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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

The synthesis and screening of the antimicrobial activity of some novel 3-(furan-2-yl)-1-(aryl)-3-(phenylthio) propan-1-one derivatives

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Abstract A series of thiophenol adducts (**3a–m**) were prepared by addition of thiophenol to chalcones (**1a–m**) in the presence of a catalytic amount of KO*t*-Bu in solvent free conditions. In addition, the antibacterial and antifungal in vitro properties were tested against some human pathogenic microorganisms by employing the disk diffusion technique. A majority of compounds were remarkably active against several of the microorganisms. Compound **3i** was determined to be the most active compound.

Keywords Thiophenol · Chalcones · Antimicrobial activity

Introduction

The preparation of sulfur-containing molecules has long been a mainstay of organic synthesis because of their broad application to organic and medicinal chemistry (Li *et al.*, 2006). The thio-Michael addition reaction has emerged as one of the most powerful tools for C–S bond formation (Fujita and Nagao, 1977). Thio-Michael addition provides a widespread synthetic utility in organic chemistry (i) for chemo-selective protection of olefinic double band in unsaturated carbonyl compounds, (Trost and Keeley, 1975), (ii) for the generation of acyl vinyl cation equivalents (Bakuzia and Bakuzis, 1981), and (iii) for the synthesis of medicinally important compounds (Kumar *et al.*, 1991). Thiol nucleophilic reagents are also known to show chemical reactivity toward chalcones, chalcon epoxides, chalcone dibromides, and their corresponding propynones. Conjugate addition of sulfur-centered nucleophiles to α,β-unsaturated carbonyls such as chalcones serves as a powerful synthetic method in this area of sulfur chemistry (Garg *et al.*, 2005; Sasai *et al.*, 1995; Lee *et al.*, 2001; Cheng and Cromer, 2002).

A large number of reports are available on the inhibitory effect of chalcone derivatives (Awasthi *et al.*, 2009; Siddiqui *et al.*, 2008; Gopalakrishnan *et al.*, 2009) on enzymes and their bacteriostatic activity (Elba, 2000). As already sulfur-containing compounds are known for their diverse pharmacologic actions, the compounds were also screened for antibacterial activity (Bhat and Singh, 1988). Furthermore, some sulfur-containing compounds were found to be antifungal and anticancer agents (Tandon *et al.*, 2004). In addition, there are numerous reports on the antifungal, antimicrobial, antiatherosclerotic (Apitz-Castro *et al.*, 1983), hypocholesterolemic, hyperlipidemic (Bordia *et al.*, 1975) anti-thrombotic, antioxidant and anti-diabetic effects (Sheela and Augusti, 1992) of sulfur compounds.

The target compounds, **3a–m**, were synthesized as depicted in Scheme 1.

Results and discussion

Chemistry

In this study, a series of novel chalcone derivatives containing thiophenol (**3a–m**) were prepared by the addition of thiophenol to chalcones (**1a–m**). The reaction of chalcones **1a–m** with thiophenol in the presence of a catalytic amount

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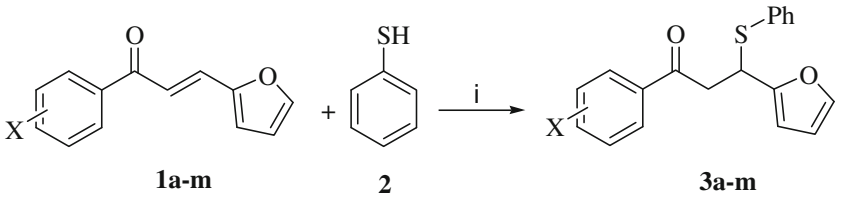

Scheme 1 Schematic representation of the synthesized compounds. **3a**: X = *o*-OCH3, **3b**: X = *m*-OCH3, **3c**: X = *p*-OCH3, **3d**: X = *o*-Cl, **3e**: X = *m*-Cl, **3f**: X = *p*-Cl, **3g**: X = *o*-Br, **3h**: X = *m*-Br, **3ı**: X = *p*-Br, **3i**: X = *o*-OH, **3j**: X = *p*-OH, **3k**: X = *o*-NO2, **3l**: X = *m*-NO2, **3m**: X = *p*-NO_2. i = reagents and conditions: 6 % mol KO*t*-Bu, r.t., 3h

(% 6 mol) of KO*t*-Bu at room temperature for 3 h gave solely the products (**3a**–**m**) of 1,4-addition of thiophenol in good yields. When this reaction was employed in a solvent like $CHCl_3$ and CH_2Cl_2, the reaction took a longer time (36 h) and resulted in low yields.

The crude products were purified on a short silica gel column, which was followed by crystallization from $CHCl_3$ /*n*-hexane (3:7), and chalcone derivatives (**1a**–**m**) were obtained in yields of 73–96%. All synthesized compounds (**3a**–**m**) are novel compounds according to our literature survey.

The structures of the synthesized compounds **3a**–**m** were identified on the basis of Fourier-transform infrared (FTIR) spectroscopy, ^{1}H nuclear magnetic resonance (NMR), and elemental analysis. Spectral values support the expected structures.

