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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and antimicrobial activities of some new 5-((3-(aryl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)-3-phenylthiazolidine-2,4-diones

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Abstract A series of nine new compounds of 5-((3-(aryl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)-3-phenylthiazolidine-2,4-diones was synthesized by Knoevenagel condensation of various 3-(aryl)-1-phenyl-1*H*-pyrazole-4-carbaldehydes with 3-phenylthiazolidine-2,4-dione in ethanol in the presence of piperidine as a catalyst. The reaction afforded the desired products in good yields. All the nine compounds were screened for their in vitro antibacterial (*Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Escherichia coli*) and antifungal (*Aspergillus niger* and *A. flavus*) activity. Biological activities of these compounds were compared with those of commercially available antibiotics, ciprofloxacin and antifungal agent fluconazole. Two compounds **3e** and **3i** were found to be most effective against *S. aureus* and *B. subtilis*. Out of the nine compounds tested for antifungal activity, five, **3c–f** and **3h** showed more than 50% inhibition against the *A. flavus*, whereas the three compounds **3a**, **3d** and **3f** showed more than 50% inhibition against *A. niger*.

Keywords Pyrazole · Thiazolidine-2,4-dione · Antibacterial activity · Antifungal activity

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Introduction

Over the years, 4-thiazolidinones have enjoyed a prominent place in heterocyclic chemistry largely due to the wide range of biological activity associated with this class of compounds (Bhargava and Chaurasia, 1969). Diverse biological activities, namely, antihyperglycemic (Lee *et al*., 2005), bactericidal (Mahalle *et al*., 2008; Bozdag-Dundar *et al*., 2008a, b), pesticidal (Hyo *et al*., 2007), fungicidal (Deohate *et al*., 2004), insecticidal (Sahu *et al*., 2007), anticonvulsant (Altintas *et al*., 2006), tuberculostatic (Thaker *et al*., 2003), anti-inflammatory (Szeto and Li, 2008; Pastromas *et al*., 2008; Murugan *et al*., 2009; Cioni and Ramelli, 2009; Sha *et al*., 2009), antithyroid and potentiation of pentobarbital induced sleeping time, etc., have been associated with thiazolidinone derivatives. Different possibilities of heterocyclic modifications (Bozdag-Dundar *et al*., 2008a, b) with a wide spectrum of pharmacological properties are the most important grounds for investigation of this class of compounds (Jeon *et al*., 2006; Chandrappa *et al*., 2008; Ramesh *et al*., 2004; Clark *et al*., 1991; Tuncbilek and Altanlar, 1999, 2006). The fifth position of thiazolidine-2,4-diones (the active methylene group) being relatively more reactive, hence most of the modification at this position exhibit a wide spectrum of pharmacological properties. There have been many reports in literature depicting that the presence of heterocyclic moieties like thienyl, furyl, pyridyl and pyrimidinyl at aforesaid position proves to be more potent and efficacious than a simple aryl group (Rawal *et al*., 2007; El-Gaby *et al*. 2009; Kaneria *et al*., 2003). These observations coupled with the fact that pyrazole derivatives (Kalluraya and Chimbalkar, 2001) possess wide spectrum of biological activities; we directed our attention to synthesize 2,4-thiazolidinones having pyrazole moiety at their fifth position.

Chemistry

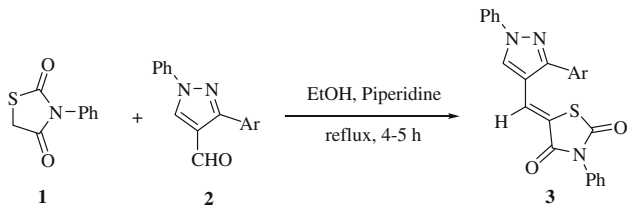
The starting material 3-phenylthiazolidine-2,4-dione (**1**) was prepared according to literature procedure in two steps starting from carbon disulphide and aniline (Furniss *et al*., 1991; Brown, 1961; Momose *et al*., 1991). 4-Formylpyrazoles (**2**) were prepared according to literature (Kira *et al*., 1969) procedure involving Vilsmeier–Haack reaction of various substituted acetophenone phenylhydrazones using $POCl_3$/DMF at 50–60°C for 4–5 h.

