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ORIGINAL ARTICLE

Synthesis and antimicrobial activity of pyrazole nucleus containing 2-thioxothiazolidin-4-one derivatives

H. B'Bhatt, S. Sharma *

Department of Chemistry, Hemchandracharya North Gujarat University, Patan 384 265, Gujarat, India

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KEYWORDS

3-(4-Chlorophenyl)-2-thioxothiazolidin-4-one;
Vilsmeier–Haack reaction;
1-Phenyl-3-(p-substituted phenyl)-1*H*-pyrazole-4-carbaldehyde;
Antibacterial activity;
Antifungal activity

Abstract A series of novel compounds of type 3-(4-chlorophenyl)-5-((1-phenyl-3-aryl-1H-pyrazol-4-yl)methylene)-2-thioxothiazolidin-4-one (**3a–h**) have been synthesized from the 3-(4-chlorophenyl)-2-thioxothiazolidin-4-one (**1**) and 1-phenyl-3-(*p*-substituted phenyl)-1*H*-pyrazole-4-carbaldehyde (**2a–h**). The structures of all the synthesized compounds have been confirmed by elemental analyses, FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. These newly synthesized compounds were screened for in vitro antibacterial activity against *Escherichia coli* (MTCC 443), *Pseudomonas aeruginosa* (MTCC 1688), *Staphylococcus aureus* (MTCC 96), and *Staphylococcus pyogenes* (MTCC 442) using commercially available antibiotics ampicillin as a standard drug. Compound **3c** was found as a potent compound against *E. coli*, compounds **3a**, **3d** and **3g** were found as a potent against *S. aureus*, while **3d** against *S. pyogenes*. For in vitro antifungal activity, these compounds were tested *against Candida albicans* (MTCC 227), *Aspergillus niger* (MTCC 282) and *Aspergillus clavatus* (MTCC 1323) using griseofulvin as a standard drug. Compounds **3b** and **3d** were found to have very good activity against *C. albicans*. Variable and modest activities were observed against the investigated strains of bacteria and fungi.

1. Introduction

Microbial diseases have emerged as a main origin of morbidity and often as suppressor of immune power over the past two decades. Microbes are responsible for several poisonous syndromes and prevalent epidemics in human civilizations. Microbial diseases such as plague, diphtheria, typhoid, cholera, pneumonia and tuberculosis have taken high toll of humanity in recent pasts (Todar, 2011). In present times, many of the accessible antimicrobial drugs are poisonous and create recurrence of diseases because they are bacteriostatic and not bactericides. These can also lead to the expansion of resistance due to the long periods of administration.

The growing potent literature of recent years demonstrated that the 2-thioxothiazolidin-4-one derivatives exhibit better pharmacological properties such as antimicrobial (Zhen-Hua et al., 2010; Habib et al., 1997; Tomasic et al., 2010; Dixit et al., 2010; Chen et al., 2010; Desai and Desai, 2006; Abdel-Halim et al., 1994; Pachhamia and Parikh, 1991), HIV-1 integrase inhibitors (Ramkumar et al., 2010) and anticonvulsant effect (Gursoy and Terzioglu, 2005). Additionally, rhodanine

* Corresponding author. Tel.: +91 2766 220932.
E-mail address: smridhee2000@yahoo.co.in (S. Sharma).

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Table 1 Antibacterial and antifungal activities of compounds **(3a–h)**.

	Bacterial strains					Fungal strains		
		E. Coli (MTCC443)	*P. aeruginosa* (MTCC 1688)	*S. aureus* (MTCC 96)	*S. pyogenes* (MTCC 442)	*C. albicans* (MTCC 227)	*A. niger* (MTCC 282)	*A. clavatus* (MTCC 1323)
Comp. Code	–R	Minimum inhibition concentration (MIC) (μg/ml)						
3a	–H	500	125	100	125	500	1000	> 1000
3b	$-CH_3$	250	500	250	125	250	200	200
3c	–OH	62.5	125	250	250	500	500	500
3d	$-NO_2$	200	200	100	100	200	> 1000	> 1000
3e	–F	500	200	500	500	1000	> 1000	> 1000
3f	–Br	100	250	200	200	1000	200	250
3g	–Cl	500	125	100	125	500	1000	> 1000
3h	$-OCH_3$	250	250	250	200	500	1000	> 1000
Ampicillin		100	100	250	100			
Griseofulvin						500	100	100

based molecules have gained much attention as small molecule inhibitors of various targets such as anti-diabetics (Murugan et al., 2009; Momose et al., 1991), aldose reductase (Bruno et al., 2002; Fujishima and Tsuboto, 2002), β-lactamase (Grant et al., 2000), cathepsin D (Whitesitt et al., 1996), PMT inhibitors (Orchard et al., 2004), PDE4 inhibitors (Irvine et al., 2008), and histidine decarboxylase (Free et al., 1971).