Antimicrobial activity

The synthesized compounds **3a**–**j** underwent general antimicrobial screening. Two yeasts (*Candida albicans* ATCC 1213 and *Candida utilis* KUEN 1031), five gram-positive bacteria (*Proteus Vulgaris* KUEN 1329, *Bacillus cereus* DSM 4312, *Bacillus subtilis* ATCC 6633, *Staphylococcus aureus* ATCC 29213, *Streptococcus Pyogenes* ATCC 176), and four gram-negative bacteria (*Escherichia coli* 111, *Pseudomonas aeruginosa* ATCC 9027, *Salmonella enteridis* ATCC 13076, and *Pseudomonas aeruginosa* ATCC 27859) were selected to evaluate the effectiveness of the test compounds (**3a**–**j**) (Table 1).

A comparison of the compounds' activity with that of standard antibiotic SCF is effectively presented in Table 1. All compounds except **3c** demonstrated significant activity against *P. vulgaris,* while **3i** has the same activity as SCF. Compound **3i** showed remarkable activity against *B. cereus*, *B. subtilis* and *St. pyogenes,* whereas the other compounds displayed moderate and very low activity. Compounds **3a**, **3b**, **3d**, **3e**, **3g**, **3h**, and **3i** demonstrated a significant level of activity against *S. aureus*. Compounds **3a** and **3b** showed moderate activity against *E. coli*, while the other compounds showed very low activity or no

Table 1 Antimicrobial activity of thiophenol derivatives (**3a**–**j**) (105 μg/disc) against the bacterial strains and *Candida* sp. isolates using the disc diffusion method

	3a	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**	**3ı**	**3i**	**3j**	SCF	MeOH
Gram-positive bacteria													
P. vulgaris KUEN 1329	**15**	**14**	–	**16**	**17**	**14**	**16**	**15**	**15**	**18**	**17**	**18**	**13**
B. cereus DSM 4312	10	–	–	11	11	10	12	13	–	15	–	26	9
B. subtilis ATCC 6633	14	12	–	15	14	–	15	–	–	17	–	23	11
S. aureus ATCC 29213	**17**	–	–	**18**	**16**	–	**17**	**16**	–	**16**	–	**22**	11
St. pyogenes ATCC 176	15	–	13	–	14	13	13	–	–	**17**	–	**19**	12
Gram-negative bacteria													
E. coli 111	**13**	**14**	10	–	–	10	10	–	–	–	10	**20**	9
P. aeruginosa ATCC 9027	15	–	13	14	15	15	15	**16**	15	14	14	**22**	10
S. enteridis ATCC 13076	**18**	**17**	–	**18**	**19**	**17**	**15**	**16**	**17**	**19**	**17**	**23**	12
P. aeruginosa ATCC 27859	**15**	–	–	**14**	**16**	–	**16**	–	–	**17**	–	**16**	12
Yeasts													
C. albicans ATCC 1213	**17**	**17**	12	**16**	**17**	14	**17**	**16**	**11**	**21**	**20**	**23**	6
C. utilis KUEN 1031	14	13	12	13	15	14	15	14	13	15	13	**22**	10

Bold values show significant antimicrobial activity when compared with that of the standard antibiotic

SCF sulbactam (30 μg) + cefoperazona (75 μg) = positive control

MeOH methanol = negative control

activity. All compounds except **3b** showed moderate activity against *P. aeruginosa* ATCC 9027. All compounds except **3c** were found to display significant activity against *S. enteridis*. Compound **3i** was more active than SCF against *P. aeruginosa* ATCC 27859, while **3e** and **3g** showed the same activity as SCF, and compounds **3a** and **3d** showed significant activity. The compounds other than **3c**, **3f**, and **3ı** demonstrated significant levels of activity against yeast strain *C. albinas*. All compounds showed moderate activity against *C. utilis*. As a result, it could be argued that the most active compound is **3i** according to the disc diffusion method.

Among the synthesized compounds, **3a–j** were subjected to MIC (minimum inhibitory concentrations) studies and the results are given in Table 2. Tetracycline, ceftriaxone, and amphicilin were chosen as positive control. MIC values were determined by serial microdilution technique in Mueller–Hinton Broth for antibacterial assay and in Sabouraud Dextrose Broth for antifungal assay.

