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Synthesis and Biological Activity of (2-Substituted-4-methylthiazol-5-yl) (4-substituted piperazin-1-yl)methanone Derivatives

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ABSTRACT. In the present study a novel series of (2-substituted-4-methylthiazol-5-yl)(4-substituted piperazin-1-yl)methanone derivatives were synthesized by reaction of 2-substituted-4-methylthiazole-5-carboxylic acid with N-substituted benzyl piperazine by using 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCl) and 1-hydroxybenzotriazole (HOBt) in DMF. All the newly synthesized compounds were characterized by spectral methods. The title compounds were screened for in vitro antibacterial activity. Most of the compounds show moderate to good antimicrobial activity.

Key words: Thiazole, Piperazine, EDCl-HOBt, Antimicrobial activity

Thiazole and their derivatives have attracted continuing interest over the years because of their varied biological activities.[1] 1,3-Thiazole nucleus containing compounds have exhibited a broad range of biological activities.[2–13] 5-Azole carboxamide derivatives showed antianoxic activity.[14] The aryl imidazolyl carboxamide derivatives were shown to be cannabinoid CB_1 receptor antagonist.[15,16] Based on these observations, a series of (2-substituted-4-methylthiazol-5-yl)(4-substituted piperazin-1-yl)methanone derivatives were synthesized and subjected to microbial screening.

The synthesis of (2-methyl, phenyl or benzyl-substituted-4-methylthiazol-5-yl)(4-phenyl or benzyl substituted piperazin-1-yl)methanone is illustrated in *Scheme* 1. Ethyl-2-chloro-3-oxobutanoate **1** on reaction with methyl, phenyl or benzyl substituted thioamides **2a–2f** afforded corresponding ethyl-2-methyl, phenyl or benzyl-substituted-4-methylthiazole-5-carboxylate which on alkaline hydrolysis furnished corresponding 2-methyl, phenyl or benzyl-substituted-4-methylthiazole-5-carboxylic acids **3a–3f.** The structures of acid **3a–3f** were confirmed by spectral data. The IR spectrum of acid **3a** displayed the broad absorption band at 2550–3400 cm^{-1} characteristic of –COOH group and a band at 1702 cm^{-1} due to stretching frequency of C=O.

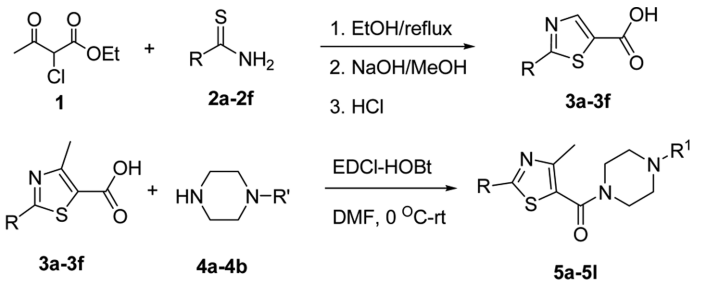
The reaction of **3a–3f** with N-aryl or benzyl substituted piperazine **4a–b** in the presence of EDC-HOBt in DMF furnished the target compounds **5a–5l** in good yields. The yields, melting points and molecular formula of synthesized compounds **5a–5l** are listed in *Table* 1. The structures of synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopy and all the spectral data are in accordance with the assumed structures.

The IR spectrum of **5d** showed the absorption band at 1699–1647 cm^{-1} and 1610–1590 cm^{-1} which indicated the presence of O=C–N (amide) and C=N functionality respectively. The ^{1}H NMR spectrum of **5d** revealed a singlet at δ 2.44 for thiazole-CH_3 protons, two peaks at δ 3.13 and 3.72 integrated for four protons of piperazine and a singlet at δ 4.24 integrated for two methylene protons of benzyl group. Seven aromatic protons resonated at δ 6.69–7.30. Further the ^{13}C NMR spectrum of **5d** revealed four signals in aliphatic region. The aromatic *ipso* carbon attached to fluorine appeared as doublet with ^1J = 244.4 Hz (C-F). The *ortho* and the *meta* carbon atoms in the same ring also appeared as doublets with ^2J = 21.3 Hz and ^3J = 8.0 Hz. All other aromatic carbon and carbonyl carbon atoms appeared between δ 115.7 and 170.3. The structure was further confirmed by LC mass spectral data which showed peak at 464.1 $(M+H)^+$.