5-((3-(Aryl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)-3-phenylthiazolidine-2,4-diones (**3a–i**) were prepared according to Scheme 1. Initially, Knoevenagel condensation was carried out starting from 3-phenylthiazolidine-2,4-dione (**1**) and 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde (**2a**) in ethanol in the presence of catalytic amount of piperidine to give the desired product (**3a**) as yellow solid in 73% yield (Scheme 1). We studied the reaction of different 1-phenyl-3-aryl-1*H*-pyrazole-4-carbaldehydes (**2b–i**) with 3-phenylthiazolidine-2,4-dione (**1**) under similar conditions, the reaction afforded the desired products **3b–i** in good yields. The geometry of **3a–i** was assumed to be (*Z*)-isomer as observed in other instances (Unangst *et al*., 1993). The physical data of these synthesized products have been summarized in Table 1.

The structures of all the heterocyclic compounds **3** synthesized were confirmed by spectral (IR, NMR) and elemental analyses. IR spectrum of product **3a** displayed disappearance of bands at 1674 cm^{-1} (due to C=O of aldehyde) and appearance of 1744, 1697 (due to C=O of thiazolidinedione). The ^1H NMR spectrum of **3a** showed singlets at δ 8.047, 8.275 for the =CH proton and pyrazolyl proton, respectively, apart from other aromatic signals. Its ^{13}C spectrum showed signals at δ 166.35, 165.19, 154.92 and 139.21 due to carbonyl groups C_2 and C_4 of thiazolidine-2,4-dione, C_3 of pyrazole and =CH carbon, respectively, apart from other signals (Fig. 1).

Biological results and discussion

A total of nine compounds **3a–i** were screened for their antibacterial and antifungal activity. All the tested compounds possessed variable antibacterial activity against



Scheme 1

Table 1 Physical data of (Z)-5-((3-(aryl)-1-phenyl-1H-pyrazol-4-yl)methylene)-3-phenylthiazolidine-2,4-diones (**3a–i**)

Compounds	Ar	MP (°C)	Yields %
3a	C_6H_5	216–217	73
3b	4-MeC_6H_4	231–232	70
3c	4-$OMeC_6H_4$	236–237	75
3d	4-ClC_6H_4	244–245	77
3e	4-BrC_6H_4	261–262	75
3f	4-FC_6H_4	246–247	70
3g	4-OHC_6H_4	260–261	78
3h	4-$NO_2C_6H_4$	259–260	71
3i	2-Thienyl	219–220	70

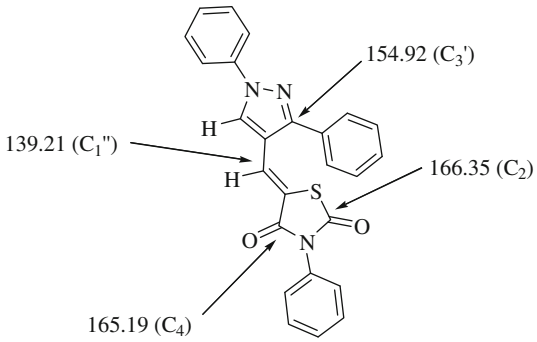


Fig. 1 Characteristic values of ^{13}C spectrum of compound **3a**

both gram-positive (*S. aureus* and *B. subtilis*) bacteria. On the basis of zone of inhibition produced against the test bacterium, compound **3e** (Ar = 4-BrC_6H_4) and **3i** (Ar = 2-thienyl) were found to be most effective against *S. aureus* showing the maximum zone of inhibition of 22 and 23 mm and *B. subtilis*, producing 21 and 20 mm, respectively. However, in case of gram-negative bacteria, none of the compounds showed any activity as shown in Table 2. In the whole series, the minimum inhibitory concentration (MIC) of various tested chemical compounds ranged between 32 and 128 μg/ml against gram-positive bacteria (Fig. 2). The compounds **3e** and **3i** were found to be best, showed the lowest MIC of 32 μg/ml against *S. aureus* and compound nos. **3e**, **3f** and **3i** showed the lowest MIC of 32 μg/ml against *B. subtilis* (Table 3). Of all the nine compounds screened, compounds **3e** and **3i** were found to be highly effective in inhibiting the growth of gram-positive bacteria.

All the nine synthesized compounds tested for their antifungal activity, five compounds, **3c–f** and **3h** showed more than 50% inhibition against the *A. flavus*, whereas three compounds **3a**, **3d** and **3f** showed more than 50% inhibition against *A. niger*. (Table 4).