As seen in the Table 2, while all compounds showed lower activity than positive controls against *P. vulgaris*, **3i** showed the same activity (MIC: 15.62 μg/ml as CEF and AMP. Moreover, **3f**, **3i**, and **3j** demonstrated better activity (MIC: 7.81 μg/ml) than CEF and AMP. Compounds **3a**, **3c** and **3ı** showed the same activity (MIC: 62.5 μg/ml) against *B. cereus,* while other compounds showed better activity (MIC: 15.62–31.25 μg/ml) than positive controls. Compound **3ı** showed the same activity (MIC: 15.62 μg/ml) as CS-T against *B. subtilis* while others demonstrated lower activity than positive controls. Compounds **3a**, **3d**, **3e**, **3g**, **3h**, **3i** and **3j** showed better activity (MIC: 7.81–31.25 μg/ml) than positive controls against *S. aureus*. Only compound **3i** showed the same activity (MIC: 3.9 μg/ml) as positive controls against *St. pyogenes*. Compounds **3a**, **3b**, **3c**, **3f**, **3g**, **3i**, and **3j** showed better activity (MIC: 15.62–62.5 μg/ml) than positive controls against *E. coli*, while others showed lower activity. Compounds **3e** and **3h** demonstrated the same activity (MIC: 15.62 μg/ml as CEF against *P. aeruginosa* ATCC 9027, while other compounds showed lower activity than positive controls. All compounds except **3c** and **3g** showed lower activity than CS-T against *S. enteridis*, while they demonstrated better activity (MIC: 15.62–62.5 μg/ml) than CEF and AMP. Except **3f** and **3h**, other compounds demonstrated better activity (MIC: 31.25–125 μg/ml) than standard against *P. aeruginosa* ATCC 27859. Compounds **3c**, **3g** and **3h** showed lower activity (MIC: >125 μg/ml) than standard against *C. albinas*, while the others demonstrated better activity (MIC: 15.62–125 μg/ml) than standard. Compounds **3b**, **3e**, and **3i** showed better activity (MIC: 7.81–15.62 μg/ml) against *C. utilis,* while the others have lower activity (MIC: ≥125–62.5 μg/ml) than standard (MIC: 7.81–15.62 μg/ml).

Concerning SAR, compound **3i** containing *o*-OH group found to be the most active compound according to the inhibition zone and MIC values. In addition, when the effects of methoxy substituent on activity against microorganism were investigated, 4-methoxy derivative **3c**

Table 2 Minimum-inhibitory concentrations (MIC, in mg/ml) of synthesized compounds (**3a–j**)

	3a	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**	**3ı**	**3i**	**3j**	MeOH	CS-T	CEF	AMP
Gram-positive bacteria															
P. vulgaris KUEN 1329	31.25	31.25	62.5	31.25	31.25	**7.81**	62.5	31.25	**15.62**	**7.81**	**7.81**	–	3.9	15.62	15.62
B. cereus DSM 4312	**31.25**	**62.5**	**62.5**	**31.25**	**31.25**	**31.25**	**31.25**	**31.25**	**62.5**	**15.62**	**31.25**	–	62.5	–	–
B. subtilis ATCC 6633	31.25	62.5	125	31.25	31.25	–	31.25	31.25	31.25	**15.62**	31.25	–	15.62	3.9	–
S. aureus ATCC 29213	**7.81**	–	–	**7.81**	**31.25**	–	**7.81**	**15.62**	–	**15.62**	**31.25**	–	125	–	–
St. pyogenes ATCC 176	31.25	7.81	–	15.62	31.25	125	–	31.25	7.81	**3.9**	7.81	–	3.9	3.9	3.9
Gram-negative bacteria															
E. coli 111	**62.5**	**31.25**	**62.5**	–	–	**62.5**	**62.5**	–	–	**15.62**	**62.5**	–	125	–	–
P. aeruginosa ATCC 9027	31.25	–	62.5	31.25	**15.62**	–	–	**15.62**	31.25	–	62.5	–	3.9	15.62	7.81
S. enteridis ATCC 13076	**15.62**	**62.5**	–	**15.62**	**15.62**	**62.5**	–	**31.25**	**62.5**	**31.25**	**62.5**	–	7.81	125	–
P. aeruginosa ATCC 27859	**62.5**	**125**	**62.5**	**125**	**62.5**	–	**31.25**	–	**31.25**	**125**	**62.5**	–	–	–	–
Yeasts															
C. albicans ATCC 1213	125	**15.62**	–	**15.62**	**15.62**	62.5	–	–	**15.62**	125	**15.62**	–	125	–	–
C. utilis KUEN 1031	125	**15.62**	125	125	**15.62**	62.5	–	–	**7.81**	125	62.5	–	15.62	15.62	7.81

Bold values show significant antimicrobial activity when compared with that of the standard antibiotic

CS-T tetracycline, *CEF* ceftriaxone, *AMP* amphiciline = positive control

MeOH methanol = negative control

–, >125 μg/ml

showed lower activity than 2- and 3-methoxy derivatives (**3a** and **3b**). In addition, 4-choloro derivative **3f** showed lower activity than 2- and 3-choloro derivatives (**3d** and **3e**). While 4-bromo derivative **3ı** showed better activity than 2- and 3-bromo derivatives against yeast strains, 2- and 3-bromo derivatives (**3g** and **3h**) demonstrated better activity than **3i** against bacteria.

