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Synthesis, characterization and antimicrobial screening of some novel chalcones and their derivative

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ABSTRACT

Synthesis of some novel 2-(4-(4-fluorophenylthio) phenyl)-4H-chromen-4-one 6a-h and 2-(4-(4-fluorophenylthio)phenyl)-3-chloro-4H-chromen-4-one 7a-h by oxidative cyclization of (E)-3-(4-(4-fluorophenylthio)phenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one 5a-h using DMSO/I2 and DMSO/CuCl2 at reflux condition has been carried out. The synthesized compounds have been characterized by melting point, FT-IR, NMR and EI-MS spectral data. All the newly synthesized derivatives have been evaluate.

1. Introduction

Chalcones are natural as well as synthetic compounds associated with the flavonoid family. These compounds are of high interest due to their use as a starting material in the synthesis of a series of heterocyclic compounds [1-2]. The chemistry of chalcones has attracted considerable attention as they are endowed with the wide spectrum of activities such as antimicrobial [3], Antiviral [4], antimalarial [5], anticancer [6], anti-inflammatory [7], anti-invasive, anti-angiogenic [8], anti-leishmanial and anti-trypanosomoal [9].

The flavonoid compounds widely occurring in plants shows interesting biological and pharmacological activities [10]. Chromones based on flavones have a wide range of application in the field of synthetic chemistry. They have been reported to exert biological effects including low toxicity and antioxidant [11], cytotoxicity [12], anticancer [13], antitumor [14] and anti-HIV activities [15]. A series of chromones have been found to shows activity against neodegenrative diseases [16]. More recently, naturally occurring chromones exhibited significant activity against MCF-7 and HepG2, cell lines in *vitro* [17]. Chromones are very important structural scaffolds and also a privileged structure for drug development [18]. Various substitutes at 2^{nd} and 3^{rd} positions are reported to have antiallergic [19] muscular relaxation and antimicrobial activity [20].

A literature survey reveals that organosulfur compounds are biologically active. The thiol group is of particular interest because of its involvement in the mechanism of a number of, enzymes, hormones and proteins [21]. The sulfur containing heterocyclic compounds are regarded as repair agents for the oxidative damage site in natural cells such as proteins, lipids, DNA and carbohydrates [22]. Fluorinated compounds are associated with antimicrobial [23], antiproliferative [24], cardiovascular disease [25], antioxidant and anti-inflammatory [26] activities.

Therefore, in view of these important biological activities, and in continuation of our research [27-30] we report the synthesis of thiophenol and fluorinated derivatives, from the analogues of (E)-3-(4-(4-fluorophenylthio)phenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one. The newly synthesized compounds were tested against Gram-negative and fungi, which showed an interesting profile of pharmacological activity.

2. Experimental

Material and methods

The melting points of all synthesized compounds were determined in open capillary tubes and were uncorrected. The purity of all compounds was checked by TLC. IR spectra were recorded on Jasco FT-IR-4100, Japan, in KBr disc, ^{1}H NMR spectra were recorded on a Varian AS 400 MHz spectrometer in CDCl3/DMSO-*d*6; chemical shifts (δ) are in ppm relative to tetramethylsilane and coupling constants (*J*) are expressed in hertz (Hz). Mass spectra were recorded on a Macro mass spectrometer (Water) by the electro-spray method (ES). Elemental analysis was performed on Perkin-Elmer EAL-240 elemental analyzer. Bandelin Sonorex (with a frequency of 35 kHz and a nominal power 200 W) ultrasonic bath was used for ultrasonic irradiation. Built-in heating at 30-80°C are thermostatically adjustable. The reaction vessel was placed inside the ultrasonic bath containing water.

General Procedure for the Synthesis of (E)-3-(4-(4-fluorophenylthio)phenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one

Aqueous KOH (0.0040mole) was added to a suspension of 1-(2-hydroxyphenyl) ethanone (0.00135mole) and 4-(4-fluorophenylthio) benzaldehyde (0.0021mole) in 10mL ethanol. The Product was filtered, washed with water by dil.sodium thiosulphate solution for several times. It was washed with water, dried under vacuum and crystallized from ethanol to afford **5 (a-h)** (**Tablel**).

General Procedure for the Synthesis of 2-(4-(4-fluorophenylthio)phenyl)-4H-chromen-4-one.

