Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Der Pharmacia Lettre, 2016, 8 (12):143-148
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-5071
USA CODEN: DPLEB4

Antibacterial and antifungal evaluation of Mannich bases of 2,4-thiazolidinedione and rhodanine

Archana Kapoor* and Neha Khare

Drug Discovery and Research Laboratory, Department of Pharmaceutical Sciences, Guru Jambeshwar University of Science and Technology, Hisar (Haryana), India

---

ABSTRACT

A series of mannich bases of thiazolidinedione and rhodanine were synthesized and characterized. The synthesized compounds were screened for their antibacterial and antifungal potential against gram positive bacteria: Staphylococcus aureus, Bacillus subtilis and gram negative bacteria: Escherichia coli and fungal strains C.albicans and A. niger by in-vitro serial dilution method. Compound MB05 (pMIC 2.3 µM/ml) found to be the most effective antibacterial agent among the synthesized derivatives it has shown the highest antibacterial activity against B.subtilis. MB02 (pMIC 2.28 µM/ml) displayed highest anti-fungal activity against C. albicans among the synthesized derivatives.

Keywords: Thiazolidinedione, antibacterial, antifungal, rhodanine, mannich bases

---

INTRODUCTION

The presence of thiazolidine ring in penicillin and related derivatives was the first recognition of its occurrence in the nature. Thiazolidine derivatives reported to show variety of biological activities such as antibacterial, antifungal [1,2,3], anti-inflammatory, anti-tuberculostatic, antitumor, anticonvulsant [4], cardio-tonic [5], besides showing promising anti-diabetic [6] activity. The medication class of thiazolidinediones (TZDs; also called as "glitazones") was introduced in late 1990's as an adjunct therapy for type II diabetes mellitus and related diseases [7]. Antibacterial activity is of particular importance given the dramatic rise of drug-resistant bacteria and paucity of new agents currently in development. One report on benzylidene thiazolidinediones identifies the key requirements for antibacterial activity to be an NH at the 3-position, a heteroatom at the 1-position and a substituted phenyl group at the 5-position [8]. The valuable properties of "glitazones" initiated us to synthesize N-substituted-5-benzylidene-2, 4- thiazolidinedione and rhodanine derivatives and evaluate their antimicrobial activity.

MATERIALS AND METHODS

Chemistry

Melting points were determined on an ELICO melting point apparatus and are uncorrected. Starting materials and the reagents used were of commercial grade and used further without purification. ^{1}H NMR (nuclear magnetic resonance) spectra were recorded at 400 MHz on a Brucker Advance II 400 spectrometer using TMS as an internal standard. Infrared spectra were recorded using KBr pellets on a Perkin-Elmer FTIR spectrophotometer. The wave number expressed in cm^{-1}. The structures of all the compounds were found to be in agreement with ^{1}H NMR and IR spectral data. The progress of the reaction was monitored by TLC using silica gel G as adsorbent.

General procedure for thiazolidine-2, 4-dione [9]

0.6mol of chloroacetic acid (56.4 g) in 60 ml of water was mixed with 0.6mol of thiourea (45.6 g) dissolved in 60 ml of water. The mixture was stirred for 15 min. to form a white precipitate, accompanied by considerable cooling.

To the contents of the flask, added slowly 60 ml of concentrated hydrochloric acid from a dropping funnel, the flask was then connected with a reflux condenser and gentle heat applied to effect complete solution, after which the reaction mixture was stirred and refluxed for 8-10 hour at 100-110°C. On cooling, the contents of the flask solidified to a cluster of white needles. The product was filtered and washed with water to remove traces of hydrochloric acid and dried. It was purified by recrystallization from ethyl alcohol.

General procedure for 4- Hydroxy-5-benzylidene-2, 4-thiazolidinedione [9]
2, 4-thiazolidinedione (22 g, 0.188mol) and 4-Hydroxy benzaldehyde (20 g, 0.188mol) were together suspended in ethanol. To this, a catalytic amount of piperidine (1 ml) was added. The mixture was stirred and refluxed. After the complete removal of water and when the temperature reached above 110°C the reaction mixture was stirred for a further1 hour. On cooling, the product precipitated out from ethanol. The compound was filtered and washed with cold dry toluene and dry ethanol.

