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Research Article

SYNTHESIS, MOLECULAR DOCKING STUDIES AND ANTIMICROBIAL ACTIVITY OF MANNICH BASES OF THIAZOLIDINE-2,4-DIONES

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ABSTRACT

The aim of study was to synthesize a new series of mannich bases of thiazolidine-2,4-diones. A new series of mannich bases of thiazolidine-2,4-diones have been synthesized by mannich base reaction between 5-substituted thiazolidine-2,4-dione, acetanilide and aromatic aldehydes. The structure of these compounds was established by IR,^{1}H NMR and Mass spectrosopy. The synthesized mannich bases of thiazolidine-2,4-diones were subjected to molecular docking studies with dihydropteroate synthase (DPHS, PDB ID: 3TYE) by using **XP GLIDE** module of Schrodinger suite and *in silico* studies by molinspiration online tool. These new compounds **(3a–3i)** were evaluated for their antimicrobial activity. The compounds **3g** and **3h** showed good activity against bacteria *Salmonella paratyphi*, *Escherichia coli* and fungi *Aspergillus niger*, *Colletotrichum coffeanum* comparable to that of standard drugs streptomycin and griseofulvin. Molecular docking studies showed the compound **3h** showed good docking score of -5.419 with target protein dihydropteroate synthase.

Keywords: Thiazolidine-2,4-diones, Antimicrobial activity, Mannich base, Molecular docking

INTRODUCTION

Development of novel synthetic antimicrobial agents is an important and challenging problem because, some microorganisms have developed resistance to available antibiotics in the market. Hence it is essential to develop new compounds for treating infectious disease[1].Thiazolidine-2,4-diones (TZDs) are important class of heterocyclic compounds, because of their various biological applications such as antihyperglycemic[2-4], tuberculostatic[5], anti-inflammatory[6], bactericidal[7-8], fungicidal[9]etc. The reported potential activities of "glitazones" initiated us to synthesize N-substituted-2,4-TZD derivatives with good antimicrobial activity.

MATERIALS AND METHODS

The chemicals and reagents were procured from sigma aldrich. By using open capillary tubes melting points were determined and are uncorrected. Purity of the all synthesized compounds was checked by using precoated TLC plates and iodine was used as visualizing agent. IR spectra were recorded on FT-IR 8400S, Fourier Transform (Shimadzu) Infrared spectrophotometer using KBr pellet method. ^{1}H NMR spectra were recorded on Bruker AVANCE (400 MHz) spectrophotometer in dimethyl sulfoxide (DMSO) using tetramethylsilane (TMS) as an internal standard. The mass spectra were recorded on Shimadzu LCMS-8030 Mass Spectrometer. Elemental analyses (C, H, and N) were performed using Perkin Elmer model 240 C analyzer.

Experimental Procedure

The schematic representation of synthesized compounds **(3a–3i)** were summarized in Figure 1. The physical data of synthesized compounds **(3a-3i)** were given in Table 1.

Synthesis of Thiazolidine-2,4-dione (1)

56.5 g of chloroacetic acid (0.6 mol) in a 60 ml of water and 45.6 g of thiourea (0.6mol) in 60 ml of water were transferred into a 250 ml round bottomed flask. The reaction mixture was stirred and cooled to form a white precipitate. To contents of the flask, added slowly 60 ml concentrated hydrochloric acid. The reaction mixture was stirred and refluxed for 8-10 hours at 100-110°C. Cooled content of the flask solidified to mass of cluster of white needles. The product was filtered and washed with water to remove traces of HCl and dried. It was recrystallized from ethanol. Yield: 73%; m.p: 124 – 126°C.

Synthesis of 5-(thiophen-2-ylmethylene) thiazolidine-2,4-dione (2a)

Into a 250 ml round bottomed flask thiophen-2-carbaldehyde (20 g, 0.188 mol) and 2,4-thiazolidinedione (22 g, 0.188 mol) were transferred and added dry toluene and 1 ml of piperidine. The reaction mixture was refluxed for 1 hour with stirring. Cooled the product, precipitate was obtained. The compound was filtered and washed with cold, dry toluene and dry ethanol. Yield: 68%; m.p: 236 – 238°C.