Chalcones (0.003 mol) was dissolved in 15 mL of DMSO and to this reaction mixture a catalytic amount of iodine was added. The reaction mixture was heated in an oil bath for 1 h at 120 ◦C. The reaction was monitored by TLC. After completion of the reaction, mixture was cooled and then 20 mL of cold water was slowly added to the flask and the separated product was filtered, washed with water by dil. sodium thiosulphate. **6 a-h** (**Table**).

General Procedure for the Synthesis of 2-(4-(4-fluorophenylthio)phenyl)-3-chloro-4H-chromen-4-one.

Chalcone (0.0007mole) was dissolved in 10mL of DMSO. To this reaction mixture catalytic amount of copper chloride was added. The reaction mixture was heated in an oil bath for 1hr at 120°C.The reaction was monitored by TLC.10mL cold water was slowly added to the flask and the separated product was filtered, washed with water by dil. Sodium thiosulphate solution for several times. It was washed with water, dried under vacuum and crystallized from ethanol to afford **7a-h** (**Tablel**).

(E)-3-(4-(4-fluorophenylthio) phenyl)-1-(5-chloro-2-hydroxy-4-methylphenyl)prop-2-en-1-one (5a):

IR (KBr) cm^{-1}: 3254 (OH), 1690 (C O), 1565, 1475;^{1}H NMR (400 MHz, DMSO): δ 2.30 (s,3H,CH_3), 6.90 (d, J = 14.20 Hz, 1H, -olefinic-H), 7.52 (t, 1H, Ar-H),7.05-7.65 (m, 7H, Ar-H), 7.68 (t, 1H, Ar-H), 7.90 (d, J = 14.40 Hz, 1H, -olefinic-H), 7.95 (d, 1H, Ar-H), 13.70 (s, 1H, OH); EC-MS: 398.05 (M^+); Anal. Calcd. for $C_{22}H_{16}ClFO_2S$: C,66.24%, H:4.04%,S: 9.65%; Found: C,66.18%, H: 4.01%,S: 9.58%.

(E)-3-(4-(4-fluorophenylthio)phenyl)-1-(2-hydroxy-3,5-dimethylphenyl)prop-2-en-1-one (5d):

IR (KBr) cm^{-1}: 3270(OH), 1693 (C O), 1545, 1470 ;^{1}H NMR (400 MHz, DMSO): δ 2.36(s,6H,CH_3),6.92 (d, J = 14.3 Hz, 1H, -olefinic-H), 7.54 (t, 1H, Ar-H),7.02-7.68 (m, 7H, Ar-H), 7.70 (t, 1H, Ar-H), 7.93 (d, J = 14.38 Hz, 1H, -olefinic-H), 7.94 (d, 1H, Ar-H), 12.90 (s, 1H, OH); EC-MS: 378.11 (M^+); Anal. Calcd. for $C_{23}H_{19}FO_2S$: C,72.99%, H, 5.06%,S: 8.47%; Found: C,72.90%, H, 5.02%,S: 8.38%.

(E)-3-(4-(4-fluorophenylthio)phenyl)-1-(5-fluoro-2-hydroxyphenyl)prop-2-en-1-one (5e):

IR (KBr) cm^{-1}: 3305(OH), 1672 (C O), 1565, 1475;^{1}H NMR (400 MHz, DMSO): δ 6.94 (d, J = 14.1 Hz, 1H, -olefinic-H), 7.50 (t, 1H, Ar-H),7.05–7.70 (m, 8H, Ar-H), 7.72 (t, 1H, Ar-H), 7.94 (d, J = 14.41Hz, 1H, -olefinic-H), 7.95(d, 1H, Ar-H), 12.95 (s, 1H, OH); EC–MS: 368.07 (M^+); Anal. Calcd. for $C_{21}H_{14}F_2O_2S$: C,68.47%, H: 3.83%,S: 8.70%; Found: C: C,68.36%, H: 3.72%,S: 8.63%.

(E)-3-(4-(4-fluorophenylthio)phenyl)-1-(5-chloro-2-hydroxyphenyl)prop-2-en-1-one (5f):

IR (KBr) cm^{-1}: 3275 (OH), 1685 (C O), 1550, 1472;^{1}H NMR (400 MHz, DMSO): δ 6.92 (d, J = 14.4 Hz, 1H,-olefinic-H), 7.53 (t, 1H, Ar-H),7.02-7.68 (m, 8H, Ar-H), 7.69 (t, 1H, Ar-H), 7.92 (d, J = 14.41Hz, 1H, -olefinic-H), 7.98(d, 1H, Ar-H), 13.0 (s, 1H, OH); EC–MS: 384.04 (M^+); Anal. Calcd. for $C_{21}H_{14}ClFO_2S$: C,65.54%, H: 3.67%,S: 8.33%; Found: C: C,65.43%, H: 3.52%,S: 8.25%.