General procedure for N-(Benzothiazol-2-yl)-2-chloroacetamide [10]
In a conical flask, 2-Amino benzothiazole (15 gm, 0.1mol) in chloroform (10 ml) was stirred and to this, chloroacetyl chloride (12.01ml, 0.15mol) was added drop wise under cold condition. Reaction mixture was stirred till completion of reaction, which was monitored by TLC.

General procedure for N-(Benzothiazol-2-yl)-2-(4-((2, 4-dioxothiazolidin-5 ylidene)methyl)phenoxyacetamide [10]
5-Benzylidene-2, 4-thiazolidinedione (22.12gm, 0.1mol) and anhydrous potassium carbonate (20.72gm, 0.15mol) in dimethyl formamide (DMF) was stirred in a flask and to this reaction mixture, N-(Benzothiazol-2-yl)-2-chloroacetamide (34.0gm, 0.15mol) in DMF was added. Reaction mixture was stirred at room temperature till the completion of reaction, which was monitored by TLC. After completion of reaction, water was added to get the solid final product.

General procedure for N-mannich bases [11]
To a solution of N-(Benzothiazol-2-yl)-2-(4-((2, 4-dioxothiazolidin-5-ylidene) methyl) phenoxy)acetamide (5.09gm, 0.01 mol) in DMF, formaldehyde (0.6ml, 0.02 mol) was added under stirring. The reaction-mixture was stirred at RT for 0.5 hr to complete the reaction of formaldehyde and yield methylol derivative of compound. To this, the solution of secondary amine in DMF was added drop wise and refluxed for 2 hr. The reaction was poured into ice cold water and filtered off and wash with hot water. Finally it was dried and purified by recrystallization from chloroform to get the desired compound.

Spectral data
(E)-5-(4-hydroxybenzylidene) thiazolidine-2, 4-dione: IR (KBr, cm^{-1}): 3405 (NH str.), 3125 (C-H str., aromatic), 1720 and 1678 (C=O str., cyclic imide), 1510 (C=C bend, aromatic), 1279 (C-O str.), 1156 (C-N str.), 614 (C-S str.); ^{1}H NMR ($DMSOd_6$) δ (ppm): 6.92 (d, 2H, aromatic), 7.46 (d, 2H, aromatic), 7.695 (s, 1H, benzylidene proton)
N-(Benzothiazol-2-yl)-2-chloroacetamide: IR (KBr, cm^{-1}): 3368 (NH str.), 1695 (C=O str., amide), 1450 (C=C bend, aromatic), 1268 (C-O str.), 1177 (C-N str.), 677 (C-Cl str.)

***N-(Benzothiazol-2-yl)-2-(4-((2, 4-dioxothiazolidin-5 ylidene)methyl)phenoxyacetamide* (TZP):** IR (KBr, cm^{-1}): 3197 (NH str.), 3065 (H-C=C str.), 1733 and 1677 (C=O str., cyclic imide), 1267 (C-O str.), 1176 (C-N str.), 611 (C-S str.); ^{1}H NMR ($DMSOd_6$) δ (ppm): 8.5 (2H, s, Ar-H), 8.3 (1H, s, NH), 7.56 (2H, s, Ar-H), 7.14 (2H, m, Ar-H), 4.68 (2H, s, CH_2)

***(E)-N-(benzo[d]thiazol-2-yl)-2-(4-((4-oxo-2-thioxothiazolidin-5-ylidene)methyl)phenoxy)acetamide* (RHP):** IR (KBr, cm^{-1}): 3190 (NH str.), 3070 (H-C=C str.), 1643 (C=O, aliphatic) and 1664 (C=O str., imide), 1271 (C-O str.), 1170 (C-N str.), 621 and 632 (C-S str.); ^{1}H NMR ($DMSOd_6$) δ (ppm): 7.96 (1H, s, NH), 7.75 (2H, s, Ar-H), 7.32 (3H, m, Ar-H), 6.68 (2H, s, Ar-H), 3.7 (2H, s, CH_2)

