Indian Journal of Chemistry
Vol. 61, June 2022, pp. 591-598

Pharmacological evaluation of some synthesized thiazolidinone derivatives containing Mannich base of sydnone and *p*-phenylenediamine

Suchitra S Savant[a], Parikshit I Vashi[b], Elit A Gamit[c], Keshav C Patel[b] & Paresh S Patel*[b]

[a] Department of Chemistry, Sheth P. T. Mahila College of Arts, Home Science and Science Unit, Vanita Vishram, Surat 395 001, India

[b] Department of Chemistry, Veer Narmad South Gujarat University, Surat 395 007, India

[c] Shri K. J. Polytechnic, Bharuch 392 001, India

E-mail: ncscpsp@gmail.com

Received 16 August 2020; accepted (revised) 23 December 2021

A series of 4-thiazolidinone derivatives incorporating Mannich base of 3-(3-nitrophenyl)sydnone have been synthesized by conventional routes and evaluated for their antimicrobial activities against *E. coli, P. aerugenosa, S. aureus, S. pyogenus, C. albicans, A. niger* and *A. clavatus*. Most of the compounds show moderate to very good biological activity. The structures of synthesized compounds **7a-j** have been elucidated by C, H, and N analysis, FT-IR, ^{1}H and ^{13}C NMR and mass spectrometry.

Keywords: Thiazolidinone, Mannich base, sydnone, antimicrobial

Medicinal chemistry concerns essentially the understanding and explanation of the mechanisms of the drugs. It explains the design and production of compounds that can be used for the prevention, treatment or cure of human and animal diseases. Medicinal chemistry includes the study of already existing drugs, their biological properties and their structure activity relationships. Mesoionic compounds are five membered heterocyclic conjugated betains. At present the most frequently used 'mesoionic' structure is of Sydnone proposed by Baker and Ollis[1,2]. The sydnone ring bears a fractional positive charge balanced by a corresponding negative charge located on covalently attached oxygen[3]. Due to the unique structure, sydnone possesses both the conjugated and polar character, which makes it sensitive to both electric and magnetic fields. Many Sydnone compounds have been found to exhibit pharmacological and biological activities viz, antibacterial[4], antitumor[5,6], antifungal[7], antimalarial[8], anti-inflammatory[9], analgesic[10], anthelmintic[11], antioxidant[12]. They also show significant response of coronary dilation test, collagen induced platelet aggregation inhibition, local anaesthetic, antiwrithing, anticonvulsant, muscle relaxation and moderate cardiotropic activity. A hydrogen atom at the 4th position of the sydnone ring allows substitution with a wide variety of electrophiles, such as bromination, nitration, acylation, and sulfonation. It seems to be possible to substitute the 4th position by electron-releasing groups such as the methylene group by Mannich reaction[13-15].

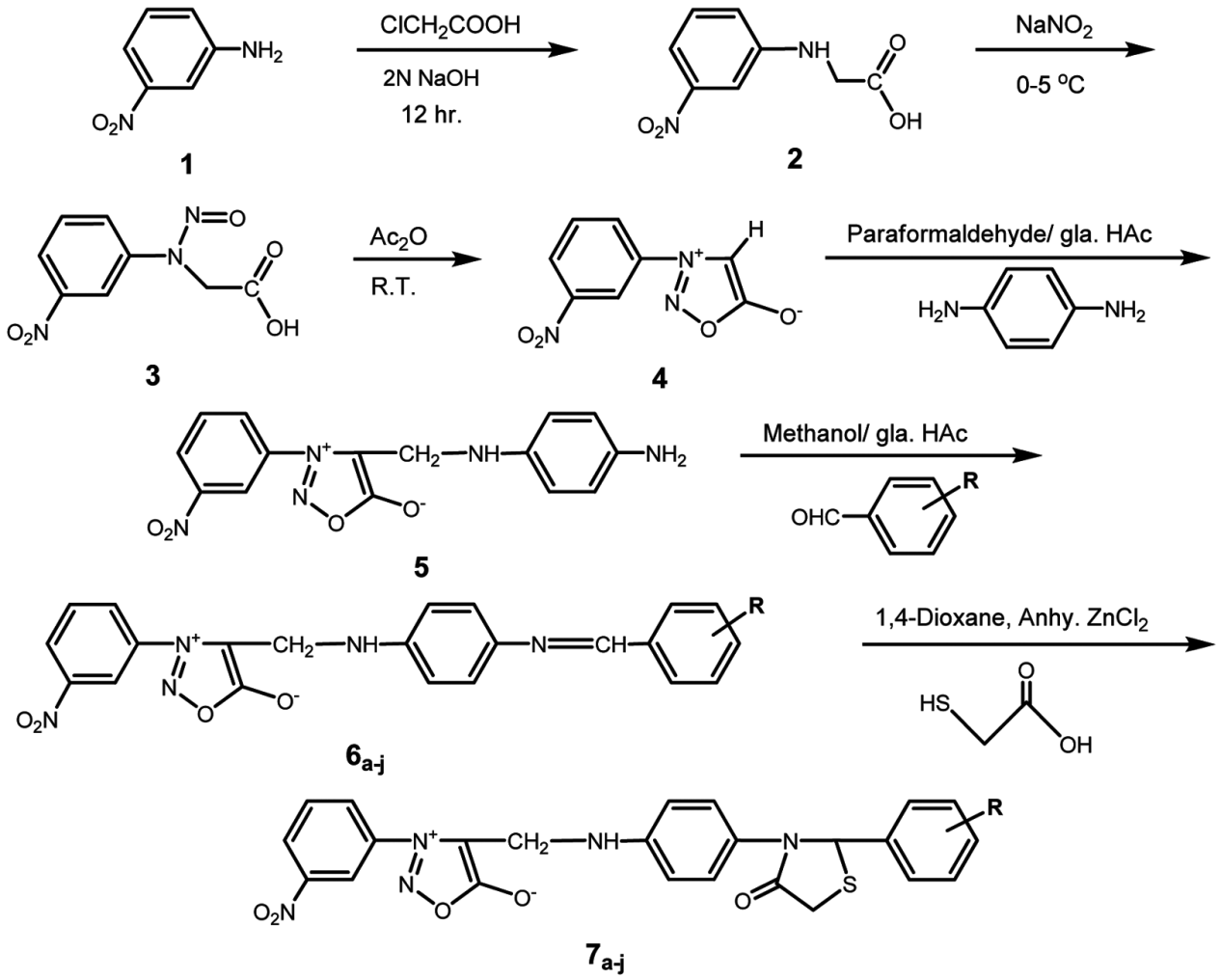
4-Thiazolidinones play a vital role due to their wide range of biological activities viz, antibacterial and antifungal[16-18], anti-inflammatory[19], antitubercular[20,21], anticonvulsant[22], antiviral[23], CNS stimulants[24], COX inhibitors[25], cytoprotective agents[26], trypanocidal and anticancer activity[27].