BIOLOGICAL ACTIVITY

Antimicrobial Activity

The in vitro antibacterial activity was performed against Gram-positive bacteria including *S. aureus, B. subtilis* and Gram-negative bacteria including *E. coli* and *K. pneumonia*. The antifungal activity was screened against fungi including *F. solani, C. lunata* and *A. niger*. To evaluate the activity of the synthesized compounds, the zone of inhibition were determined. The in vitro antimicrobial screen-



1 2a-2f 3a-3f 3a-3f 4a-4b 5a-5l

Compound	R	R^1	Compound	R	R^1
5a	CH_3	2,4-$(Cl)_2C_6H_3$	**5g**	CH_3	4-$ClC_6H_4CH_2$
5b	C_6H_5	2,4-$(Cl)_2C_6H_3$	**5h**	C_6H_5	4-$ClC_6H_4CH_2$
5c	4-$ClC_6H_4CH_2$	2,4-$(Cl)_2C_6H_3$	**5i**	4-$ClC_6H_4CH_2$	4-$ClC_6H_4CH_2$
5d	4-$FC_6H_4CH_2$	2,4-$(Cl)_2C_6H_3$	**5j**	4-$FC_6H_4CH_2$	4-$ClC_6H_4CH_2$
5e	2,4-$(Cl)_2C_6H_3CH_2$	2,4-$(Cl)_2C_6H_3$	**5k**	2,4-$(Cl)_2C_6H_3CH_2$	4-$ClC_6H_4CH_2$
5f	3,4-$(MeO)_2C_6H_3CH_2$	2,4-$(Cl)_2C_6H_3$	**5l**	3,4-$(MeO)_2C_6H_3CH_2$	4-$ClC_6H_4CH_2$

***Scheme* 1.**

***Table* 1.** Yield and physical data of compounds **5a**–**5l**

Compound	R	R^1	Mp (ºC)	Yield (%)	Molecular Formula
5a	CH_3	2,4-$(Cl)_2C_6H_3$	82–84	70	$C_{16}H_{17}Cl_2N_3OS$
5b	C_6H_5	2,4-$(Cl)_2C_6H_3$	136–138	72	$C_{21}H_{19}Cl_2N_3OS$
5c	4-$ClC_6H_4CH_2$	2,4-$(Cl)_2C_6H_3$	128–130	70	$C_{22}H_{20}Cl_3N_3OS$
5d	4-$FC_6H_4CH_2$	2,4-$(Cl)_2C_6H_3$	86–88	70	$C_{22}H_{20}Cl_2FN_3OS$
5e	2,4-$(Cl)_2C_6H_3CH_2$	2,4-$(Cl)_2C_6H_3$	68–70	65	$C_{22}H_{19}Cl_4N_3OS$
5f	3,4-$(MeO)_2C_6H_3CH_2$	2,4-$(Cl)_2C_6H_3$	89–91	74	$C_{24}H_{25}Cl_2N_3O_3S$
5g	CH_3	4-$ClC_6H_4CH_2$	78–79	75	$C_{17}H_{20}ClN_3OS$
5h	C_6H_5	4-$ClC_6H_4CH_2$	83–85	65	$C_{22}H_{22}ClN_3OS$
5i	4-$ClC_6H_4CH_2$	4-$ClC_6H_4CH_2$	86–88	65	$C_{23}H_{23}Cl_2N_3OS$
5j	4-$FC_6H_4CH_2$	4-$ClC_6H_4CH_2$	160–162	70	$C_{23}H_{23}ClFN_3OS$
5k	2,4-$(Cl)_2C_6H_3CH_2$	4-$ClC_6H_4CH_2$	132–135	75	$C_{23}H_{22}Cl_3N_3OS$
5l	3,4-$(MeO)_2C_6H_3CH_2$	4-$ClC_6H_4CH_2$	78–80	60	$C_{25}H_{28}ClN_3O_3S$