Pyrazolo[3,4-*d*]pyrimidines are of considerable chemical and pharmacological importance as purine analogs (Ghorab et al., 2009; Bhat et al., 1981; Zacharie et al., 1996). Various compounds with related structures also possessed anti-tumor and antileukemia activities (Anderson et al., 1990; Avila et al., 1986). On the other hand, substituted pyridazines are often used in medicine because of their pronounced bactericidal and fungicidal effects (Contreras et al., 1999).

We report here, the synthesis of a series of novel rhodanine derivatives containing pyrazole moiety. The synthesized compounds have been structurally established with modern analytical tools like IR, NMR and mass spectroscopy with an aim to find new and more potent antibacterial and antifungal agents.

2. Experimental section

2.1. General

The melting points of the synthesized products were determined using Mettler Toledo FP 62 melting point apparatus (Metter Toledo-Switzerland) and were used without correction. The FT-IR spectra were recorded on a Perkin Elmer Spectrum GX FT-IR System (USA) in a KBr disk. ^1H and ^{13}C spectra (solvent DMSO-d_6) were recorded on 200 MHz Bruker Avance DPX 200 NMR system. TMS was used as an internal standard. The mass spectra were scanned on a Shimadzu QP2010 spectrometer (equipped with a direct inlet probe) operating at 70 eV. Elemental analysis was performed on Perkin Elmer CHNS (O) analyzer (PE-2400 Series II-USA). Analytical TLC was performed on silica gel GF 254.

2.2. Biological assay

2.2.1. Antibacterial activity

The newly synthesized compounds were screened for their antibacterial activity against gram positive bacteria *Staphylococcus aureus* (MTCC-96) and *Streptococcus pyogenes* (MTCC-442) and gram negative bacteria *Escherichia coli* (MTCC-443) and *Pseudomonas aeruginosa* (MTCC-1688). Antibacterial activity was carried out by serial broth dilution method (Pier et al., 1997)|. The standard strains used for the antimicrobial activity were procured from the Institute of Microbial Technology, Chandigarh, India. Compounds (**3a–h**) were screened for their antibacterial activity in triplicate against *E. coli, S. aureus, P. aeruginosa,* and *S. pyogenes* at different concentrations of 1000, 500, 250, 100 (Table 1). The drugs which were found to be active in primary screening were diluted to obtain required concentrations to get more close result. The growths of bacterial cultures were monitored after 24 and 48 h. The lowest concentration, which showed no growth after spot subculture was considered as MIC for each drug. Also, the highest dilution showing at least 99% inhibition is taken as MIC. The test mixture selected for this assay contained 10^8 cells/ml. The standard drug used for this study was ampicillin and it showed MIC at 100, 100, 250, and 100 μg/ml against *E. coli, P. aeruginosa, S. aureus,* and *S. pyogenes*, respectively.

2.2.2. Antifungal activity

Same compounds were tested for antifungal activity in triplicate against *Candida albicans*, *Aspergillus niger*, and *Aspergillus clavatus* at various concentrations of 1000, 500, 250, and 100 μg/ml as shown in (Table 1). The results were recorded in the form of primary and secondary screening. The synthesized compounds were diluted at 1000 μg/ml concentration, as a stock solution. The synthesized compounds which were found to be active in this primary screening were further tested in a second set of dilution against all microorganisms. The lowest concentration, which showed no growth after spot subculture and highest dilution showing at least 99% inhibition was considered as MIC for each drug. Antibiotic griseofulvin was used as a standard drug for antifungal activity study. It showed MIC at concentrations 500, 100 and 100 μg/ml for *C. albicans*, *A. niger* and *A. clavatus*, respectively.

2.3. General synthetic method

2.3.1. Synthesis of 3-(4-chlorophenyl)-2-thioxothiazolidin-4-one (1)

Synthesis of 3-(4-chlorophenyl)-2-thioxothiazolidin-4-one **(1)** was carried according to the procedure reported earlier

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(Redemann, 1947). Characterization data were obtained using various analytical tools and were compared well with literature values. (It is reported as supplementary data).

2.3.2. Synthesis of 1-phenyl-3-(p-substituted phenyl)-1H-pyrazole-4-carbaldehydes (2a–h)

The compounds of 1-phenyl-3-(p-substituted phenyl)-1*H*-pyrazole-4-carbaldehydes **(2a–h)** have been synthesized according to the method reported in the literature (Fieser et al., 1940; Prakash et al., 2011a,b). Characterization data have shown a good correlation with literature values and data of representative compound are attached herewith as supplementary data.

2.3.3. Synthesis of 3-(4-chlorophenyl)-5-((1-phenyl-3-aryl-1H-pyrazol-4-yl) methylene)-2-thioxothiazolidin-4-one (3a–h)

All the compounds (**3a–h**) were synthesized according to the Knoevenagel condensation reaction (Song et al., 2012).

