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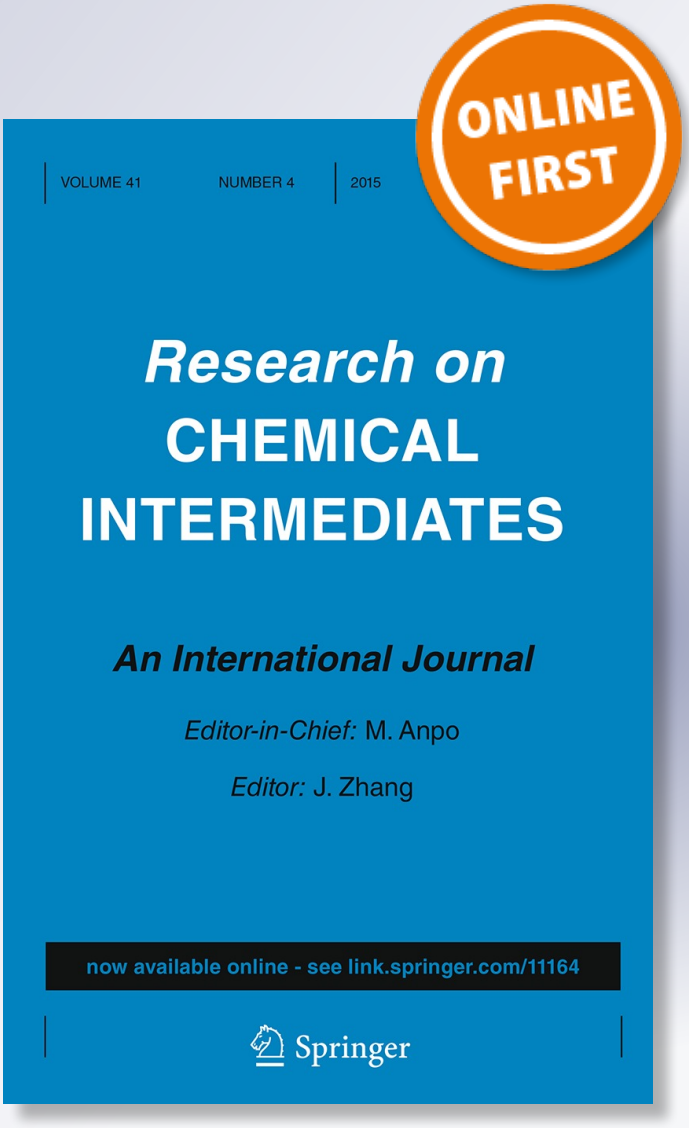

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One-pot multicomponent synthesis of novel thiazolylhydrazone derivatives and their antimicrobial activity

G. Rajitha[1] · V. Ravibabu[1] · G. Ramesh[1] · B. Rajitha[1] · R. Jobina[2] · B. Siddhardha[2] · S. Vijaya Laxmi[3]

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Abstract A series of novel thiazolylhydrazone derivatives (**4a–f**, **6a–f**) were synthesized via one-pot multicomponent condensation of 1,3-indandione (**1**), thiosemicarbazide (**2**) and 3-(2-bromoacetyl)-2*H*-chromen-2-ones (**3a–f**)/2-bromo-1-(4-substituted-phenyl)ethanone (**5a–f**). All the synthesized compounds were characterized by spectral and elemental analyses. All the synthesized compounds were evaluated for their in vitro antimicrobial activity. Antibacterial activity results revealed that compound **6d**, possessing 4-methylphenyl on thiazole ring, has shown equipotent activity against *K. pneumoniae* (ZOI 22 mm, MIC 50 μg/ml) on comparing with the standard drug Streptomycin. Compounds **4a–f**, **6a**, **6b**, and **6d** against *P. aeruginosa* and compounds (**4a–d**) against *S. pyogenes* have shown promising antibacterial activity with ZOI ranging from 14 to 17 mm. Antifungal activity results revealed that, compound **6d** has shown maximum zone of inhibition against four fungal strains *C. albicans*, *C. glabrata*, *A. niger*, and *A. parasiticus* with ZOI 19, 16, 20, and 20 mm, respectively, on comparing with the standard drug clotrimazole.