***Table* 2.** Antibacterial screening results of the compounds **5a**–**5l** (Zone diameter of growth inhibition in mm)

Compd.	*S. aureous*		*B. subtilis*		*E. coli*		*K. pneumonia*	
Conc. μg/ml	100	200	100	200	100	200	100	200
5a	26	30	24	27	25	29	23	26
5b	26	29	29	31	**31**	**34**	28	31
5c	24	27	27	29	28	29	26	28
5d	10	12	10	13	9	12	8	10
5e	**33**	**36**	**37**	**39**	**39**	**44**	**34**	**37**
5g	**36**	**39**	**34**	**37**	**31**	**34**	**29**	**33**
5h	**31**	**34**	**32**	**35**	**37**	**38**	**34**	**36**
5i	9	12	8	13	7	12	6	10
5j	28	31	28	32	27	33	26	29
5k	**38**	**43**	**37**	**41**	**36**	**40**	**37**	**39**
5l	7	9	8	9	7	9	6	8
Ciprofloxacin	34	38	36	42	40	45	37	42
Chloramphenicol	35	39	38	41	40	44	42	45

ing results of tested compounds are listed in *Table* 2 and 3.

Most of the synthesized compounds (except compounds **5d**, **5i** and **5l**) exhibited moderate to excellent antimicrobial activities. It is noteworthy that compounds **5e** and **5k** (R = 2,4-$(Cl)_2C_6H_3CH_2$–, R^1 = 2,4-$(Cl)_2C_6H_3$– and 4-$ClC_6H_4CH_2$, respectively), compound **5g** (R = CH_3–, R^1 = 4-$ClC_6H_4CH_2$–)

***Table* 3.** Antifungal screening results of the compounds **5a–5l** (Zone diameter of growth inhibition in mm)

Compd.	*F. solani*		*C. lunata*		*A. niger*	
Conc. µg/ml	100	200	100	200	100	200
5a	16	19	17	20	15	18
5b	19	21	22	24	17	21
5c	24	27	23	25	20	24
5d	29	32	27	31	22	24
5e	16	19	17	19	15	16
5g	14	19	14	18	13	17
5h	17	20	18	22	16	21
5i	17	19	18	23	18	21
5j	21	23	18	20	17	21
5k	16	20	15	17	16	19
5l	24	26	24	27	18	20
Ketoconazole	38	42	38	42	38	42

and **5h** (R = C_6H_5–, R^1 = 4-$ClC_6H_4CH_2$–) showed excellent activity against all bacterial strain as compared to standard drugs. Even compounds **5a**, **5b**, **5c** and **5j** showed good antibacterial activities against most of the strains.

The result of antifungal activity revealed that all the tested compounds show moderate to good antifungal activity as compared to the standard drug ketoconazole. Compound **5c** (R = 4-$ClC_6H_4CH_2$–, R^1 = 2,4-$(Cl)_2C_6H_3$–), **5d** (R = 4-$FC_6H_4CH_2$–, R^1 = 2,4-$(Cl)_2C_6H_3$–) and **5l** (R = 3,4-$(MeO)_2$ $C_6H_3CH_2$–, R^1 = 4-$ClC_6H_4CH_2$–) exhibited good activities against all the fungal species. However compounds **5d**, **5i** and **5l** were inactive against bacterial strain but showed good antifungal activity.

Thus, it is concluded that compounds with R = CH_3–, C_6H_5– and 2,4-di$ClC_6H_3CH_2$– show good to excellent antibacterial activity.

EXPERIMENTAL

Melting points were determined in an open capillary on Veego melting point apparatus and are uncorrected. The purity of the compounds was checked on silica gel-G plates. The compounds **5a–l** was purified on silica gel (100–200) column chromatography using ethyl acetate: hexane (2:8) as eluent. Infrared spectra (cm^{-1}) were recorded in KBr on a Shimadzu Model FTIR-435 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 solution on a Varian Mercury YH-300 spectrometer operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C. Chemical shifts are expressed relative to tetramethylsilane (TMS) and were reported as δ (ppm). Mass spectral (MS) measurements were made on a Jeol-JMS-DX 303 mass spectrometer. The isotopic peak at M+2 was observed in the mass spectrum of all the compounds due to S, Br and/or Cl.