Thus, we decided to incorporate these three important species, sydnone, Mannich base and 4-thiazolidinones with a view to improve their antimicrobial activities.

Results and Discussion

Chemistry

The multi-component condensation of a primary amine or secondary amine and enolizable carbonyl compound with the aim to synthesized aminomethylated products are referred to as the Mannich Reaction. The synthesis of 4-thiazolidinone derivatives **7a-j** containing Mannich base of sydnone is shown in Scheme I. We focused on the synthesis of Mannich base by reacting 3-(3-nitrophenyl)sydnone **4** with *p*-phenylene diamine. Synthesis of 3-(3-nitrophenyl)sydnone **4** comprises of three steps procedure viz, condensation with chloroacetic acid, nitrosation and cyclodehydration[6]. 3-(3-Nitrophenyl)sydnone **4** was reacted with



Scheme I

paraformaldehyde and *p*-phenylene diamine to give 4-(((4-aminophenyl)amino)methyl)-3-(3-nitrophenyl) sydnone **5**[12]. This on further condensed with substituted aldehydes **a-j** in presence of gla. HAc to give desired Schiff base **6a-j**. These Schiff base derivatives were treated with thioglycolic acid in presence of anh. $ZnCl_2$ to yield 4-thiazolidinones **7a-j**.

Elemental analysis and spectral data were used to confirm the structures of synthesized compounds. 3-(3-Nitrophenyl)sydnone **4** showed two characteristics IR absorption bands at 3108 cm^{-1} and 1752 cm^{-1} due to C-H and >C=O stretching of the sydnone. ^{1}H NMR (DMSO d_6) spectra of compound **4** showed sharp singlet peak at δ 7.42 ppm, characteristics band for active proton at 4th position of sydnone. T he absence of this sharp peak in 4-(((4-aminophenyl)amino)methyl)-3-(3-nitrophenyl) sydnone **5** confirms the formation of Mannich base. IR spectra of compound **5** showed two characteristics band at 3269 cm^{-1} and 2860 cm^{-1} due to -CH_2- and -NH- of Mannich base. ^{1}H NMR (DMSO-d_6) spectra of compound **5** showed singlet at δ 4.59 ppm due to -NH_2, which was disappeared in compounds **6a-j** due to the formation of Schiff base derivatives. The -C=N- stretching of Schiff base in compounds **6a-j** found between 1665-1595 cm^{-1} which was not seen in the spectra of compounds **7a-j** due to the formation of thiazolidinone ring. >C=O stretching of 4-thiazolidinone in compounds **7a-j** was observed between 1738-1674 cm^{-1}. Some additional peaks appear due to substitution in aromatic ring. ^{13}C NMR spectra showed characteristics signal for the carbonyl carbon of sydnone around δ 168.7ppm, methylene carbon around δ 49 ppm.

Experimental Section

All the chemicals used were of analytical grade and the solvents were distilled before use. All the melting points reported are uncorrected and were recorded using an electro-thermal melting point apparatus. The structure of synthesized compounds was confirmed by elemental analysis (C, H, N) which was performed on Thermo Scientific FLASH 2000 at G.N.F.C. (Gujarat Narmada Valley Fertilizer Company Ltd., Bharuch). Infrared spectra were recorded with FT-IR Spectrophotometer Perkin Elmer in the frequency range 4000-400 cm^{-1} with samples embedded in KBr disks. Proton nuclear magnetic resonance (^{1}H NMR) spectra of the compound were recorded with a Bruker Advance II 400Hz NMR and carbon (^{13}C) NMR spectra of the compounds were recorded with a Bruker Avance II 400 NMR spectrometer using DMSO-d_6 as a solvent and tetramethyl silane(TMS) as an internal reference at Sophisticated Analytical Instrument Facilities (SAIF), Chandigarh. Thin-layer chromatography analysis were performed using aluminium backed Silica-gel plates (Merck 60 F524) and examined under short wave ultraviolet (UV) light.