Keywords 1,3-Indandione · Antimicrobial activity · Thiazolylhydrazones · 3-(2-Bromoacetyl)-2*H*-chromen-2-ones

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Introduction

In recent decades, bacterial and fungal infections have increased at an alarming level, causing deadly diseases and wide-spread epidemics in humans, resulting in 13 million deaths each year worldwide [1, 2]. However, the emergence and spread of bacterial resistance represent a severe global problem. Consequently, there is an urgent need to widen new antimicrobial agents, which have a broad spectrum of activity against the resistant micro-organisms. The current literature is enriched with progressive findings about the synthesis and pharmacological action of fused heterocycle. Schiff bases are one such class of compounds well reported to have antimicrobial activities [3]. The imine group is responsible for the antimicrobial activity, and several studies have shown that the presence of lone pair electrons in an SP^2 hybridized nitrogen atom of azomethine group plays a significant chemical and biological role [4].

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry. These are convergent reactions in which three or more starting materials react to form a product, provide a most powerful platform to access speed, diversity, as well as complexity in a limited number of reaction steps [5–7]. MCRs contribute to the requirements of an environmentally friendly process by reducing the number of synthetic steps, energy consumption, and waste production.

Thiazole moiety is a prevalent scaffold in a number of naturally occurring and synthetic molecules with attractive biological activities such as anticancer [8], anticonvulsant [9], anti-HIV [10], anti-inflammatory [11], antioxidant [12], antitubercular [13], antitumor [14], and cytotoxicity activities [15]. Further, thiazoles have emerged as a new class of potent antimicrobial agents, which are reported to inhibit bacteria by blocking the biosynthesis of certain bacterial lipids [16]. Thiazole is a parent material for various chemical compounds including sulfur drugs, biocides, fungicides, dyes, and chemical reaction accelerators. Synthetic drugs belonging to the thiazole family include the antimicrobial agents sulfathiazole and acinitrazole [17], antibiotic penicillin, anti-HIV drug ritonavir [18], the antidepressant pramipexole [19], antineoplastic agents bleomycin and tiazofurin [20], the antiasthmatic drug cinalukast [21], antiulcer agent nizatidine [22], and non-steroidal anti-inflammatory drug meloxicam [23]. Similarly, coumarin derivatives also posses a wide range of biological properties such as anticancer, anticoagulant, anti-inflammatory, antimicrobial, antioxidant, antiviral, and central nervous system activities [24]. Warfarin, a naturally occurring coumarin derivative and dicoumarol, a synthetic analogue, are used as anticoagulant [25].

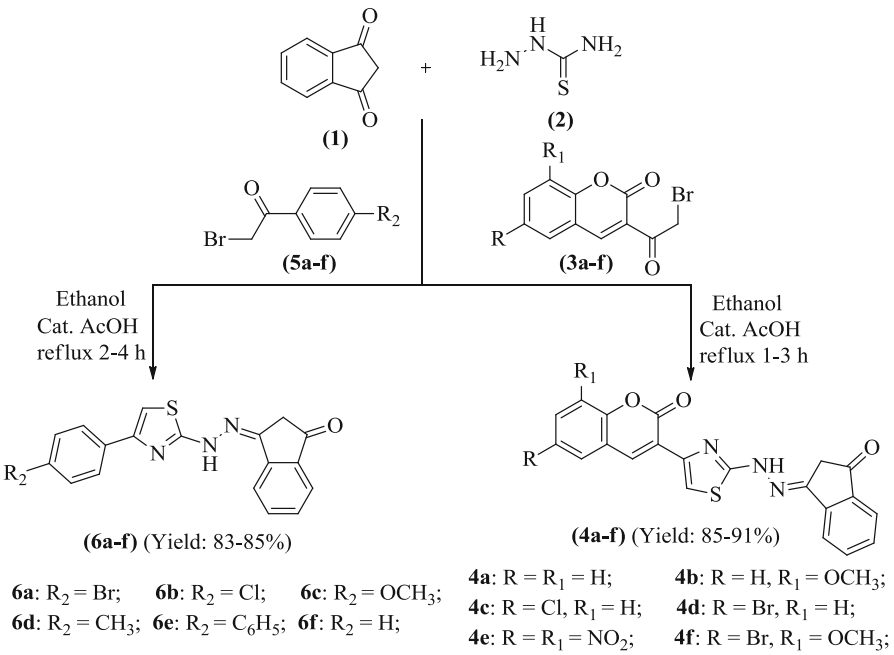
In the light of the aforesaid findings and in continuation of author's efforts to synthesize thiazole ring-containing heterocyclic compounds [26–30], we herein report the synthesis of 1,3-indandione incorporated thiazolylhydrazones derivatives and evaluation of their antimicrobial activity.