General Procedure

2-Methyl, phenyl or benzyl substituted-4-methylthiazole-5-carboxylic acid (3a–3f)

Mixture of 2-chloro-3-oxo ethyl butanoate (0.05 mol) and substituted thioamides (0.055 mol) in methanol (50 mL) was refluxed for 5–6 hours. After completion of the reaction, as monitored on TLC, 2N NaOH (20 mL) was added and refluxed further for 4 hours. Methanol was distilled off and the mixture was acidified with 4N HCl to pH 2. The precipitated product was filtered, washed with water and recrystallized from aqueous ethanol.

(2-methyl, phenyl or benzyl-substituted-4-methylthiazol-5-yl)(4-phenyl or benzyl substituted piperazin-1-yl)methanone (5a–5l)

A mixture of 2-substituted-4-methylthiazole-5-carboxylic acid (**3a–f)** (1 mmol), DIPEA (0.35 mL, 2 mmol), HOBt (0.14 g, 1 mmol) in DMF (10 mL) was cooled to 0 ºC. To this N-aryl or benzyl piperazine (**4a–b)** (1 mmol) was added followed by EDC.HCl (0.19 g, 1 mmol) at 0 ºC and stirred overnight at room temperature. The reaction was quenched with water and the product was filtered, washed with water and purified by column chromatography using ethyl acetate:hexane (2:8).

(4-(2,4-Dichlorophenyl)piperazin-1-yl)(2,4-dimethylthiazol-5-yl)methanone (5a)

IR (KBr): 3056, 2971, 2911, 2802, 1631, 1542, 1480, 1417, 1251, 1130, 1006, 934, 830, 822 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): 2.42 (s, 3H), 2.68 (s, 3H), 3.18 (s, 4H), 3.76 (s, 4H), 6.72 (m, 1H), 6.95 (s, 1H), 7.24–7.45 (m, 1H); ^{13}C

NMR ($CDCl_3$, 75 MHz): 15.0, 20.1, 48.1, 49.3, 115.4, 121.6, 126.8, 127.0, 128.9, 132.5, 149.3, 151.7, 164.2, 168.5; LCMS: 370.0 $(M+H)^+$. Anal. calcd. for $C_{16}H_{17}Cl_2N_3OS$: C, 51.90; H, 4.63; N, 11.35. Found: C, 51.79; H, 4.51; N, 11.22.

(4-(2,4-Dichlorophenyl)piperazin-1-yl)(4-methyl-2-phenylthiazol-5-yl)methanone (5b)

IR (KBr): 2991, 2891, 2850, 1616, 1541, 1438, 1365, 1242, 1151, 1010, 947, 850, 813 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 2.44 (s, 3H), 3.11 (s, 4H), 3.71 (s, 4H), 6.66 (dd, J = 3 and 9 Hz, 1H), 6.88, (d, J = 3 Hz, 1H), 7.21 (d, J = 9 Hz, 1H), 7.35−7.37 (m, 3H), 7.81−7.85 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): 16.6, 49.1, 115.9, 117.9, 123.3, 123.7, 126.5, 129.0, 130.5, 130.6, 132.7, 132.9, 150.0, 153.1, 162.6, 167.9; LCMS: 432.1 $(M+H)^+$. Anal. calcd. for $C_{21}H_{19}Cl_2N_3OS$: C, 58.34; H, 4.43; N, 9.72. Found: C, 58.26; H, 4.37; N, 9.59.