To the solution of 3-(4-chlorophenyl)-2-thioxothiazolidin-4-one (10 mM) (**1**) in ethanol and anhydrous sodium acetate (10 mM), 1-phenyl-3-(*p*-substituted phenyl)-1*H*-pyrazole-4-carbaldehyde (**2a–h**) (10 mM) was added. The reaction mixture was heated and refluxed for 6 h. A bright yellow crystalline product was obtained and the excess solvent was removed under reduced pressure. Crude product was washed with water and isolated by filtration. It was recrystallized from ethanol to give compounds (**3a–h**).

2.4. Physical and spectral data

2.4.1. 3-(4-chlorophenyl)-5-((1,3-diphenyl-1H-pyrazol-4-yl)methylene-2-thioxothiazolidin-4-one) (3a)

Yield 59%; yellow crystalline solid; mp 196–198 °C; IR (KBr, cm^{-1}) *v*: 3113, 3066 (Ar–H stretching, pyrazole –H stretching), 1725 (C═O stretching), 1579, 1499, 1443 (C═N, C═C, aromatic ring), 1332 (C═S stretching), 693 (C–S–C linkage); ^{1}H NMR (DMSO-d_6) δ (ppm): 8.91 (s, 1H, –C═CH group in the pyrazole ring), 8.11-7.06 (m, 15H, Ar–H, C–NH, –C═CH); ^{13}C NMR (DMSO-d_6) δ: 193.6, 180.6, 166.3, 152.6, 138.8, 134.4, 134.3, 132.2, 130.9, 130.6, 129.8, 129.6, 129.6, 129.1, 128.0, 123.0, 122.8, 119.8, 115.8; MS: *m/z*: 473 (M^+, % abundance = 2%), 469, 438, 276, 215, 122; analytical calculations for $C_{25}H_{16}ClN_3OS_2$ (473.0): C, 63.35; H, 3.40; N, 8.87; S, 13.53. found: C, 63.59; H, 3.61; N, 8.98; S, 13.71.

2.4.2. 3-(4-chlorophenyl)-5-((1-phenyl-3-tolyl-1H-pyrazol-4-yl) methylene-2-thioxothiazolidin-4-one) (3b)

Yield 89%; yellow crystalline solid; mp 199–201 °C; IR (KBr, cm^{-1}) *v*: 3100, 3030 (Ar–H stretching, pyrazole –H stretching), 1716 (C═O stretching), 1587, 1525, 1443 (C═N, C═C, aromatic ring), 1339 (C═S stretching), 685 (C–S–C linkage); ^{1}H NMR (DMSO-d_6) δ (ppm): 8.88 (s, 1H, –C═CH group in pyrazole ring), 8.11-7.38 (m, 14H, Ar–H, C–NH, –C═CH), 2.41 (s, 3H, Ar–H); ^{13}C NMR (DMSO-d_6) δ: 193.8, 166.9, 154.5, 146.3, 139.3, 134.6, 131.2, 130.1, 130.0, 129.1, 128.0, 123.5, 122.2, 119.9, 116.0, 21.3; MS: *m/z*: 487(M^+, % abundance = 30%), 290, 257, 187, 154; analytical calculations for $C_{26}H_{18}ClN_3OS_2$ (487.1): C, 63.99; H, 3.72; N, 8.61; S, 13.14. Found: C, 63.81; H, 3.64; N, 8.51; S, 13.23.

2.4.3. 3-(4-chlorophenyl)-5-((3-(4-hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl)methylene-2-thioxothiazolidin-4-one) (3c)

Yield 59%; yellow crystalline solid; mp 261–263 °C; IR (KBr, cm^{-1}) *v*: 3110, 3030 (Ar–H stretching, pyrazole –H stretching), 1724 (C═O stretching), 1594, 1521, 1438 (C═N, C═C, aromatic ring), 1345 (C═S stretching), 685 (C–S–C linkage); ^{1}H NMR (DMSO-d_6) δ (ppm): 8.69 (s, 1H, ═CH group in pyrazole ring), 8.28-7.33 (m, 15H, Ar–H, C–NH, –C═CH); ^{13}H NMR (DMSO-d_6) δ: 190.6, 168.0, 150.6, 148.0, 138.6, 134.7, 133.0, 131.3, 130.6, 123.51, 123.1, 122.7, 121.6, 120.6, 119.5, 115.6; MS: *m/z*: 490 (M^+, % abundance = 2%), 379, 292, 249, 156; analytical calculations for $C_{25}H_{16}ClN_3O_2S_2$ (490.0): C, 61.28; H, 3.29; N, 8.58; S, 13.09. Found: C, 61.32; H, 3.41; N, 8.49; S, 13.22.