Table 2 In vitro antibacterial activity of compounds (**3a–i**) through agar well diffusion method

Compounds	Diameter of growth of inhibition zone (mm)[a]			
	S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*
3a	18.6	19.3	–	–
3b	18.3	19.6	–	–
3c	18.6	16.6	–	–
3d	20.6	18.3	–	–
3e	21.6	20.6	–	–
3f	19.3	20.6	–	–
3g	20.3	18.3	–	–
3h	20.6	18.3	–	–
3i	22.3	21.6	–	–
Ciprofloxacin	26.0	24.0	25.0	22.0

– No activity, [a] values including diameter of the well (8 mm) are means of three replicates

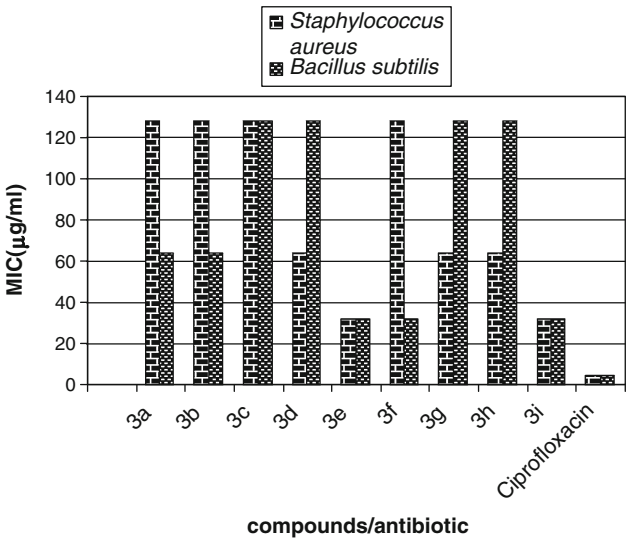


Fig. 2 Comparison of MIC of test compounds with antibiotic up to MIC 128 (μg/ml)

Table 3 MIC (μg/ml) of compounds (**3a–i**) by using macro dilution method

Compounds	*S. aureus*	*B. subtilis*
3a	128	64
3b	128	64
3c	128	128
3d	64	128
3e	32	32
3f	128	32
3g	64	128
3h	64	128
3i	32	32
Ciprofloxacin	5	5

Table 4 In vitro antifungal activity of compounds (**3a–i**) through poisoned food method

Compounds	Mycelial growth inhibition (%)	
	A. flavus	*A. niger*
3a	50	55.5
3b	50	44.4
3c	66.6	50
3d	61.1	55.5
3e	55.5	38.8
3f	55.5	55.5
3g	44.4	50
3h	61.1	50
3i	33.3	50
Fluconazole	77.7	81.1

Experimental

All the reagents were purchased from commercial sources and were used without further purification. Melting points were taken on slides in an electrical apparatus Labindia visual melting range apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brucker 300 MHz instrument using TMS as an internal standard. IR spectra were recorded on a Perkin–Elmer 1800 FT-IR spectrophotometer.

Preparation of (Z)-5-((3-(aryl)-1-phenyl-1*H*-pyrazol-4-yl) methylene)-3-phenylthiazolidine-2,4-diones (**3**)

General procedure

A mixture of 1,3-diphenyl-1*H*-pyrazol-4-carboxaldehyde (**2a**, 1 g, 4 mmol) and 3-phenylthiazolidine-2,4-dione (**1**, 1.01 g, 5 mmol) in ethanol (20 ml) and 2–3 drops of piperidine, was refluxed 4–5 h. A solid was separated out of the reaction mixture within 15–20 min and the refluxing was continued for 4–5 h to complete the reaction. The reaction mixture was cooled to room temperature, filtered and washed with ethanol to give the pure product **3a** (1.3 g, 76% yield).

The other derivatives **3b–i** were synthesized by adopting the similar procedure.