(E)-3-(4-(4-fluorophenylthio)phenyl)-1-(3,5-dichloro-2-hydroxyphenyl)prop-2-en-1-one (5g):

IR (KBr) cm^{-1}: 3303(OH), 1695 (C O), 1637, 1587;^{1}H NMR (400 MHz, DMSO): δ 6.96 (d, J = 14.3 Hz, 1H, -olefinic-H), 7.52 (t, 1H, Ar-H),7.06–7.64 (m, 7H, Ar-H), 7.85 (t, 1H, Ar-H), 7.89 (d, J = 14.41Hz, 1H, -olefinic-H), 7.92(d, 1H, Ar-H), 12.83 (s, 1H, OH); EC–MS: 418.1 (M^+); Anal. Calcd. for $C_{21}H_{13}Cl_2FO_2S$: C,60.15%, H: 3.13%,S: 7.65%; Found: C: C,60.09%, H: 3.07%,S: 7.52%.

2-(4-(4-fluorophenylthio)phenyl)-6-chloro-7-methyl-4H-chromen-4-one (6a):

IR (KBr) cm^{-1}: 1645 (C=O), 1565, 1486 (C=C); ^{1}HNMR (400 MHz, CDCl3): *δ* 2.35 (s, 3H, CH_3), 6.70 (s, 1H, Ar-H), 7.24 (s, 1H, Ar-H), 7.25-7.80 (m, 8H, Ar-H), 7.82 (s, 1H, Ar-H); EC-MS: 397.04 (M^+) Anal. Calcd. For $C_{22}H_{14}ClFO_2S$: C: 66.58, H: 3.56,S: 8.08%; Found: C: 66.42, H: 3.43, S: 8.02%.

2-(4-(4-fluorophenylthio)phenyl)-6,8-dimethyl-4H-chromen-4-one (6d)

IR (KBr) cm^{-1}: 1640 (C=O), 1570, 1485 (C=C); ^{1}H NMR (400 MHz, CDCl3): *δ* 2.24 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 6.58-6.90 (s, 2H, Ar-H), 7.02-7.45 (m, 6H, Ar-H), 7.20-7.32 (d, 3H, Ar-H); EC-MS: 377.10 (M^+); Anal. Calcd. for $C_{23}H_{17}FO_2S$: C: 73.38, H: 4.55%, S: 8.52%; Found: C: 73.27, H: 4.46%, S: 8.46%.

2-(4-(4-fluorophenylthio)phenyl)-6-fluoro-4H-chromen-4-one (6e)

IR (KBr) cm^{-1}: 1654 (C=O), 1579, 1478 (C=C); ^{1}H NMR (400 MHz, CDCl3): *δ* 6.80 (d, 1H, Ar-H), 6.92 (s, 1H, Ar-H), 7.14 (d, 1H, Ar-H). 7.20-7.52 (m, 8H, Ar-H), 7.34 (d, 1H, Ar-H); EC-MS: 367.06 (M^+); Anal. Calcd. for $C_{21}H_{12}F_2O_2S$: C: 68.84%, H: 3.30%, S: 8.75%; Found: C: 68.72%, H: 3.24%, S: 8.67%.

2-(4-(4-fluorophenylthio)phenyl)-6-chloro-4H-chromen-4-one (6f)

IR (KBr) cm^{-1}: 1630 (C=O), 1565, 1492 (C=C); ^{1}H NMR (400 MHz, CDCl3): *δ* 6.80 (s, 1H, Ar-H), 6.90 (d, 1H, Ar-H), 6.95-7.15 (m, 7H, Ar-H), 7.45-7.56 (d, 3H, Ar-H); EC-MS: 359.07 (M^+); Anal. Calcd. for $C_{21}H_{12}ClFO_2S$: C: 65.88%, H: 3.16%, S: 8.38%; Found: C: 65.74%, H: 3.04%, S: 8.24%.