Similarly compounds **2b – 2i** were prepared by adopting similar procedure using appropriate substituted aldehydes.

Synthesis of 3-(4-(dimethylamino) phenyl)-3-(2,4-dioxo-5-(thiophen-2-ylmethylene)thiazolidin-3-yl)-N-phenylpropanamide (3a)

In a 250 ml round bottomed flask 5-(thiophen-2-ylmethylene) thiazolidine-2,4-dione (**2a)** (0.1 mol), 4-dimethyl amino benzaldehyde (0.1 mol) and acetanilide (0.1 mol) were suspended in an ethanol. The reaction mixture was refluxed for 5 hours. The reaction mixture was cooled and poured into ice cold water and precipitate was separated by filtration and dried. It was recrystallized from absolute ethanol[10-11].

Similarly compounds **3b – 3i** were prepared by adopting similar procedure using appropriate aromatic aldehydes.

3-(4-(dimethylamino)phenyl)-3-(2,4-dioxo-5-(thiophen-2-ylmethylene)thiazolidin-3-yl)-N-phenylpropanamide(3a):
Yield: 78% ; m.p: 231-233ºC; IR (KBr, $\nu_{max, Cm^{-1}}$) 3427 (NH), 3038 (Ar C-H), 1721 (C=O), 1333 (C-N), 684 (C-S);^{1}H NMR (400 MHz, DMSO – d_6) δ: 2.08 (s, 1H, CH), 2.52 (s, 6H, $N(CH_3)_2$) , 4.18 (s, 2H, CH_2) , 7.52–8.16 (m, 12H, Ar C-H), 7.82 (s, 1H, R-CH=C), 10.03 (s, 1H, NH); EI-MS m/z: 478 (M+1); Anal. Calcd. For $C_{25}H_{23}N_3O_3S_2$: C, 62.87; H, 4.85; N, 8.8; Found: C, 62.42; H, 4.16; N, 8.6.

3-(2,4-dioxo-5-(thiophen-2-ylmethylene)thiazolidin-3-yl)-3-(4-nitrophenyl)-N-phenylpropanamide (3b):
Yield: 70%;m.p: 261-263ºC;IR (KBr, $\nu_{max, Cm^{-1}}$) 3467 (NH), 3086 (Ar C-H), 1709 (C=O), 1356 (C-N), 687 (C-S); ^{1}H NMR (400 MHz, DMSO – d_6) δ: 2.28 (s, 1H, CH), 4.18 (s, 2H, CH_2), 7.40–7.80 (m, 12H, Ar C-H), 7.33 (s, 1H, R-CH=C), 10.09 (s,1H,NH); EI-MS m/z: 480 (M+1); Anal. Calcd. For $C_{23}H_{17}N_3O_5S_2$: C, 57.61; H, 3.57; N, 8.76; Found: C, 57.42; H, 3.16; N, 8.4.

3-(2,4-dioxo-5-(thiophen-2-ylmethylene)thiazolidin-3-yl)-3-(4-methylphenyl)-N-phenylpropanamide(3c):
Yield: 78%; m.p: 251-253 ºC; IR (KBr, $\nu_{max, Cm^{-1}}$) 3456 (NH), 3112 (Ar C-H), 1714 (C=O), 1346 (C-N), 678 (C-S); ^{1}H NMR (400 MHz, DMSO – d_6) δ: 2.19 (s, 1H, CH), 3.52 (s, 3H, CH_3) , 4.19 (s, 2H, CH_2) , 7.62–8.24 (m, 12 H, Ar C-H), 8.51 (s, 1H, R-CH=C), 10.34 (s, 1H, NH); EI-MS m/z: 449 (M+1); Anal. Calcd. For $C_{24}H_{20}N_2O_3S_2$: C, 64.26; H, 4.49; N, 6.25; Found: C, 64; H, 4.36; N, 6.19.

