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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and antimicrobial screening of 4-thiazolidinone and 2-azetidinone derivatives of piperazine

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Abstract The Schiff's bases **3a–3h** were synthesized by reacting substituted/unsubstituted aromatic aldehydes **2a–2h** with 1-(2-aminoethyl)-piperazine **1.** A series of novel aryl-3-(2-piperazin-1-ylethyl)-1,3-thiazolidin-4-one **4a–4h** and 3-chloro-1-{2-[4-(chloroacetyl)piperazin-1-yl]ethyl}-4-arylazetidin-2-one **5a–5h** were synthesized from the Schiff's bases of 1-(2-aminoethyl)-piperazine **3a–3h.** The structures of synthesized compounds were confirmed by analytical (C, H, and N) and spectral (FT-IR, ^{1}H NMR, ^{13}C NMR, and Mass) data. The compounds **4a–4h** and **5a–5h** were screened for antimicrobial activity. The compounds **4a**, **4d**, **4f**, **4g**, **5a**, **5d**, **5f**, and **5g** exhibited substantially significant antibacterial as well as antifungal activity.

Keywords Piperazine · Schiff bases · 4-Thiazolidinone · 2-Azetidinone · Antimicrobial activity

Introduction

Piperazine and substituted piperazine derivatives have been found to possess diverse biological activities like antimicrobial (Chandra *et al.*, 2006; Chaudhary *et al.*, 2006; Foroumadi *et al.*, 2006, 2007; Tomar *et al.*, 2007), antiplasmodial (Cunico *et al.*, 2009; Martyn *et al.*, 2010; Ryckebusch *et al.*, 2003, 2005), anti-inflammatory (Papadopoulou *et al.*, 2005), antioxidant (Kimura *et al.*, 2004), antihistaminic (Choo *et al.*, 1999; Terzioglu *et al.*, 2004; Yoo *et al.*, 2010), and antipsychotic activity (Bali *et al.*, 2009, 2010). The penicillins and cephalosporins are widely used therapeutic agents against bacterial infection and diseases. The antimicrobial activity of these compounds is mainly associated with the β-lactam ring. They inhibit the cell wall synthesis by binding with membrane-bound bacterial transpeptidase, also known as penicillin binding proteins (PBP's). The 2-azetidinones possess β-lactamase inhibitory activity and hence became an attractive nucleus for development of new antimicrobial agents. Numerous 2-azetidinone derivatives were reported to exhibit antibacterial and antifungal activity (Arnould *et al.*, 1992; Halve *et al.*, 2007; Keri *et al.*, 2009). The 4-thiazolidinones are of great interest in diverse areas of medicinal chemistry because of their different pharmacological activities like antimicrobial (Vicini *et al.*, 2008), anti-HIV (Chen *et al.*, 2009; Rao *et al.*, 2004; Rawal *et al.*, 2005), anticancer (Abdel-Aziz *et al.*, 2010; Lv *et al.*, 2010) and antihypertensive activity (Bhandari *et al.*, 2009).

Microbial infections are now a days more common than during the first half of the century. Although, a number of different classes of antibacterial and antifungal agents have been discovered during last two decades the use is limited due to development of microbial resistance. This situation highlights the need for development of novel, potent, and safe antimicrobial agents. Therefore, in continuation of our studies on synthesis of 4-thiazolidinone and 2-azetidinone heterocycles (Shingade *et al.*, 2011), we were interested to synthesize 4-thiazolidinone and 2-azetidinone derivatives of piperazine with a view to find the antimicrobial efficacy.

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Results and discussion

Chemistry

The synthetic routes of compounds are outlined in Scheme 1. The 1-(2-aminoethyl)-piperazine **1** was condensed with different substituted/unsubstituted aromatic aldehydes **2a–2h** in acetonitrile yielded the corresponding Schiff bases **3a–3h**. The Schiff bases **3a–3h**, undergoes cyclization with thioglycolic acid in the presence of anhydrous $ZnCl_2$ to afford aryl-3-(2-piperazin-1-ylethyl)-1,3-thiazolidin-4-one **4a–4h.** The compound 3-chloro-1-{2-[4-(chloroacetyl)piperazin-1-yl]ethyl}-4-arylazetidin-2-one **5a–5h** were obtained by cyclization of Schiff's bases **3a–3h** with chloroacetyl chloride in the presence of triethylamine (Et_3N). The thiazolidi-4-ones and azetidi-2-ones were formed by cycloaddition mechanism (Soleiman, 2011).

The formation of Schiff bases **3a–3h** were confirmed by the presence of a band at 1,638–1,650 cm^{-1} for (N=CH) in the IR spectrum, appearance of a singlet between δ 8.4–8.8 for one proton of (N=CH) in the ^1H NMR spectra and a peak at δ 160.7–163.9 for one carbon of (N=CH) in the ^{13}C NMR spectra.