General procedure for the synthesis of the compounds 7a-j

Synthesis of (3-nitrophenyl)glycine 2

This step, a condensation, involved neutralizing an aqueous solution of chloroacetic acid (0.94 g, 0.01 mol) with an equimolar equivalent of 10% NaOH and adding this solution to an aqueous solution of 3-nitro aniline **1** (1.38 g, 0.01 mol) over a period of 4 h. This reaction mixture was heated for 10 h and the clear liquor was then filtered while hot to remove any decomposition product and refrigerated overnight. The resulting crystals were again filtered to obtain (3-nitrophenyl) glycine **2**. Yield 87%, m.p. 145-147 ºC. IR: (KBr) ν (cm^{-1}): 3465 (O-H str. of acid), 1773 (>C=O of acid), 1601, 1507 (C=C of aromatic), 1514 (asym.), 1323(sym.) (-NO_2); ^{1}H NMR (DMSO-d_6): δ (ppm): 4.07 (s, 2H, -CH_2-), 6.34 (s, 1H, -NH-), 7.25 (d, 1H, Ar-H), 7.37 (t, 1H, Ar-H), 7.59 (d, 1H, Ar-H),7.66 (s, 1H, Ar-H), 13.12 (s, 1H, -COOH); ^{13}C NMR (DMSO-d_6): δ (ppm): 45.91 (-CH_2-), 106.45 (Ar-C), 112.29 (Ar-C), 119.57 (Ar-C), 130.38 (Ar-C), 148.54 (Ar-C of C-N), 148.72 (Ar-C of C-N), 171.98 (>C=O of acid).

Synthesis of N-(3-nitrophenyl)-N-nitrosoglycine 3

To an ice-cooled solution of (3-nitrophenyl) glycine **2** (1.96 g, 0.01 mol) in 40 mL of water, a solution of sodium nitrite (0.69 g, 0.01 mol) in 5 mL of water was added drop by drop with stirring. After stirring for another 2 h and leaving the solution to stand overnight, the reaction mixture was filtered through a Buckner funnel, and the nitroso compound was precipitated by adding concentrated hydrochloric acid to the filtrate. Yellowish needles were obtained as product, yield 87%, m.p.154-157 ºC. IR: (KBr) ν (cm^{-1}): 3461 (O-H of acid), 1774 (>C=O of acid), 1616, 1513 (C=C of aromatic), 1597 (N=O str.),1524 (asym.), 1335 (sym.) (-NO_2); ^{1}H NMR (DMSO-d_6): δ (ppm): 4.05 (s, 2H, -CH_2-), 6.85(d, 1H, Ar-H), 7.39 (t, 1H, Ar-H), 7.55 (d, 1H, Ar-H), 7.62 (s, 1H, Ar-H), 13.08(s, 1H, COOH); ^{13}C NMR (DMSO-d_6): δ (ppm): 62.25 (-CH_2-), 113.11 (Ar-C), 122.49 (Ar-C), 129.52 (Ar-C), 130.42 (Ar-C), 143.33 (Ar-C of C-N), 148.75 (Ar-C of C-N), 173.08(>C=O of acid).

Synthesis of 3-(3-nitrophenyl)sydnone 4

A mixture of N-(3-nitrophenyl)-N-nitrosoglycine **3** (2.835 g, 0.0126 mol) and acetic anhydride (15 mL) was stirred at room temperature for 12 h in the dark. The solution was poured slowly into cold water which was very well stirred. The pH of the content was adjusted to 7.0 with 10% Sodium bicarbonate solution. The crude sydnone obtained was washed well with water, dried and recrystallized from 95% ethanol afforded a yield of 92% of light yellow needles, m.p. 147-149 ºC.IR: (KBr) ν (cm^{-1}): 3108 (C-H of sydnone), 1752 (>C=O of sydnone), 1622, 1517 (C=C of aromatic), 1518 (asym.), 1327 (sym.) (-NO_2); ^{1}H NMR(DMSO-d_6): δ (ppm): 4.05(s,1H,-CH- of sydnone), 7.59 (t, 1H, Ar-H), 8.19 (d, 1H, Ar-H), 8.25 (s, 1H, Ar-H); ^{13}C NMR (DMSO-d_6):δ (ppm): 114.71 (Ar-C), 123.43 (C_4 of sydnone), 126.69 (Ar-C), 132.31(Ar-C), 136.55 (Ar-C), 139.44 (Ar-C of C-N), 147.93(Ar-C of C-N), 169.18(C_5 of sydnone).

Synthesis of 4-(((4-aminophenyl)amino)methyl)-3-(3-nitrophenyl)sydnone 5

The mixture of compound 3-(3-nitrophenyl)sydnone **4** (2.07 g, 0.01 mol), paraformaldehyde (0.25 g, 0.00833 mol) and *p*-phenylenediamine (1.296g, 0.012 mol) were added to 10 mL of acetic acid and 10 mL ethanol and whole mixture was heated at 70 ºC for 3 h. After cooling ethanol was distilled off, 20 mL of water was added and neutralized with aqueous sodium bicarbonate to afford the crude product.