2-(4-(4-fluorophenylthio)phenyl)-6,8-dichloro-4H-chromen-4-one (6g)

IR (KBr) cm^{-1}: 1640 (C=O), 1572, 1490 (C=C); ^{1}H NMR (400 MHz, DMSO): *δ* 6.72 (s, 1H, Ar-H), 7.30 (d, 1H, Ar-H), 7.32-7.60 (m, 8H, Ar-H), 7.78 (d, 1H, Ar-H); EC-MS: 417.9 (M^+) Anal. Calcd. for $C_{21}H_{11}Cl_2FO_2S$: C: 60.44%, H: 2.66%, S: 7.68%; Found: C: 60.32%, H: 2.54%, S: 7.52%.

2-(4-(4-fluorophenylthio)phenyl)-3,6-dichloro-7-methyl-4H-chromen-4-one (7a):

IR (KBr) cm^{-1}: 1642 (C=O), 1554, 1467 (C=C); ^{1}HNMR (400 MHz, CDCl3): *δ* 2.32 (s, 3H, CH_3), 7.18 (s, 1H, Ar-H), 7.18-7.60 (m, 8H, Ar-H), 7.78 (s, 1H, Ar-H); EC-MS: 431.0 (M^+) Anal. Calcd. For $C_{22}H_{13}Cl_2FO_2S$: C: 61.26, H: 3.04, S: 7.43%; Found: C: 61.14, H: 3.02, S: 7.32%.

2-(4-(4-fluorophenylthio)phenyl)-3-chloro-6,8-dimethyl-4H-chromen-4-one (7d)

IR (KBr) cm-1: 1640 (C=O), 1570, 1485 (C=C); ^{1}H NMR (400 MHz, CDCl3): δ 2.32 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 7.02-7.45 (m, 7H, Ar-H), 7.20-7.32 (d, 3H, Ar-H); EC-MS: 411.0 (M^+); Anal. Calcd. for $C_{23}H_{16}ClFO_2S$: C: 67.23, H: 3.92%,S: 8.63%; Found: $C_{23}H_{16}ClFO_2S$: C: 67.12, H: 3.82%,S: 8.54%.

2-(4-(4-fluorophenylthio)phenyl)-3-chloro-6-fluoro-4H-chromen-4-one (7e)

IR (KBr) cm-1: 1649 (C=O), 1587, 1488 (C=C); ^{1}H NMR (400 MHz, CDCl3): δ 6.97 (d, 1H, Ar-H), 7.1 (d, 1H, Ar-H). 7.01-7.63 (m, 8H, Ar-H), 7.69 (d, 1H, Ar-H); EC-MS: 401 (M^+); Anal. Calcd. for $C_{21}H_{11}ClF_2O_2S$: C: 62.93%, H: 2.77%,S: 8.00%; Found: C: 62.85%, H: 2.64%,S: 7.95%.

2-(4-(4-fluorophenylthio)phenyl)-3,6-dichloro-4H-chromen-4-one (7f)

IR (KBr) cm-1: 1648 (C=O), 1585, 1486 (C=C); ^{1}H NMR (400 MHz, CDCl3): δ 6.86 (s, 1H, Ar-H), 6.95 (d, 1H, Ar-H), 7.02-7.65 (m, 7H, Ar-H), 7.42-7.67 (d, 2H, Ar-H); EC-MS: 359.07 (M^+); Anal. Calcd. for $C_{21}H_{11}Cl_2FO_2S$: C: 60.44%, H: 2.66%, S: 7.68%; Found: C: 60.32%, H: 2.54%, S: 7.58%.

