of glaucoma), and Sulfamethizole (III), Cefazedone (IV), Cefazolin (V), Ceftezole (VI) (which are used as antibacterial drugs) [3].

In recent years the chase for the novel drug has evolved from sophisticated procedures involving computational techniques. Molecular docking is a computational chemistry tool that has a clear, intuitive definition of finding the structure and binding energy of a protein-ligand complex when the spatial structures of the protein and the ligand are known [4]. In the present study, the novel derivatives of thiadiazole have been synthesized

and were docked for possible targets followed by antimicrobial and anti-inflammatory activities to understand the probable binding interactions of ligands with their target proteins by availing facilities of V-life MDS 3.0 (Molecular Design Suite) software.

MATERIALS AND METHODS:

Synthesis: Analytical grade solvents and commercially available reagents were used without further purification. The completion of the reaction and purity of the compounds was monitored by TLC. Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on Alpha ECO ATR spectrophotometer. ^{1}H and ^{13}C NMR spectra were determined by Bruker Avance II 400 NMR spectrometer in DMSO and are expressed in parts per million (δ, ppm) downfield from tetramethylsilane (internal standard). NMR data are given as multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet) and a number of protons. The mass spectra (70 eV) were obtained on a Q-TOF Micromass (LC-MS) Instrument.



SCHEME 1: SYNTHESIS OF 2-(5-(1H-indol-3-yl)-1, 3, 4-thiadiazol-2-ylimino)-5(substituted benzylidene) thiazolidin-4-one analogues 7(a-j)

Synthesis of Indole-3-thiosemicarbazone (3): A solution of indole-3-aldehyde (1.45g, 0.01M) and thiosemicarbazide (0.91g, 0.01M) was prepared in methanol (20 ml), refluxed for 5 h. It was recrystallized from hot methanol to achieve pure indole-3-thiosemicarbazone. The solvent system used for TLC was n-Hexane: ethyl acetate (8:2) [5].

Synthesis of 5-(1H-indol-3-yl)-1,3,4-thiadiazol-2-amine (4): Ferric chloride solution (0.8gm, 0.005mol) in water was added to indole-3-thiosemicarbazone (2.18 g, 0.01 mol) solution with constant stirring and heated for 45 min at the temperature 80 - 90 ºC. The solution was filtered followed by the addition of (0.1 mol) citric acid and (0.05 mol) sodium citrate and neutralized by adding aq. NH_3 and product were recrystallized from 50% ethanol. The solvent system selected for TLC was *n*-hexane: ethyl acetate (8:2) [5, 6].

Synthesis of (5-(1H-indol-3-yl)-1,3,4-thiadiazol-2- yl) -2 -chloroacetamide (5): Chloroacetyl chloride was added dropwise to indole-1, 3, 4-thiadiazol-2-amine (2.16 g, 0.01 mol) in pyridine and after an instant reaction the contents were stirred for half hour which leads to the formation of precipitates. Precipitates were recrystallized from ethanol. The solvent system used for TLC was *n*-hexane: ethyl acetate (8:2) [5].

Synthesis of 2- (5- (1H-indol-3 -yl) -1, 3, 4-thiadiazol -2- ylimino) thiazolidin -4 -one (6): Indole- (1, 3, 4-thiadiazol-2-yl) -2-chloroacetamide (0.01 mol, 2.92) was refluxed with ammonium thiocyanate (3.8 g, 0.05 mol) in 50 ml of ethanol for 3 h, the product obtained was filtered and re-crystallized with 50% ethanol. The solvent system used for TLC was *n*-hexane: ethyl acetate (8:2) [7].

General method of synthesis of 2-(5-(1H-indol-3-yl) -1, 3, 4- thiadiazol-2-ylimino)-5-(substituted benzylidene) thiazolidine-4-one 7 (a-j): A mixture of equal mols of 2- (5-(1H-indol-3-yl)-1, 3, 4-thiadiazol-2 -ylimino) thiazolidine-4-one (6) with prerequisite benzaldehydes was refluxed for 5-7 h by adding anhydrous sodium acetate, CH_3COONa in glacial acetic acid, CH_3COOH (20 ml) and then crushed ice was added to solution to obtain the precipitates of the product. The compound was recrystallized, and purity was determined with *n*-hexane: ethyl acetate (8:2) solvent system [7].

Pharmacological Evaluation: The Institutional Animal Ethics Committee checked all the processes and protocols employed in the present investigation (Reg. no. CPCSEA-MMCP/IAEC/15/15) and agreed with the recommendations of the CPCSEA, Ministry of Forests and Environment, Government of India.

Antimicrobial Activity: The *in-vitro* antibacterial and antifungal activities were screened by the two-fold serial dilution technique and disc diffusion method against gram-positive bacteria: *Staphylococcus aureus* (MTCC 3160), *Bacillus subtilis* (MTCC 2061), and gram-negative bacteria *Escherichia coli* (MTCC 1652), *Pseudomonas aeruginosa* (MTCC 741), and fungal strains: *Candida albicans* (MTCC 183) and *Aspergillus niger* (MTCC 2110). Ciprofloxacin and Clotrimazole were employed as reference drugs for antibacterial and antifungal activity correspondingly.