Results and discussion

Chemistry

A series of novel thiazolylhydrazones derivatives (**4a–f**, **6a–f**) were synthesized via one-pot multicomponent condensation of 1,3-indandione (**1**), thiosemicarbazide (**2**), and 3-(2-bromoacetyl)-2*H*-chromen-2-ones (**3a–f**)/2-bromo-1-(4-substituted-phenyl)ethanone (**5a–f**) in ethanol using catalytic amount of acetic acid under reflux conditions. The starting compounds substituted 3-(2-bromoacetyl)-2*H*-chromen-2-ones were prepared according to the literature procedure [31]. The starting compounds 2-bromo-1-(4-substituted-phenyl)ethanones (**5a–f**) are commercially available. The synthetic strategies adopted for the synthesis of the target compounds are depicted in Scheme 1.

The assignment of structure for compounds (**4a–f**, **6a–f**) was supported by IR, NMR, and mass spectral studies as well as elemental analysis. In infrared spectroscopic analysis of compound **4c**, the appearance of bands at 3,394, 1,723, 1,605, and 1,110 cm^{-1} corresponds to NH, lactone (C=O), imine (C=N), thiazole (C–S) stretching frequencies, respectively. In case of ^{1}H NMR spectrum, the singlets at 8.49 and 11.74 ppm confirm the presence of coumarin 4th proton and NH proton respectively. ^{13}C NMR and spectroscopic analyses also confirmed the structural identity, with resonances observed at 168.36, 158.28, 150.88, and 146.31 ppm, corresponding to thiazolyl carbon, δ-lactone carbonyl carbon, imine



Scheme 1 Synthesis of novel thiazolylhydrazone derivatives (**4a–f**, **6a–f**)

carbon, and coumarin 4th carbon, respectively. Molecular ion peak from the mass spectrum as well as elemental analyses further confirmed the product formation.

Biological evaluation

Antimicrobial evaluation

All the target compounds (**4a–f**, **6a–f**) were initially evaluated for their in vitro antibacterial activity against different bacterial (Gram-positive bacteria such as *Staphylococcus aureus*, *Streptococcus pyogenes*, and Gram-negative bacteria such as *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* and in vitro antifungal activity against fungal strains such as *Candida albicans*, *Candida glabrata*, *Aspergillus niger*, and *Aspergillus parasiticus*. Streptomycin for bacteria and clotrimazole for fungi are taken as standard drugs. Zone of inhibition (mm) and minimum inhibitory concentration (MIC in μg/ml) values were determined at 150 μg/ml for analogs and 30 μg/ml for standard.

In vitro antibacterial activity results (Table 1) revealed that compound **6d**, possessing 4-methylphenyl on the thiazole ring, has shown equipotent activity against *K. pneumoniae* (ZOI 22 mm, MIC 50 μg/ml) on comparing with the standard drug streptomycin. Compounds **4a–f**, **6a**, **6b** and **6d** have shown promising antibacterial activity against *P. aeruginosa* with ZOI ranging from 14 to 17 mm. Compounds (**4a–d**) have also exhibited promising activity against Gram-positive bacteria *S. pyogenes* with the zone of inhibition ranging from 14 to 17 mm.