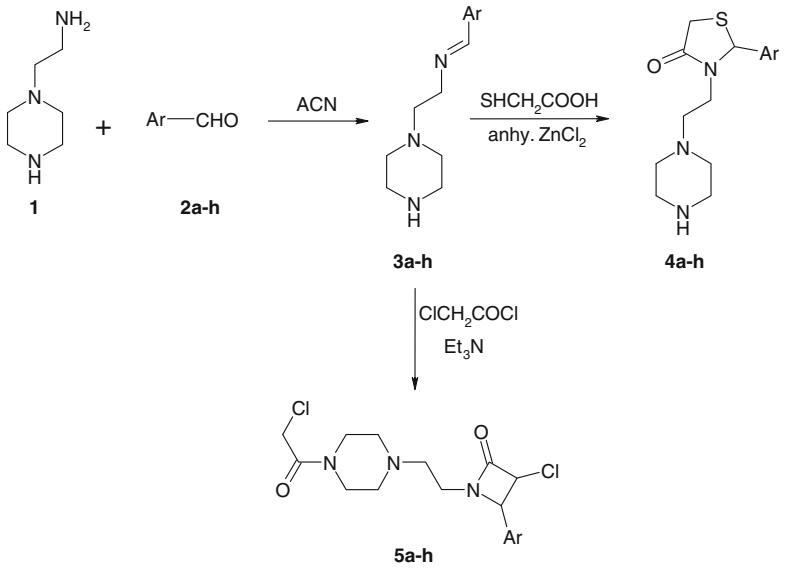
The appearance of band between 1,700 and 1,733 cm^{-1} for (C=O β-thialactam), singlets at δ 3.25–3.9 for two protons of (CH_2 of thiazolidinone ring) and at δ 5.0–5.5 for one proton of (CH–Ar) and peaks at δ 31.7–34.5 for one carbon of (CH_2 of thiazolidinone ring), at δ 52.5–63.7 for one carbon of (–CH–Ar), and at δ 171–171.3 for one carbon of (C=O β-thialactam) in IR, ^1H NMR, and ^{13}C NMR spectra, respectively, confirmed the formation of 4-thiazolidinone derivatives **4a–4h**. The formation of 2-azetidinone derivatives **5a–5h** was evidenced by the appearance of a band at 1,720–1,740 cm^{-1} for (C=O β-lactam), 1,700–1,710 cm^{-1} for (C=O), and 735–760 cm^{-1} for (C–Cl) in IR spectra. The formation of 2-azetidinone derivatives **5a–5h** was also supported by the presence of singlet at δ 4.12–4.78 for one proton of (CH–Cl) and a singlet at δ 5.4–5.6 for one proton of (CH–Ar) in ^1H NMR spectra and peaks at δ 60.7–62.8 for one carbon of (CH–Cl), δ 54.2–61.2 for one carbon of (CH–Ar), and at δ 166–166.7 for one carbon of (C=O β-lactam) in ^{13}C NMR spectra.

Antimicrobial activity

All the synthesized compounds were screened for their possible antibacterial and antifungal activities by determining MIC values in μg mL^{-1} against selected strains. The MIC values were determined by broth dilution method (Srinivas *et al.*, 2006). The antibacterial and antifungal activities (MIC) were determined using Ciprofloxacin and Clotrimazole as standard control and the results are presented in Tables 1 and 2, respectively. The MIC values of **12** derivatives against tested organisms exhibited significant activity with a degree of variation. The compound **4a**, **4d**, **4f**, **4g**, **5a**, **5d**, **5f,** and **5g** exhibited substantially significant activity. The compound **4c**, **4e**, **5c,** and **5e** showed significant activity, while compound **4b**, **4h**, **5b,** and **5h** are found to be inactive against all screened strains of bacteria and fungi.

Conclusion

In the present study, we report a simple and highly effective method for synthesis of Schiff bases from 1-(2-aminoethyl)-piperazine, while the 4-thiazolidinones and 2-azetidinones were synthesized by conventional methods



Scheme 1 *a* 3-hydroxy-4-methoxyphenyl, *b* 2-hydroxyphenyl, *c* 3-hydroxyphenyl, *d* 4-hydroxyphenyl, *e* phenyl, *f* 4-hydroxy-3-methoxyphenyl, *g* 4-methoxyphenyl, and *h* 2-furan

Table 1 Antibacterial activity of the compounds: MIC in μg mL^{-1}

Comp. code	Name of microorganism (MIC in μg mL^{-1})												
	B. subtilis	*S. epidermidis*	*M. luteus*	*S. aureus*	*S. hominis*	*B. pumilus*	*B. cereus*	*P. vulgaris*	*P. mirabilis*	*S. typhi*	*K. pneumonia*	*E. coli*	*P. aeruginosa*
4a	9.37	9.37	9.37	9.37	9.37	9.37	4.68	9.37	9.37	9.37	4.68	9.37	9.37
4b	75	75	150	150	75	150	75	150	150	75	75	75	75
4c	37.5	18.75	18.75	37.5	37.5	37.5	18.75	37.5	18.75	18.75	37.5	37.5	37.5
4d	4.68	9.37	9.37	9.37	9.37	9.37	9.37	4.68	9.37	9.37	9.37	4.68	9.37
4e	37.5	75	75	37.5	37.5	75	37.5	18.75	37.5	18.75	37.5	37.5	37.5
4f	9.37	9.37	4.68	9.37	9.37	9.37	9.37	9.37	9.37	9.37	9.37	9.37	9.37
4g	9.37	9.37	9.37	9.37	4.68	9.37	4.68	9.37	9.37	4.68	9.37	9.37	9.37
4h	75	300	75	150	75	150	150	150	150	75	150	75	75
5a	4.68	9.37	4.68	9.37	9.37	9.37	9.37	9.37	9.37	4.68	9.37	9.37	9.37
5b	150	150	75	75	150	75	150	75	75	75	150	150	75
5c	18.75	18.75	18.75	37.5	37.5	37.5	37.5	18.75	37.5	37.5	37.5	18.75	37.5
5d	9.37	9.37	9.37	9.37	9.37	9.37	9.37	4.68	9.37	9.37	9.37	4.68	9.37
5e	75	37.5	18.75	18.75	37.5	18.75	18.75	37.5	18.75	37.5	37.5	37.5	18.75
5f	9.37	9.37	4.68	9.37	9.37	9.37	9.37	9.37	9.37	4.68	9.37	9.37	4.68
5g	9.37	4.68	9.37	9.37	4.68	9.37	9.37	9.37	9.37	9.37	9.37	4.68	9.37
5h	150	75	150	150	75	75	75	75	150	150	75	75	150
Standard[a]	2.34	2.34	2.34	2.34	2.34	2.34	2.34	2.34	2.34	2.34	2.34	2.34	2.34