Serial Dilution Method: Minimum inhibitory concentration (MIC) with micro broth dilutions technique using Mueller-Hinton broth and Sabouraud's broth was used for screening *in-vitro* antibacterial and antifungal activities. Test compounds and standard drugs were dissolved in dimethyl sulfoxide (DMSO) at a concentration of 1 mg/ml, and further dilutions obtained different concentrations of 50, 25, 12.5, 6.25, 3.12, 1.56, 0.78 µg/ml. Strains were inoculated in Mueller Hinton broth for antibacterial activity, and Sabouraud's broth for antifungal activity and the inoculum size in the test mixture was approximately 10^6 colony forming units (CFU)/ml. Tubes containing bacterial strains were kept at 37 ± 10 °C for 24 h, and tubes carrying fungal strains were kept at 25 °C for 7 days.

All the experiments were performed three times. The tubes displaying turbidity were observed, and the minimum inhibitory concentration (MIC) for the synthesized derivatives was found out [8, 9].

Disc Diffusion Method: Disc diffusion method was used for the evaluation of cytotoxicity of test compounds. Nutrient agar medium was cooled, and bacterial and fungal suspension (10^6 CFU/ml 0.5 McFarland standards) was added to it and was poured into Petri plates. Discs of approximately 6 mm in diameter were prepared by Whatman filter paper no. 1 and these discs were sterilized in a hot air oven for 1 h at 140 °C.

These sterile discs formerly dipped with a solution of test compounds with 100µg/disc were wisely located on the agar plates. The inverted plates were incubated for 24 h at 37°C. The entire tests were performed in triplicates to calculate the mean of the diameter of inhibition [10, 11].

Anti-inflammatory Activity: This task was performed with the paw edema method [15]. Wistar rats of either sex (150-200 g) were distributed into three groups (control, drug-treated, and standard of six animals each) and were fasted for 12 h. Normal saline: tween 80 (95:5) was given to control group while the standard group received Diclofenac sodium 10 mg/kg intraperitoneally and the test groups received the synthesized compounds at the dose of 50 mg/kg orally 1h before the carrageenan injection.

Each mouse was given the 0.1 ml injection of recently prepared suspension of carrageenan (1% in 0.9% saline) underneath the plantar aponeurosis of the right hind paw1h before and 1h, 2h, 3h, and 4h after administration of carrageenan the paw volume of every rat was measured with the aid of plethysmometer (Model 7140, Ugo Basile, Italy). The percent inflammation of paw was calculated according to the formula given below [12, 13, 14, 16].

$$\Delta T = T_t - T_0$$

$$\% \text{ inflammation} = \Delta T/T_0 \times 100$$

$$\% I = 100 - \% \text{ inflammation}$$

Where T_t = the right hind paw thickness at time t, T_0= the right hind paw thickness before sub-planter injection of carrageenan.

Molecular Docking Study: Molecular docking experiment to investigate the binding modes of synthesized derivatives was performed by using the Molecular Design Suite (V-Life MDS 3.0 software package, version 3.0; from V-life Sciences, Pune, India), on a Windows 7, Windows Server 2008 R2 (operating system version 6.1), Genuine Intel Computer ID: 783232402132454023. All the structures of compounds and standard drugs were sketched using the 2D draw application provided in the main window and then all the SDF and Mol files as 2D files were converted into 3D structures. Monte Carlo search method was adopted to generate conformers and to reduce the energy of the system [17].

All the conformers were then optimized using the (Merck Molecular Force Field) MMFF parameter, and then a molecular docking study was performed on the X-ray crystal structure of described proteins [14, 18]. The crystal structures of proteins of microbes *Aspergillus niger* (PDB code-1UKC, Resolution: 2.1 Å), *Bacillus subtilis* (PDB code- 1I6W, Resolution: 1.5 Å), *Candida albicans* (PDB code-1IYK Resolution: 2.3 Å), *Escherichia coli* (PDB Code-2CCZ, Resolution: 2.7 Å *Pseudomonas aeruginosa* (PDB Code-1U1T, Resolution: 1.9 Å), *Staphylococcus aureus* (PDB Code-1BDD) and enzyme cyclooxygenase-2 (PDB Code-1CX2, Resolution: 3.0 Å) were downloaded from RCSB protein data bank. The downloaded proteins were analyzed by Geometry Check, Ramachandran Plot, and Cavity Identification, *etc*.

The reference ligand was extracted from monomer, and water molecules were detached. The positions of side chain hydrogens were optimized up to the rms gradient 1 by aggregating the other part of the receptor using Merck Molecular Force Field (MMFF). Then, conformers generated by Monte Carlo method were put as one batch in GRIP docking wizard selected from the Biopredicta module [19]. In Grip docking window various parameters were set as rotation angle as 30^o by which the ligand will be rotated for different poses, a number of placements as 30 and ligand wise results as 5 to obtain 5 top poses for each ligand and scoring function as dock score. The conformers found with their best score were saved in the output folder. The optimized ligands were then tested for numerous interactions of the ligand with a receptor having hydrogen bonding and other types of other interactions like hydrophobic bonding and Van der Waal's interaction [20].