Recrystallization from 95% ethanol yielded 96% of title compound as crystalline solid. M.P. 207-209 ºC.IR: (KBr) ν (cm^{-1}): 3269 (-NH-), 2932, 2860, (-CH_2- of Mannich base), 1749 (>C=O of sydnone), 1628, 1508 (C=C of aromatic), 1525 (asym.), 1332 (sym.) (-NO_2); ^{1}H NMR(DMSO-d_6): δ (ppm): 4.29 (s, 2H, -CH_2- of Mannich base), 4.59 (s, 2H, -NH_2), 6.08 (d, 2H, Ar-H), 6.54 (d, 2H, Ar-H), 6.76 (s, 1H,-NH-), 7.59 (t, 1H, Ar-H), 8.22 (d, 2H, Ar-H),8.27 (s, 1H, Ar-H); ^{13}C NMR (DMSO-d_6): δ (ppm): 49.03 (-CH_2- of Mannich base), 114.72 (Ar-C), 117.11 (Ar-C), 118.53 (Ar-C), 126.71 (Ar-C), 132.33 (Ar-C), 136.48 (Ar-C),136.83 (Ar-C of C-N), 139.41 (Ar-C), 142.4 (C_4 of sydnone), 147.91 (Ar-C of C-N), 168.75 (C_5 of sydnone).

Synthesis of compounds 6a-j

The Schiff base derivatives were synthesized by the equimolar reaction between 4-(((4-aminophenyl) amino)methyl)-3-(3-nitrophenyl)sydnone **5** and various substituted aldehydes **a-j**. Each reactant was dissolved in a minimum amount of methanol, then mixed together and followed by addition of catalytic amount of glacial acetic acid. The solution was refluxed for 8 hr then cooled to room temperature and poured into ice cold water. The solid product was filtered, dried and recrystallized from ethanol.

Synthesis of compounds 7a-j

A mixture of 4-(((4-(3-substituted-benzylidine) amino)phenyl)amino)methyl)-3-(3-nitr-ophenyl) sydnone (0.005 mol) **6a-j** and thioglycolic acid (0.92 g, 0.01 mol) in 1,4-dioxane (50 mL), containing a pinch of anhy. $ZnCl_2$ was refluxed for about 10-12 hrs. The reaction mixture then heated to distil out the solvent. The remaining mass was then cooled and poured over crushed ice and stirred well. The solid thus obtained was filtered, washed with 5% sodium bicarbonate solution followed by water wash, dried and recrystallized from methanol.

All the 4-thiazolidinone derivatives were synthesized by the same procedure. The physical constants of synthesized **7a-j** are given in Table I and antimicrobial activities are given in Table II.

7a: IR: (KBr) ν (cm^{-1}): 3436 (Ar-OH), 3275 (-NH-), 2932, 2863, (-CH_2- of Mannich base), 1755 (>C=O of sydnone), 1698 (>C=O of 4-thiazolidinone), 1634, 1509 (C=C of aromatic), 1527 (asym.), 1343 (sym.) (-NO_2), 1403(bending) (-CH_2- of 4-thiazolidinone), 1244, 1052 (C-O-C of -OCH_3), 1241 (-N-C- of tertiary amine of 4-thiazolidinone), 721 (-S-C- of 4-thiazolidinone); ^{1}H NMR (DMSO-d_6): δ (ppm): 3.76 (s, 3H, -OCH_3), 4.03 (q, 2H, -CH_2- of thiazolidinone), 4.33 (s, 2H, -CH_2- of Mannich base), 6.45 (s, 1H, >CH- of thiazolidinone), 6.66 (d,

Table I — Physical constants and Elemental analysis data of compound 7a-j

Compd	-R	Yield (%)	m.p. ºC	Mol. formula Mol. Wt. (g/mol)	Elemental analysis		
					C	H	N
7a	3 -OCH_3, 4 -OH	76	141-143	$C_{25}H_{21}N_5O_7S$ 535.53	56.01 (56.07)	3.63 (3.95)	13.01 (13.08)
7b	3 -OCH_3, 2 -OH	78	167-169	$C_{25}H_{21}N_5O_7S$ 535.53	56.01 (56.07)	3.59 (3.95)	13.00 (13.08)
7c	2 -OH	71	138-140	$C_{24}H_{19}N_5O_6S$ 505.51	56.98 (57.02)	3.46 (3.79)	13.48 (13.85)
7d	4 -NO_2	82	152-154	$C_{24}H_{18}N_6O_7S$ 534.50	53.62 (53.93)	3.12 (3.39)	15.49 (15.72)
7e	3,4 -di OCH_3	86	143-146	$C_{26}H_{23}N_5O_7S$ 549.56	56.72 (56.82)	4.13 (4.22)	12.65 (12.74)
7f	4 -OCH_3	79	210-212	$C_{25}H_{21}N_5O_6S$ 519.53	57.44 (57.80)	4.01 (4.07)	13.22 (13.48)
7g	4 -CH_3	81	166-168	$C_{25}H_{21}N_5O_5S$ 503.53	53.55 (59.63)	4.12 (4.20)	13.81 (13.91)
7h	2 -Cl	80	182-184	$C_{24}H_{18}ClN_5O_5S$ 523.95	54.97 (55.02)	3.38 (3.46)	13.29 (13.37)
7i	4 -Cl	74	162-164	$C_{24}H_{18}ClN_5O_5S$ 523.95	54.93 (55.02)	3.37 (3.46)	13.25 (13.37)
7j	2 -F	72	159-161	$C_{24}H_{18}FN_5O_5S$ 507.50	56.69 (56.80)	3.46 (3.58)	13.67 (13.80)