***(E)-N-(benzo[d]thiazol-2-yl)-2-(4-((2,4-dioxo-3-(piperazin-1-ylmethyl)thiazolidin-5-ylidene)methyl)phenoxy) acetamide* (MB01):** IR (KBr, cm^{-1}): 3402 (NH str.), 2935 (H-C=C str.), 1664 (C=O str., imide), 1459 (CH_2 str.), 1278 (C-O str.), 1169 (C-N str.), 620 (C-S str.); ^{1}H NMR ($DMSOd_6$) δ (ppm): 8.25 (2H, s, Ar-H), 7.95 (1H, s, NH), 7.10 (3H, m, Ar-H), 6.8 (3H, m, Ar-H), 3.34 (2H, s, CH_2), 2.5 (4H, m, CH_2)

***(E)-N-(benzo[d]thiazol-2-yl)-2-(4-((3-((diphenylamino)methyl)-2,4-dioxothiazolidin-5-ylidene)methyl) phenoxy) acetamide* (MB02):** IR (KBr, cm^{-1}): 3385 (NH str.), 3045 (H-C=C str.), 1680 and 1656 (C=O str., cyclic imide), 1494 (C=C bend, aromatic), 1477 (CH_2, bend), 1234 (C-O str.), 1172 (C-N str.), 615 (C-S str.); ^{1}H NMR ($DMSOd_6$) δ (ppm): 8.14 (1H, s, NH), 7.2 (4H, m, Ar-H), 7.07 (6H, d, Ar-H), 6.8 (1H, s, H-C=C)

***(E)-N-(benzo[d]thiazol-2-yl)-2-(4-((3-((dimethylamino)methyl)-2,4-dioxothiazolidin-5-ylidene)methyl) phenoxy) acetamide (*MBO3*)*:** IR (KBr, cm^{-1}): 3381 (NH str.), 3061 (H-C=C str.), 1664 (C=O str., imide), 1593 (C=C bend, aromatic), 1471 (CH_2, bend), 1273 (C-O str.), 1176 (C-N str.), 619 (C-S str.); ^1H NMR ($DMSOd_6$) δ (ppm): 7.9 (1H, s, NH), 7.72 (4H, m, Ar-H), 7.33 (4H, m, Ar-H), 6.84 (1H, s, H-C=C), 3.4 (4H, s, CH_2), 2.5 (6H, s, CH_3)

***(E)-N-(benzo[d]thiazol-2-yl)-2-(4-((3-((4-methylpiperazin-1-yl)methyl)-2,4-dioxothiazolidin-5-ylidene)methyl) phenoxy)acetamide (*MB04*)*:** IR (KBr, cm^{-1}): 3288 (NH str.), 3062 (H-C=C str.), 1681 and 1598 (C=O str., cyclic imide), 1494 (C=C bend, aromatic), 1377 (CH_3, bend), 1273 (C-O str.), 1188 (C-N str.), 617 (C-S str.); ^1H NMR ($DMSOd_6$) δ (ppm): 8.1 (2H, s, Ar-H), 7.96 (1H, s, NH), 7.17 (4H, m, Ar-H), 6.98 (1H, s, H-C=C), 3.42 (4H, s, CH_2), 2.5 (8H, s, CH_2), 2.2 (3H, s, CH_3)

***(E)-N-(benzo[d]thiazol-2-yl)-2-(4-((3-((diethylamino)methyl)-2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy) acetamide (*MBO5*)*:** IR (KBr, cm^{-1}): 3413 (NH str.), 2921 (CH_3 str., aliphatic), 1666 (C=O str., imide), 1494 (C=C bend, aromatic), 1377 (CH_3, bend), 1273 (C-O str.), 1188 (C-N str.), 617 (C-S str.)