RESULTS AND DISCUSSION:

Chemistry: In the current study, series of derivatives 7(a-j) was synthesized according to the **Scheme 1**. Firstly, Thiosemicarbazones (3) were prepared by refluxing indole aldehyde (1) with thiosemicarbazide (2) [5]. Secondly, 5-(1H-indol-3-yl)-1,3,4-thiadiazol-2-amine (4) was obtained in good yields by cyclization of appropriately substituted thiosemicarbazones (3) in the presence of ferric chloride as reported in the literature [6, 8]. Chloroacetamides (5) were obtained by reaction of 5-(1H-indol-3-yl)-1, 3, 4-thiadiazol-2-amine (4) with chloroacetyl chloride [5]. The intermediate (5-(1H-indol-3-yl)-1, 3, 4-thiadiazol-2-yl)-2-chloroacetamide (5) was reacted with ammonium thiocyanate to afford 2-(5-(1H-indol-3-yl)-1, 3, 4-thiadiazol-2-ylimino)thiazolidine-4-one [7]. In the last step, 2-(5-(1H-indol-3-yl)-1,3,4-thiadiazol-2-ylimino) thiazolidine-4- one (6) was refluxed with substituted aldehydes and yielded the final compounds 7(a-j) [7].

In the IR spectrum of derivatives 7(a-j), the N-H and C=O stretching bands were detected at 3100-3500 cm^{-1} and 1660-1700 cm^{-1}, respectively [29, 30]. In the thiadiazole ring C=N and C-N stretching in the range of 1560-1660 cm^{-1} and 1500-1550 cm^{-1} were observed. Moreover, the bands characteristic for (C=C Ar) and (C-H Ar) are at 1450-1660 cm^{-1} and 2820-2810cm^{-1} respectively [21, 22, 24, 25].

The structures were confirmed with the assistance of ^{1}H NMR spectroscopy which gave a characteristic peak of all the hydrogens present. When analyzed the ^{1}H NMR spectra of this compound, the indole ring NH proton singlet came at δ 10-12 δ (s, 1H, indole), and the NH proton for (s, 1H, thiazolidinone) was observed at δ 8-9 ppm. The protons of aromatic rings were obtained as a multiplet at δ 7.89-7.13 ppm.

A singlet NH δ 8-9 ppm (s, 1H, thiazolidinone) indicated that the bond was made at the 5th position of the thiazolidinone instead of third position [24]. In ^{13}C NMR spectrum of compounds 7(a-j) a bunch of signals shown in the region δ 149.58-112.97 ppm which are assigned to aryl carbons. The chemical shift in ^{13}C-NMR spectra at δ 169.14 and 159.8 are attributed to the presence of C=O and C=N. The chemical shift in the range of δ 60-50 indicates the presence of methoxy carbon [23, 24]. The mass spectrum of compounds showed molecular ion peaks corresponding to molecular weights.

A general multistep procedure for the synthesis of unreported titled compounds 7(a-j) was executed according to **Scheme 1**. The physicochemical data of the series is provided in the observation section in **Table 1**.

TABLE 1: THE PHYSICOCHEMICAL PROPERTIES OF NOVEL COMPOUNDS 7(a-j)

S. no.	Compound name	R	Molecular formula	Molecular weight	Melting point	Yield (%)	R_f value	Physical appearance
1	7a	H	$C_{20}H_{13}N_5OS_2$	403.48	190-192	72	0.68	Yellow powder
2	7b	4-Cl	$C_{20}H_{12}ClN_5OS_2$	437.93	210-212	77	0.63	Yellow powder
3	7c	2-Cl	$C_{20}H_{12}ClN_5OS_2$	437.93	182-184	71	0.71	Yellow powder
4	7d	2-OCH_3	$C_{21}H_{15}N_5O_2S_2$	433.51	225-227	67	0.78	Yellow powder
5	7e	3-OCH_3	$C_{21}H_{15}N_5O_2S_2$	433.51	188-190	78	0.67	Yellow powder
6	7f	4-Br	$C_{21}H_{15}N_5O_2S_2$	482.38	242-244	66	0.66	Yellow powder
7	7g	2-NO_2	$C_{20}H_{12}N_6O_3S_2$	448.48	201-203	69	0.61	Yellow powder
8	7h	4-CH_3	$C_{21}H_{15}N_5OS_2$	417.51	195-197	71	0.59	Yellow powder
9	7i	4-$N(CH_3)_2$	$C_{22}H_{18}N_6OS_2$	446.55	221-223	68	0.69	Yellow powder
10	7j	4-OH	$C_{20}H_{13}N_5O_2S_2$	419.48	179-181	83	0.58	Yellow powder

Spectral Data:

2-(5-(1H-indol-3-yl)-1, 3,4-thiadiazol-2-ylimino)-5- benzylidenethiazolidin-4 -one (7a): Molecular formula: $C_{20}H_{13}N_5OS_2$; Mol. wt.: 403.48; FT-IR (KBr, cm^{-1}): 3176 (NH str), 3020 (C-H Ar str), 2831 (C-H str), 1679 (C=O str), 1639, 1587, 1482 (C=C Ar str), 1650 (C=N str), 1052 (N-N), 691(C-S bend); ^{1}H NMR (DMSO-*d*6, 400 MHz): 11.12(s, 1H, indole, H_1), 9.14(s, 1H, thiazolidinone H_3), 7.83-7.41 (m, 4H, ArH of ring A), 7.39-6.85 (m, 5H, ArH of ring B), 6.84(s, 1H, CH, indole H_2), 6.83 (s, 1H, benzylidene H_4); MS ES+ (ToF): *m/z* 403.06; CHN analysis: Calc.- C, 59.54; H, 3.25; N, 17.36. Found- C, 59.50; H, 3.21; N, 17.32.