Table II — Antimicrobial activity of compounds 7a-j

Compd	Gram –positive		Gram-negative		Fungla strains		
	S. pyogenes	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. niger*	*A. clavatus*
7a	100	100	100	200	500	500	1000
7b	200	250	80	100	500	200	300
7c	250	250	200	250	1000	1000	500
7d	60	60	80	80	200	60	125
7e	250	200	100	250	1000	500	500
7f	200	80	250	100	250	500	1000
7g	60	100	100	125	250	200	300
7h	125	100	250	250	1000	1000	300
7i	80	60	60	80	200	80	250
7j	250	250	125	250	300	500	1000
Gentamycin	0.05	1	0.25	0.5	–	–	–
Ampicillin	100	100	250	100	–	–	–
Chloramphenicol	50	50	50	50	–	–	–
Ciprofloxacin	25	25	50	50	–	–	–
Norfloxacin	10	10	10	10	–	–	–
Nystatin	–	–	–	–	100	100	100
Greseofulvin	–	–	–	–	500	100	100

2H, Ar-H), 6.74 (d, 2H, Ar-H), 6.79 (s, 1H, -NH-), 6.93 (d, 1H, Ar-H), 7.32 (d, 1H, Ar-H), 7.45 (s, 1H, Ar-H), 7.63 (t, 1H, Ar-H), 8.23 (d, 2H, Ar-H), 8.27 (s, 1H, Ar-H), 9.97 (s, 1H, -OH); ^{13}C NMR (DMSO-d_6): δ(ppm): 33.52(-CH_2- of 4-thiazolidinone), 49.01(-CH_2- of -CH_2-NH-), 56.11(C of –OCH_3), 72.89(C_4 of 4-thiazolidinone), 114.18(Ar-C), 114.67(Ar-C),115.51(Ar-C),117.91(Ar-C),122.42(Ar-C), 126.74(Ar-C), 130.11(Ar-C of -C-N-), 132.22 (Ar-C), 132.36(Ar-C),132.81(Ar-C), 136.54(Ar-C),139.47(Ar-C of -C-N), 142.44(C_4-sydnone), 144.88(Ar-C of -C-N-), 147.08 (Ar-C of -C-O-), 147.41(Ar-C of -C-O-), 147.92(Ar-C of -C-N-), 168.71(C_4-sydnone), 171.22(>C=O of 4–thiazolidinone); MS *m/z* (rel. int.%): 536.5$(M+1)^+$.

7b: IR: (KBr) ν (cm^{-1}): 3427 (Ar-OH), 3269 (-NH), 2923, 2869, (-CH_2- of Mannich base), 1751 (>C=O of sydnone),1693 (>C=O of 4-thiazolidinone), 1513 (C=C of aromatic), 1528 (asym.), 1349 (sym.) (-NO_2), 1411(bending)(-CH_2- of 4-thiazolidinone), 1257, 1064 (C-O-C of -OCH_3), 1237(-N-C- of tertiary amine of 4-thiazolidinone), 729(-S-C- of 4-thiazolidinone); ^{1}H NMR (DMSO-d_6): δ (ppm): 3.84 (s, 3H, -OCH_3), 4.01 (q, 2H, -CH_2- of thiazolidinone), 4.28 (s, 2H, -CH_2- of Mannich base), 6.43(s, 1H, >CH- of thiazolidinone), 6.67 (d, 2H, Ar-H), 6.73 (d, 2H, Ar-H), 6.74(d, 1H, Ar-H), 6.78 (s, 1H, -NH-), 6.79 (d, 1H, Ar-H), 6.82 (t, 1H, Ar-H), 7.63 (t, 1H, Ar-H), 8.24 (d, 2H, Ar-H), 8.28 (s, 1H, Ar-H), 9.56 (s, 1H, -OH); ^{13}C NMR (DMSO-d_6): δ (ppm): 33.51 (-CH_2- of 4-thiazolidinone), 49.01(-CH_2- of -CH_2-NH-),56.11 (C of -OCH_3),66.72 (C_4 of 4-thiazolidinone), 110.18 (Ar-C), 114.71 (Ar-C), 117.91 (Ar-C), 119.11(Ar-C),120.28(Ar-C), 122.17(Ar-C),126.71 (Ar-C),130.12 (Ar-C of -C-N-),132.21 (Ar-C), 132.31 (Ar-C), 136.51(Ar-C), 139.41 (Ar-C of -C-N),142.42 (C_4-sydnone),144.91 (Ar-C of -C-N-), 145.15 (Ar-C of -C-O-), 147.88 (Ar-C of -C-O-),147.93 (Ar-C of -C-N-),168.73 (C_4-sydnone), 171.22 (>C=O of 4–thiazolidinone); MS *m/z* (rel. int.%): 536.5 $(M+1)^+$.

7c: IR: (KBr) ν (cm^{-1}): 3424 (Ar-OH), 3256 (-NH), 2913, 2859, (-CH_2- of Mannich base), 1742 (>C=O of sydnone), 1681 (>C=O of 4-thiazolidinone), 1503 (C=C of aromatic), 1521 (asym.), 1342 (sym.) (-NO_2), 1403(bending) (-CH_2- of 4-thiazolidinone), 1228(-N-C- of tertiary amine of 4-thiazolidinone), 722(-S-C- of 4-thiazolidinone); ^{1}H NMR (DMSO-d_6): δ (ppm): 4.02 (q, 2H, -CH_2- of thiazolidinone), 4.30 (s, 2H, -CH_2- of Mannich base), 6.41(s, 1H, >CH- of thiazolidinone), 6.64 (d, 2H, Ar-H), 6.71 (d, 2H, Ar-H), 6.79 (s, 1H, -NH-), 6.84 (d, 1H, Ar-H), 6.89 (t, 1H, Ar-H), 7.07 (t, 1H, Ar-H), 7.12 (t, 1H, Ar-H), 7.61 (t, 1H, Ar-H), 8.22 (d, 2H, Ar-H), 8.28 (s, 1H, Ar-H), 9.68 (s, 1H, -OH); ^{13}C NMR (DMSO-d_6):