***(E)-N-(benzo[d]thiazol-2-yl)-2-(4-((3-((dibenzylamino)methyl)-2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy) acetamide (MB06)*:** IR (KBr, cm^{-1}): 3406 (NH str.), 1664 (C=O str., imide), 1506 (C=C bend, aromatic), 1467(-CH_2-), 1250 (C-O str.), 1176 (C-N str.), 622(C-S str.); ^1H NMR ($DMSOd_6$) δ (ppm): 7.95 (1H, s, NH), 7.68 (4H, m, Ar-H), 7.09 (4H, m, Ar-H), 3.34 (4H, s, CH_2), 2.5 (4H, s, CH_2), 1.2 (6H, s, CH_3)

***(E)-N-(benzo[d]thiazol-2-yl)-2-(4-((4-oxo-3-(piperazin-1-ylmethyl)-2-thioxothiazolidin-5-ylidene)methyl) phenoxy) acetamide (*MB07*)*:** IR (KBr, cm^{-1}): 3240 and 3304 (NH str.), 3078 (H-C=C str.), 1666 (C=O str., amide), 1460 (CH_2, bend), 1278 (C-O str.), 1159 (C-N str.), 646 (C-S str.)

***(E)-N-(benzo[d]thiazol-2-yl)-2-(4-((3-((4-methylpiperazin-1-yl)methyl)-4-oxo-2-thioxothiazolidin-5-ylidene) methyl) phenoxy)acetamide (*MB08*)*:** IR (KBr, cm^{-1}): 3213 (NH str.), 3061 (H-C=C str.), 1664 (C=O str., amide), 1481 (C=C bend, aromatic), 1465 (CH_2 bend), 1365 (CH_3, bend), 1278 (C-O str.), 1151 (C-N str.), 624 (C-S str.); ^1H NMR ($DMSOd_6$) δ (ppm): 8.23 (2H, s, Ar-H), 7.89 (1H, s, NH), 7.23 (4H, m, Ar-H), 6.91 (1H, s, H-C=C), 3.38 (4H, s, CH_2), 2.43 (8H, s, CH_2), 2.32 (3H, s, CH_3)

***(E)-N-(benzo[d]thiazol-2-yl)-2-(4-((3-((dimethylamino)methyl)-4-oxo-2-thioxothiazolidin-5-ylidene)methyl)phenoxy)acetamide (*MB09*)*:** IR (KBr, cm^{-1}): 3381 (NH str.), 3061 (H-C=C str.), 1664 (C=O str., amide), 1593 (C=C bend, aromatic), 1471 (CH_2, bend), 1273 (C-O str.), 1176 (C-N str.); ^1H NMR ($DMSOd_6$) δ (ppm): 7.85 (1H, s, NH), 7.69 (4H, m, Ar-H), 7.39 (4H, m, Ar-H), 6.78 (1H, s, H-C=C), 3.5 (4H, s, CH_2), 2.8 (6H, s, CH_3)

***(E)-5-(4-hydroxybenzylidene)-2-thioxothiazolidin-4-one (*RHB*)*:** IR (KBr, cm^{-1}): 3383 (NH str.), 3101 (C-H str., aromatic), 1685 (C=O str., amide), 1506 (C=C bend, aromatic), 1282 (C-O str.), 1174 (C-N str.), 624 (C-S str.); ^1H NMR ($DMSOd_6$) δ (ppm): 10.4 (1H, s, NH), 7.13 (3H, m, Ar-H), 6.68 (2H, m, Ar-H)

Antimicrobial activity

The antimicrobial evaluation of synthesized compounds was performed against gram positive *Staphylococcus aureus* (MTCC 3160), *Bacillus subtilis* (MTCC2063), gram negative *Escherichia coli* (MTCC40) and fungal strain of *Candida alibicans* (MTCC183), *Aspergillus niger* (MTCC281) using serial dilution method [12,13].

Antibacterial assay

Antibacterial activity of synthesized derivatives was tested against gram positive *Staphylococcus aureus, Bacillus subtilis* and gram negative *Escherichia coli* by in-vitro serial dilution method using Nutrient Broth I.P. Fresh culture of respective bacteria was obtained by inoculation in double strength Nutrient Broth I.P. followed by incubation at 37± 1°C. The standard drug ciprofloxacin and the test compounds were dissolved in DMSO to obtain the concentration of 100µg/ml. 1 ml of sterilized media were poured into the sterilized test tubes. The stock solution (100µg/ml) of thiazolidinedione and rhodanine derivatives were serially diluted to give the concentration 50-1.56 µg/ml and then inoculated with 100µl of suspension of respective organism in sterile saline and the tubes were incubated at 37± 1°C. The MIC was determined by the lowest concentration of the sample that prevented the development of turbidity.