Experimental

Chemistry

Melting points were measured on Electrothermal 9100 apparatus. IR spectrums (KBr disc or $CHCl_3$) were recorded on a Jasco FT/IR-430 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX-400 instrument. As internal standards served TMS (δ 0.00) for ^1H NMR and $CDCl_3$ (δ 77.0) for ^{13}C NMR spectroscopy *J* values are given in Hz. The multiplicities of the signals in the ^1H NMR spectra are abbreviated by s (singlet), d (doublet), t (triplet), q (quarted), m (multiplet), br (broad) and combinations thereof. Elemental analyses were obtained from a LECO CHNS 932 Elemental Analyzer. All column chromatographies were performed on silica gel (60-230 mesh, Merck).

*General procedure for the synthesis of **3a–3m***

To a magnetically stirred mixture of chalcone derivative (1 mmol) and thiophenol (2 and/or 3 mmol) was added a catalytic amount of KO*t*-Bu (6% mol) and the reaction mixture was stirred at room temperature for 3 h. Then, the mixture was washed with dilute HCl and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and removed the solvent in vacuum. The residue was purified on a silica gel column, eluted with $CHCl_3$/*n*-hexane (3:7) and/or crystallized in $CHCl_3$/*n*-hexane (3:7).

Data

3-(Furan–2-yl)-1-(2-methoxyphenyl)-3-(phenylthio)propan-1-one (**3a**): Brown oil, yield: 93%. **^{1}H-NMR** (400 MHz, $CDCl_3$, ppm): δ 7.68 (dd, *J* = 7.7, 1.8 Hz, 1H, H10), 7.48 (dd, *J* = 15.6, 1.8 Hz, 1H, H12), 7.48 (dd, *J* = 1.7, 1.1 Hz, 1H, H2), 7.37–7.33 (m, 2H, H14, H15), 7.30–7.26 (m, 2H, H17, H18), 7.02–6.95 (m, 2H, H11, H13), 6.23 (dd, *J* = 3.2, 1.8 Hz, H3), 6.01 (d, *J* = 3.2 Hz, 1H, H4), 4.96 (dd, *J* = 8.0, 6.5 Hz, H6), 3.99 (s, 3H, –OCH_3), 3.77 (dd, *J* = 17.5, 8.1 Hz, 1H, H7), 3.58 (dd, *J* = 17.5, 6.4 Hz, 1H, H7). **^{13}C-NMR** (100 MHz, $CDCl_3$, ppm): δ 198.6, 158.6, 153.8, 141.8, 133.9, 133.8, 130.6, 128.7, 127.9, 120.7, 111.5, 110.2, 107.1, 55.5, 47.4, 41.8. **IR**: (KBr cm^{-1}) 3073, 2942, 2838, 1673, 1596, 1484, 1465, 1436, 1288, 1243, 754, 692. **Anal. Cald** for $C_{20}H_{18}O_3S$: C, 70.98; H, 5.36; S, 9.47. Found: C, 70.83; H, 5.12; S, 9.33.

3-(Furan–2-yl)-1-(3-methoxyphenyl)-3-(phenylthio)propan-1-one (**3b**): Brown oil, yield: 81%. **^{1}H-NMR** (400 MHz, $CDCl_3$, ppm): δ 7.54–7.12 (m, 10H, H2, H10, H11, H12, H13, H14, H15, H17, H16, H18), 6.25 (dd, *J* = 3.2, 1.8 Hz, H3), 6.05 (d, *J* = 3.2 Hz, 1H, H4), 5.03 (dd, *J* = 7.7, 6.5 Hz, H6), 3.84 (s, 3H, –OCH_3), 3.75 (dd, *J* = 17.3, 7.8 Hz, 1H, H7), 3.53 (dd, *J* = 17.3, 6.3 Hz, 1H, H7). **^{13}C-NMR** (100 MHz, $CDCl_3$, ppm): δ 196.4, 159.9, 153.3, 141.9, 137.9, 133.8, 129.7, 128.9, 128.1, 120.7, 119.9, 112.3, 110.3, 107.4, 55.4, 42.1, 41.6. **IR**: (KBr cm^{-1}) 3073, 3004, 2938, 2834, 1685, 1596, 1583, 1482, 1430, 1288, 1259, 1041, 1012, 786, 740, 692. **Anal. Cald** for $C_{20}H_{18}O_3S$: C, 70.98; H, 5.36; S, 9.47. Found: C, 70.83; H, 5.19; S, 9.33.

3-(Furan–2-yl)-1-(4-methoxyphenyl)-3-(phenylthio)propan-1-one (**3c**): Yellow solid, yield: 95%, mp 64–67°C. **^{1}H-NMR** (400 MHz, $CDCl_3$, ppm): δ 7.93 (d, *J* = 8.9 Hz, 2H, AA', H10, H13), 7.37–7.27 (m, 6H, H2, H14, H15, H16, H17, H18), 6.95 (d, *J* = 8.9 Hz, 2H, XX', H11, H12), 6.24 (dd, *J* = 3.2, 1.8 Hz, 1H, H3), 6.04 (d, *J* = 3.2 Hz, 1H, H4), 5.02 (dd, *J* = 7.8, 6.3 Hz, 1H, H6), 3.87 (s, 3H), 3.67 (dd, *J* = 17.0, 7.9 Hz, 1H, H7), 3.51 (dd, *J* = 17.0, 6.3 Hz, 1H, H7). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 195.0, 163.7, 153.4, 141.9, 133.7, 133.4, 130.5, 129.7, 128.8, 128.0, 113.8, 110.3, 107.4, 55.5, 41.7, 41.6. **IR**: (KBr cm^{-1}) 3421, 1675, 1600, 1509, 1438, 1419, 1261, 1172, 771, 750, 692. **Anal. Cald** for $C_{20}H_{18}O_3S$: C, 70.98; H, 5.36; S, 9.47. Found: C, 70.84; H, 5.12; S, 9.41.