2.4.4. 3-(4-chlorophenyl)-5-((3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene-2-thioxothiazolidin-4-one) (3d)

Yield 64%; yellow crystalline solid; mp > 300 °C; IR (KBr, cm^{-1}) *v*: 3121, 3085 (Ar–H stretching, pyrazole –H stretching), 1719 (C═O stretching), 1600, 1530, 1446 (C═N, C═C, aromatic ring), 1345 (C═S stretching), 684 (C–S–C linkage); ^{1}H NMR (DMSO-d_6) δ (ppm): 8.81 (s, 1H, ═CH group in pyrazole ring), 8.47-7.41 (m, 14H, Ar–H, C–NH, –C═CH); ^{13}C NMR (DMSO-d_6) δ: 193.7, 166.6, 150.6, 148.0, 138.6, 134.7, 133.0, 131.7, 131.31, 129.5, 128.4, 127.5, 126.7, 123.5, 123.1, 122.7, 121.6, 120.6, 119.6, 115.6; MS: *m/z*: 518 (M^+, % abundance = 31%), 321, 275, 242, 169; analytical calculations for $C_{25}H_{15}ClN_4O_3S_2$ (519.0): C, 57.86; H, 2.91; N, 10.80; S, 12.36. Found: C, 57.76; H, 2.70; N, 10.89; S, 12.42.

2.4.5. 3-(4-chlorophenyl)-5-((3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene-2-thioxothiazolidin-4-one) (3e)

Yield 81%; yellow crystalline solid; mp 224–226 °C; IR (KBr, cm^{-1}) *v*: 3101, 3059 (Ar–H stretching, pyrazole –H stretching), 1718 (C═O stretching), 1596, 1526, 1442 (C═N, C═C, aromatic ring), 1345 (C═S stretching), 686 (C–S–C linkage); ^{1}H NMR (DMSO-d_6) δ (ppm): 8.92 (s, 1H, ═CH group in the pyrazole ring), 8.10-7.49 (m, 14H, Ar–H, C–NH, –C═CH); ^{13}C NMR (DMSO-d_6) δ: 193.3, 166.3, 163.6, 161.6, 152.9, 138.6, 134.1, 131.0, 130.7, 129.5, 129.3, 128.6, 127.6, 122.7, 122.1, 119.4, 116.1, 115.9; MS: *m/z*: 492 (M^+, % abundance = 10%), 294, 233, 191, 147; analytical calculations for $C_{25}H_{15}ClFN_3OS_2$ (492.0): C, 61.03; H, 3.07; N, 8.54; S, 13.03;. Found: C, 61.22; H, 3.23; N, 8.69; S, 13.24.

2.4.6. 5-((3-(4-bromophenyl)-1-phenyl-1H-pyrazol-4-yl) methylene)-3-(4-chlorophenyl)-2-thioxothiazolidin-4-one (3f)

Yield 61%; yellow crystalline solid; mp 237–239 °C; IR (KBr, cm^{-1}) *v*: 3119, 3063 (Ar–H stretching, pyrazole –H stretching), 1719 (C═O stretching), 1590, 1524, 1439 (C═N, C═C, aromatic ring, 1341 (C═S stretching), 687 (C–S–C linkage); ^{1}H NMR (DMSO-d_6) δ (ppm): 8.90 (s, 1H, ═CH group in the pyrazole ring), 8.11-7.45 (m, 14H, Ar–H, C–NH, –C═CH); ^{13}C NMR (DMSO-d_6) δ: 193.8, 180.8, 166.8, 152.8, 139.0, 134.6, 134.5, 132.5, 131.17, 130.8, 130.1, 129.9, 129.3, 128.2, 123.0, 120.0, 116.1; MS: *m/z*: 552(M^+, % abundance = 25%), 356, 275, 231, 169; analytical calculations for $C_{25}H_{15}BrClN_3OS_2$ (552.9): C, 54.31; H, 2.73; N, 7.60; S, 11.60. Found: C, 54.18; H, 2.67; N, 7.79; S, 11.76.