Antifungal Assay

The antifungal activity of synthesized compounds was evaluated against *C.albicans* and *A. niger*. The Activity was determined by *in-vitro* serial dilution method similar to anti-bacterial assay using Sabouraud Dextrose Broth I.P. as nutrient medium. The inoculated test tubes were incubated at 37±1°C and 25±1°C for a period of 2 days and 7 days

in case of *C.albicans* and *A.niger* respectively. The activity of the synthesized compounds was compared with standard drug Fluconazole.

Table I: Physicochemical Characterization of the Synthesized Compounds

S.No.	Product code	Molecular formula	Molecular weight	Melting Point	R_f	% yield
1.	TZP	$C_{19}H_{13}O_4N_3S_2$	411.454	168-180	0.61	58.4
2.	RHP	$C_{19}H_{13}O_3N_3S_3$	427.52	170-185	0.86	60.3
3.	MB01	$C_{24}H_{23}O_4N_5S_2$	509.601	62-64	0.73	67.89
4.	MB02	$C_{32}H_{24}O_4N_4S_2$	592.687	56-60	0.72	48.56
5.	MB03	$C_{22}H_{20}O_4N_4S_2$	468.549	54-58	0.65	56.7
6.	MB04	$C_{25}H_{25}O_4N_5S_2$	523.627	60-64	0.70	44.9
7.	MB05	$C_{34}H_{28}O_4N_4S_2$	620.741	63-65	0.82	78.25
8.	MB06	$C_{24}H_{24}O_4N_4S_2$	496.602	55-57	0.76	62.8
9.	MB07	$C_{24}H_{23}O_3N_5S_3$	525.666	58-62	0.60	53.65
10.	MB08	$C_{25}H_{25}O_3N_5S_3$	539.693	60-65	0.79	70.48
11.	MB09	$C_{22}H_{20}O_3N_4S_3$	484.614	55-59	0.57	64.45
12.	RHB	$C_{10}H_7O_2NS_2$	237.298	150-155	0.67	78.42

TLC Mobile Phase: Benzene:Methanol ; 8.5:1.5 (v/v)

RESULTS AND DISCUSSION

Chemistry

The mannich bases of thiazolidinedione and rhodanine derivatives were synthesized using scheme 1 and scheme 2 respectively. Thiazolidinedione and rhodanine was condensed with benzaldehyde by Knoevenagel condensation to form 5-benzylidene thiazolidinedione and 5-benzylidene rhodanine which was condensed with acetamide derivative of 2-aminobenzothiazole (**2)** to form compound **3**. This compound was further reacted with formaldehyde by stirring and then refluxed with desired secondary amines to get the mannich bases. The completion of reaction was confirmed by single spot TLC. The synthesized derivatives were characterized by their physical parameters such as R_f, melting point and % yield.The results are summarized in Table I.

Scheme I: The general synthetic scheme for synthesis of mannich bases of thiazolidinedione and rhodanine derivatives