1-(2-Chlorophenyl)-3-(Furan-2-yl)-3-(phenylthio)propan-1-one (**3d**): Brown oil, yield: 87%. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.55–7.21 (m, 10H, H2, H10, H11, H12, H13, H14, H15, H17, H16, H18), 6.26 (dd, *J* = 3.2, 1.8 Hz, H3), 6.06 (d, *J* = 3.2 Hz, 1H, H4), 4.97 (t, *J* = 7.3 Hz, H6), 3.72 (dd, *J* = 17.2, 7.8 Hz, 1H, H7), 3.60 (dd, *J* = 17.2, 6.9 Hz, 1H, H7). **^{13}C-NMR** (100 MHz, $CDCl_3$, ppm): δ 199.5, 153.1, 142.0, 138.8, 133.9, 133.1, 132.1, 130.9, 130.5, 129.4, 129.2, 128.9, 128.2, 127.5, 127.2, 127.0, 110.4, 107.6, 46.4, 42.0. **IR**: (KBr cm^{-1}) 3058, 1693, 1589, 1502, 1477, 1434, 1284, 1218, 1149, 1012, 771, 738, 690. **Anal. Cald** for $C_{19}H_{15}ClO_2S$: C, 66.56; H, 4.41; S, 9.35; Found: 66.40; H, 4.32; S, 9.23.

1-(3-Chlorophenyl)-3-(Furan-2-yl)-3-(phenylthio)propan-1-one (**3e**): Brown oil, yield: 90%. **^{1}H-NMR** (400 MHz, $CDCl_3$, ppm): δ 7.90 (t, *J* = 1.7 Hz, 1H, H14), 7.81 (dt, *J* = 7.8, 1.1 Hz, 1H, H10), 7.57–7.41 (m, 2H, H11, H12), 7.39–7.27 (m, 6H, H2, H14, H15, H17, H16, H18), 6.25 (dd, *J* = 3.2, 1.8 Hz, H3), 6.05 (d, *J* = 3.2 Hz, 1H, H4), 4.98 (dd, *J* = 7.6, 6.5 Hz, 1H, H6), 3.69 (dd, *J* = 17.3, 7.8 Hz, 1H, H7), 3.52 (dd, *J* = 17.3, 6.4 Hz, 1H, H7).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ 195.4, 153.1, 142.0, 138.1, 133.8, 133.3, 130.0, 129.1, 128.9, 128.2, 128.1, 127.4, 127.1, 126.2, 110.3, 107.5, 42.1, 41.6. **IR**: (KBr cm^{-1}) 3062, 2923, 2852, 1689, 1600, 1571, 1477, 1438, 1423, 1284, 1220, 1014, 786, 738, 690. **Anal. Cald** for $C_{19}H_{15}ClO_2S$: C, 66.56; H, 4.41; S, 9.35. Found: 66.50; H, 4.22; S, 9.28.

1-(4-Chlorophenyl)-3-(Furan-2-yl)-3-(phenylthio)propan-1-one (**3f**): Yellow solid, yield: 90%, mp 74–76°C. **^{1}H-NMR** (400 MHz, $CDCl_3$, ppm): δ 7.74 (d, J = 13.4 Hz, 2H, AA', H10, H13), 7.30 (d, J = 13.4 Hz, 2H, XX', H11, H12), 7.25–7.14 (m, 6H, H2, H14, H15, H16, H17, H18), 6.12 (dd, J = 3.2, 1.8 Hz, 1H, H3), 5.93 (d, J = 3.2 Hz, 1H, H4), 4.88 (dd, J = 7.6, 6.5 Hz, 1H, H6), 3.56 (dd, J = 17.2, 7.8 Hz, 1H, H7), 3.40 (dd, J = 17.2, 6.4 Hz, 1H, H7). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 195.4, 153.2, 142.0, 139.8, 134.8, 133.8, 133.2, 129.6, 129.0, 128.9, 128.2, 110.4, 107.5, 42.0, 41.6. **IR**: (KBr cm^{-1}) 3361, 3058, 2904, 1687, 1589, 1400, 1224, 1093, 938, 819, 692. **Anal. Cald** for $C_{19}H_{15}ClO_2S$: C, 66.56; H, 4.41; S, 9.35. Found: 66.53; H, 4.38; S, 9.30.