Characterization data of synthesized compounds (**3a–i**)

*(Z)-3-Phenyl-5-((1,3-diphenyl-1H-pyrazol-4-yl) methylene)thiazolidine-2,4-dione (**3a**)*

IR cm^{-1} (KBr): 1744, 1697, 1597, 1535, 1497, 1358, 1219, 1173, 1142 and 1065. ^{1}H NMR δ (300 MHz, $CDCl_3$): 8.275 (s, 1H, Pyrazolyl-H), 8.047 (s, 1H CH=), 7.860–7.835 (m, 2H), 7.721–7.700 (m, 2H), 7.586–7.362 (m, 11H). ^{13}C

NMR δ (300 MHz, $CDCl_3$): 166.35, 165.19, 154.92, 139.21, 132.81, 131.47, 129.71, 129.40, 129.24, 129.12, 128.97, 127.74, 127.38, 127.31, 125.55, 119.64, 119.42 and 116.24. Elemental analysis: calculated for $C_{25}H_{17}N_3O_2S$; C 70.90, H 4.05, N 9.92; Found C 70.75, H 3.98, N 9.99.

*(Z)-3-Phenyl-5-((1-phenyl-3-p-tolyl-1H-pyrazol-4-yl) methylene)thiazolidine-2,4-dione (**3b**)*

IR cm^{-1} (KBr): 1744, 1690, 1605, 1497, 1450, 1358, 1227, 1149 and 1072. ^1H NMR δ (300 MHz, $CDCl_3$): 8.260 (s, 1H, Pyrazolyl-H), 8.041 (s, 1H CH=), 7.855–7.827 (m, 2H), 7.611–7.326 (m, 12H), 2.452 (s, 1H, CH_3). ^{13}C NMR δ (300 MHz, $CDCl_3$): 166.39, 165.19, 155.00, 139.25, 139.11, 132.84, 129.67, 129.38, 129.21, 128.83, 128.58, 127.65, 127.32, 125.73, 119.61, 119.19, 116.19 and 21.39. Elemental analysis: calculated for $C_{26}H_{19}N_3O_2S$; C 68.64, H 4.34, N 9.61; Found C 68.58, H 4.27, N 9.71.

*(Z)-5-((3-(4-Methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl) methylene)-3-phenylthiazolidine-2,4-dione (**3c**)*

IR cm^{-1} (KBr): 1744, 1690, 1605, 1520, 1450, 1350, 1296, 1250 and 1165. ^1H NMR δ (300 MHz, $CDCl_3$): 8.248 (s, 1H, Pyrazolyl-H), 8.030 (s, 1H CH=), 7.847–7.821 (m, 2H), 7.657–7.628 (d, 2H, $J = 8.7$ Hz), 7.576–7.478 (m, 5H), 7.453–7.361 (m, 3H), 7.073–7.044 (d, 2H, $J = 8.7$ Hz), 3.893 (s, 3H, OCH_3). ^{13}C NMR δ (300 MHz, $CDCl_3$): 166.40, 165.22, 160.40, 154.80, 139.25, 132.79, 130.22, 129.70, 129.39, 129.23, 127.67, 127.30, 125.78, 123.90, 119.62, 119.09, 116.08, 114.45 and 55.41. Elemental analysis: calculated for $C_{26}H_{19}N_3O_3S$; C 66.25, H 4.05, N 8.95; Found C 66.30, H 4.09, N 8.94.

*(Z)-5-((3-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-4-yl) methylene)-3-phenylthiazolidine-2,4-dione (**3d**)*

IR cm^{-1} (KBr): 1744, 1690, 1628, 1597, 1535, 1498, 1450, 1358, 1219, 1173, 1142, 1095 and 1065. ^1H NMR δ (300 MHz, $CDCl_3$): 8.260 (s, 1H, Pyrazolyl-H), 7.974 (s, 1H CH=), 7.838–7.813 (m, 2H), 7.666–7.638 (m, 2H), 7.584–7.429 (m, 8H), 7.404–7.358 (m, 2H). ^{13}C NMR δ (300 MHz, $CDCl_3$): 166.18, 165.11, 153.67, 139.14, 135.31, 132.72, 130.14, 129.97, 129.76, 129.42, 129.29, 129.21, 127.91, 127.48, 127.26, 124.90, 119.92, 119.69 and 116.20. Elemental analysis: calculated for $C_{25}H_{16}N_3O_2SCl$; C 65.57, H 3.49, N 9.18; Found C 65.54, H 3.46, N 9.15.