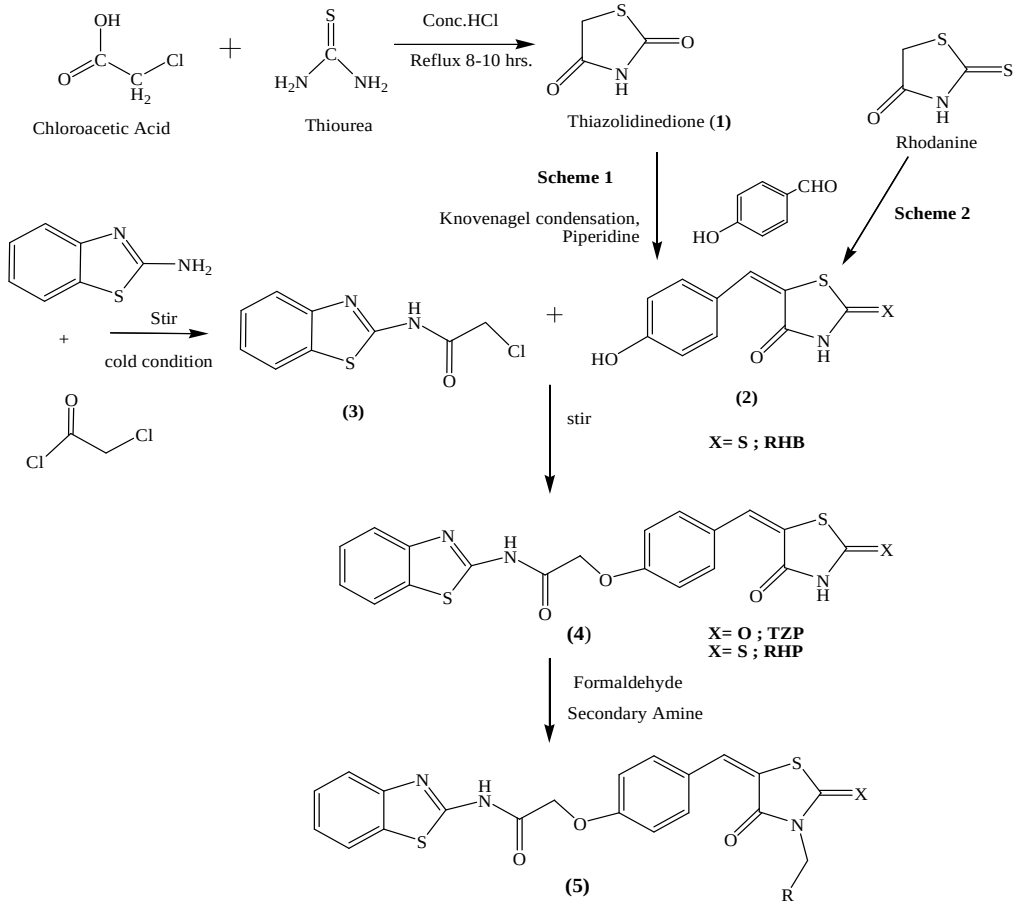
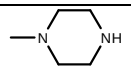
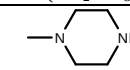
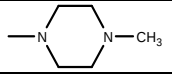
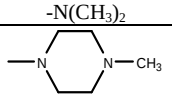


Table II: pMIC values (µM/ml) of synthesized derivatives of 2, 4-thiazolidinedione and rhodanine

S. No.	Product code	R	X	S.No.	Product code	R	X
1.	TZP	-	O	**7.**	MB05	$-N(CH_2.C_6H_5)_2$	O
2.	RHP	-	S	**8.**	MB06	$-N(CH_2.CH_3)_2$	O
3.	MB01		O	**9.**	MB07		S
4.	MB02	$-N(C_6H_5)_2$	O	**10.**	MB08		S
5.	MB03	$-N(CH_3)_2$	O	**11.**	MB09	$-N(CH_3)_2$	S
6.	MB04		O	**12.**	RHB	-	S

Consistent IR, ^{1}HNMR data confirmed the structure of the synthesized compounds to be correct. The absence of O-H peak at 3600 cm^{-1} in TZP confirmed the formation of ether linkage in the pharmacophore. The IR spectrum of benzylidene 2, 4-thiazolidinedione illustrated the presence of H-C=C bond at 3065cm^{-1} which confirmed the unsaturation at C-5 in all the synthesized derivatives. The IR spectra of synthesized derivatives (MB01-MB09) exhibited the absorption bands for aromatic ring vibrations in the region of 3150-3050 cm^{-1}. The carbonyl stretching band was observed at 1680 and 1664 cm^{-1}.The $-CH_2-$ bend was observed at 1465cm^{-1} which confirmed the presence of methylene group in mannich bases. The synthesized compounds also showed C-O str. in the range of 1270-1278cm^{-1}, C-N str. in the range of 1100-1200cm^{-1} and C-S str. in the range of 620-630cm^{-1} which indicated the synthesis of respective compounds.