MIC minimum inhibitory concentration

[a] Ciprofloxacin

Table 2 Antifungal activity of the compounds: MIC in μg mL^{-1}

Comp. code	Name of microorganism (MIC in μg mL^{-1})										
	A. niger	*A. awamori*	*C. albicans*	*A. alternate*	*M. canis*	*R. solani*	*T. longiformis*	*F. solani*	*T. viride*	*A. flavus*	*A. fumigatus*
4a	18.75	9.37	9.37	18.75	9.37	9.37	18.75	18.75	18.75	9.37	9.37
4b	300	300	150	150	300	150	300	300	300	150	150
4c	37.5	37.5	37.5	75	37.5	37.5	37.5	75	37.5	37.5	37.5
4d	18.75	18.75	9.73	18.75	18.75	18.75	9.73	9.73	18.75	18.75	9.37
4e	75	75	37.5	75	37.5	37.5	75	37.5	75	75	37.5
4f	9.73	9.73	18.75	9.73	18.75	18.75	9.73	9.73	18.75	18.75	18.75
4g	18.75	9.73	9.73	18.75	18.75	9.73	18.75	18.75	9.73	18.75	9.73
4h	300	150	300	300	300	150	300	300	150	150	150
5a	18.75	18.75	18.75	9.73	18.75	18.75	9.73	18.75	18.75	18.75	18.75
5b	300	300	300	300	300	300	300	300	300	300	300
5c	37.5	75	37.5	37.5	75	37.5	75	37.5	37.5	75	75
5d	9.37	9.37	18.75	18.75	9.37	9.37	18.75	18.75	9.37	9.37	9.37
5e	75	75	75	37.5	75	75	37.5	75	75	75	75
5f	18.75	18.75	9.37	18.75	18.75	9.37	9.37	18.75	18.75	9.37	18.75
5g	18.75	9.37	18.75	9.37	18.75	9.37	9.37	18.75	18.75	9.37	9.37
5h	150	150	300	150	150	300	300	150	300	300	300
Standard[a]	2.34	4.68	2.34	1.17	4.68	2.34	4.68	4.68	2.34	2.34	4.68

MIC minimum inhibitory concentration

[a] Clotrimazole

reported previously. The activity data revealed that the compounds **4a**, **4d**, **4f**, **4g**, **5a**, **5d**, **5f**, and **5g** having electron releasing substitution at 4th position of the phenyl ring exhibit good antibacterial as well as antifungal activity. The compounds **4c** and **5c** were having electron releasing substituents at 3rd position of the phenyl ring and the compounds **4e** and **5e** having phenyl ring exhibit decreased but moderate activity. The compounds **4b**, **4h**, **5b,** and **5h** possessing electron releasing substituents at 2nd position of phenyl ring and heterocyclic ring are found to be inactive. In conclusion, the electron releasing substituent at the 4th position may enhance activity, while the same substituent at 3rd position may decrease the activity slightly. The electron releasing substituent at 2nd position may completely decrease the antimicrobial activity.

Experimental protocols

General

The 1-(2-aminoethyl)-piperazine was procured from Sigma Aldrich, India. All other reagents and solvents used in study are of analytical grade and have been procured locally. The progress of the reaction is monitored by TLC and the products are purified through recrystallization. The melting points (m.p.) were determined in one-end-open capillary method and are uncorrected. IR spectra were recorded on Shimadzu FT-IR 8400-S spectrophotometer using potassium bromide (KBr) pellet. The ^{1}H NMR spectra were acquired on Varian AMX 300 NMR instrument using D_2O or DMSO-d_6 as the solvent and TMS as the internal reference (chemical shifts in δ, ppm); ^{13}C NMR was performed on Varian AMX 300 (100 MHz) spectrometer using solutions in D_2O or DMSO-d_6 and mass spectra were acquired on API 2000 spectrometer. The elemental analysis (C, H, and N) of compounds was performed on Elementar Vario EL III elemental analyzer.

General procedure for synthesis of *N*-(arylmethylidene)-2-piperazin-1-ylethanamine (**3a–h**)

Equimolar quantities of 1-(2-aminoethyl)-piperazine (**1**, 0.1 mol) and the substituted/unsubstituted aromatic aldehydes (**2a–2h**, 0.1 mol) in acetonitrile were stirred for half an hour. The product thus obtained was filtrated and purified by washing with acetonitrile to afford compounds (**3a–h**).

*2-Methoxy-5-{[(2-piperazin-1-ylethyl)imino]methyl}phenol (**3a**)*

Yield 89 %; m. p. 158 °C. IR (KBr, cm^{-1}): 3390 (OH), 3225 (NH), 3043 (CH aromatic), 2962 (CH aliphatic), 2825 (CH aliphatic), 1640 (C=N), 1249 (C–O–C); ^{1}H NMR (D_2O) δ in ppm: 2.0 (s, 1H), 2.3–2.4 (t, 4H), 2.6–2.7 (m, 4H), 2.8–2.9 (t, 2H), 3.6–3.7 (t, 2H), 3.9 (s, 3H), 7.2–7.3 (m, 2H), 7.4 (s, 1H), 8.7 (s, 1H), 9.8 (s, 1H); ^{13}C NMR (D_2O) δ in ppm: 160.9, 152.4, 147.2, 133.9, 123.0, 115.1, 112.3, 59.7, 57.2, 54.9, 52.7, 45.9. Anal. Calcd. for $C_{14}H_{21}N_3O_2$: C: 63.85, H: 8.04, N: 15.96; Found: C: 63.10, H: 7.85, N: 16.09 %.

*2-{[(2-Piperazin-1-ylethyl)imino]methyl}phenol (**3b**)*

Yield 78 %; m. p. 130 °C. IR (KBr, cm^{-1}): 3390 (OH), 3267 (NH), 2958 (CH aromatic), 2837 (CH aliphatic), 2735 (CH aliphatic), 1635 (C=N); ^{1}H NMR (D_2O) δ in ppm: 1.9 (s, 1H), 2.3–2.4 (t, 4H), 2.6–2.7 (m, 6H), 3.6–3.7 (t, 2H), 7.1–7.2 (m, 2H), 7.5–7.6 (t, 1H), 7.7–7.8 (d, 1H), 8.5 (s, 1H), 11.2 (s, 1H); ^{13}C NMR (D_2O) δ in ppm: 161.3, 157.7, 132.9, 131.0, 124.6, 121.5, 117.8, 59.5, 54.6, 52.7, 46.2. Anal. Calcd. for $C_{13}H_{19}N_3O$: C: 66.92, H: 8.21, N: 18.01; Found: C: 67.08, H: 8.15, N: 17.60 %.