*(Z)-5-((3-(4-Bromophenyl)-1-phenyl-1H-pyrazol-4-yl) methylene)-3-phenylthiazolidine-2,4-dione (**3e**)*

IR cm^{-1} (KBr): 1744, 1690, 1605, 1528, 1497, 1443, 1366, 1219, 1165, 1072 and 1011. ^1H NMR δ (300 MHz, $CDCl_3$): 8.264 (s, 1H, Pyrazolyl-H), 7.973 (s, 1H CH=), 7.842–7.815 (m, 2H), 7.685–7.657 (m, 2H), 7.601–7.410 (m, 8H), 7.383–7.359 (m, 2H). ^{13}C NMR δ (300 MHz, $CDCl_3$): 132.16, 130.39, 129.76, 129.41, 127.49, 127.26 and 119.69. Elemental analysis: calculated for $C_{25}H_{16}N_3O_2SF$; C 59.88, H 3.19, N 8.38; Found C 59.86, H 3.16, N 8.35.

*(Z)-5-((3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl) methylene)-3-phenylthiazolidine-2,4-dione (**3f**)*

IR cm^{-1} (KBr): 1744, 1690, 1597, 1497, 1450, 1358, 1227, 1142 and 1065. ^1H NMR δ (300 MHz, $CDCl_3$): 8.264 (s, 1H, Pyrazolyl-H), 7.980 (s, 1H CH=), 7.845–7.819 (m, 2H), 7.712–7.666 (m, 2H), 7.627–7.357 (m, 8H), 7.282–7.201 (m, 2H). ^{13}C NMR δ (300 MHz, $CDCl_3$): 166.21, 165.16, 153.95, 139.16, 132.73, 130.80, 130.69, 129.75, 129.41, 129.28, 127.86, 127.62, 127.41, 127.27, 125.09, 119.67, 116.20, 116.15 and 115.91. Elemental analysis: calculated for $C_{25}H_{16}N_3O_2SF$; C 68.02, H 3.63, N 9.52; Found C 68.00, H 3.64, N 9.53.

*(Z)-5-((3-(4-Hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl) methylene)-3-phenylthiazolidine-2,4-dione (**3g**)*

IR cm^{-1} (KBr): 3279, 1728, 1666, 1605, 1528, 1497, 1435, 1358, 1273, 1196, 1173, 1142 and 1072. ^1H NMR δ (300 MHz, DMSO-d_6): 9.253 (bs, 1H, OH), 8.205 (s, 1H, Pyrazolyl-H), 7.891 (s, 1H CH=), 7.749–7.746 (m, 2H), 7.433–7.284 (m, 10H), 6.911–6.895 (m, 2H). ^{13}C NMR δ (300 MHz, DMSO-d_6): 167.12, 165.41, 158.81, 154.47, 139.26, 133.58, 130.55, 130.07, 129.60, 128.46, 127.85, 124.29, 122.38, 120.30, 119.78, 116.24 and 115.65. Elemental analysis: calculated for $C_{25}H_{17}N_3O_3S$; C 68.33, H 3.87, N 9.56; Found C 68.35, H 3.84, N 9.52.

*(Z)-5-((3-(4-Nitrophenyl)-1-phenyl-1H-pyrazol-4-yl) methylene)-3-phenylthiazolidine-2,4-dione (**3h**)*

IR cm^{-1} (KBr): 1744, 1697, 1597, 1528, 1504, 1358, 1227, 1149, 1111 and 1080. ^1H NMR δ (300 MHz, $CDCl_3$): 8.415–8.384 (d, 2H, $J = 8.7$ Hz), 8.307 (s, 1H, Pyrazolyl-H), 7.980 (s, 1H CH=), 7.936–7.907 (d, 2H, $J = 8.7$), 7.861–7.830 (m, 2H), 7.617–7.443 (m, 6H), 7.390–7.361 (m, 2H). ^{13}C NMR δ (300 MHz, $CDCl_3$): 137.93, 129.86, 129.56, 129.46, 128.27, 127.81, 127.22, 124.19, 123.90, 119.78 and 116.58. Elemental analysis: calculated for $C_{25}H_{17}N_4O_4S$; C 63.96, H 3.62, N 11.94; Found C 63.92, H 3.61, N 11.92.