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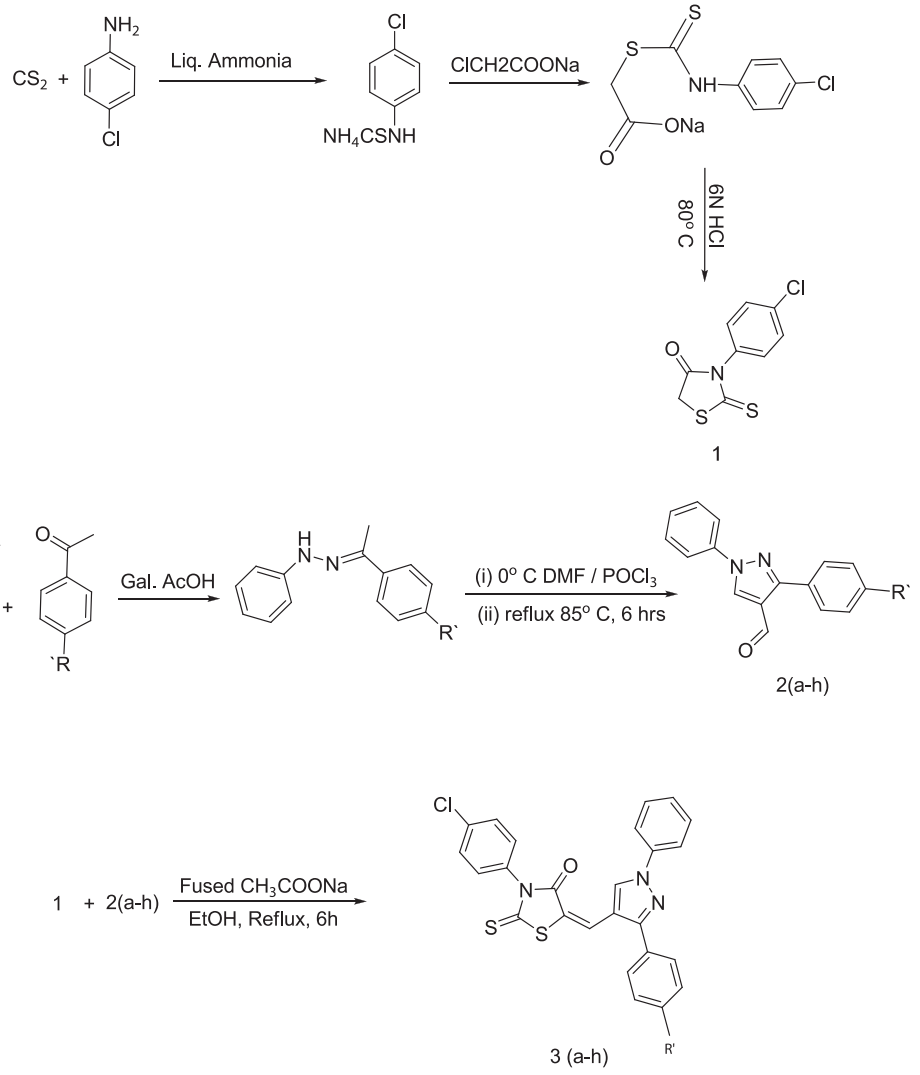
*2.4.7. 3-(4-chlorophenyl)-5-((3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene-2-thioxothiazolidin-4-one) (**3g**)*

Yield 76%; yellow crystalline solid; mp 240–242 °C; IR (KBr, cm^{-1}) *v*: 3095, 3060 (Ar–H stretching, pyrazole –H stretching), 1730 (C=O stretching), 1594, 1496, 1430 (C=N, C=C, aromatic ring), 1342 (C=S stretching), 683 (C–S–C linkage); ^{1}H NMR (DMSO-d_6) δ (ppm): 8.91 (s, 1H, =CH group in the pyrazole ring), 8.11-7.45 (m, 14H, Ar–H, C–NH, –C=CH); ^{13}C NMR (DMSO-d_6) δ: 193.8, 166.8, 153.1, 134.5, 131.2, 130.9, 130.4, 130.1, 129.90, 129.6, 129.3, 128.2, 123.1, 122.9, 120.0, 116.1; MS: *m/z*: 508 (M^+, % abundance = 12%), 310, 275, 231, 169; analytical calculations for $C_{25}H_{15}Cl_2N_3OS_2$ (508.4): C, 59.06; H, 2.97; N, 8.26; S, 12.61. Found: C, 59.11; H, 2.82; N, 8.19; S, 12.51.

*2.4.8. 3-(4-chlorophenyl)-5-((3-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)methylene-2-thioxothiazolidin-4-one) (**3h**)*

Yield 81%; yellow crystalline solid; mp 213–215 °C; IR (KBr, cm^{-1}) *v*: 3103, 3036 (Ar–H stretching, pyrazole –H stretching), 1712 (C=O stretching), 1586, 1520, 1439 (C=N, C=C, aromatic ring), 1338 (C=S stretching), 684 (C–S–C linkage); ^{1}H NMR (DMSO-d_6) δ (ppm): 8.86 (s, 1H, =CH group in the pyrazole ring), 8.10-7.12 (m, 14H, Ar–H, C–NH, –C=CH), 3.84 (s, 3H, Ar–OCH_3); ^{13}C NMR (DMSO-d_6) δ: 193.3, 166.4, 160.0, 153.8, 138.6, 134.1, 130.7, 130.0, 129.5, 129.3, 128.5, 127.5, 123.2, 121.6, 119.4, 115.4, 114.4, 55.2; MS: *m/z*: 504 (M^+, % abundance = 12%), 306, 263, 169, 111; analytical calculations for $C_{26}H_{18}ClN_3O_2S_2$ (504.0): C, 61.96; H, 3.60; N, 8.34; S, 12.72. Found: C, 61.83; H, 3.42; N, 8.19; S, 12.91.