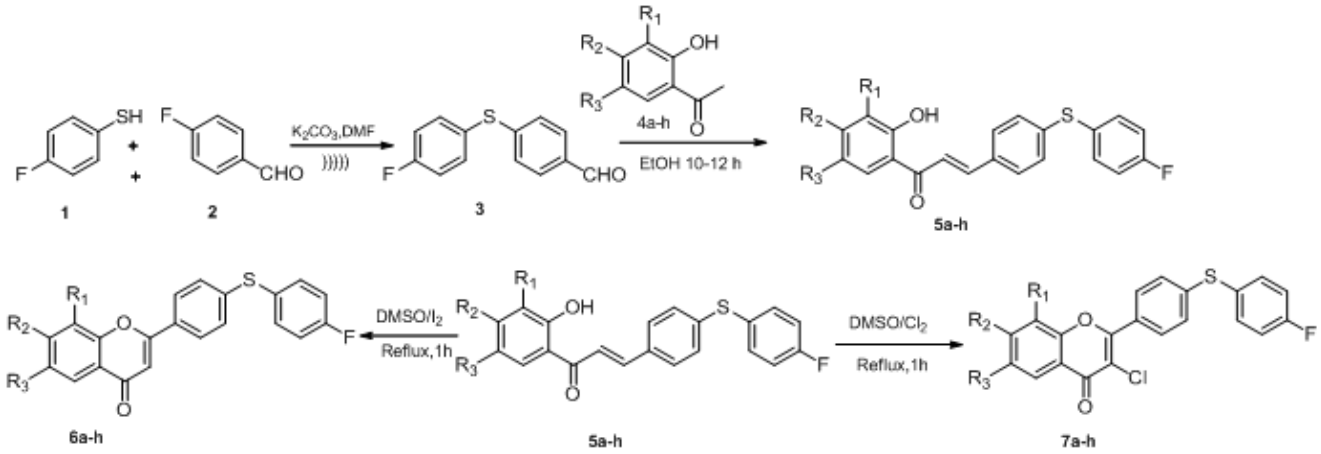
2-(4-(4-fluorophenylthio)phenyl)-3,6,8-trichloro-4H-chromen-4-one (7g)

IR (KBr) cm-1: 1642 (C=O), 1567, 1478 (C=C); ^{1}H NMR (400 MHz, DMSO): δ 6.84 (s, 1H, Ar-H), 7.25 (d, 1H, Ar-H), 7.26-7.67 (m, 7H, Ar-H), 7.69 (d, 1H, Ar-H); EC-MS: 417.9 (M^+) Anal. Calcd. for $C_{21}H_{10}Cl_3FO_2S$: C: 55.84%, H: 2.23%, S: 7.10%; Found: C: 55.78%, H: 2.12%, S: 7.02%.

3. Results and Discussion

Chemistry

The synthetic route for the preparation of 2-(4-(4-Fluorophenylthio)phenyl)-4H-chromen-4-one **6**(**a-h**) and 2-(4-(4-Fluorophenylthio)phenyl)-3-chloro-4H-chromen-4-one **7**(**a-h**) are shown in Scheme 1. 4-F-thiophenol (**1**) was treated with 4-flurobenzaldehyde (**2**) in DMF and K_2CO_3 under ultrasonication yielded 4-(4-fluorophenylthio)benzaldehyde (**3**). The 4-(4-fluorophenylthio)benzaldehyde (**3**) was subjected to a base-catalyzed Claisen-Schmidt condention reaction 26 with appropriate o-hydroxy acetophenones **4(a–h**) generating (E)-3-(4-(4-fluorophenylthio)phenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one **5(a–h)**. 2-(4-(4-Fluorophenylthio) phenyl)-4H-chromen-4-one **6**(**a-h**) and 2-(4-(4-Fluorophenylthio)phenyl)-3-chloro-4H-chromen-4-one **7**(**a-h**) were prepared by the oxidative cyclization of corresponding (E)-3-(4-(4-fluorophenylthio)phenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one5(a-h)in DMSO/$I_2$and DMSO/$CuCl_2$ at reflux condition shown in scheme.



Scheme 1. Synthesis of chalcones and their derivatives **5a-h, 6a-h and 7a-h**

4. Spectral Discussion

The structural assignment of all newly synthesized compounds 5a-h, 6a-h and 7a-h was confirmed by IR, ^{1}NMR, Mass spectral studies and elemental analysis. The IR spectrum of 5g showed a characteristic absorption band at 3300 cm^{-1} due to OH stretching. Its ^{1}H NMR spectrum exhibited the presence of olefinic protons as a doublet at δ = 6.96 and 7.89 regions with a mutual coupling constant value (*J* = 14.41 & 14.30 Hz). These observed coupling constant values indicate the presence of the *E, E*-configuration. The phenolic OH is highly deshielded and appears at δ = 12.83 ppm. The mass spectrum of (E)-3-(4-(4-fluorophenylthio)phenyl)-1-(3,5-dichloro-2-hydroxyphenyl)prop-2-en-1-one showed (M^+) peak at 418.1.The IR spectra of prepared 6a revealed the disappearance of the respective OH stretching absorption due to ring cyclization and also showed a characteristic absorption band at 1600 cm^{-1}and 1645 cm^{-1}, respectively due to C=O stretching. The ^{1}H NMR spectrum of 6a revealed the characteristic CH_2 proton of the chromone ring appearing at δ = 6.70 ppm. The mass spectrum of 2-(4-(4-fluorophenylthio)phenyl)-6-chloro-7-methyl-4H-chromen-4-one showed (M^+) peak at 397.04. The IR spectrum of 7c showed a characteristic absorption band at 1645 cm^{-1} correspond to C=O. Its ^{1}H NMR spectrum exhibited doublet at δ = 6.97 and 7.69 ppm characteristic of two aromatic protons, The mass spectrum of 7e showed (M^+) peak at 401.0.