The ^{1}HNMR spectrum of benzylidene derivatives of thiazolidinedione and rhodanine displayed the characteristic peak at δ 7.1 for unsaturation at C-5 of the ring and NH peak at δ 10.0. The pharmacophore showed the peak at δ 4.7 for $-CH_2$ which confirmed the condensation of 2-amino benzothiazole ring with benzylidene thiazolidinedione and rhodanine, with the peaks for aromatic hydrogen at δ 7.2 and δ 7.7. The NH peak at 8.0 for amide linkage at benzothiazole and NH peak at δ 10.0 for unsubstituted N-3 can be easily distinguished in the spectrum of TZP and RHP. The mannich bases of thiazolidinedione gave characteristic peak for $-CH_2$ at δ 2.2-3.5 which confirmed the methylene group between secondary amines and N-3. The absence of NH peak at δ 10.0 further confirms the substitution at N-3 of thiazolidinedione and rhodanine instead of at amide linkage of benzothiazole which was also one of the probable sites for substitution of secondary amine. The peaks of respective amines containing hydrogens were also noted. The spectral data thus confirmed the synthesis of mannich bases of thiazolidinedione and rhodanine derivatives with repective amines at N-3 of TZP and RHP.

Antimicrobial activity

Minimum inhibitory concentration (MIC) is the lowest concentration of an antimicrobial agent which will inhibit the visible growth of a micro-organism after overnight incubation. The *in-vitro* antimicrobial activity of the novel synthesized thiazolidinedione and rhodanine derivatives were evaluated against gram positive *B.subtilis*, *S.aureus* and gram negative bacterial strain *E.coli*, and anti-fungal activity against different strains of fungi *C. albicans*, *A. niger* by *in-vitro* serial dilution method. The pMIC values of synthesized derivatives are given in Table II.

S.No.	Product code	$pMIC_{B.s.}$	$pMIC_{S.a.}$	$pMIC_{E.c}$	$pMIC_{C.a.}$	$pMIC_{A.n.}$
1.	TZP	1.82	1.52	1.22	1.52	**1.82**
2.	RHP	1.84	1.53	1.23	**1.84**	1.53
3.	MB01	1.61	1.61	1.31	1.61	1.61
4.	MB02	1.68	**1.68**	1.37	**2.28**	**2.28**
5.	MB03	1.87	1.57	1.27	**1.87**	1.57
6.	MB04	1.62	1.62	1.32	**1.92**	1.62
7.	MB05	**2.3**	1.39	1.39	**2**	1.39
8.	MB06	**1.9**	1.6	1.3	1.6	1.6
9.	MB07	**1.92**	1.32	1.62	**1.92**	**1.92**
10.	MB08	**1.94**	1.64	**1.64**	1.64	1.64
11.	MB09	1.89	1.59	1.29	1.59	1.59
12.	RHB	1.58	1.28	0.98	1.28	1.28
13.	STD.	**2.33**[a]	**2.33**[a]	**2.33**[a]	**1.99**[b]	**1.99**[b]

Standard a-Ciprofloxacin, Standard b-Fluconazole

The results obtained showed that MB05 is equipotent to standard against gram positive *B. subtilis* with pMIC 2.3µM/ml and showed good activity against fungal strain *C. albicans.* All compounds showed moderate to good activity against *B. subtilis.* Compounds MB02 and MB08 were found to be more active against *S. aureus* as

compared to other synthesized derivatives. The derivatives were less active against *E. coli*. The antifungal results showed that MB02 depicted the excellent inhibition against *C.albicans* and *A.niger* with pMIC 2.28µM/ml.

From the results of antimicrobial evaluation, SAR can be deduced as follows:

- The derivatives of thiazolidinedione and rhodanine showed superior anti-fungal activity. MB02 was more potent than standard Fluconazole with pMIC 2.28 µM/ml against *C. albicans*, *A. niger* and also showed good activity against *S. aureus.* This may be due to presence of aromatic substituent *viz.* diphenylamine at N-3 of thiazolidinedione.
- In case of *B. subtilis*, MB05 emerged as an active compound for antimicrobial activity which can be again be attributed to the aromatic substitution of dibenzylamine at N-3 of thiazolidinedione.
- Presence of alicyclic and aliphatic ring through methylene group at N-3 showed moderate to significant activity against *B. subtilis* and *S. aureus.* (MB08, MB07, MB06, MB03, MB04 and MB01 with pMIC 1.94, 1.92, 1.9, 1.87, 1.62 and 1.61µM/ml respectively).
- The role of heterocyclic ring i.e. benzothiazole linked to the pharmacophore via amide linkage in enhancing the antimicrobial activity is clearly evident from anti-fungal activity (against C. albicans) and moderate anti-bacterial activity (against B. subtilis) of RHP with pMIC of 1.84 µM/ml.
- Mannich bases (MB01-MB09) displayed better activity than their respective thiazolidinedione and rhodanine pharmacophore i.e. TZP and RHP.
- It has also been observed that N-3 substitution of thiazolidinedione and rhodanine derivatives displayed better activity than their respective pharmacophores.
- The methylene linkage between NH of thiazolidinedione ring and secondary amines can also be responsible for good antimicrobial activity.