	3a	*3b*	*3c*	*3d*	*3e*	*3f*	*3g*	*3h*
R`	**-H**	**-CH_3**	**-OH**	**-NO_2**	**-F**	**-Br**	**-Cl**	**-OCH_3**

Scheme 1 Schematic representation of synthesis of 3-(4-chlorophenyl)-5-((1-phenyl-3-aryl 1*H*-pyrazol-4-yl) methylene)-2-thioxothiazolidin-4-one (**3a–h**).

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3. Results and discussion

3.1. Chemistry

The synthetic route followed for the preparation of the novel 3-(4-chlorophenyl)-5-((1-phenyl-3-aryl-1*H*-pyrazol-4-yl) methylene)-2-thioxothiazolidin-4-one (**3a–h**) derivatives is illustrated in Scheme 1. The compound 3-(4-chlorophenyl)-2-thioxothiazolidin-4-one (**1**) was synthesized from the reaction of carbon disulfide, ammonia, and chloroacetic acid **(1)** (Redemann, 1947). The ketones on treatment with phenyl hydrazine formed required Schiff's bases. The Schiff's bases of ketones on treatment with dimethyl formamide and phosphorous oxychloride underwent cyclization reaction forming pyrazole derivatives and got formylated on to the pyrazole ring **(2a–h)** (Fieser et al., 1940). The final compounds 3-(4-chlorophenyl)-5-((1-phenyl-3-aryl-1*H*-pyrazol-4-yl)methylene)-2-thioxothiazolidin-4-one (**3a–h**) were synthesized with 3-(4-chlorophenyl)-2-thioxothiazolidin-4-one (**1**) and 1-phenyl-3-(*p*-substituted phenyl)-1*H*-pyrazole-4-carbaldehyde (**2a–h**) (Scheme 1). All the synthesized compounds were characterized by FT-IR, ^{13}C and ^{1}H NMR and GC–MS. The expected IR spectra were assigned to the synthesized compounds (**3a–h**). The band observed around 1350–1320 cm^{-1} was attributed to –C═S stretching vibration of the thiazole ring. Bands at about 1600–1560 cm^{-1} were attributed to –C═N stretching vibration of pyrazole moiety. Strong bands in the region 1740–1700 cm^{-1} was due to –C═O stretching of the amide group. ^{1}H and ^{13}C NMR and mass spectral data of compounds (**3a–h**) are shown in Section 2. The ^{1}H NMR spectra showed the most characteristics olefinic proton C═CH deshielded at δ = 8.9–8.6 ppm in the pyrazole ring (Fig. 1). ^{13}C NMR spectra show chemical shift around 193–190 due to the presence of –C═S in the rhodanine ring. Chemical shift at 168–166 represents the –C═O in the rhodanine ring and at 154–150 represents the –C═N in the pyrazole ring (Fig. 2). All these compounds were subjected to C, H, N and S analysis.

3.2. Antimicrobial activity

Antimicrobial study of synthesized compounds was performed against two gram negative bacterial strains namely *E. coli,* and *P. aeruginosa* and two gram positive bacterial stains *namely S. aureus,* and *S. pyogenes* and against three different fungi e.g. *C.*

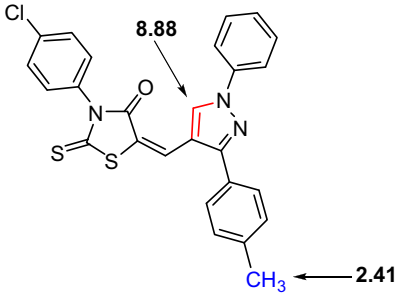

Figure 1 ^{1}H NMR chemical shift (δ) representation for compound **3b**.

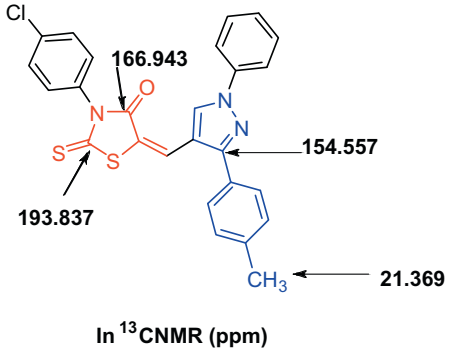

Figure 2 ^{13}C NMR chemical shift (δ) representation for compound **3b**.