δ(ppm): 33.52 (-CH_2- of 4-thiazolidinone),49.06 (-CH_2- of -CH_2-NH-),66.41 (C_4 of 4-thiazolidinone), 114.71(Ar-C),115.78 (Ar-C),117.89 (Ar-C),118.12 (Ar-C), 121.19 (Ar-C),126.7(Ar-C),128.0 (Ar-C),128.45 (Ar-C),130.11 (Ar-C of -C-N-),132.21 (Ar-C), 132.29 (Ar-C),136.49 (Ar-C), 139.39 (Ar-C of -C-N),142.40 (C_4-sydnone),144.91 (Ar-C of -C-N),147.89 (Ar-C of -C-N-), 153.67 (Ar-C of -C-O),168.77(C_4-sydnone),171.26 (>C=O of 4-thiazolidinone); MS *m/z* (rel. int.%): 506.4 $(M+1)^+$.

7d: IR: (KBr) ν (cm^{-1}): 3249 (-NH-), 2928, 2845, (-CH_2- of Mannich base), 1761 (>C=O of sydnone), 1689 (>C=O of 4-thiazolidinone),1635, 1519 (C=C of aromatic), 1537 (asym.), 1355 (sym.) (-NO_2) 1411(bending) (-CH_2- of 4-thiazolidinone), 1241(-N-C- of tertiary amine of 4-thiazolidinone), 734(-S-C- of 4-thiazolidinone); ^{1}H NMR (DMSO-d_6): δ (ppm): 4.04 (q, 2H, -CH_2- of thiazolidinone), 4.32 (s, 2H, -CH_2- of Mannich base), 6.43(s, 1H, >CH- of thiazolidinone), 6.65 (d, 2H, Ar-H), 6.73 (d, 2H, Ar-H), 6.79 (s, 1H, -NH-), 7.52 (d, 2H, Ar-H), 7.62 (t, 1H, Ar-H), 8.19 (d, 2H, Ar-H), 8.20 (d, 2H, Ar-H), 8.25 (s, 1H, Ar-H); ^{13}C NMR (DMSO-d_6): δ (ppm): 33.55 (-CH_2- of 4-thiazolidinone), 49.08 (-CH_2- of -CH_2-NH-),72.58 (C_4 of 4-thiazolidinone), 114.67 (Ar-C),117.89 (Ar-C),123.81 (Ar-C),126.74 (Ar-C),129.61 (Ar-C),130.08 (Ar-C of -C-N-),132.22 (Ar-C), 132.27 (Ar-C), 136.51 (Ar-C),139.43 (Ar-C of -C-N),142.41 (C_4-sydnone),144.89 (Ar-C of -C-N-),145.33 (Ar-C),146.31 (Ar-C of -C-N-),147.90 (Ar-C of -C-N-),168.71 (C_4-sydnone),171.19 (>C=O of 4-thiazolidinone); MS *m/z* (rel. int.%): 535.3 $(M+1)^+$.

7e: IR: (KBr) ν (cm-1): 3253 (-NH-), 2919, 2858, (-CH_2- of Mannich base), 1756 (>C=O of sydnone), 1695 (>C=O of 4-thiazolidinone), 1634, 1516 (C=C of aromatic), 1533 (asym.), 1353 (sym.) (-NO_2), 1419(bending) (-CH_2- of 4-thiazolidinone), 1247(-N-C- of tertiary amine of 4-thiazolidinone), 1232, 1031 (C-O-C of methoxy), 734(-S-C- of 4-thiazolidinone);^{1}H NMR (DMSO-d_6): δ (ppm): 3.76(s, 3H,-OCH_3), 3.82 (s, 3H, -OCH_3); 4.02 (q, 2H, -CH_2- of thiazolidinone), 4.31 (s, 2H, -CH_2- of Mannich base), 6.42(s, 1H, >CH- of thiazolidinone), 6.66 (d, 2H, Ar-H), 6.71 (d, 2H,Ar-H), 6.78 (s, 1H, -NH-), 6.86 (d, 1H, Ar-H), 7.53 (d, 1H, Ar-H), 7.61 (t, 1H, Ar-H), 8.22 (d, 2H, Ar-H), 8.27 (s, 2H, Ar-H); ^{13}C NMR (DMSO-d_6): δ(ppm): 33.48 (-CH_2- of 4-thiazolidinone), 49.05 (-CH_2- of -CH_2-NH-), 56.14 (C of -OCH_3), 72.91 (C_4 of 4-thiazolidinone), 112.32 (Ar-C),113.81 (Ar-C), 114.67 (Ar-C), 117.89 (Ar-C),122.02 (Ar-C), 126.66 (Ar-C),130.11 (Ar-C of -C-N-),132.21 (Ar-C),132.31 (Ar-C),132.52 (Ar-C),136.48 (Ar-C), 139.39 (Ar-C of -C-N), 142.44 (C_4-sydnone), 144.87 (Ar-C of -C-N-),147.94 (Ar-C of -C-N-),148.22 (Ar-C of -C-O-), 149.71(Ar-C of -C-O-), 168.70(C_4-sydnone), 171.23(>C=O of 4-thiazolidinone); MS *m/z* (rel. int.%): 550.2 $(M+1)^+$.