*3-{[(2-Piperazin-1-ylethyl)imino]methyl}phenol (**3c**)*

Yield 85 %; m. p. 180–182 °C. IR (KBr, cm^{-1}): 3390 (OH), 3215 (NH), 3055 (CH aromatic), 2821 (CH aliphatic), 2673 (CH aliphatic), 1640 (C=N); ^{1}H NMR (D_2O) δ in ppm: 2.0 (s, 1H), 2.35–2.5 (t, 4H), 2.7–2.9 (m, 6H), 3.7–3.8 (t, 2H), 7.0–7.1 (d, 1H), 7.3–7.45 (m, 2H), 7.62 (s, 1H), 8.72 (s, 1H), 9.47 (s, 1H); ^{13}C NMR (D_2O) δ in ppm: 160.8, 158.4, 141.0, 130.2, 121.9, 118.3, 114.9, 59.6, 54.9, 52.8, 46.2. Anal. Calcd. for $C_{13}H_{19}N_3O$: C: 66.92, H: 8.21, N: 18.01; Found: C: 66.97, H: 8.19, N: 17.90 %.

*4-{[(2-Piperazin-1-ylethyl)imino]methyl}phenol (**3d**)*

Yield 92 %; m. p. 162 °C. IR (KBr, cm^{-1}): 3400 (OH), 3200 (NH), 3010 (CH aromatic), 2860 (CH aliphatic), 2845 (CH aliphatic), 1638 (C=N); ^{1}H NMR (D_2O) δ in ppm: 1.9 (s, 1H), 2.3–2.4 (t, 4H), 2.6–2.7 (m, 6H), 3.6–3.7 (t, 2H), 6.76–6.9 (d, 2H), 7.6–7.8 (d, 2H), 8.7 (s, 1H), 10.2 (s, 1H); ^{13}C NMR (D_2O) δ in ppm: 162.1, 160.5, 130.8, 129.1, 116.0, 59.8, 55.2, 53.5, 46.3. Anal. Calcd. for $C_{13}H_{19}N_3O$: C: 66.92, H: 8.21, N: 18.01; Found: C: 67.00, H: 7.93, N: 18.10 %.

*N-[phenylmethylidene]-2-piperazin-1-ylethanamine (**3e**)*

Yield 88 %; m. p. 170–172 °C. IR (KBr, cm^{-1}): 3200 (NH), 3012 (CH aromatic), 2924 (CH aliphatic), 2850 (CH aliphatic), 1639 (C=N); ^{1}H NMR (D_2O) δ in ppm: 2.0 (s, 1H), 2.35–2.5 (t, 4H), 2.6–2.8 (m, 6H), 3.6–3.75 (t, 2H), 7.37–7.48 (t, 2H), 7.6–7.72 (t, 1H), 7.9–8.0 (d, 2H), 8.8 (s, 1H); ^{13}C NMR (D_2O) δ in ppm: 160.9, 136.4, 132.1, 130.5,

128.7, 59.6, 54.8, 53.1, 46.5. Anal. Calcd. for $C_{13}H_{19}N_3$: C: 71.85, H: 8.81, N: 19.34; Found: C: 71.60, H: 8.50, N: 19.60 %.

*2-Methoxy-4-{[(2-piperazin-1-ylethyl)imino]methyl}phenol (**3f**)*

Yield 75 %; m. p. 148 °C. IR (KBr, cm^{-1}): 3400 (OH), 3225 (NH), 3043 (CH aromatic), 2962 (CH aliphatic), 2825 (CH aliphatic), 1640 (C=N), 1270 (C–O–C); ^{1}H NMR (D_2O) δ in ppm: 2.0 (s, 1H), 2.3–2.4 (t, 4H), 2.6–2.7 (m, 4H), 2.8–2.9 (t, 2H), 3.6–3.7 (t, 2H), 3.9 (s, 3H), 7.15–7.27 (d, 2H), 7.52 (s, 1H), 8.7 (s, 1H), 11.3 (s, 1H); ^{13}C NMR (D_2O) δ in ppm: 160.7, 151.2, 149.5, 133.5, 122.9, 117.3, 112.2, 59.3, 57.4, 55.1, 53.3, 46.4. Anal. Calcd. for $C_{14}H_{21}N_3O_2$: C: 63.85, H: 8.04, N: 15.96; Found: C: 63.56, H: 7.94, N: 16.10 %.

*N-[(4-methoxyphenyl)methylidene]-2-piperazin-1-ylethanamine (**3g**)*

B. P. 210 °C. IR (KBr, cm^{-1}): 3275 (NH), 3072 (CH aromatic), 2955 (CH aliphatic), 2839 (CH aliphatic), 1645 (C=N), 1253 (C–O–C); ^{1}H NMR (D_2O) δ in ppm: 1.9 (s, 1H), 2.3–2.4 (t, 4H), 2.5–2.72 (m, 6H), 3.4–3.52 (t, 2H), 3.9 (s, 3H), 7.55–7.65 (d, 2H), 7.8–7.9 (d, 2H), 8.8 (s, 1H); ^{13}C NMR (D_2O) δ in ppm: 162.7, 160.8, 130.2, 128.3, 114.5, 59.2, 56.9, 55.0, 53.1, 46.2. Anal. Calcd. for $C_{14}H_{21}N_3O$: C: 67.98, H: 8.56, N: 16.99; Found: C: 68.15, H: 8.35, N: 16.88 %.

*N-[furan-2-ylmethylidene]-2-piperazin-1-ylethanamine (**3h**)*

B. P. 178 °C. IR (KBr, cm^{-1}): 3270 (NH), 3020 (CH aromatic), 2935 (CH aliphatic), 2812 (CH aliphatic), 1650 (C=N), 1155 (C–O–C); ^{1}H NMR (D_2O) δ in ppm: 1.9 (s, 1H), 2.3–2.4 (t, 4H), 2.5–2.72 (m, 6H), 3.4–3.52 (t, 2H), 6.5–6.65 (t, 1H), 6.9–7.02 (d, 1H), 7.7–7.8 (d, 1H), 8.4 (s, 1H); ^{13}C NMR (D_2O) δ in ppm: 163.9, 149.2, 144.5, 119.0, 112.4, 59.2, 54.8, 50.7, 46.6. Anal. Calcd. for $C_{11}H_{17}N_3O$: C: 63.74, H: 8.27, N: 20.27; Found: C: 63.83, H: 7.90, N: 20.10 %.