3-(2,4-dioxo-5-(thiophen-2-ylmethylene)thiazolidin-3-yl) 3-**(4-chlorophenyl)-N-phenylpropanamide(3d):**
Yield: 67%;m.p: 206-208ºC; IR (KBr, $\nu_{max, Cm^{-}}$1) 3456 (NH), 3077 (Ar C-H), 1679 (C=O), 1326 (C-N), 682 (C-S); ^{1}H NMR (400 MHz, DMSO – d_6) δ: 2.08 (s, 1H, CH),4.14 (s, 2H, CH_2) , 7.62–7.90 (m, 12 H, Ar C-H), 7.59 (s, 1H, R-CH=C), 11.01 (s, 1H, NH). EI-MS m/z: 470 (M+1); Anal. Calcd. For $C_{23}H_{17}N_2O_3S_2Cl$: C, 58.9; H, 3.65; N, 5.97; Found: C, 58.42; H, 3.16; N, 5.89.

3-(2,4-dioxo-5-(thiophen-2-ylmethylene)thiazolidin-3-yl)-3-(4-methoxyphenyl)-N-phenylpropanamide(3e):
Yield:75%; m.p: 227-229ºC; IR (KBr, $\nu_{max, Cm^{-1}}$) 3447 (NH), 3126 (Ar C-H), 1682 (C=O), 1378 (C-N), 646 (C-S); ^{1}H NMR (400 MHz,DMSO – d_6) δ:2.08 (s, 1H, CH),3.76 (s, 3H, OCH_3), 4.21 (s, 2H, CH_2) , 7.62–7.90 (m, 12 H, Ar C-H), 8.19 (s, 1H, R-CH=C), 11.11 (s, 1H, NH); EI-MS m/z: 466 (M+1); Anal. Calcd. For $C_{27}H_{24}N_2O_5S$: C, 66.38; H, 4.95; N, 5.73; Found: C, 66.34; H, 4.89; N, 5.68.

3-(2,4-dioxo-5-(thiophen-2-ylmethylene)thiazolidin-3-yl)-3-(3,4-dimethoxyphenyl)-N-phenylpropanamide(3f):
Yield: 81%;m.p: 237-238ºC; IR (KBr, $\nu_{max, Cm^{-1}}$) 3398 (NH), 3087 (Ar C-H), 1718 (C=O), 1345 (C-N), 668 (C-S); ^{1}H NMR (400 MHz,DMSO – d_6) δ: 2.06 (s, 1H, CH), 3.82 (s, 6H, $(OCH_3)_2$), 4.18 (s, 2H, CH_2) , 7.24–7.90 (m, 11 H, Ar C-H) 8.13 (s, 1H, R-CH=C), 10.11 (s, 1H, NH); EI-MS m/z: 495 (M+1); Anal. Calcd. For $C_{25}H_{22}N_2O_5S_2$: C, 60.71; H, 4.48; N, 5.66; Found: C, 60.34; H, 4.39; N, 5.62.

3-(5-(3,4-dimethoxybenzylidene)-2,4-dioxothiazolidin-3-yl)-N,3-diphenylpropanamide(3h):
Yield: 73%; m.p: 218-220ºC; IR (KBr, $\nu_{max, Cm^{-1}}$) 3448 (NH), 3092 (Ar C-H), 1696 (C=O), 1358 (C-N), 688 (C-S); ^{1}H NMR (400 MHz, DMSO – d_6) δ: 2.18 (s, 1H, CH), 3.62 (s, 6H, $(OCH_3)_2$), 4.14 (s, 2H, CH_2) , 7.24–7.96 (m, 13 H, Ar C-H), 8.23 (s, 1H, R-CH=C), 11.18 (s, 1H, NH); EI-MS m/z: 489 (M+1). Anal. Calcd. For $C_{27}H_{24}N_2O_5S$: C, 66.38; H, 4.95; N, 5.73; Found: C, 66.34; H, 4.89; N, 5.68.