2-(5-(1H-indol-3-yl)-1, 3,4-thiadiazol-2-ylimino)-5-(4-chlorobenzylidene) thiazolidin-4 -one (7b): Molecular formula: $C_{20}H_{12}ClN_5OS_2$; Mol. wt.: 437.93; FT-IR (KBr, cm^{-1}): 3339 (NH str), 3071 (C-H Ar str), 2825 (C-H str), 1679 (C=O str), 1652, 1587, 1482 (C=C Ar str), 1357(C=N str), 1068 (N-N), 744 (C-Cl bend), 632 (C-S bend); ^{1}H NMR (DMSO-*d*6, 400 MHz): 11.12(s, 1H, indole H_1), 9.01(s, 1H, thiazolidinone H_3), 8.45-7.59 (m, 4H, ArH of ring A), 7.42-7.39 (m, 4H, ArH of ring B), 7.35 (s, 1H, CH, indole H_2), 6.99 (s, 1H, CH, benzylidene H_4); MS ES+ (ToF): *m/z (*M+ 437.02), (M+2 439); CHN analysis: Calc.- C, 54.82; H, 2.72; N, 15.94. Found- C, 54.79; H, 2.69; N, 15.90.

2-(5-(1H-indol-3-yl)-1, 3,4-thiadiazol-2-ylimino)-5- (2-chlorobenzylidene) thiazolidin-4-one (7c): Molecular formula: $C_{20}H_{12}ClN_5OS_2$; Mol. wt.: 437.93; FT-IR (KBr, cm^{-1}): 3339 (NH str), 3069 (C-H Ar str), 2829 (C-H str), 1697 (C=O str), 1652, 1532, 1496 (C=C Ar str), 1360(C=N str) 1086 (N-N), 744(C-Cl bend), 633(C-S bend); ^{1}H NMR (DMSO-d6, 400 MHz): 11.13 (s, 1H, indole H_1), 9.62(s, 1H, thiazolidinone H_3), 7.70-7.42 (m, 4H, ArH of ring A), 7.40-7.24(m, 4H, ArH of ring B), 7.23(s, 1H, CH, indole H_2), 6.99 (s, 1H, CH, benzylidene H_4); MS ES+ (ToF): m/z 437.02; CHN analysis: Calc.- C, 54.85; H, 2.76; N, 15.99. Found- C, 54.81; H, 2.72; N, 15.95.

2-(5-(1H-indol-3-yl)-1, 3,4-thiadiazol-2-ylimino)-5-(2-methoxybenzylidene)thiazolidin-4-one (7d): Molecular formula: $C_{21}H_{15}N_5O_2S_2$; Mol. wt.: 433.51; FT-IR (KBr, cm^{-1}): 2997 (C-H Ar str), 2850 (C-H str), 1710 (C=O str), 1616, 1554, 1481

(C=C Ar str), 1370(C=N str) 1274(C-O str), 1071 (N-N), 664 (C-S bend); ^{1}H NMR (DMSO-d6, 400 MHz): 11.26 (s, 1H, indole H_1), 9.06 (s, 1H, thiazolidinone H_3), 9.01-7.53(m, 4H, ArH of ring A), 7.52-6.97 (m, 4H, ArH of ring B), 6.96(s, 1H, CH, indole H_2), 6.94 (s, 1H, CH, benzylidene H_4), 3.79 (s, 3H, OCH_3); ^{13}CNMR (DMSO-d_6, 75 MHz, δ ppm): 168.45, 153.45, 139.40, 134.18, 133.01, 132.23, 129.96, 129.01, 128.56, 127.94, 122.24, 119.95, 109.42, 40.05, 39.93.MS ES+ (ToF): m/z 435.2, other m/z values 404.3, 302.3, 301.3, 202.1, 118.9, 102.09; CHN analysis: Calc.-C, 58.18; H, 3.49; N, 14.79. Found- C, 58.14; H, 3.45; N, 16.12.

2-(5-(1H-indol-3-yl)-1, 3,4-thiadiazol-2-ylimino)-5-(3-methoxybenzylidene)thiazolidin-4 -one (7e): Molecular formula: $C_{21}H_{15}N_5O_2S_2$; Mol. wt.: 433.51; FT-IR (KBr, cm^{-1}): 3206 (NH str), 3057 (C-H Ar str), 2942 (C-H str), 1702 (C=O str), 1640, 1587, 1492 (C=C Ar str), 1365(C=N str) 1234(C-O str), 1061 (N-N), 671 (C-S bend); ^{1}H NMR (DMSO-d6, 400 MHz): 11.93 (s, 1H, indole H_1), 9.00 (s, 1H, thiazolidinone H_3), 8.91-7.56 (m, 4H, ArH of ring A), 7.54-7.16 (m, 4H, ArH of ring B), 7.15 (s, 1H, CH, indole H_2), 7.00 (s, 1H, CH, benzylidene H_4), 3.17 (s, 3H, OCH_3); MS ES+ (ToF): m/z 433.07; CHN analysis: Calc.- C, 58.18; H, 3.49; N, 16.16. Found- C, 58.14; H, 3.43; N, 16.11.

2-(5-(1H-indol-3-yl)-1, 3,4-thiadiazol-2-ylimino)-5- (4-bromobenzylidene) thiazolidin-4-one (7f): Molecular formula: $C_{20}H_{12}BrN_5OS_2$; Mol. wt.: 482.38; FT-IR (KBr, cm^{-1}): 2997 (C-H Ar str), 2850 (C-H str), 1711(C=O str), 1650, 1526, 1481 (C=C Ar str), 1370(C=N str) 1071 (N-N), 624 (C-S bend) 548 (C-Br bend); ^{1}H NMR (DMSO-d6, 400 MHz): 11.12 (s, 1H, indole H_1), 9.00 (s, 1H, thiazolidinone H_3), 7.89-7.70 (m, 4H, ArH of ring A), 7.64-6.70 (m, 4H, ArH of ring), 7.69 (s, 1H, CH, indole H_2), 6.74 (s, 1H, CH, benzylidene H_4); MS ES+ (ToF): m/z (M+482.06), (M+2 484); CHN analysis: Calc.- C, 49.80; H, 2.51; N, 14.52. Found- C, 49.76; H, 2.48; N, 14.48.