Table 1. Physical data of compounds 4a-h, 6a-h, 8a-h and **9a-h**

Entry	R1	R2	R3	Yield	MP (°C)
5a	H	CH_3	Cl	72	165-167
5b	H	H	CH_3	83	101-103
5c	H	H	H	69	140-142
5d	CH_3	H	CH_3	78	133-135
5e	H	H	F	76	135-137
5f	H	H	Cl	82	141-143
5g	Cl	H	Cl	75	118-120
5h	H	H	Br	86	102-104
6a	H	CH_3	Cl	70	167-169
6b	H	H	CH_3	65	102-104
6c	H	H	H	85	110-112
6d	CH_3	H	CH_3	75	95-97
6e	H	H	F	71	103-105
6f	H	H	Cl	67	110-112
6g	Cl	H	Cl	70	175-177
6h	H	H	Br	73	90-92
7a	H	CH_3	Cl	83	125-127
7b	H	H	CH_3	78	115-117
7c	H	H	H	72	108-110
7d	CH_3	H	CH_3	68	90-92
7e	H	H	F	65	83-85
7f	H	H	Cl	74	150-152
7g	Cl	H	Cl	73	140-142
7h	H	H	Br	67	131-133

Antibacterial activity

The compounds were dissolved in dimethyl sulfoxide (DMSO) at a concentration of 1 mg/mL. Antibacterial activity of DMSO against the test organisms was investigated and was found to be nil. Molten nutrient agar (15 cm3) kept at 45°C was then poured into the Petri dishes and allowed to solidify. A total of 10-mL diameter holes were then punched carefully using a sterile cork borer and completely filled with the test solutions. The plates were incubated for 24 h at 37°C. After 24 h, the inhibition zone that appeared around the holes in each plate was measured. Antibacterial and antifungal activity was determined by measuring the diameter of inhibition zone and examining the minimum inhibitory concentration (MIC). Activity of each compound was compared with control solvent. The observed data of antibacterial and antifungal activity of compounds are given in Table II. The compounds **7a**, **7b**, **7c**, **7d** and **7f** show excellent antifungal activity against Aspergillus flavus. Likewise, compounds **5a** showed moderate activity against Escherichia coli. Although with respect to solvent as control, all the tested compounds were found nil activity, so result of all preliminary study indicated that the substituted 2-(4-(4-fluorophenylthio)phenyl)-3-chloro-4H-chromen-4-one moiety represent a new class of pharmacophor for broad spectrum antifungal activity.

Table 2. *In vitro* antibacterial screening of compounds (**5a-h**), (**6a-h**), and (**7a-h**)

Antibacterial and antifungal zone of inhibition (mm)		
Gram-negative Bacteria		Fungi
Compd	*E. Coli*	*A.flavus*
5a	**03**	**-**
5b	**-**	**-**
5c	**-**	**-**
5d	**-**	**-**
5e	**-**	**-**
5f	**-**	**-**
5g	**-**	**-**
5h	**-**	**-**
6a	**-**	**-**
6b	**-**	**-**
6c	**-**	**-**
6d	**-**	**-**
6e	**-**	**-**
6h	**-**	**-**
7a	**-**	**13**
7b	**-**	**15**
7c	**-**	**15**
7d	**-**	**17**
7e	**-**	**-**

7f	**-**	**02**
7g	**-**	**-**
7h	**-**	**-**
Control (Solvent)	**Nil**	**Nil**

5. Conclusions

In summary, this work demonstrates a rapid and efficient method for the synthesis of novel title compounds **5a-h**, **6a-h** and **7a-h** under reflux condition. All the newly synthesized compounds have been characterized by ^{1}H NMR, mass, IR spectra and elemental analysis. The compounds have been evaluated for their antibacterial and antifungal activities.

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