3-(5-benzylidene-2,4-dioxothiazolidin-3-yl)-3-(4-chlorophenyl)-N-phenylpropanamide(3i):
Yield: 74%; m.p: 234-236ºC; IR (KBr, $\nu_{max, Cm^{-1}}$) 3457 (NH), 3084 (Ar C-H), 1711 (C=O), 1366 (C-N), 677 (C-S); ^{1}H NMR (400 MHz, DMSO – d_6) δ: 2.18 (s, 1H, CH),4.16 (s, 2H, CH_2) , 7.62–7.94 (m, 14 H, Ar C-H), 7.81 (s, 1H, R-CH=C), 10.36 (s, 1H, NH); EI-MS m/z: 450 (M+1). Anal. Calcd. For $C_{24}H_{18}N_2O_3SCl$: C, 64.07; H, 4.03; N, 6.23; Found: C, 64; H, 4.; N, 6.18.

Molecular docking

Molecular docking studies were performed using various modules of Schrodinger using XP Glide. The 3D X-ray crystal structure of enzyme DHPS (Dihydropteroate synthase) imported in to maestro v 9.0 and receptor grid of 20x20x20 A° with its ligand (PDB ID: 3TYE) was obtained from the Protein Data Bank (PDB). The enzyme was prepared for docking studies involves i) ligand molecule was removed from the enzyme active site. ii) Hydrogen atoms were added to the structure with their standard geometry iii) The obtained model was used in predicting the ligand enzyme interaction at the active site[12-15].

***In silico* studies**

By using Molinspiration online tool the ADME properties of synthesized compounds were determined. (http://www. molinspiration.com/cgi-bin/properties)[16]. The % oral absorption was calculated according to the formula.

$$\%ABS=109-(0.345 \times TPSA)$$

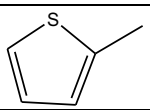
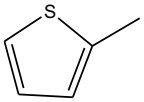
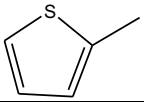
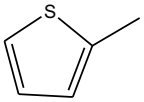
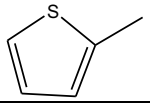
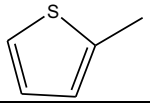
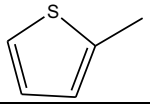
Lipinski's rule of five (RO5) is used to evaluate whether the chemical compound possess the properties of drug likeness (i.e. orally active) in humans. As per the rule the compound possessing log P in −0.4 to +5.6 range, molar refractivity 40–130, molecular weight 180–500, number of atoms 20–70 and TPSA >140. All the designed compounds obeyed Lipinski rule of five suggesting good oral bioavailability for the title compounds (Table 3). The compounds with bioactivity score>0 are considered to be active and those with scores ranging from -0.5 to 0 are considered to be moderately active[17]. (Table 4)

Biological Evaluation of Antimicrobial Activity

The antimicrobial activity of the prepared compounds was determined by cup plate method (Agar diffusion method) by measuring zone of inhibition at a concentration of 50 µg/ml against gram negative *Salmonella paratyphi, Pseudomonas aeruginosa, Escherichia coli, Proteus mirabilis, gram positive*

Bacillus subtilis, Streptococcus pyogene bacteria and fungi *Aspergillus niger*, *Penicillium notatum* and *Colletotrichum coffeanum*. Streptomycin and Griseofulvin were used as standard drugs at a concentration of 50 µg/ml.

Table 1: Physical data of title compounds 3a – 3i

Compound	Molecular Formula	R	R_1	Molecular Weight (gm)	m.p. (°C)	%Yield	R_f value
3a	$C_{25}H_{23}N_3O_3S_2$		4-$N(CH_3)_2$	477	231-233	78	0.61
3b	$C_{23}H_{17}N_3O_5S_2$		4-NO_2	479	261-263	70	0.74
3c	$C_{24}H_{20}N_2O_3S_2$		4-CH_3	448	251-253	78	0.62
3d	$C_{23}H_{17}N_2O_3S_2Cl$		4-Cl	468	206-208	67	0.63
3e	$C_{24}H_{20}N_2O_4S_2$		4-OCH_3	465	227-229	75	0.65
3f	$C_{25}H_{22}N_2O_5S_2$		3,4-di methoxy	494	237-238	81	0.62
3g	$C_{24}H_{21}N_3O_3S_2$		4-$NHCH_3$	463	232-234	76	0.63
3h	$C_{27}H_{24}N_2O_5S$	3,4-di methoxy phenyl	H	488	218-220	73	0.67
3i	$C_{24}H_{18}N_2O_3SCl$	Phenyl	4-Cl	449	234-236	74	0.70

m.p: Melting point; %Yield: Percentage yield; R_f value: Retention factor;