2-(5-(1H-indol-3-yl)-1, 3,4-thiadiazol-2-ylimino)-5- (2-nitrobenzylidene) thiazolidin-4 -one (7g): Molecular formula: $C_{20}H_{12}BrN_5OS_2$; Mol. wt.: 448.38; FT-IR (KBr, cm^{-1}): 3013 (C-H Ar str), 2895(C-H str), 1711(C=O str), 1656, 1519, 1479 (C=C Ar str), 1376(C=N str), 1328 (NO_2), 1080 (N-N), 644 (C-S bend); ^{1}H NMR (DMSO-d6, 400 MHz): 11.40 (s, 1H, indole H_1), 9.05(s, 1H, thiazolidinone H_3), 7.92-7.39 (m, 4H, ArH of ring A), 7.34-6.80 (m, 4H, ArH of ring B), 7.21 (s, 1H, CH, indole H_2), 6.79 (s, 1H, CH, benzylidene H_4); MS ES+ (ToF): m/z (M+ 448.04); CHN analysis: Calc.- C, 53.56; H, 2.70; N, 18.74. Found- C, 53.52; H, 2.66; N, 18.70.

2-(5-(1H-indol-3-yl)-1, 3,4-thiadiazol-2-ylimino)-5- (2-methylbenzylidene)thiazolidin -4- one (7h): Molecular formula: $C_{21}H_{15}N_5OS_2$; Mol. wt.: 417.51; FT-IR (KBr, cm^{-1}): 3285 (NH str), 3154 (C-H Ar str), 2967 (C-H str), 2929 (C-H str in CH_3), 1717 (C=O str), 1601, 1516, 1482 (C=C Ar str), 1301(C=N str), 1024 (N-N), 617 (C-S bend); ^{1}H NMR (DMSO-d6, 400 MHz): 11.13 (s, 1H, Indole H_1), 9.06 (s, 1H, thiazolidinone H_3), 7.99-7.70 (m, 4H, ArH of ring A), 7.69-7.33 (m, 4H, ArH of ring B), 7.31 (s, 1H, CH, indole H_2), 6.99 (s, 1H, CH, benzylidene H_4), 2.50 (s, 3H, CH_3); MS ES+ (ToF): m/z 417.07, 319.29,318.2, 302.2, 301.1, 218.2, 202.1, 102.0, 88; CHN analysis: Calc.- C, 60.41; H, 3.62; N, 16.77. Found- C, 60.38; H, 3.58; N, 16.74.

2- (5-(1H-indol-3-yl)-1,3,4-thiadiazol-2-ylimino)-5- (4-dimethyaminolbenzylidene) thiazolidin -4-one (7i): Molecular formula: $C_{22}H_{18}N_6OS_2$; Mol. wt.: 446.55; FT-IR (KBr, cm^{-1}): 3157 (NH str), 3031 (C-H Ar str), 2934 (C-H str in CH_3gp), 1726 (C=O str), 1620, 1540, 1482 (C=C Ar str), 1413 (C-N str., aryl tertiary amine), 1301(C=N str), 1045 (N-N), 643 (C-S bend); ^{1}H NMR (DMSO-d6, 400 MHz): 11.06 (s, 1H, indole H_1), 9.14 (s, 1H, thiazolidinone H_3), 8.86-7.39 (m, 4H, ArH of ring A), 6.99-6.86 (m, 4H, ArH of ring B), 7.28 (s, 1H, CH, indole H_2), 6.84 (s, 1H, CH, benzylidene H_4), 2.61 (s, 6H, N $(CH_3)_2$); ^{13}CNMR (DMSO-d_6, 75 MHz, δ ppm): 153.09, 143.39, 136.29, 135.32, 128.84, 128.81, 128.20, 126.53, 125.51, 39.91; MS ES+ (ToF): m/z (M+1447.80); CHN analysis: Calc.-C, 59.17; H, 4.06; N, 18.82. Found- C, 59.12; H, 4.02; N, 18.78.

2-(5-(1H-indol-3-yl)-1, 3,4-thiadiazol-2-ylimino)-5- (4-hydroxybenzylidene)thiazolidin-4-one (7j): Molecular formula: $C_{20}H_{13}N_5O_2S_2$; Mol. Wt.: 419.48; FT-IR (KBr, cm^{-1}): 3489(OH str), 3190 (NH str), 2998 (C-H Ar str), 2870 (C-H str), 1647, 1594, 1479 (C=C Ar str), 1296(C=N str), 1068 (N-

N), 681 (C-S bend); ^{1}H NMR (DMSO-d6, 400 MHz): 11.58 (s, 1H$_1$, indole H$_1$), 8.86 (s, 1H, thiazolidinone, H$_3$), 8.63-7.61 (m, 4H, ArH of ring A), 7.59-6.99 (m, 4H, ArH of ring B), 6.84 (s, 1H, CH, indole H$_2$), 6.79(s, 1H, CH, benzylidene H$_4$), 4.22 (s, 1H, OH); MS ES+ (ToF): m/z 419.05; CHN analysis: Calc.- C, 57.26; H, 3.12; N, 16.70. Found- C, 57.22; H, 3.08; N, 16.3.