1-(2-Bromophenyl)-3-(furan-2-yl)-3-(phenylthio)propan-1-one (**3g**): Brown oil, yield: 73%. **^{1}H-NMR** (400 MHz, $CDCl_3$, ppm): δ = 7.51–7.13 (m, 10H, H2, H10, H11, H12, H13, H14, H15, H17, H16, H18), 6.11 (dd, J = 3.2, 1.8 Hz, H3), 5.90 (d, J = 3.2 Hz, 1H, H4), 4.77 (t, J = 7.3 Hz, H6), 3.53 (J = 17.2, 7.9 Hz, 1H, H7), 3.41 (J = 17.2, 6.8 Hz, 1H, H7). **^{13}C-NMR** (100 MHz, $CDCl_3$, ppm): δ 196.3, 153.0, 142.0, 138.3, 136.2, 133.8, 133.1, 131.2, 130.2, 129.0, 128.9, 128.1, 127.5, 127.1, 126.6, 123.0, 110.4, 107.5, 42.1, 41.6. **IR**: (KBr cm^{-1}) 3118, 3058, 2923, 1700, 1600, 1587, 1301, 1282, 1220, 1012, 754, 738, 690. **Anal. Cald** for $C_{19}H_{15}BrO_2S$: C, 58.92; H, 3.90; S, 8.28. Found: C, 58.86; H, 3.71; S, 8.19.

1-(3-Bromophenyl)-3-(furan-2-yl)-3-(phenylthio)propan-1-one (**3h**): Brown oil, yield: 83%. **^{1}H-NMR** (400 MHz, $CDCl_3$, ppm): δ 7.27–7.13 (m, 10H, H2, H10, H11, H12, H13, H14, H15, H17, H16, H18), 6.12 (dd, J = 3.1, 1.9 Hz, H3), 5.93 (d, J = 3.2 Hz, 1H, H4), 4.85 (t, J = 6.7 Hz, H6), 3.55 (dd, J = 17.3, 7.8 Hz, 1H, H7), 3.39 (dd, J = 16.7, 6.4 Hz, 1H, H7). **^{13}C-NMR** (100 MHz, $CDCl_3$, ppm): δ 195.3, 153.4, 142.0, 138.3, 136.2, 133.8, 133.1, 131.2, 130.2, 128.9, 128.1, 126.6, 123.1, 110.4, 107.5, 42.1, 41.6. **IR**: (KBr cm^{-1}) 3367, 3118, 3062, 3018, 2923, 1691, 1600, 1565, 1477, 1421, 1220, 1014, 786, 746, 692. **Anal. Cald** for $C_{19}H_{15}BrO_2S$: C, 58.92; H, 3.90; S, 8.28. Found: C, 58.82; H, 3.78; S, 8.14.

1-(4-Bromophenyl)-3-(furan-2-yl)-3-(phenylthio)propan-1-one (**3ı**): Brown oil, yield: 96%. **^{1}H-NMR** (300 MHz, $CDCl_3$, ppm): δ 7.82 (d, J = 8.6 Hz, 2H, AA', H10, H13), 7.63 (d, J = 8.6 Hz, 2H, XX', H11, H12), 7.40–7.28 (m, 6H, H2, H14, H15, H16, H17, H18), 6.25 (dd, J = 3.1, 1.9 Hz, 1H, H3), 6.03 (d, J = 3.2 Hz, 1H, H4), 4.98 (dd, J = 7.5, 6.7 Hz, 1H, H6), 3.68 (dd, J = 17.2, 7.8 Hz, 1H, H7), 3.51 (dd, J = 17.3, 6.4 Hz, 1H, H7). **^{13}C-NMR** (75 MHz, $CDCl_3$, ppm): δ 195.6, 153.1, 142.0, 135.3, 133.8, 133.1, 132.0, 129.6, 128.9, 128.7, 128.1, 127.4, 110.3, 107.4, 41.9, 41.6. **IR**: (KBr cm^{-1}) 3446, 3058, 2972, 1685, 1601, 1585, 1562, 1477, 1228, 1070, 1008, 741, 690. **Anal. Cald** for $C_{19}H_{15}BrO_2S$: C, 58.92; H, 3.90; S, 8.28. Found: C, 58.84; H, 3.81; S, 8.11.

3-(Furan–2-yl)-1-(2-hydroxyphenyl)-3-(phenylthio)propan–1-one (**3i**): Brown oil, yield: 88%. **^{1}H-NMR** (300 MHz, $CDCl_3$, ppm): δ 12.10 (s, 1H, OH), 7.75 (dd, J = 8.1, 1.5 Hz, 1H, H10), 7.54–7.47 (m, 1H, H2, H13), 7.39–7.29 (m, 2H, H14, H15, H16, H17, H18), 7.02–6.98 (m, 2H, H11–H12), 6.27 (dd, J = 3.2, 1.9 Hz, H3), 6.06 (d, J = 3.2 Hz, 1H, H4), 4.98 (dd, J = 7.7, 6.4 Hz, H6), 3.75 (dd, J = 17.3, 7.8 Hz, 1H, H7), 3.39 (dd, J = 17.3, 6.3 Hz, 1H, H7). **^{13}C-NMR** (75 MHz, $CDCl_3$, ppm): δ 202.4, 162.5, 152.9, 142.1, 136.7, 133.9, 132.9, 129.1, 129.0, 128.9, 128.2, 127.4, 119.2, 119.0, 110.4, 107.5, 41.5, 41.4. **IR**: (KBr cm^{-1}) 3141, 3124, 2372, 2343, 1639, 1581, 1552, 1214, 1159, 1016, 968, 744, 651. **Anal. Cald** for $C_{19}H_{16}O_3S$: C, 70.35; H, 4.97; S, 9.88. Found: C, 70.13; H, 4.86; S, 9.72.