Table 2: Molecular docking score and binding energy of title compounds 3a-3i

S.No.	DHPS (3TYE) with Compound	Docking score	Binding free energy (kcal/mol)
1	**3a**	-3.33	-48.116
2	**3b**	-3.245	-43.26
3	**3c**	-2.068	-49.498
4	**3d**	-3.34	-43.246
5	**3e**	-3.212	-41.88
6	**3f**	-3.513	-44.27
7	**3g**	-3.725	-64.84
8	**3h**	-5.419	-48.673
9	**3i**	-1.604	-50.018
10	Crystal ligand (XTZ)	-8.332	-63.875

Table 3: Analysis of Lipinski rule of 5 for title compounds 3a-3i

Code	log P	TPSA	% abs	n atoms	MW	n ON	n OHNH	n Violations	n Rotb	Molar volume
3a	4.21	71.41	84	33	477	6	1	0	7	413.95
3b	4.06	114	70	33	479	8	1	0	7	391.38
3c	4.55	68.17	85	31	448	5	1	0	6	384.6
3d	4.78	68.17	85	31	468	5	1	0	6	381.58
3e	4.16	77.41	82	32	465	6	1	0	7	393.59
3f	3.75	86.64	79	34	494	7	1	0	8	419.13
3g	3.96	86.20	79	32	463	6	2	0	7	397.01
3h	3.85	86.84	79	35	489	7	1	0	8	428.42
3i	4.88	68.17	85	32	463	5	1	0	6	390.87

log P**:** Partition coefficient; TPSA: Topological polar surface area; % abs: percentage of absorption; n atoms: no of atoms; n ON: No. of hydrogen bond acceptors; n OHNH: No. of hydrogen bond donors; n Rotb: No. of rotatable bonds;

Table 4: Bio active scores of title compounds 3a-3i

S. No	Code	GPCR	ICM	KI	NRL	PI	EI
1	**3a**	-0.48	-0.85	-0.43	-0.74	-0.55	-0.31
2	**3b**	-0.60	-0.87	-0.57	-0.83	-0.63	-0.38
3	**3c**	-0.55	-0.94	-0.51	-0.83	-0.61	-0.36
4	**3d**	-0.52	-0.89	-0.49	-0.82	-0.60	-0.34
5	**3e**	-0.54	-0.92	-0.49	-0.79	-0.59	-0.35
6	**3f**	-0.52	-0.88	-0.47	-0.77	-0.59	-0.33
7	**3g**	-0.47	-0.83	-0.40	-0.77	-0.53	-0.30
8	**3h**	-0.45	-0.75	-0.41	-0.58	-0.53	-0.28
9	**3i**	-0.45	-0.73	-0.42	-0.61	-0.53	-0.28

GPCR: G-protein coupled receptor ligand; ICM: Ion Channel Modulator; KI: Kinase Inhibitor; NRL: Nuclear Receptor Ligand; PI: Protease Inhibitor; EI: Enzyme Inhibitor.