7f: IR: (KBr) ν (cm^{-1}): 3254 (-NH-), 2969, 2835 (-CH_2- of Mannich base), 1747 (>C=O of sydnone), 1687 (>C=O of 4-thiazolidinone), 1519 (asym.), 1355 (sym.) (-NO_2), 1411(bending) (-CH_2- of 4-thiazolidinone), 1239(-N-C- of tertiary amine of 4-thiazolidinone), 1228, 1036 (C-O-C of methoxy), 723(-S-C- of 4-thiazolidinone); ^{1}H NMR (DMSO-d_6): δ (ppm): 3.82 (s, 3H, 2-OCH_3), 4.01 (q, 2H, -CH_2- of thiazolidinone), 4.33 (s, 2H, -CH_2- of Mannich base), 6.44(s, 1H, >CH- of thiazolidinone), 6.64 (d, 2H, Ar-H), 6.72 (d, 2H, Ar-H), 6.79 (s, 1H, -NH-), 6.88 (d, 2H, Ar-H), 7.60 (t, 1H, Ar-H), 7.84 (d, 2H, Ar-H), 8.21 (d, 2H, Ar-H), 8.25 (s, 1H, Ar-H);^{13}C NMR x (Ar-C of -C-N), 142.39 (C_4-sydnone),144.89 (Ar-C of -C-N-),147.88 (Ar-C of -C-N-),168.73 (C_4-sydnone),171.20 (>C=O of 4–thiazolidinone); MS *m/z* (rel. int.%): 524 $(M+1)^+$.

7i: IR: (KBr) ν (cm^{-1}): 3251(-NH-), 2963, 2852 (-CH_2- of Mannich base), 1739 (>C=O of sydnone), 1699 (>C=O of 4-thiazolidinone),1556 (asym.), 1363 (sym.) (-NO_2), 1422(bending) (-CH_2- of 4-thiazolidinone),1245 (-N-C- of tertiary amine of 4-thiazolidinone), 781 (C-Cl), 736(-S-C- of 4-thiazolidinone); ^{1}H NMR (DMSO-d_6): δ (ppm): 4.04 (q, 2H, -CH_2- of thiazolidinone), 4.33 (s, 2H, -CH_2- of Mannich base), 6.43(s, 1H, >CH- of thiazolidinone), 6.65 (d, 2H, Ar-H), 6.72 (d, 2H, Ar-H), 6.78 (s, 1H, -NH-), 7.22 (d, 2H, Ar-H),7.38 (d, 2H, Ar-H), 7.62 (t, 1H, Ar-H), 8.22 (d, 2H, Ar-H), 8.27 (s, 1H, Ar-H); ^{13}C NMR (DMSO-d_6): δ (ppm): 33.47 (-CH_2- of 4-thiazolidinone),49.01(-CH_2- of -CH_2-NH-), 72.56 (C_4 of 4-thiazolidinone),114.71 (Ar–C), 117.88 (Ar–C),126.71 (Ar-C), 128.72(Ar-C),130.11 (Ar-C), 130.08 (Ar-C of -C-N-),132.20 (Ar-C),132.26 (Ar-C),132.71 (C of -C-Cl),137.31(Ar-C),136.54 (Ar-C),139.42 (Ar-C of -C-N), 142.37 (C_4-sydnone), 144.90 (Ar-C of -C-N-), 147.92 (Ar-C of -C-N-), 168.70 (C_4-sydnone),171.21 (>C=O of 4-thiazolidinone); MS *m/z* (rel. int.%): 524$(M+1)^+$.

7j: IR: (KBr) ν (cm^{-1}): 3236(-NH-), 2952, 2829 (-CH_2- of Mannich base), 1739 (>C=O of sydnone),

1702 (>C=O of 4-thiazolidinone), 1553 (asym.), 1341 (sym.) (-NO_2), 1425(bending) (-CH_2- of 4-thiazolidinone), 1241(-N-C- of tertiary amine of 4-thiazolidinone),1168 (C-F), 739(-S-C- of 4-thiazolidinone); ^{1}H NMR (DMSO-d_6): δ (ppm): 4.01 (q, 2H, -CH_2- of thiazolidinone), 4.31 (s, 2H, -CH_2- of Mannich base), 6.42(s, 1H, >CH- of 4-thiazolidinone), 6.66 (d, 2H, Ar-H), 6.73 (d, 2H, Ar-H), 6.77 (s, 1H, -NH-), 7.11 (t, 1H, Ar-H), 7.27(d, 1H, Ar-H), 7.64 (d, 2H, Ar-H), 7.61 (t, 1H, Ar-H), 7.72 (t, 1H, Ar-H), 8.21 (d, 2H, Ar-H), 8.28 (s, 1H, Ar-H); ^{13}C NMR (DMSO-d_6): δ(ppm): 33.49 (-CH_2- of 4-thiazolidinone), 49.01 (-CH_2- of -CH_2-NH-),65.81 (C_4 of 4-thiazolidinone), 101.81 (Ar-C), 114.67 (Ar-C), 115.42 (Ar-C), 117.87 (Ar-C), 124.19 (Ar-C), 126.68 (Ar-C),128.73 (Ar-C),130.09 (Ar-C of -C-N-), 130.26 (Ar-C),132.22 (Ar-C),132.31 (Ar-C),136.52 (Ar-C),139.41 (Ar-C of -C-N),142.43(C_4-sydnone),144.91 (Ar-C of -C-N-),147.88 (Ar-C of -C-N-),161.23 (Ar-C of -C-F), 168.66(C_4-sydnone),171.21 (>C=O of 4-thiazolidinone); MS *m/z* (rel. int.%): 508.5 $(M+1)^+$.