Table 1 In vitro antibacterial activity of thiazolylhydrazone derivatives **(4a–f**, **6a–f)**

S. no.	Anolog	*S. aureus*		*S. pyogenes*		*P. aeruginosa*		*K. pneumoniae*	
		ZOI	MIC	ZOI	MIC	ZOI	MIC	ZOI	MIC
1	**4a**	8	200	14	100	14	100	13	100
2	**4b**	8	200	15	100	14	100	8	200
3	**4c**	10	200	17	50	16	50	8	200
4	**4d**	8	200	15	100	15	100	8	200
5	**4e**	8	200	8	200	15	100	8	200
6	**4f**	8	200	8	200	14	100	8	200
7	**6a**	12	100	8	200	14	100	8	200
8	**6b**	13	100	8	200	17	50	8	200
9	**6c**	8	200	8	200	8	200	8	200
10	**6d**	10	200	12	100	14	100	22	50
11	**6e**	8	200	8	200	8	200	14	100
12	**6f**	8	200	8	200	8	200	14	100
13	**Streptomycin**	22	25	21	12.5	20	12.5	22	50

Zone of inhibition values (mm) and MIC values were given in μg/ml for analogs (**4a–f**, **6a–f**) and positive control drugs (streptomycin) were measured at 150 and 30 μg/ml, respectively. Bacterial strains: Gram-positive: *S. aureus—Staphylococcus aureus*, *S. pyogenes—Streptococcus pyogenes*, Gram-negative: *P. aeruginosa—Pseudomonas aeruginosa* and *K. pneumoniae—Klebsiella pneumonia*

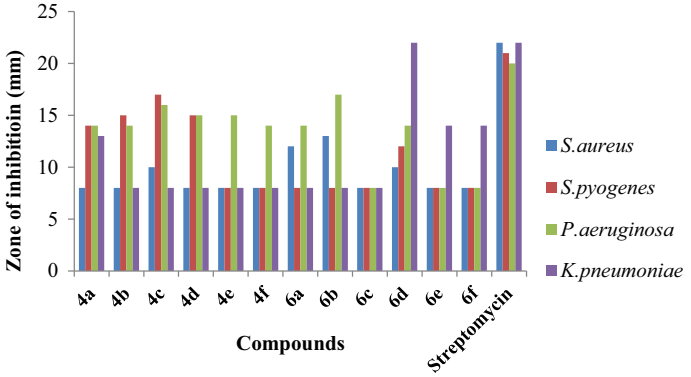


Fig. 1 Preliminary antibacterial activity of thiazolylhydrazones (**4a–f**, **6a–f**)

Table 2 In vitro antifungal activity of thiazolylhydrazone derivatives (**4a–f**, **6a–f**)

S. no.	ZOI				
	Anolog	*C. albicans*	*C. glabrata*	*A. niger*	*A. parasiticus*
1	**4a**	8	8	10	10
2	**4b**	8	8	8	8
3	**4c**	10	12	10	8
4	**4d**	8	8	12	12
5	**4e**	10	12	14	8
6	**4f**	8	10	8	8
7	**6a**	8	12	10	10
8	**6b**	8	8	14	14
9	**6c**	8	8	8	8
10	**6d**	19	16	20	20
11	**6e**	12	10	14	10
12	**6f**	8	10	10	10
13	**Clotrimazole**	24	22	20	20

Zone of inhibition values (mm) for analogs (**4a–f**, **6a–f**) and positive control drugs (clotrimazole) were measured at 150 and 30 μg/ml, respectively. Fungal strains: *C. albicans*—*Candida albicans*, *C. glabrata*—*Candida glabrata*, *A. niger*—*Aspergillus niger*, *A parasiticus*—*Aspergillus parasiticus*

Remaining compounds have shown moderate antibacterial activity against all the bacterial strains (Fig. 1). In vitro antifungal activity results (Table 2) revealed that the compound **6d** exhibited maximum zone of inhibition against four fungal strains *C. albicans*, *C. glabrata*, *A. niger*, and *A. parasiticus* with ZOI 19, 16, 20, and 20 mm, respectively, on comparing with the standard drug clotrimazole. The remaining compounds have shown moderate antifungal activity against all the fungal strains (Fig. 2). Thus, compound **6d** can be considered as a new lead compound for further development of more potent antimicrobial agents.