(2-(4-Chlorobenzyl)-4-methylthiazol-5-yl)(4-(2,4-dichlorophenyl)piperazin-1-yl)methanone (5c)

IR (KBr): 3059, 2930, 2879, 2823, 1631, 1475, 1427, 1365, 1271, 1240, 1157, 1089, 1016, 956, 873 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 2.41 (s, 3H), 3.16 (s, 4H), 3.61 (s, 4H), 3.84 (s, 2H), 6.75 (dd, J = 2.4 and 8.4 Hz, 1 H), 7.00 (d, J = 2.4 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.37−7.42 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): 14.9, 41.0, 47.9, 51.0, 115.2, 117.8, 125.0, 125.5, 128.1, 128.8, 130.6, 131.4, 131.6, 134.3, 148.9, 152.0, 164.5, 169.1; LCMS: 480.0 $(M+H)^+$. Anal. calcd. for $C_{22}H_{20}Cl_3N_3OS$: C, 54.95; H, 4.19; N, 8.74. Found: C, 54.88; H, 4.11; N, 8.63.

(2-(4-Fluorobenzyl)-4-methylthiazol-5-yl)(4-(2,4-dichlorophenyl)piperazin-1-yl)methanone (5d)

IR (KBr): 3076, 2908, 2831, 1947, 1506, 1435, 1348, 1246, 1138, 1006, 852, 763 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 2.44 (s, 3H), 3.13 (s, 4H), 3.72 (s, 4H), 4.24 (s, 2H), 6.71 (dd, J = 2.75 and 9 Hz, 1H), 6.83, (d, J = 2.70 Hz, 1H), 7.01 (t, J = 8.7 Hz, 2H), 7.24–7.30 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): 16.2, 38.4, 48.6, 48.8, 115.4, 117.6, 122.8, 124.0, 130.3, 130.5, 132.5, 132.6, 132.7, 149.9, 151.7, 161.5, 162.4, 170.3; LCMS: 464.1 $(M+H)^+$. Anal. calcd. for $C_{22}H_{20}Cl_2FN_3OS$: C, 56.90; H, 4.34; N, 9.05. Found: C, 56.80; H, 4.23; N, 8.94.

(2-(2,4-Dichlorobenzyl)-4-methylthiazol-5-yl)(4-(2,4-dichlorophenyl)piperazin-1-yl)methanone (5e)

IR (KBr): 3084, 2928, 2833, 1631, 1558, 1487, 1242, 997, 954, 856, 788 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 2.36 (s, 3H), 3.06 (s, 4H), 3.64 (s, 4H), 4.29 (s, 2H), 6.64 (dd, J = 3 and 9 Hz, 1H), 6.86, (d, J = 3 Hz, 1H), 7.13−7.23 (m, 3H), 7.33 (d, J = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 16.4, 29.6, 36.4, 49.0, 115.4, 117.9, 123.2, 124.2, 127.5, 129.5, 130.5, 131.9, 132.8, 133.4, 134.0, 134.7, 150.0, 151.9, 162.5, 168.1; LCMS: 514.0 $(M+H)^+$. Anal. calcd. for $C_{22}H_{19}Cl_4N_3OS$: C, 51.28; H, 3.72; N, 8.15. Found: C, 51.20; H, 3.60; N, 8.04.

(2-(3,4-Dimethoxybenzyl)-4-methylthiazol-5-yl)(4-(2,4-dichlorophenyl)piperazin-1-yl)methanone (5f)

IR (KBr): 3031, 2965, 2910, 2824, 1631, 1524, 1418, 1315, 1251, 1140, 1089, 1006, 750, 819 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 2.43 (s, 3H), 3.14 (s, 4H), 3.73 (s, 4H), 3.86 (s, 3H), 3.87 (s, 3H), 4.19 (s, 2H), 6.72 (dd, J = 3 and 9 Hz, 1H), 6.80−6.87, (m, 3H), 6.94 (d, J = 3 Hz, 1H), 7.28 (d, J = 9 Hz 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 15.4, 39.2, 46.4, 51.1, 56.2, 56.3, 115.2, 117.0, 117.6, 119.1, 123.4, 125.2, 126.0, 128.1, 129.5, 131.5, 145.8, 148.4, 149.7, 152.2, 163.1, 168.2; LCMS: 506.1 $(M+H)^+$. Anal. calcd. for $C_{24}H_{25}Cl_2N_3O_3S$: C, 56.92; H, 4.98; N, 8.30. Found: C, 56.78; H, 4.86; N, 8.19.