Table 5: Antimicrobial activity data of title compounds 3a-3i at 50 µg/ml

S.No	Compound Code	Zone of inhibition (mm)								
		Gram negative				Gram positive		Fungal		
		SP	***PA***	***EC***	***PM***	***BS***	***S.pyogenes***	***AN***	***PN***	***CC***
1	**3a**	20	19	18	11	15	17	13	17	15
2	**3b**	NA	NA	15	11	22	17	12	NA	14
3	**3c**	18	19	NA	18	13	NA	NA	19	11
4	**3d**	NA	NA	12	NA	13	14	16	16	NA
5	**3e**	20	18	16	12	20	NA	20	19	22
6	**3f**	22	9	19	12	10	11	16	13	NA
7	**3g**	24	20	25	20	21	17	20	19	22
8	**3h**	26	22	27	21	22	14	21	18	24
9	**3i**	NA	NA	10	NA	12	16	NA	11	10
10	**Streptomycin**	30	32	32	33	28	30	NT	NT	NT
11	**Griseofulvin**	NT	NT	NT	NT	NT	NT	25	30	35

SP: Salmonella paraytphi; *PA*: *Pseudomonas aeruginosa*; *EC*: *Escherichia coli*; *BS*: *Bacillus subtilis*; *S.pyogenes*: *Streptococcus pyogenes*; *AN* : *Aspergillus niger*; *PN*: *Penicillium notatum*; *CC*: *Colletotrichum coffeanum*; NT: Not tested; NA: Not Active.

In vitro antimicrobial activity

Cup Plate Method

Antimicrobial activity was performed by cup plate method by measuring zone of inhibition. Muller Hinton agar media for bacterial strain and Sabouraud dextrose agar (SDA) for fungal strain was used as culture medium & dimethyl sulfoxide (DMSO) was used as solvent control. The test organisms were inoculated in nutrient broth and were incubated at 34-37°C for 48 hours, it was stored in refrigerator. The stock culture was maintained. Bacterial and fungal inoculum was prepared by transferring a loop full of stock culture to the nutrient broth in conical flask. The flask was incubated at 34-37°C for 24 hours before experimentation[18-20].

A volume of 25 ml of sterile hot agar medium was poured in each plate and allowed to harden on a level surface. The agar plates were inoculated with 24-hour test inoculums by spreading uniformly with sterile cotton swabs. The plates were then allowed to dry in the inverted position in an incubator for 30 mins. Afterwards they were removed, and bore were made on the medium using sterile borer. A volume of 0.1 ml of test solution was added to respective bores. Streptomycin at a concentration ken as standard drug. A control having only DMSO in the cup was maintained in each plate. The petri plates were kept in the refrigerator at 4°C for 15 mins for diffusion to take place. Afterwards they were incubated at 37°C for 24 hours and zones of inhibition were observed and measured using a scale. Similarly, the antifungal activity of synthesized compounds was determined by cup plate method using Sabouraud dextrose broth and the petri plates were incubated at 37°C for 48 hours and determined the zone of inhibition. Griseofulvin was used as a standard drug at a concentration of 50 µg/ml [21-22]. The various antimicrobial activity results of synthesized compounds were showed in the Table 5.

RESULTS & DISCUSSION

Chemistry

2,4-TZD (**1**) was synthesized with chloroacetic acid and thiourea in hot water. 5-substituted-2,4-thiazolidinedione (**2**) was obtained with Knoevenagel condensation of 2,4-TZD (**1**) and aromatic aldehyde in Toluene in presence of piperidine. A series of 3-(2,4-dioxo-5-(substituted-2-ylmethylene)thiazolidin-3-yl)-3-(substituted phenyl)- N-phenylpropanamide **(3a-3i)** were synthesized by mannich reaction between 5-(substituted-2-ylmethylene) thiazolidine-2,4-dione (**2**), aromatic aldehyde and acetanilide in few ml of ethanol.

The structure of the title compounds was elucidated by ^{1}H NMR, Mass and IR spectroscopy. All spectral data were in accordance with the assumed structures. IR spectra of the compounds **(3a-3i)** showed NH stretching at 3467-3398 cm−1, aromatic stretching at 3112-3077 cm−1, C = O stretching bonds at 1721-1679 cm−1, C-N stretching at 1378-1326 cm−1 and C-S stretching at 687-646 cm−1 respectively. ^{1}H NMR spectra of the compounds **(3a-3i)** showed CH protons at 2.08-2.19 ppm, methylene protons at 4.14-4.18 ppm, aromatic protons at 7.1-7.9 ppm and NH protons at 10.0-11.34 ppm. The mass spectrum of the compounds **(3a-3i)** showed (M+1) ion peak between 449-495 m/z. The C, H and N analyse of title compounds were in good agreement with the calculated values.