Antimicrobial Activity

Control of microbial population is necessary to prevent transmission of disease, infection, decomposition, contamination and spoilage caused by them. This was one of the purposes of our present work. The synthesized compounds were screened for their *in vitro* antibacterial activity against Gram positive and Gram negative bacterial strains, compounds were also screened for their *in vitro* antifungal activity. Gram positive bacteria viz., *Staphylococcus aureus, Streptococcus pyogenes,* gram negative bacteria viz., *Escherichia coli* and *Pseudomonas aeruginosa* were used in this assay. Gentamycin, Ampicillin, Chloramphenicol, Ciprofloxacin and Norfloxacin were used as standard antimicrobial compounds. The antifungal activity was screened *in vitro* against pathogenic yeast, *Candida albicans,* and moulds like *Aspergillus niger* and *Aspergillus clavatus.* Antifungal compounds, Nystatin and Griseofulvin, were used as standard. The investigation was carried out by Minimum Inhibitory Concentration (MIC) by Broth Dilution Method.

Compound 7_d (R=4-NO_2) and 7_i (R = 4 -Cl) showed excellent activity against all bacterial strains and *A. niger*. Compound 7_g (R=4-CH_3) is more active against *S. pyogenes*. Compound 7_f (R=4-OCH_3) is most active against Gram positive bacteria *S. aureus*, Compound7_b(R=3-OCH_3, 2-OH) is highly active against Gram negative bacterial strain viz., *E. coli*. All other compounds were showed moderate to good activity and some are inactive against all strains.

Acknowledgement

The authors would like to express their gratitude to the Department of Chemistry, Veer Narmad South Gujarat University, Surat for providing basic research facilities. The authors wish to thank to UGC-BSR-SAP for financial assistance.

References

1 Baker W & Ollis W D, *Quart Rev Chem Soc,* 11 (1957**)** 15.
2 Ollis W D & Ramsden C A, *Advances in Heterocyclic Chemistry,* (Academic Press, New York) 1976, pp.3.
3 Brookes P & Walker J, *J Chem Soc*, (1957) 4409.
4 Thanh N D, Duc H T, Duyen V T, Tuonq P M & Quoc N V, *Chem Cent J,* 9 (2015) 60.
5 Tegginamath G, Kamble mailto:kamchem9@gmail.comR R, Taj T, Kattimani P P & Meti G Y, *Med Chem Res,* 22 (2013) 4367.
6 Dunkley C S & Thoman C J, *Bioorg Med Chem Lett*, 13 (2003) 2899.
7 Bansode S & Kamble R, *Med Chem Res*, 21 (2012) 867.
8 Nyberg W H & Cheng C C, *J Med Chem*, 8 (1965) 531.
9 Wagner H & Hill J B, *J Med Chem*, 17 (1974) 1337.
10 Jagadeesh K & Revankar S P, *Int J Sci Appl Res*, 2(7) (2015) 11.
11 Kalluraya B, Rahiman M A & Banji D, *Indian J Chem*, 41B (2002) 1712.
12 Shih M H & Ke F Y, *Bioorg Med Chem*, 12 (2004) 4633.
13 Yeh M-Y, Tien H-J, Chou J T & Nonaka T, *Bull Chem Soc Japan*, 54 (1981) 947.
14 Rahiman M A & Kalluraya B, *J Ind Council Chem*, 25 (2008) 10.
15 Savaliya P P, Akbari V K, Modi J A & Patel K C, *Med Chem Res*, 22 (2013) 5789.
16 Akbari V K, Chothani N J, Patel Y M & Patel K C, *Indian J Chem*, 54B (2015) 93.
17 Baboo P, Gautam G & Gupta S K, *Int Res J Pharm*, 8 (2017) 121
18 Joshi P, Mahajan D & Chejaraa D, *Indian J Chem*, 59B (2020) 710.
19 Vigorita M, Ottana R, Monforte F, Maccari R, Trovato A, Monforte M T & Taivano M F, *Bioorg Med Chem Lett*, 11 (2001) 2791.
20 Mistry B M & Jauhari, *Med Chem Res*, 22 (2013) 647.
21 Pathak R B, Chovatia P T & Parekh H H, *Bioorg Med Chem Lett*, 22(15) (2012) 5129.
22 Capan G, Ulusoy N, Ergenc N, Ekinci A C & Vidin A, *Farmaco*, 51 (1996) 729.
23 Barbosa V A, Barea P, Mazia R S, Ueda-Nakamura T, da Costa W F, Foglio M A, Ruiz A L T G, de Carvalho J E,

Vendramini-Costa D B, Nakamura C V & Sarragitto M H, *Eur J Med Chem*, 29 (2016) 1093.

24 Kumar D, Kumar V, Mundlia J, Pradhan D & Malik S, *Cent Nerv Syst Agents Med Chem,*15 (2015) 23-27.

25 Atta-Allah S R, Nassar I F & El-Sayed W A, *J Pharmacol Ther Res,* 5 (2020) 1.

26 Ilkiv I, Lesyk R & Sklyarov O, *J Appl Pharm Sci,* 7 (2017) 199.

27 Holota S, Kryshchyshyn A, Derkach H, Trufin Y, Demchuk I, Gzella A, Grellier P & Lesyk R, *Bioorg Chem*, 86 (2019) 126.