*(Z)-3-Phenyl-5-((1-phenyl-3-(thiophen-2-yl)-1H-pyrazol-4-yl)methylene)thiazolidine-2,4-dione (**3i**)*

IR cm^{-1} (KBr): 1744, 1690, 1597, 1528, 1497, 1458, 1404, 1358, 1296, 1234, 1196, 1149, 1072 and 1049. ^1H NMR δ

(300 MHz, $CDCl_3$): 8.232 (s, 1H, Pyrazolyl-H), 8.194 (s, 1H CH=), 7.836–7.809 (m, 2H), 7.579–7.371 (m, 10H), 7.213–7.184 (m, 2H). ^{13}C NMR δ (300 MHz, $CDCl_3$): 166.21, 165.13, 148.85, 139.02, 133.09, 132.77, 129.71, 129.39, 129.25, 128.85, 128.63, 127.98, 127.86, 127.53, 127.43, 127.28, 127.17, 124.80, 119.97, 119.65 and 116.04. Elemental analysis: calculated for $C_{23}H_{15}N_3O_2S_2$; C 64.33, H 3.49, N 9.79; Found C 64.31, H 3.47, N 9.77.

Biological assay

Test microorganisms

Four bacteria, *S. aureus* (MTCC 96), *B. subtilis* (MTCC 121) (gram-positive), *E. coli* (MTCC 1652) and *P. aeruginosa* (MTCC 741) (gram-negative) procured from MTCC, Chandigarh and two fungi, *A. niger* and *A. flavus*, the ear pathogens isolated from the Kurukshetra patients, were used in this study.

In vitro antibacterial activity

The antibacterial activity of synthesized compounds was evaluated by the agar well diffusion method. All the cultures were adjusted to 0.5 McFarland standard, which is visually comparable to a microbial suspension of approximately 1.5×10^8 CFU/ml. 20 ml of Mueller–Hinton agar medium was poured into each petri plate and the agar plates were swabbed with 100 µl inocula of each test bacterium and kept for 15 min for adsorption. Using sterile cork borer of 8 mm diameter, wells were bored into the seeded agar plates and these were loaded with a 100 µl volume with concentration of 4.0 mg/ml of each compound reconstituted in the dimethylsulphoxide (DMSO). All the plates were incubated at 37°C for 24 h. Antibacterial activity of each synthetic compound was evaluated by measuring the zone of growth inhibition against the test organisms with zone reader (Hi Antibiotic zone scale). DMSO was used as a negative control whereas ciprofloxacin was used as a positive control. This procedure was performed in three replicate plates for each organism (Ahmad and Beg, 2001; Andrews, 2001).

Determination of minimum inhibitory concentration of synthesized compounds

The MIC is the lowest concentration of an antimicrobial compound that will inhibit the visible growth of a microorganism after overnight incubation. MIC of the various compounds against bacterial strains was tested through a macro dilution tube method as recommended by NCCLS (2000). In this method, various test concentrations of synthesized compounds were made from 128 to 0.25 µg/ml in sterile tubes no. 1–10. 100 µl sterile Mueller–Hinton Broth (MHB) was poured in each sterile tube followed by the addition of 200 µl test compound in tube 1. Twofold serial dilutions were carried out from the tube no. 1 to the tube no. 10 and excess broth (100 µl) was discarded from the last tube no. 10. To each tube, 100 µl of standard inoculums (1.5×10^8 CFU/ml) was added. Ciprofloxacin was used as control. Turbidity was observed after incubating the inoculated tubes at 37°C for 24 h.

In vitro antifungal activity

The antifungal activity of the synthesized compounds was evaluated by poisoned food technique. The moulds were grown on Sabouraud dextrose agar (SDA) at 25°C for 7 days and used as inocula. 15 ml of molten SDA (45°C) was poisoned by the addition of 100 µl volume of each compound having concentration of 4.0 mg/ml, reconstituted in the DMSO, poured into a sterile petri plate and allowed it to solidify at room temperature. The solidified poisoned agar plates were inoculated at the centre with fungal plugs (8 mm diameter), obtained from the actively growing colony and incubated at 25°C for 7 days. DMSO was used as the negative control whereas fluconazole was used as the positive control. The experiments were performed in triplicates. Diameter of the fungal colonies was measured and expressed as percent mycelial inhibition determined by applying the formula (Al-Burtamani *et al*., 2005).

$$\text{Inhibition of mycelial growth}\% = (\text{dc} - \text{dt})/\text{dc} \times 100$$

where, dc = average diameter of fungal colony in negative control plates, dt = average diameter of fungal colony in experimental plates.

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