Antimicrobial activity

The compounds **(3a-3i)** were evaluated for their invitro antimicrobial activity by the agar diffusion (cup plate) method by measuring zone of inhibition. The results of antimicrobial evaluation (Table 5) revealed that some of the compounds showed moderate to good bacterial and fungal inhibition. The

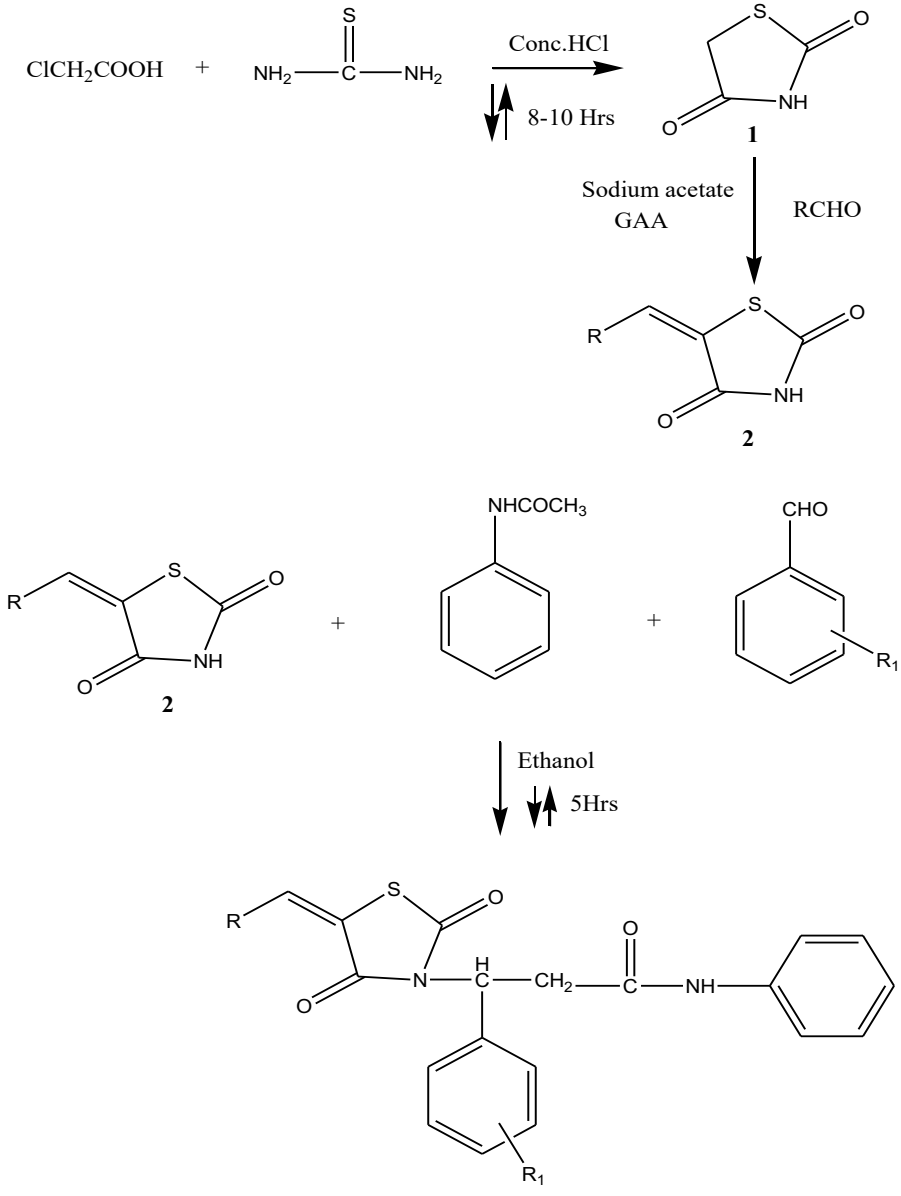
compounds **3g** and **3h** showed good activity against *S. paratyphi* and *E. coli* with zone of inhibition ranging from 24-27 mm. The compounds **3a**, **3e** and **3f** showed moderate activity against *S. paratyphi* with zone of inhibition ranging from 20-22 mm. The compounds **3e**, **3g** and **3h** showed good antifungal activity against *A. niger* and *C. coffeanum* with zone of inhibition ranging from 20-24 mm. The results were in accordance with previous studies, which indicated that 4-hydroxy-3-methoxy and 4-dimethyl amino substituents on benzylidene ring showed good antimicrobial activity[7].