Synthesis of 2-aryl-3-(2-piperazin-1-ylethyl)-1,3-thiazolidin-4-one (**4a–h**) (Shingade *et al.*, 2011)

*2-(3-Hydroxy-4-methoxyphenyl)-3-(2-piperazin-1-ylethyl)-1,3-thiazolidin-4-one (**4a**)*

Yield 73 % (ethanol); m. p. 185 °C. IR (KBr, cm^{-1}): 3390 (OH), 3225 (NH), 3043 (CH aromatic), 2962 (CH aliphatic), 2825 (CH aliphatic), 1733 (C=O), 1271 (C–O–C), 710 (C–S–C); ^{1}H NMR ($DMSOd_6$) δ in ppm: 1.9–2.1 (s, 1H), 2.3–2.4 (t, 4H), 2.6–2.76 (m, 4H), 2.8–2.9 (t, 2H), 3.25 (s, 2H), 3.6–3.7 (t, 2H), 3.9 (s, 3H), 5.4 (s, 1H), 6.85–6.95 (s, 1H), 7.3–7.4 (m, 2H), 9.83 (s, 1H); ^{13}C NMR ($DMSOd_6$) δ in ppm: 171.2, 148.5, 147.0, 132.8, 122.1, 114.9, 112.7, 63.7, 55.8, 54.2, 46.3, 42.2, 36.9, 33.9. Anal. Calcd. For $C_{16}H_{23}N_3O_3S$: C: 56.95, H 6.87, N 12.45, S 9.50; Found: C: 56.87, H 6.95, N 12.56, S 9.43 %. MS: $[M]^+$ at *m/z* 337.

*2-(2-Hydroxyphenyl)-3-(2-piperazin-1-ylethyl)-1,3-thiazolidin-4-one (**4b**)*

Yield 68 % (ethanol); m. p. 284–285 °C. IR (KBr, cm^{-1}): 3400 (OH), 3200 (NH), 2958 (CH aromatic), 2837 (CH aliphatic), 2735 (CH aliphatic), 1728 (C=O), 700 (C–S–C); ^{1}H NMR ($DMSOd_6$) δ in ppm: 1.85–2.0 (s, 1H), 2.3–2.4 (t, 4H), 2.6–2.73 (m, 6H), 3.25–3.3 (s, 2H), 3.6–3.7 (t, 2H), 5.3 (s, 1H), 7.05–7.2 (m, 2H), 7.5-7.6 (t, 1H), 7.68–7.78 (d, 1H), 11.2 (s, 1H); ^{13}C NMR ($DMSOd_6$) δ in ppm: 171.2, 153.8, 130.1, 128.6, 124.2, 121.3, 116.1, 54.9, 52.5, 46.4, 42.2, 36.8, 33.9. Anal. Calcd. For $C_{15}H_{21}N_3O_2S$: C: 58.61, H 6.89, N 13.67, S 10.43; Found: C: 58.67, H 7.05, N 13.59, S 10.36 %. MS: $[M]^+$ at *m/z* 307.

*2-(3-Hydroxyphenyl)-3-(2-piperazin-1-ylethyl)-1,3-thiazolidin-4-one (**4c**)*

Yield 86 % (methanol); m. p. 158 °C. IR (KBr, cm^{-1}): 3390 (OH), 3215 (NH), 3055 (CH aromatic), 2943 (CH aliphatic), 2821 (CH aliphatic), 1700 (C=O), 680 (C–S–C); ^{1}H NMR ($DMSOd_6$) δ in ppm: 1.95–2.1 (s, 1H), 2.3–2.45 (t, 4H), 2.7–2.9 (m, 6H), 3.35–3.45 (t, 2H), 3.7 (s, 2H), 7.02–7.1 (d, 2H), 7.15–7.25 (d, 1H), 7.35 (s, 1H), 7.6–7.7 (t, 1H), 9.35 (s, 1H); ^{13}C NMR ($DMSOd_6$) δ in ppm: 171.3, 156.9, 140.6, 130.0, 119.6, 116.3, 114.5, 64.1, 54.8, 46.2, 42.2, 37.1, 34.2. Anal. Calcd. For $C_{15}H_{21}N_3O_2S$: C: 58.61, H 6.89, N 13.67, S 10.43; Found: C: 58.55, H 6.78, N 13.61, S 10.49 %. MS: $[M]^+$ at *m/z* 307.

*2-(4-Hydroxyphenyl)-3-(2-piperazin-1-ylethyl)-1,3-thiazolidin-4-one (**4d**)*

Yield 79 % (methanol); m. p. 208–210 °C. IR (KBr, cm^{-1}): 3400 (OH), 3200 (NH), 3044 (CH aromatic), 2960 (CH aliphatic), 2845 (CH aliphatic), 1705 (C=O), 660 (C–S–C); ^{1}H NMR ($DMSOd_6$) δ in ppm: 1.85–1.97 (s, 1H), 2.3–2.4 (t, 4H), 2.6–2.72 (m, 6H), 3.48 (s, 2H), 3.6–3.7 (t, 2H), 5.0 (s, 1H), 6.76–6.88 (d, 2H), 7.6-7.75 (d, 2H), 10.1-10.3 (s, 1H); ^{13}C NMR ($DMSOd_6$) δ in ppm: 171.3, 158.0, 136.4, 130.7, 115.9, 63.5, 54.8, 46.5, 42.4, 37.1, 34.5. Anal. Calcd. For $C_{15}H_{21}N_3O_2S$: C: 58.61, H 6.89, N 13.67, S 10.43; Found: C: 58.56, H 6.79, N 13.57, S 10.39 %. MS: $[M]^+$ at *m/z* 307.