Pharmacological Evaluation: The synthesized derivatives 7(a-j) were assessed for their *in-vitro* antibacterial activity against Gram-positive, Gram-negative bacterial and fungal strains by MIC and disc diffusion method and anti-inflammatory activity on carrageenan-induced paw edema model using albino mice.

Antimicrobial Activity: Ciprofloxacin and Clotrimazole were taken as reference drugs for antibacterial and antifungal activity. Compounds 7d, 7e, 7h, and 7i were observed with good activity against *B. subtilis* with 20-21 mm zone of inhibition and 12.5-6.25 µg/ml MIC. For bacterial strain *S. aureus* compounds 7d, 7h and 7i were proved as good inhibitors with 22-24 mm zone of inhibition and MIC 12.5-6.25 µg/ml. In case of gram-negative bacteria *E. coli* 7d, 7e, 7g, 7h and 7i were found with greater activity with 21-24 mm zone of inhibition and 12.5-6.25 µg/ml MIC. For *P. aeruginosa* three compounds 7d, 7e and 7h were observed with good activity with 20-21mm zone of inhibition and 12.5 µg/ml MIC. In case of antifungal activity, compound 7d and 7i have shown good activity against the fungal strain *A. niger* with 12.5 µg/ml MIC and 21-23 mm zone of inhibition. For antifungal strain, *C. albicans* compounds 7c, 7d, 7e, and 7i were also observed as good inhibitors with 19-21 mm zone of inhibition and 12.5-6.25 mm zone of inhibition. The results of antimicrobial activity for compounds 7(a-j) are shown in **Table 2** and **Table 3** for MIC and zone of inhibition, respectively.

TABLE 2: MINIMUM INHIBITION CONCENTRATION (MIC) FOR THE NOVEL SYNTHESIZED COMPOUNDS 7(a-j)

		MIC range (µg/ml)					
S. no.	**Compound name**	***B. subtilis***	***S. aureus***	***E. coli***	***P. aeruginosa***	***A. niger***	***C. albicans***
1	7a	25	25	25	25	50	25
2	7b	50	50	50	50	25	50
3	7c	50	50	50	25	25	12.5
4	7d	6.25	6.25	12.5	12.5	12.5	12.5
5	7e	12.5	25	12.5	12.5	50	6.25
6	7f	25	50	50	50	25	50
7	7g	25	25	6.25	50	25	25
8	7h	6.25	12.5	6.25	12.5	25	25
9	7i	12.5	6.25	12.5	25	12.5	6.25
10	7j	50	50	50	50	25	50
11	Ciprofloxacin	6.25	6.25	6.25	12.5	-	-
12	Clotriamazole	-	-	-	-	12.5	6.25

(-)- Not Determined

TABLE 3: ANTIMICROBIAL ACTIVITY OF NOVEL SYNTHESIZED COMPOUNDS 7(A-J) BY DISC DIFFUSION METHOD

S. no.	**Compound Name**	**Conc. (µg/ml)**	***B. subtilus***	***S. aureus***	***E. coli***	***P. aeruginosa***	***A. niger***	***C. albicans***
1	7a	100	17±0.81	18±0.58	18±0.58	19±0.96	13±0.58	16±0.81
2	7b	100	11±0.53	14±0.81	13±0.67	16±0.85	18±0.67	13±0.67
3	7c	100	12±0.67	11±0.58	11±0.81	18±0.67	18±0.67	19±0.67
4	7d	100	21±0.54	24±0.81	24±0.67	20±0.56	21±0.58	21±0.58
5	7e	100	20±0.64	19±0.58	24±0.67	21±0.65	14±0.81	24±0.54
6	7f	100	12±0.64	11±0.54	12±0.81	11±0.58	18±0.54	12±0.54
7	7g	100	18±0.45	19±0.54	21±0.54	13±0.67	16±0.58	17±0.81
8	7h	100	22±0.81	22±0.56	22±0.67	20±0.64	16±0.54	16±0.56
9	7i	100	21±0.76	23±0.58	24±0.43	18±0.56	23±0.65	22±0.58
10	7j	100	11±0.56	13±0.45	12±0.56	13±0.64	17±0.65	12±0.78
11	Ciprofloxacin	100	24±0.78	26±0.57	25±0.68	22±0.88	-	-
12	Clotrimazole	100	-	-	-	-	25±0.56	23±0.45

(-)- Not Determined. The results are the mean ± SD (n=3).

Anti-inflammatory Activity: The anti-inflammatory activity of the novel derivatives 7 (a-j) was assessed by the carrageenan-induced paw edema method of Winter *et al*. The percentage inhibition was calculated after 1h, 2h, 3h, and 4h. Compounds 7d and 7h with the methoxy substitution on phenyl ring were found as active derivatives of the series, exhibited 49.86% and 49.88% inhibition respectively. Compounds 7e and 7i also displayed the moderate activity 47.25% and 47.53% respectively as associated to the standard drug Diclofenac sodium. The percentages of edema reduction given by the tested compounds, Diclofenac sodium, as a reference drug, at a dose of 10 mg/kg by carrageenan-induced paw edema method are depicted in **Table 4**.