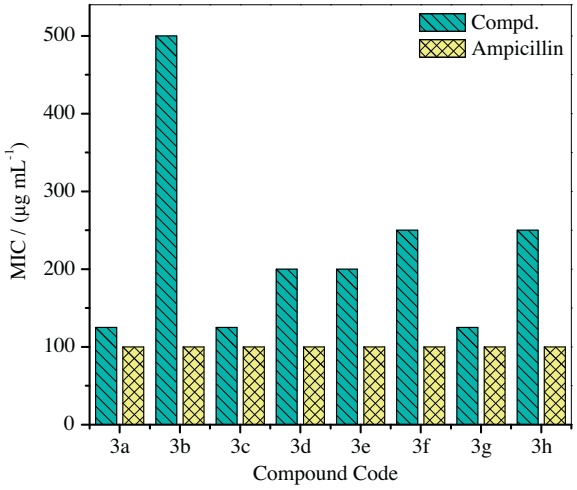

Figure 3 Graphical representation of "MIC" values comparison of synthesized compounds 3-(4-chlorophenyl)-5-((1-phenyl-3-aryl-1*H*-pyrazol-4-yl)methylene)-2-thioxothiazolidin-4-one (**3a–h**) for the *Pseudomonas aeruginosa* bacterial strain.

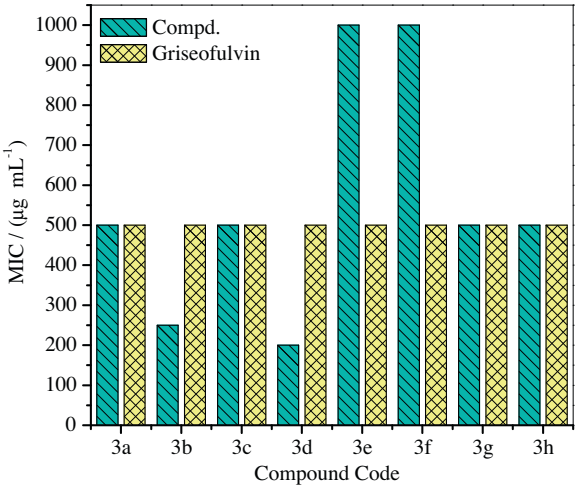

Figure 4 Graphical representation of "MIC" values comparison of synthesized compounds 3-(4-chlorophenyl)-5-((1-phenyl-3-aryl-1*H*-pyrazol-4-yl)methylene)-2-thioxothiazolidin-4-one (**3a–h**) for the *Candida albicans* fungal strain.

albicans, A. niger and *A. clavatus*. The standard antibiotics namely ampicillin and griseofulvin were used as positive control for bacteria and fungi, respectively. Solvent control was also checked to know the effect of the solvent on growth of microbes. The results were recorded for each tested compounds as the minimum inhibition concentration (MIC).

The results of antibacterial screening of newly synthesized compounds are presented in (Table 1) (Fig. 3 and Fig. 4). From the results, it has been revealed that all the tested compounds possess moderate to good antimicrobial activity against selected bacteria strains (*E. coli, S. aureus, P. aeruginosa,* and *S. pyogenes*). On the basis of zone of inhibition test against test bacterium, *E. coli*, compound **3c** (R′ = 4-OH) was found to have very good activity and compound **3f** (R′ = 4-Br) possessed good activity, while compound **3d** (R′ = 4-NO_2) showed moderate activity when compared with the standard drug ampicillin. In case of *P. aeruginosa*, compounds **3a** (R′ = 4-H), **3c** (R′ = 4-OH) and **3g** (R′ = 4-Cl) possessed moderate activity as compared to the standard drug ampicillin. For, *S. aureus*, compound **3d** (R′ = 4-NO_2) was potent as it showed very good activity while other compounds like **3b** (R′ = 4-CH_3), **3c** (R′ = 4-OH), **3f** (R′ = 4-Br) and **3h** (R′ = 4-OCH_3) possessed only good activity when compared to the standard drug ampicillin. For, *S. pyogenes*, compound **3d** (R′ = 4-NO_2) revealed good activity and compounds **3a** (R′ = 4-H), **3b** C and **3g** (R′ = 4-Cl) showed moderate activity in comparison to the standard drug ampicillin. It is also concluded that compounds **3c** (R′ = 4-OH) and **3d** (R′ = 4-NO_2) showed better antibacterial activity in comparison with their parent compound (Fig. 5 and Fig. 6). The reason for different sensitivities between gram-positive and gram-negative bacteria could be ascribed to the morphological difference between these micro-organisms. Gram-negative bacteria have an outer phospholipidic membrane carrying the structural lipopolysaccharide components. This makes the cell wall impermeable to lipophilic solutes, while porins constitute a selective barrier to the hydrophilic solutes with an exclusion limit of about 600 Da (Nikaido and Vaara, 1985). The Gram-positive bacteria had been found to be more susceptible since they have only an outer peptidoglycan layer which is not an effective permeability barrier (Scherrer, 1971).