(4-(4-Chlorobenzyl)piperazin-1-yl)(2,4-dimethylthiazol-5-yl)methanone (5g)

IR (KBr) 3060, 2976, 2908, 2808, 1639, 1546, 1487, 1429, 1265, 1138, 1006, 935, 831, 756 cm^{-1}; ^1H NMR: 2.37 (s, 7H), 2.60 (s, 3H), 3.59 (s, 4H), 4.23 (s, 2H), 7.15−7.34 (m, 4H); ^{13}C NMR: 15.1, 20.2, 48.9, 59.1, 65.3, 116.0, 128.9, 130.5, 132.9, 135.1, 152.0, 164.5, 168.3; LCMS: 350.1 $(M+H)^+$. Anal. calcd. for $C_{17}H_{20}ClN_3OS$: C, 58.36; H, 5.76; N, 12.01. Found: C, 58.23; H, 5.67; N, 11.89.

(4-(4-Chlorobenzyl)piperazin-1-yl)(4-methyl-2-phenylthiazol-5-yl)methanone (5h)

IR (KBr): 3065, 2956, 2900, 2815, 1630, 1484, 1440, 1321, 1250, 1005, 865, 815 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 2.26 (s, 4H), 2.35 (s, 3H), 3.49 (s, 4H), 4.09 (s, 2H), 7.01−7.24 (m, 7H), 7.74−7.77 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): 18.1, 51.5, 74.7, 77.2, 119.4, 126.2, 127.4, 128.4, 128.7, 130.2, 133.6, 140.1, 140.6, 152.2, 162.2, 167.6; LCMS: 412.1 $(M+H)^+$. Anal. calcd. for $C_{22}H_{22}ClN_3OS$: C, 64.14; H, 5.38; N, 10.20. Found: C, 64.08; H, 5.31; N, 10.09.

(2-(4-Chlorobenzyl)-4-methylthiazol-5-yl)(4-(4-chlorobenzyl)piperazin-1-yl)methanone (5i)

IR (KBr): 3068, 2949, 2912, 2809, 1628, 1504, 1478, 1324, 1248, 1006, 860, 809 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 2.32 (s, 3H), 2.60 (s, 4H), 3.32 (s, 4H), 4.21 (s, 2H), 4.23 (s, 2H), 7.15–7.36 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz): 14.2, 47.7, 51.2, 61.2, 127.2, 127.5, 128.3, 128.5, 128.9, 129.7,

131.2, 132.6, 133.8, 135.5, 140.4, 153.2, 168.9; LCMS: 460.1 $(M+H)^+$. Anal. calcd. for $C_{23}H_{23}Cl_2N_3OS$: C, 60.00; H, 5.04; N, 9.13. Found: C, 59.88; H, 5.00; N, 9.02.

(4-(4-Chlorobenzyl)piperazin-1-yl)(2-(4-fluorobenzyl)-4-methylthiazol-5-yl)methanone (5j)

IR (KBr): 3051, 2908, 2823, 1629, 1487, 1305, 1240, 1132, 1006, 846, 746 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 2.41 (s, 4H), 2.44 (s, 3H), 3.62 (s, 4H), 4.24 (s, 2H), 4.26 (s, 2H), 7.03 (t, J = 8.4 Hz, 2H), 7.20–7.40 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): 16.2, 38.5, 51.6, 60.1, 75.0, 115.5, 124.5, 127.5, 128.6, 128.9, 130.4, 132.8, 141.0, 151.3, 160.2, 163.5, 170.0; LCMS: 444.1 $(M+H)^+$. Anal. calcd. for $C_{23}H_{23}ClFN_3OS$: C, 62.22; H, 5.22; N, 9.46. Found: C, 62.09; H, 5.17; N, 9.33.