3-(Furan–2-yl)-1-(4-hydroxyphenyl)-3-(phenylthio)propan–1-one (**3j**): Yellow solid, yield: 95%, mp 98–102°C. **^{1}H-NMR** (300 MHz, $CDCl_3$, ppm): δ 7.87 (d, J = 8.4 Hz, 2H, AA', H10, H14), 7.36–7.26 (m, 6H, H2, H14, H15, H16, H17, H18), 6.89 (d, J = 8.4 Hz, 2H, XX', H11, H12), 6.24–6.22 (m, 1H, H3), 6.02 (d, J = 3.2 Hz, 1H, H4), 4.98 (t, J = 7.1 Hz, 1H, H6), 3.68 (dd, J = 17.0, 7.9 Hz, 1H, H7), 3.51 (dd, J = 17.0, 6.3 Hz, 1H, H7). **^{13}C-NMR** (75 MHz, $CDCl_3$, ppm): δ 195.9, 160.8, 153.2, 141.9, 133.7, 133.1, 130.9, 129.47, 129.0, 128.8, 128.0, 127.5, 115.5, 110.3, 107.4, 41.8, 41.6. **IR**: (KBr cm^{-1}) 3211, 3119, 2362, 2338, 1648, 1604, 1589, 1514, 1234, 1171, 1014, 959, 740, 690. **Anal. Cald** for $C_{19}H_{16}O_3S$: C, 70.35; H, 4.97; S, 9.88. Found: C, 70.25; H, 4.91; S, 9.83.

3-(Furan–2-yl)-1-(2-nitrophenyl)-3-(phenylthio)propan–1-one (**3k**): Brown oil, yield: 73%. **^{1}H-NMR** (400 MHz, $CDCl_3$, ppm): δ 8.11–8.08 (m, 1H, H13), 7.71–7.68 (m, 1H, H10), 7.54–7.45 (m, 2H, H11, H12), 7.35–7.22 (m, 2H, H2, H14, H15, H16, H17, H18), 6.27 (dd, J = 3.2, 2.0 Hz, H3), 6.06 (d, J = 3.2 Hz, 1H, H4), 4.90 (t, J = 8.0 Hz, H6), 3.59 (dd, J = 17.2, 8.0 Hz, 1H, H7), 3.46 (dd, J = 17.2, 6.4 Hz, 1H, H7). **^{13}C-NMR** (100 MHz, $CDCl_3$, ppm): δ 199.2, 152.6, 142.0, 137.4, 137.0, 134.2, 133.7, 130.7, 129.1, 128.9, 128.2, 127.6, 127.4, 127.2, 124.3, 110.4, 107.8, 46.1, 41.6. **IR**: (KBr cm^{-1}) 3648, 3088, 2863, 1693, 1634, 1561, 1487, 1416, 1223, 1030, 1010, 748, 674. **Anal. Cald** for $C_{19}H_{15}NO_4S$: C, 64.58; H, 4.28; N, 3.96; S, 9.07. Found: C, 63.40; H, 4.12; N, 3.76; 9.01.

3-(Furan–2-yl)-1-(3-nitrophenyl)-3-(phenylthio)propan–1-one (**3l**): Brown oil, yield: 79%. **^{1}H-NMR** (400 MHz, $CDCl_3$, ppm): δ 8.72 (t, J = 1.9 Hz, H14), 8.43–8.38 (m,

1H, H12), 8.23 (dt, J = 7.8, 1.1 Hz, 1H, H10), 7.65 (t, J = 7.9 Hz, H11), 7.38–7.28 (m, 6H, H2, H14, H15, H16, H17, H18), 6.24 (dd, J = 3.3, 1.8 Hz, H3), 6.07 (d, J = 3.2 Hz, 1H, H4), 4.98 (t, J = 7.0 Hz, H6), 3.75 (dd, J = 17.3, 7.6 Hz, 1H, H7), 3.59 (dd, J = 17.3, 6.4 Hz, 1H, H7). **^{13}C-NMR** (100 MHz, $CDCl_3$, ppm): δ 194.7, 152.7, 148.4, 142.1, 137.9, 133.8, 133.6, 132.9, 130.0, 129.1, 128.3, 127.6, 127.4, 127.1, 123.0, 110.4, 107.6, 42.3, 41.5. **IR**: (KBr cm^{-1}) 3445, 3080, 2923, 2852, 1697, 1614, 1531, 1477, 1438, 1348, 1223, 1087, 1014, 738, 691. **Anal. Cald** for $C_{19}H_{15}NO_4S$: C, 64.58; H, 4.28; N, 3.96; S, 9.07. Found: C, 64.34; H, 4.21; N, 3.88; S, 8.99.