CONCLUSION

A series of mannich bases of novel derivatives of thiazolidinedione and rhodanine were synthesized and characterized. The synthesized compounds were screened for their *in-vitro* antimicrobial evaluation. MB05 (pMIC 2.3µM/ml) and MB02 (pMIC 2.282.3µM/ml) showed highest antimicrobial activity against *B. subtilis* and *A. niger* respectively. It can be further concluded that the mannich bases have better antimicrobial activity and the aromatic amines substituted at N-3 of thiazolidinedione and rhodanine enhances the antimicrobial activity. MB07 and MB08 showed good antimicrobial highlighting the presence of heterocyclic ring to be good for activity. It can be generalized from the above discussed point that, heterocyclic ring, benzothiazole is evidently contributing towards the antimicrobial activity. This may be due to the increase in lipophilic nature of the ring. Further, N-3 substituted derivatives are displaying significant activity than N-unsubstituted compound which are similar to results obtained by Neeru *et al* [7]. Aromatic substitution at N-3 has shown better activity than alicyclic and aliphatic substitution.

REFERENCES

[1] I.M. Labouta, H. Salma, O. Ehsba, E. Kader, El-Churbini. *Eur. J. Med. Chem.* **1987**, 22, 485- 489.
[2] A.J.S. Goes, M.C.A. DeLima, S.L. Galdino, I.R. Pitta, C. Luu-Ducc, *Ann. Pharm. Francaises.*, **1991**, 49, 92-98.
[3] M.C.A. DeLima, D.L.B. Costa, A.J.S. Goes, S.L. Galdino, I.R. Pitta, C. Luu-Ducc, *Pharmazie.*, **1992**, 47, 182-184.
[4] S.A.H. Eel-Feky, *Pharmazie.*, **1993**, 48, 28-34.
[5] A. Andreani, M. Rambaldi, A. Locatelli, A. Leoni, R. Bossa, M. Chiericozzi, I. Galatulas, G. Salvatore, *Eur. J. Med. Chem.* **1993**, 28, 825-9.
[6] B.C.C. Cantello, M.A. Cawthorne, G.P. Cottam, P.T. Duff, D. Haigh, R.M. Hindley, C.A. Lister, S.A. Smith, P.L. Thurlby, *J. Med. Chem.* **1994**, 37, 3977-85.
[7] N. Malik, D.N. Prasad, *Iranian J. Pharmaceut. Sci.* **2012**, 8, 209-214.
[8] O. Zvarec, S.W. Polyak, W. Tieu, K. Kuan. *Bioorg. Med. Chem. Lett.* **2012**, 22, 2720-2722.
[9] S.R. Pattan, P. Kekare, A. Patil, A. Nikalje, B.S. Kittur, *Iranian J. Pharmaceut. Sci.*, **2009**, 5, 225-230.
[10] A.P.G. Nikalje, *European J. Exp. Biol.*, **2012**, 2, 1302-1314.
[11] O.P. Sharma, D.P. Pathak, *Int. J. Pharmaceut. Front. Res.*, **2011**, 1, 18-28.
[12] G.M. Eliopoulos, A. Gardella, R.C. Moellering, *Am. Soc. Microbiol.*, **1984**, 25, 331-335.
[13] Indian Pharmacopoeia, Published by The Indian Pharmacopoeia commission; Government of India, Ministry of Health and Family Welfare, **2007**, Vol. 1, page no. 45-55.