(2-(2,4-Dichlorobenzyl)-4-methylthiazol-5-yl)(4-(4-chlorobenzyl)piperazin-1-yl)methanone (5k)

IR (KBr): 3070, 2970, 2910, 2808, 1627, 1545, 1477, 1440, 1311, 1257, 1099, 1006, 864, 813 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 2.30 (s, 7H), 3.49 (s, 4H), 4.12 (s, 2H), 4.23 (s, 2H), 7.06–7.29 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz): 16.2, 36.3, 51.6, 74.9, 124.5, 127.3, 127.5, 128.6, 128.9, 129.4, 131.8, 133.5, 133.8, 134.6, 140.4, 141.2, 151.3, 162.2, 167.7; LCMS: 494.1 $(M+H)^+$. Anal. calcd. for $C_{23}H_{22}Cl_3N_3OS$: C, 55.82; H, 4.48; N, 8.49. Found: C, 55.69; H, 4.36; N, 8.35.

(2-(3,4-Dimethoxybenzyl)-4-methylthiazol-5-yl)(4-(4-chlorobenzyl)piperazin-1-yl)methanone (5l)

IR (KBr): 3024, 2974, 2918, 2810, 1626, 1533, 1429, 1317, 1249, 1141, 1095, 1004, 754, 709 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 2.37 (s, 4H), 2.62 (s, 3H), 3.58 (s, 4H), 3.83 (s, 6H), 4.17 (s, 2H), 4.21 (s, 2H), 6.81 (t, J = 8.4 Hz, 2H), 7.15–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): 15.2, 39.8, 48.0, 55.3, 56.2, 56.3, 64.3, 115.1, 116.8, 117.5, 123.3, 128.8, 129.7, 130.5, 132.9, 133.6, 146.0, 148.6, 152.1, 163.1, 168.2; LCMS: 485.2 $(M+H)^+$. Anal. calcd. for $C_{25}H_{28}ClN_3O_3S$: C, 61.78; H, 5.81; N, 8.65. Found: C, 61.64; H, 5.70; N, 8.49.

Antimicrobial Activity

The synthesized compounds **5a–5l** were screened for their in vitro antimicrobial activity against the standard strains *B. subtilis, S. aureus* (Gram-positive) and *E. coli*, *K. pneumonia* (Gram-negative) by the disk diffusion method.[17,18] Disks measuring 6 mm in diameter were punched from whatman no.1 filter paper. Batches of 100 disks were dispensed to each screw-caped bottle and sterilized by dry heat at 145 °C for one hour. The test compounds were prepared with 100 μg/mL and 200 μg/mL concentration in dimethyl sulfoxide (DMSO). Disks of each concentration were placed in nutrient agar medium inoculated with fresh bacteria strains separately. Ciprofloxacin and Chloramphenicol was used as positive controls and DMSO was used as negative control. The incubation was carried out at 37 °C for 24 h. The diameter of the zone of growth inhibition around each well was measured after incubation using vernier caliper.

The compounds were screened for their antifungal activity against *F. solani*, *C. lunata* and *A. niger* in DMSO by disc diffusion method under standard conditions using Sabourad Dextrose Agar medium as described by NCCLS.[19] Sterile filter paper discs (6 mm diameter) containing specific amount of anti fungal agent (100 μg for the synthesized compounds) were placed on the surface of an agar plate inoculated with the standardized suspension of microorganisms tested. The plates were incubated at 37 °C for 2 days for evaluating antifungal activity. The diameters of inhibition zones (in mm) were measured. Ketoconazole was used as positive control.

CONCLUSION

In summary, we have synthesized a series of novel (2-methyl, phenyl or benzyl-substituted-4-methylthiazol-5-yl)(4-phenyl or benzyl substituted piperazin-1-yl)methanone (**5a–5l**) and screened for their antimicrobial activity. The in vitro antimicrobial results revealed that the compounds **5e**, **5g**, **5h** and **5k** show significant antibacterial activity while compounds **5a**, **5b**, **5c** and **5j** showed good antibacterial activities. All the tested compounds showed moderate to good antifungal activity. The antimicrobial activity results make them interesting lead molecules for further synthetic and biological evaluation. Further studies are in progress to acquire more information regarding structure activity relationship.

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