Molecular docking Studies

Molecular docking studies of title compounds were carried out on target protein DHPS (PDB Id: 3TYE) and the data (Table 2) reveals all the synthesized compounds showed docking scores ranging from -1.604 to -5.419 kcal/mol. The synthesized compound **3h** showed good binding score of -5.419 predicted by using XP GLIDE. This data provides the type of interactions within the target protein. (Figure 2-3).

***In silico* studies**

Computation of molecular descriptors such as log P, topological surface area, number of hydrogen bond donors and acceptors and the bioactivity scores for G-protein coupled receptor (GPCR) ligand, ion channel modulator, kinase inhibitor, nuclear receptor ligand, protease inhibitor and enzyme inhibitor were calculated by using Molinspiration online tool (http://www.molinspiration.com/cgi-bin/properties). The *in silico* data reports all the compounds obey the Lipinski rule of five. The oral bioavailability of title compounds assessed by Molinspiration online kit, showed good oral bioavailability between 70-85% and also have good bioactive scores towards the ion channel modulator and nuclear receptor ligand than other types of mechanisms. (Table 3 & 4)



R = 2-Thiophenyl, Phenyl
R_1 = 4-$N(CH_3)_2$, 4-NO_2, 4-CH_3, 4-Cl, 4-OCH_3, 3,4-di methoxy, 4-$NHCH_3$, 4-H, 4-Cl

Figure 1: Schematic representation of mannich bases of thiazolidine-2,4-diones

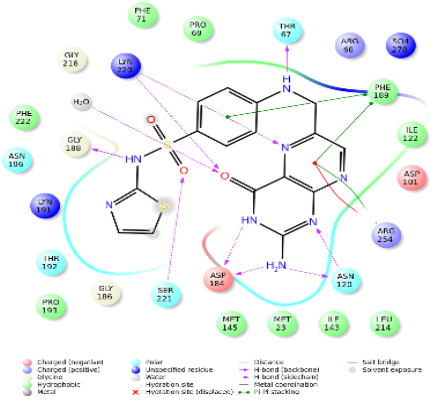


Figure 2: 2D Interaction of standard compound with Active site of 3TYE target

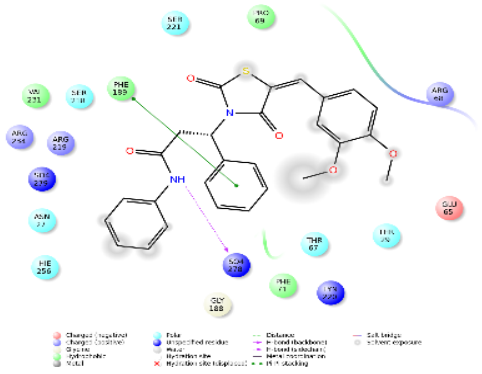


Figure 3: 2D Interaction of 3h compound with Active site of 3TYE

CONCLUSION

Our present work brings forth a method for the synthesis of nine Mannich bases **3a–3i** using conventional procedures. The compounds **3g** and **3h** showed good activity against gram negative bacteria *Salmonella paratyphi*, *Escherichia coli* and fungi *Aspergillus niger*, *Colletotrichum coffeanum*, comparable to that of standard. These compounds could be selected as a lead compounds for further development of antimicrobial agents.

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