*2-Phenyl-3-(2-piperazin-1-ylethyl)-1,3-thiazolidin-4-one (**4e**)*

Yield 81 % (ethanol); m. p. 265–266 °C. IR (KBr, cm^{-1}): 3205 (NH), 3060 (CH aromatic), 2924 (CH aliphatic), 2850 (CH aliphatic), 1700 (C=O), 680 (C–S–C); ^{1}H NMR ($DMSOd_6$) δ in ppm: 1.95–2.05 (s, 1H), 2.35–2.47 (t, 4H), 2.6–2.8 (m, 6H), 3.65 (s, 2H), 3.7–3.82 (t, 2H), 5.2 (s, 1H), 7.35-7.47 (t, 1H), 7.6–7.72 (t, 2H), 7.9–8.0 (d, 2H); ^{13}C NMR ($DMSOd_6$) δ in ppm: 171.0, 144.1, 130.6, 127.7, 126.8, 63.7, 54.7, 46.1, 42.3, 36.7, 34.1. Anal. Calcd. For $C_{15}H_{21}N_3OS$: C: 61.82, H 7.26, N 14.42, S 11.00; Found: C: 61.75, H 7.31, N 14.50, S 10.94 %. MS: $[M]^+$ at *m/z* 291.

*2-(4-Hydroxy-3-methoxyphenyl)-3-(2-piperazin-1-ylethyl)-1,3-thiazolidin-4-one (**4f**)*

Yield 59 % (ethanol); m. p. 124–126 °C. IR (KBr, cm^{-1}): 3400 (OH), 3220 (NH), 3045 (CH aromatic), 2960 (CH aliphatic), 2830 (CH aliphatic), 1710 (C=O), 1260 (C–O–C), 700 (C–S–C); ^{1}H NMR ($DMSOd_6$) δ in ppm: 1.95–2.05 (s, 1H), 2.3–2.4 (t, 4H), 2.6–2.8 (m, 6H), 3.3 (s, 2H), 3.6–3.7 (t, 2H), 3.9 (s, 3H), 5.4 (s, 1H), 7.05–7.18 (d, 1H), 7.3–7.4 (d, 1H), 7.54 (s, 1H), 11.18 (s, 1H); ^{13}C NMR ($DMSOd_6$) δ in ppm: 171.2, 149.2, 147.3, 132.7, 122.4, 116.2, 114.3, 63.7, 56.2, 54.1, 46.3, 42.1, 36.8, 33.7. Anal. Calcd. For $C_{16}H_{23}N_3O_3S$: C: 56.95, H 6.87, N 12.45, S 9.50; Found: C: 57.00, H 6.81, N 12.49, S 9.58 %. MS: $[M]^+$ at *m/z* 337.

*2-(4-Methoxyphenyl)-3-(2-piperazin-1-ylethyl)-1,3-thiazolidin-4-one (**4g**)*

Yield 88 % (ethanol); m. p. 248–250 °C. IR (KBr, cm^{-1}): 3285 (NH), 3072 (CH aromatic), 2955 (CH aliphatic), 2839 (CH aliphatic), 1700 (C=O), 1253 (C–O–C), 710 (C–S–C); ^{1}H NMR ($DMSOd_6$) δ in ppm: 1.85–1.97 (s, 1H), 2.3–2.4 (t, 4H), 2.5–2.73 (m, 6H), 3.3 (s, 2H), 3.4–3.55 (t, 2H), 3.9 (s, 3H), 5.47 (s, 1H), 7.55–7.65 (d, 2H), 7.8–7.9 (d, 2H); ^{13}C NMR ($DMSOd_6$) δ in ppm: 171.2, 159.2, 136.3, 129.6, 114.0, 63.5, 56.6, 54.7, 46.3, 42.2, 36.9, 34.1. Anal. Calcd. For $C_{16}H_{23}N_3O_2S$: C: 59.78, H 7.21, N 13.07, S 9.98; Found: C: 59.83, H 7.14, N 13.00, S 10.05 %. MS: $[M]^+$ at *m/z* 321.

*2-Furan-2-yl-3-(2-piperazin-1-ylethyl)-1,3-thiazolidin-4-one (**4h**)*

Yield 63 % (methanol); m. p. 138^{o}C. IR (KBr, cm^{-1}): 3124 (NH), 3065 (CH aromatic), 2935 (CH aliphatic), 2818 (CH aliphatic), 1705 (C=O), 1155 (C–O–C), 756 (C–S–C); ^{1}H NMR ($DMSOd_6$) δ in ppm: 1.85–1.97 (s, 1H), 2.3–2.4 (t, 4H), 2.5–2.73 (m, 6H), 3.3 (s, 2H), 3.4–3.55 (t, 2H), 5.2 (s, 1H), 6.2–6.3 (d, 1H), 6.4–6.5 (t, 1H), 7.6–7.7 (d, 1H); ^{13}C NMR ($DMSOd_6$) δ in ppm: 171.3, 151.6, 142.2, 110.5, 107.1, 55.4, 53.6, 46.3, 39.8, 36.4, 31.7. Anal. Calcd. For $C_{13}H_{19}N_3O_2S$: C: 55.49, H 6.81, N 14.93, S 11.40; Found: C: 55.56, H 6.88, N 15.00, S 11.32 %. MS: $[M]^+$ at *m/z* 281.

Synthesis of 3-chloro-1-{2-[4-(chloroacetyl)piperazin-1-yl]ethyl}-4-arylazetidin-2-one (**5a–h**)

To a stirred solution of *N*-[(1)-arylmethylidene]-2-piperazin-1-ylethanamine (**3a–h,** 0.1 mol) in dioxan (100 mL), chloroacetylchloride (0.2 mol) was added dropwise at 0–5 °C temperature in the presence of triethylamine. The reaction mixture was stirred for about 8 h and the precipitate of amine hydrochloride was filtered off. The excess of dioxan was distilled off. The mass thus obtained was cooled, poured in ice-cold water, filtered, washed, dried, and recrystallized from appropriate solvents to furnish compounds **5a–h.**

*3-Chloro-1-{2-[4-(chloroacetyl)piperazin-1-yl]ethyl}-4-(3-hydroxy-4-methoxyphenyl)azetidin-2-one (**5a**)*