3-(Furan–2-yl)-1-(4-nitrophenyl)-3-(phenylthio)propan-1-one (**3m**): Brown oil, yield: 85%. **^{1}H-NMR** (400 MHz, $CDCl_3$, ppm): δ 8.25 (d, J = 8.7 Hz, 2H, AA', H10, H13), 8.03 (d, J = 8.7 Hz, 2H, XX', H11, H12), 7.35–7.25 (m, 6H, H2, H14, H15, H16, H17, H18), 6.24 (dd, J = 3.1, 1.9 Hz, 1H, H3), 6.07 (d, J = 3.1 Hz, 1H, H4), 4.98 (t, J = 7.0 Hz, 1H, H6), 3.75 (dd, J = 17.5, 7.6 Hz, 1H, H7), 3.60 (dd, J = 17.5, 6.4 Hz, 1H, H7). **^{13}C-NMR** (100 MHz, $CDCl_3$, ppm): δ 195.3, 152.9, 150.4, 142.1, 140.8, 136.9, 133.8, 133.0, 129.1, 129.0, 128.3, 127.4, 127.2, 123.9, 110.5, 107.6, 42.6, 41.5. **IR**: (KBr cm^{-1}) 3111, 3073, 3019, 2907, 2857, 1886, 1696, 1525, 1344, 1319, 1207, 1012, 854, 740, 691. **Anal. Cald** for $C_{19}H_{15}NO_4S$: C, 64.58; H, 4.28; N, 3.96; S, 9.07. Found: C, 64.40; H, 4.16; N, 3.55; S, 9.03.

Microbiology

Preparation of microorganisms

A total of 11 microbial cultures belonging to nine bacterial and two fungal species were used in this study (Table 1). The cultures were grown in Mueller–Hinton Broth (Merck) for all the bacterial strains for 24 h of incubation at 36°C. *C. albicans* and *C. utilis* were grown in Sabouraud Dextrose Broth (Merck) in incubation for 24 h at 25°C.

Disc diffusion assay

Antimicrobial tests were carried out by disk diffusion method (Karaman *et al.*, 2003; Murray *et al.*, 1995) using 100 µl of suspension containing 10^8 CFU/ml of bacteria and 10^6 CFU/ml of yeast spread on Nutrient Agar (NA), Sabouraud Dextrose Agar (SDA) and Potato Dextrose Agar (PDA) medium, respectively. The blank discs (Oxoid = 6 mm in diameter) were impregnated with 20 µl of each substance (105 µg/disc) and placed on inoculated agar. Negative controls were prepared using the same solvents (Methanol) employed to dissolve each substance. Sulbactam (30 µg) + Cefoperazona (75 µg) (105 µg/disc) was used as positive reference standard to determine the sensitivity of a strain for each microbial species tested. The inoculated plates were incubated at 36°C for 24 h for clinical bacterial strains, 48 h for yeast, and 72 h for fungal strains. Antimicrobial activity was evaluated by measuring the zone of inhibition against the test organisms. Each assay in this experiment was repeated twice.

Microdilution assay

The minimum inhibitory concentration (MIC) values were also studied for the microorganisms, which were determined to be sensitive to the substances tested in the disc diffusion assay. Inocula of microorganisms were prepared using 12-h broth cultures, and suspensions were adjusted to 0.5 McFarland standard turbidity. Each substance dissolved in methanol was first diluted to the highest concentration (500 µg/ml) to be tested, and then serial twofold dilutions were made in a concentration range of 3.9–500 µg/ml in 10-ml sterile test tubes containing nutrient broth. This process was also repeated for the antibiotic and methanol. MIC values of the compounds against bacterial strains and *Candida* sp. isolates were determined on the basis of a micro-well dilution method (Zgoda and Porter 2001). 112-well plates were prepared by dispensing into each well 75 µl of nutrient broth and 5 µl of the inoculums. 75 µl of chalcone derivative to be tested initially was prepared at a concentration of 500 µg/ml and was added into the first wells. Then, 75 µl of their serial dilutions was transferred into eight consecutive wells. The last well containing 150 µl of nutrient broth without compound and 5 µl of the inoculums on each strip was used as negative control. Tetracycline, ceftriaxone, and amphicilin (antibiotics) at a concentration range of 500–3.9 µg/ml was prepared in nutrient broth and used as standard drug for positive control. The final volume in each well was 155 µl. The 112-well plates were incubated at 36°C for 24 h. The MIC results were repeated at least twice.

Conclusion

In conclusion, a novel series of 14 thiophenol derivatives (**3a**–**m**) were prepared by the addition of thiophenol to chalcones (**1a**–**m**) in the presence of potassium-tertiary-butoxide (KO*t*-Bu) in solvent free conditions. Among these compounds, the biological activities of **3a**–**j** were screened against 11 different human pathogenic microorganisms. The majority of the compounds were found to be active.

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