TABLE 4: ANTI-INFLAMMATORY ACTIVITY OF NOVEL SYNTHESIZED COMPOUNDS 7(a-j)

		Paw edema volume Mean ±SEM (% inhibition)							
S. no.	Comp. Name	1 h	% age inhibition	2h	% age inhibition	3h	% age inhibition	4h	% age inhibition
1	7a	0.24±0.0058	28.12	0.25±0.0045	40.53	0.26±0.0098	39.53	0.25±0.0045	41.86
2	7b	0.25±0.0060	26.00	0.30.004±40	25.25	0.32±0.0096	23.25	0.34±0.0034	44.25
3	7c	0.24±0.0065	24.57	0.31±0.0058	27.58	0.35±0.0065	25.58	0.27±0.0035	41.67
4	7d	0.26±0.0056	23.67	0.33±0.0058	29.58	0.36±0.0078	23.25	0.32±0.0037	49.86
5	7e	0.24±0.0054	28.76	0.37±0.0068	24.25	0.34±0.0056	23.25	0.36±0.0045	47.25
6	7f	0.23±0.0045	24.00	0.26±0.0068	40.86	0.31±0.0065	25.58	0.31±0.0056	36.58
7	7g	0.28±0.0060	28.00	0.29±0.0056	34.88	0.28±0.0058	37.20	0.24±0.00	37.88
8	7h	0.26±0.0040	28.70	0.31±0.0045	55.58	0.31±0.0060	25.58	0.27±0.0046	49.88
9	7i	0.22±0.0045	24.37	0.21±0.0068	36.51	0.27±0.0067	41.86	0.28±0.0060	47.53
10	7j	0.24±0.0048	25.00	0.21±0.0058	44.18	0.25±0.0065	48.83	0.24±0.0058	46.86
11	Control	0.32	-	0.43±0.0058	-	0.43±0.0049	-	0.46±0.0111	-
12	Standard	0.21	34.234	0.25±0.0120	41.43563	0.26±0.0037	39.56747	0.23±0.0037	50.03455

Statistical Analysis: All the results were expressed as mean ± Standard Error Mean (SEM). Statistical analysis was done by using one way ANOVA followed by Dunnett's 't' test and critical range for significant difference between two groups of observations was taken as *p<0.05, **p<0.01, compared with control.

Docking Studies: Molecular docking experiment was performed on all 10 derivatives of the series and standard drugs Ciprofloxacin for *B. subtilis, S. aureus, E. coli,* and *P. aeruginosa*, Clotrimazole for *A. niger and C. albicans* and Diclofenac sodium for COX-2 enzyme in order to determine the binding affinity with different amino acids as well as to compare the inhibitory activity with reference drugs. Docking score of all ligands is presented in **Table 5** and **Table 6**.

Interactions of some compounds with receptors are shown in **Fig. 1, 2 and 3**. Hydrogen bonding and hydrophobic interactions are shown with dotted lines in blue and green colors respectively. The outcomes of docking studies with a protein of microbe *Bacillus subtilis* indicated that thiadiazole core of these compounds held in the active pocket by forming the hydrogen bonding and hydrophobic interactions with the residues ASP274A, ARG315A, ASN273A, LEU142A, TYR59A, and LEU210A.

Hydrophobic interactions observed with the docking studies of the protein of microbe *Staphylococcus aureus* were between the ranges of -79.607330 kcal/mol to -51.543966 kcal/mol. With the protein of microbe *Escherichia coli* minimum score has been obtained for ligand 7a with the dock score of -65.100042 kcal/mol with five hydrogen bonds between amino acids LYS82A (2.258088), LYS82A (1.464833), LYS82A (2.2409490), MET90B (2.465678), MET90B (2.529953) and 11N, 12N, 17S, 20N, 28O.

Significant results were obtained with a protein of microbe *Pseudomonas aeruginosa* where compound 7d was again found to have a minimum score of -84.955955 kcal/mol with only 1 hydrophobic interaction with methoxy group substituted on benzylidene ring. With protein of microbe *Aspergillus niger* dock score of all compounds is below -64.831006 kcal/mol and minimum score was -86.894380 kcal/mol for ligands 7b, 7c, and 7h. Protein of microbe *Candida albicans* has shown comparatively moderate results with other receptors with the minimum binding score of -50.446960 kcal/mol for ligands 7b and 7d. Dock score in wide range was observed for enzyme COX-2 between -98.848370kcal/mol to -33.060505 kcal/mol.

TABLE 5: DOCK SCORES OF TARGET CONFORMER FOR ENZYMES *BACILLUS SUBTILIS, STAPHYLOCOCCUS AUREUS, ESCHERICHIA COLI*

S. no.	Compound name	*Bacillus subtilus*		*Staphylococcus aureus*		*Escherichia coli*	
		Dock Score	H-Bonds	Dock Score	H-Bonds	Score	H-Bonds
1	7a	-66.79677	2	-73.463187	0	-65.100042	3
2	7b	-67.39583	3	-51.543966	0	-56.088490	3
3	7c	-74.04369	2	-67.606134	2	-65.593788	2
4	7d	-75.96989	2	-79.607330	2	-51.543966	2
5	7e	-63.52672	0	-58.115880	2	-58.115880	3
6	7f	-62.98215	0	-60.139739	2	-60.139739	1
7	7g	-71.0355	0	-55.921860	0	-55.921860	1
8	7h	-67.9819	0	-61.049597	3	-61.049597	1
9	7i	-65.6066	0	-64.831006	3	-54.575649	0
10	7j	-72.6234	1	-78.613446	3	-57.690267	2
11	Standard	-44.262284	2	-32.858136	1	-55.444237	0