Yield 72 % (ethanol); m. p. 215 °C. IR (KBr, cm^{-1}): 3400 (OH), 3020 (CH aromatic), 2970 (CH aliphatic), 2800 (CH aliphatic), 1735, 1705 (C=O), 1265 (C–O–C), 750 (C–Cl); ^{1}H NMR ($DMSOd_6$) δ in ppm: 2.4–2.5 (t, 4H), 2.6–2.7 (t, 2H), 3.18–3.3 (t, 2H), 3.4–3.5 (t, 4H), 3.92 (s, 3H), 4.13 (s, 2H), 4.67–4.75 (d, 1H), 5.6 (s, 1H), 7.08–7.15 (m, 2H), 7.4 (s, 1H), 9.4–9.6 (s, 1H); ^{13}C NMR ($DMSOd_6$) δ in ppm: 166.4, 164.5, 148.4, 146.3, 132.0, 120.5, 114.7, 112.8, 62.8, 61.2, 56.3, 54.1, 46.9, 45.3, 41.1, 37.4. Anal. Calcd. For $C_{18}H_{23}Cl_2N_3O_4$: C: 56.69, H 3.08, N 11.67; Found: C: 56.60, H 2.98, N 11.56 %. MS: $[M]^+$ at *m/z* 415.

*3-Chloro-1-{2-[4-(chloroacetyl)piperazin-1-yl]ethyl}-4-(2-hydroxyphenyl)azetidin-2-one (**5b**)*

Yield 84 % (ethanol); m. p. 208–210 °C. IR (KBr, cm^{-1}): 3390 (OH), 3040 (CH aromatic), 2960 (CH aliphatic), 2830 (CH aliphatic), 1730, 1710 (C=O), 745 (C–Cl); ^{1}H NMR ($DMSOd_6$) δ in ppm: 2.3–2.4 (t, 4H), 2.5–2.62 (t, 2H), 3.1-3.2 (t, 2H), 3.38–3.5 (t, 4H), 4.15 (s, 2H), 4.7–4.8 (d, 1H), 5.57 (s, 1H), 7.1–7.24 (m, 2H), 7.36–7.5 (m, 2H), 9.65 (s, 1H); ^{13}C NMR ($DMSOd_6$) δ in ppm: 166.7, 164.6, 155.0, 129.3, 127.4, 125.7, 121.3, 115.8, 62.7, 56.2, 54.2, 46.4, 44.5, 40.8, 37.4. Anal. Calcd. For $C_{17}H_{21}Cl_2N_3O_3$: C: 52.86, H 5.48, N 10.88; Found: C: 52.90, H 5.42, N 10.92 %. MS: $[M]^+$ at *m/z* 385.

*3-Chloro-1-{2-[4-(chloroacetyl)piperazin-1-yl]ethyl}-4-(3-hydroxyphenyl)azetidin-2-one (**5c**)*

Yield 72 % (ethanol); m. p. 222–224 °C. IR (KBr, cm^{-1}): 3380 (OH), 3035 (CH aromatic), 2950 (CH aliphatic), 2800 (CH aliphatic), 1725, 1700 (C=O), 760 (C–Cl); ^{1}H NMR ($DMSOd_6$) δ in ppm: 2.39–2.5 (t, 4H), 2.6–2.7 (t, 2H), 3.18–3.27 (t, 2H), 3.4–3.5 (t, 4H), 4.13 (s, 2H), 4.68–4.76 (d, 1H), 5.6 (s, 1H), 7.08–7.16 (d, 1H), 7.2–7.3 (d, 1H), 7.4 (s, 1H), 7.65–7.74 (t, 1H), 9.5 (s, 1H); ^{13}C NMR ($DMSOd_6$) δ in ppm: 166.0, 164.4, 156.8, 139.7, 129.9, 120.3, 115.2, 113.7, 62.3, 60.9, 54.0, 46.9, 45.3, 40.8, 37.4. Anal. Calcd. For $C_{17}H_{21}Cl_2N_3O_3$: C: 52.86, H 5.48, N 10.88; Found: C: 52.91, H 5.55, N 10.85 %. MS: $[M]^+$ at *m/z* 385.

*3-Chloro-1-{2-[4-(chloroacetyl)piperazin-1-yl]ethyl}-4-(4-hydroxyphenyl)azetidin-2-one (**5d**)*

Yield 75 % (ethanol); m. p. 258–260 °C. IR (KBr, cm^{-1}): 3400 (OH), 3030 (CH aromatic), 2965 (CH aliphatic), 2850 (CH aliphatic), 1730, 1705 (C=O), 740 (C–Cl); ^{1}H NMR ($DMSOd_6$) δ in ppm: 2.4–2.5 (t, 4H), 2.6–2.7 (t, 2H), 3.18-3.28 (t, 2H), 3.4–3.5 (t, 4H), 4.13 (s, 2H), 4.6–4.7 (d, 1H), 5.4 (s, 1H), 7.1–7.2 (d, 2H), 7.4–7.5 (d, 2H), 9.5 (s, 1H); ^{13}C NMR ($DMSOd_6$) δ in ppm: 166.7, 164.3, 157.1, 130.8, 128.0, 115.9, 62.5, 61.0, 54.0, 46.6, 44.7, 40.9, 37.3. Anal. Calcd. For $C_{17}H_{21}Cl_2N_3O_3$: C: 52.86, H 5.48, N 10.88; Found: C: 52.81, H 5.54, N 10.81 %. MS: $[M]^+$ at *m/z* 385.

*3-Chloro-1-{2-[4-(chloroacetyl)piperazin-1-yl]ethyl}-4-phenylazetidin-2-one (**5e**)*

Yield 90 % (ethanol); m. p. 91–93 °C. IR (KBr, cm^{-1}): 3030 (CH aromatic), 2930 (CH aliphatic), 2860 (CH aliphatic), 1725, 1700 (C=O), 735 (C–Cl); ^{1}H NMR ($DMSOd_6$) δ in ppm: 2.4–2.5 (t, 4H), 2.6–2.7 (t, 2H), 3.2–3.29 (t, 2H), 3.4–3.5 (t, 4H), 4.12 (s, 2H), 4.6–4.7 (d, 1H), 5.4 (s, 1H), 7.22–7.34 (t, 1H), 7.48–7.6 (t, 2H), 7.78–7.85 (d, 2H); ^{13}C NMR ($DMSOd_6$) δ in ppm: 166.4, 164.3, 138.4, 130.8, 128.9, 127.1, 62.4, 60.8, 54.2, 47.0, 45.4, 40.8, 37.6. Anal. Calcd. For $C_{17}H_{21}Cl_2N_3O_2$: C: 55.14, H 5.72, N 11.35; Found: C: 55.19, H 5.80, N 11.31 %. MS: $[M]^+$ at *m/z* 369.