3.3. Antifungal activity

Antifungal screening of newly synthesized compounds is summarized in Table 1. All the compounds were also tested for their in vitro antifungal activity against three different fungal strains namely *C. albicans*, *A. niger* and *A. clavatus*. Griseofulvin was used as a reference drug for comparison of the activity of the tested compounds and the results were recorded as the percentage of the mycelial growth inhibitions. From the results, it has been revealed that most of the compounds possessed remarkable antifungal activity against selected fungal strains. For, *C. albicans,* compounds **3b** (R′ = 4-CH_3) and **3d** (R′ = 4-NO_2) showed very good activity and compounds **3a** (R′ = 4-H), **3c** (R′ = 4-OH), **3g** (R′ = 4-Cl) and **3h** (R′ = 4-OCH_3) showed good activity as compared to the standard drug griseofulvin. For, *A. niger* strains, compounds **3b** (R′ = 4-CH_3) and **3f** (R′ = 4-Br) possessed moderate activity as compared to the standard drug. In case of *A. clavatus,* compounds **3b** (R′ = 4-CH_3) and **3f** (R′ = 4-Br) represented as moderately potential molecule as compared to the standard drug griseofulvin.

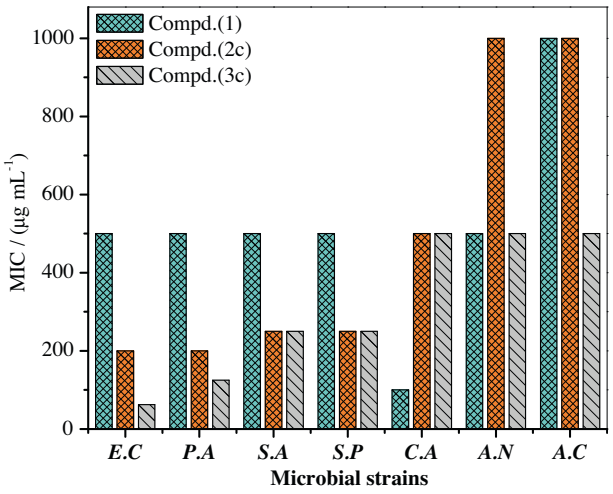

Figure 5 Graphical representation of "MIC" values comparison of synthesized 3-(4 chlorophenyl)-5-((3-(4-hydroxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene-2-thioxothiazolidin-4-one) (**3c**) with 3-(4-chlorophenyl)-2-thioxothiazolidin-4-one (**1**) and (3-(4-chlorophenyl)-5-((3-(4-hydroxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl) methylene)-2-thioxothiazolidin-4-one (**2c**) for said bacterial and fungal strain.

4. Conclusions

A series of compounds 3-(4-chlorophenyl)-5-((1-phenyl-3-aryl-1*H*-pyrazol-4-yl) methylene)-2-thioxothiazolidin-4-one

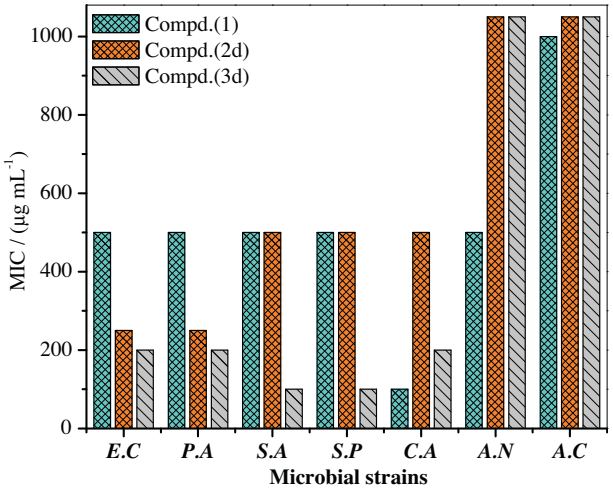

Figure 6 Graphical representation of "MIC" values comparison of synthesized 3-(4-chlorophenyl)-5-((3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene-2-thioxothiazolidin-4-one) (**3d**) with 3-(4-chlorophenyl)-2-thioxothiazolidin-4-one (**1**) and3-(4-chlorophenyl)-5-((3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)-2-thioxothiazolidin-4-one (**2d**) for said bacterial and fungal strain.

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(**3a–h**) have been synthesized from 3-(4-chlorophenyl)-2-thioxothiazolidin-4-one (**1**) and 1-phenyl-3-(*p*-substituted phenyl)-1*H*-pyrazole-4-carbaldehydes (**2a–h**). Analytical and spectral data (FT-IR, ^{1}H-NMR, ^{13}C-NMR, GC–MS) of all the synthesized compounds are in full agreement with the proposed structure. Comparison of the antimicrobial results of synthesized compounds (**3a–h**) has revealed that the addition of pyrazole derivatives in 3-(4-chlorophenyl)-2-thioxothiazolidin-4-one (**1**) has improved their antimicrobial activities. The series of compounds synthesized as 3-(4-chlorophenyl)-5-((1-phenyl-3-aryl-1*H*-pyrazol-4-yl) methylene)-2-thioxothiazolidin-4-one (**3a–h**) exhibited moderate to very good antimicrobial activities. The reason for different sensitivities between gram-positive and gram-negative bacteria could be ascribed to the morphological difference between these micro-organisms.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.arabjc.2013.05.029.

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