TABLE 6: DOCK SCORES OF TARGET CONFORMER FOR ENZYMES *PSEUDOMONAS AERUGINOSA, ASPERGILLUS NIGER, CANDIDA ALBICANS,* CYCLOOXYGENASE-2

S. no.	Compound name	*Pseudomonas aeruginosa* PDB Code-1U1T		*Aspergillus niger* PDB code-1UKC		*Candida albicans* PDB code-1IYK		Cyclooxygenase-2 PDB Code-1CX2	
		Dock Score	H-Bonds	Dock Score	H-Bonds	Dock Score	H- Bonds	Dock Score	H- Bonds
1	7a	-73.463187	1	-79.268774	2	-14.912808	2	-68.80160	2
2	7b	-79.607330	0	-86.959770	4	-50.446960	1	-88.84837	4
3	7c	-67.606134	0	-86.944741	5	-4.075683	2	-33.06050	5
4	7d	-84.955988	0	-80.949435	5	-50.376131	5	-98.74997	0
5	7e	-79.892793	0	-84.955955	1	-15.775861	1	-78.74997	3
6	7f	-74.597778	0	-79.892793	3	-29.012663	3	-77.21470	5
7	7g	-86.894380	0	-74.597778	1	-50.198061	1	-67.91393	0
8	7h	-68.411965	0	-86.894380	0	-42.367110	2	-71.00667	0
9	7i	-64.831076	0	-68.411965	0	2.329014	0	-78.48878	0
10	7j	-78.613446	3	-64.831006	0	-38.768996	1	-63.81946	0
11	Standard	-55.74433	1	-45.9856	1	-	1	-	1

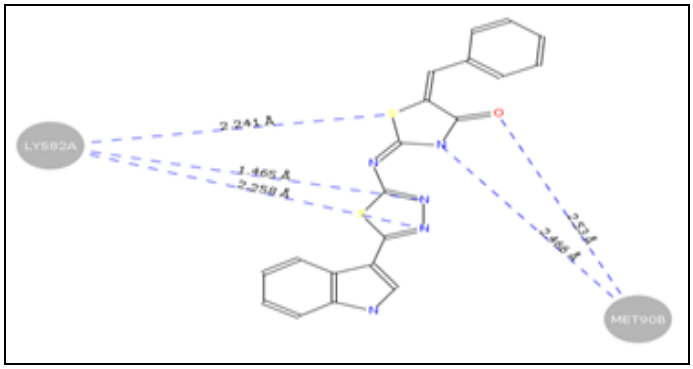


FIG. 1: LIGAND 7a IN THE CAVITY OF PROTEIN *ESCHERICHIA COLI*

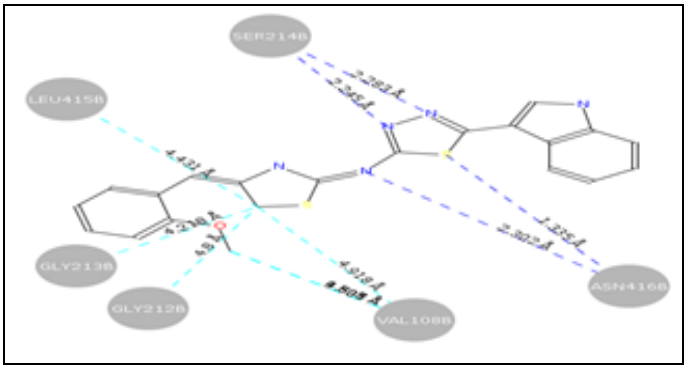


FIG. 2: LIGAND 7d IN THE CAVITY OF PROTEIN *CANDIDA ALBICANS*

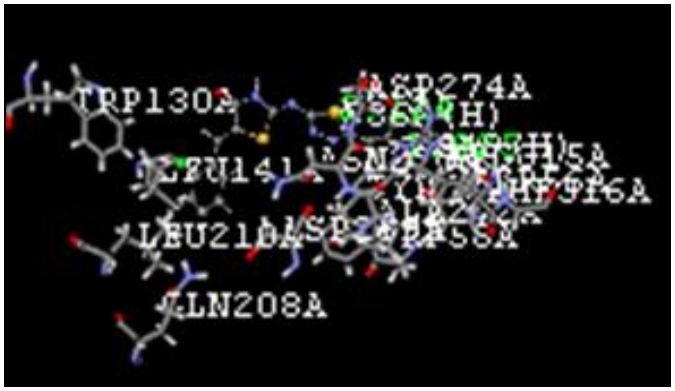


FIG. 3: LIGAND 7e IN THE CAVITY OF PROTEIN *ASPERGILLUS NIGER* SHOWN WITH BALL AND STICK MODEL IN THE ACTIVE SITE OF PROTEIN WITH GRIP DOCKING

CONCLUSION: By docking study and biological activities the synthesized compounds were found to have a promising antimicrobial activity and anti-inflammatory activity. Various spectroscopic methods clarified the structures of all synthesized compounds. Compounds 7d and 7h were found to be active derivatives of the series due to the presence of methoxy substitution on the phenyl ring, exhibited 49.86% and 49.88% inhibition respectively as compared with Diclofenac sodium. The anti-microbial activity of synthesized compounds was assessed by serial twofold dilution technique, and disc diffusion method and promising results were obtained. The docking score of the synthesized compounds correlates with biological activity.

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