*3-Chloro-1-{2-[4-(chloroacetyl)piperazin-1-yl]ethyl}-4-(4-hydroxy-3-methoxyphenyl)azetidin-2-one (**5f**)*

Yield 69 % (methanol); m. p. 175 °C. IR (KBr, cm^{-1}): 3390 (OH), 3040 (CH aromatic), 2950 (CH aliphatic), 2840 (CH aliphatic), 1740, 1705 (C=O), 1270 (C–O–C), 750 (C–Cl); ^{1}H NMR ($DMSOd_6$) δ in ppm: 2.4–2.5 (t, 4H), 2.6–2.7 (t, 2H), 3.2–3.3 (t, 2H), 3.4–3.5 (t, 4H), 3.8 (s, 3H), 4.13 (s, 2H), 4.6–4.7 (d, 1H), 5.4 (s, 1H), 7.2-7.32 (m, 2H), 7.7 (s, 1H), 11.02 (s, 1H); ^{13}C NMR ($DMSOd_6$) δ in ppm: 166.5, 164.6, 149.1, 147.2, 132.1, 120.3, 115.5, 111.2, 62.6, 61.0, 56.4, 54.0, 47.7, 45.8, 41.2, 37.4. Anal. Calcd. For $C_{18}H_{23}Cl_2N_3O_4$: C: 51.93, H 5.57, N 10.09; Found: C: 52.00, H 5.51, N 10.02 %. MS: $[M]^+$ at *m/z* 415.

*3-Chloro-1-{2-[4-(chloroacetyl)piperazin-1-yl]ethyl}-4-(4-methoxyphenyl)azetidin-2-one (**5g**)*

Yield 78 % (ethanol); m. p. 166–168 °C. IR (KBr, cm^{-1}): 3040 (CH aromatic), 2950 (CH aliphatic), 2840 (CH aliphatic), 1735, 1705 (C=O), 1250 (C–O–C), 760 (C–Cl); ^{1}H NMR ($DMSOd_6$) δ in ppm: 2.39–2.49 (t, 4H), 2.6–2.7 (t, 2H), 3.17-3.3 (t, 2H), 3.4–3.5 (t, 4H), 3.93 (s, 3H), 4.23 (s, 2H), 4.6-4.72 (d, 1H), 5.4 (s, 1H), 7.2–7.3 (d, 2H), 7.45–7.55 (d, 2H); ^{13}C NMR ($DMSOd_6$) δ in ppm: 166.5, 164.3, 158.7, 130.8, 127.7, 114.1, 62.3, 60.6, 55.9, 53.8, 47.1, 45.2, 40.9, 37.2. Anal. Calcd. For $C_{18}H_{23}Cl_2N_3O_3$: C: 54.01, H 5.79, N 10.50; Found: C: 53.96, H 5.71, N 10.56 %. MS: $[M]^+$ at *m/z* 399.

*3-Chloro-1-{2-[4-(chloroacetyl)piperazin-1-yl]ethyl}-4-furan-2-ylazetidin-2-one (**5h**)*

Yield 81 % (methanol); m. p. 154–155 °C. IR (KBr, cm^{-1}): 3030 (CH aromatic), 2940 (CH aliphatic), 2800 (CH aliphatic), 1720, 1700 (C=O), 1270 (C–O–C), 740 (C–Cl); ^{1}H NMR ($DMSOd_6$) δ in ppm: 2.32–2.43 (t, 4H), 2.53–2.62 (t, 2H), 3.1–3.2 (t, 2H), 3.4–3.5 (t, 4H), 4.16 (s, 2H), 4.7-4.78 (d, 1H), 5.43 (s, 1H), 6.4–6.56 (m, 2H), 7.6–7.7 (d, 1H); ^{13}C NMR ($DMSOd_6$) δ in ppm: 166.3, 164.5, 151.1, 141.4, 111.0, 109.2, 60.7, 58.4, 53.9, 46.5, 43.0, 40.9, 36.6. Anal. Calcd. For $C_{15}H_{19}Cl_2N_3O_3$: C: 50.01, H 5.32, N 11.66; Found: C: 49.95, H 5.28, N 11.57 %. MS: $[M]^+$ at *m/z* 359.

Antibacterial and antifungal activity (MIC-minimum inhibitory concentration)

The microbial strains were procured from the National Chemical Laboratory (NCL), Pune, India. The synthesized compounds were screened against the following bacterial strains: *Bacillus subtilis* ATCC 6633, *Staphylococcus epidermidis* ATCC 12228, *Micrococcus luteus* ATCC 4698, *Staphylococcus aureus* ATCC 25923, *Staphylococcus hominis* ATCC 27844, *Bacillus pumilus* ATCC 14884, *Bacillus cereus* ATCC 11778, *Proteus vulgaris* ATCC 13315, *Proteus mirabilis* ATCC 49565, *Salmonella typhi* ATCC 19430, *Klebsiella pneumonia* ATCC 13883, *Escherichia coli* ATCC 25922, and *Pseudomonas aeruginosa* ATCC 10145.

The synthesized compounds were also screened against the following fungal strains: *Aspergillus niger* ATCC 9142, *Aspergillus awamori* ATCC 22342, *Candida albicans* ATCC 10231, *Alternaria alternate* ATCC 66868, *Microsporum canis* ATCC 11622, *Rhizoctonia solani* ATCC 76131, *Trichophyton longiformis* ATCC 22397, *Aspergillus flavus* ATCC 15517, *Fusarium solani* ATCC 38136, and *Trichoderma viride* ATCC 52440.

The minimum inhibitory concentration was done by broth dilution method (Shingade *et al.*, 2011; Srinivas *et al.*, 2006).

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