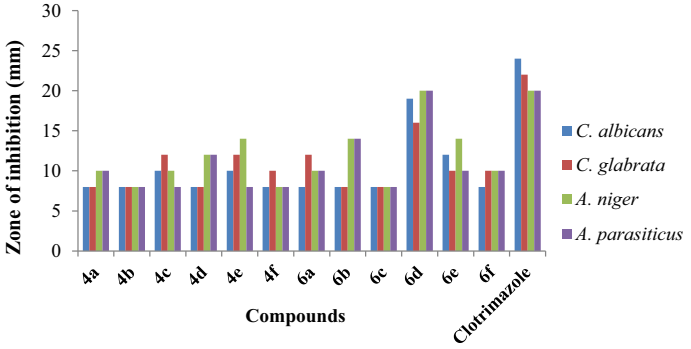


Fig. 2 Preliminary antifungal activity of thiazolylhydrazones (**4a–f**, **6a–f**)

Conclusions

In conclusion, we have synthesized a series of novel thiazolylhydrazone derivatives via one-pot multicomponent synthesis of 1,3-indandione, thiosemicarbazide and 2-bromo-1-(4-substituted-phenyl)ethanone/3-(2-bromoacetyl)-2*H*-chromen-2-ones and evaluated for their in vitro antimicrobial activity. Antibacterial activity data revealed that compound **6d** has shown equipotent activity against *K. pneumoniae* (ZOI 22 mm, MIC 50 μg/ml) on comparing with standard drug streptomycin. Antifungal activity data revealed that compound **6d** also exhibited maximum activity against four fungal strains *C. albicans*, *C. glabrata*, *A. niger*, and *A. parasiticus* with ZOI 19, 16, 20, and 20 mm. Thus, compound **6d** can be considered as a lead compound for further development of more potent antimicrobial agent.

Experimental

Materials and methods

All the reagents were purchased from Aldrich/Merck and used without further purification. Melting points were determined in open capillaries using Stuart SMP30 apparatus and are uncorrected. The progress of the reactions as well as purity of the compounds was monitored by thin-layer chromatography with F_{254} silica-gel precoated sheets using hexane/ethyl acetate (7/3) as eluent. IR spectra were recorded on a Perkin-Elmer 100S spectrophotometer using KBr pellets. NMR spectra were recorded on Bruker 400-MHz spectrometer using DMSO-d_6 as solvent and TMS as internal standard. Elemental analyses were performed on a Carlo Erba modal EA1108 and mass spectra were recorded on a Jeol JMSD-300 spectrometer.

*General procedure for the synthesis of substituted thiazolylhydrazones (**4a–f**)*

To a mixture of 1,3-indandione (**1**, 1 mmol), thiosemicarbazide (**2**, 1 mmol) and substituted 3-(2-bromoacetyl)-2*H*-chromen-2-ones (**3a–f**, 1 mmol) in 10 ml ethanol, catalytic amount of acetic acid was added and refluxed for 1–3 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the solid separated out was filtered and washed with hot ethanol, which afforded an analytically pure product without recrystallization.

Spectral data

*3-(2-(2-(3-Oxo-2,3-dihydro-1H-inden-1-ylidene)hydrazinyl)thiazol-4-yl)-2H-chromen-2-one (**4a**)* Yellow solid, Yield 89 %; M.P. 258–260 °C; IR (KBr υ_{max} cm^{-1}): 3,230 (N–H), 1,705, 1,698 (C=O), 1,606 (C=N), 1,562 (C=C), 1,105 (C–S); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.52 (s, 2H), 7.41 (t, $J = 7.6$ Hz, 1H), 7.47 (d, $J = 8.0$ Hz, 1H), 7.59–7.65 (m, 2H), 7.75–7.85 (m, 4H), 7.94 (d, $J = 7.6$ Hz, 1H), 8.58 (s, 1H), 11.69 (s, 1H); MS (ESI) *m/z*: 388 [M+H]+; Anal. calcd. for $C_{21}H_{13}N_3O_3S$: C, 65.11; H, 3.38; N, 10.85. Found: C, 65.01; H, 3.23; N, 10.97.

*8-Methoxy-3-(2-(2-(3-oxo-2,3-dihydro-1H-inden-1-ylidene)hydrazinyl)thiazol-4-yl)-2H-chromen-2-one (**4b**)* Brown solid, Yield 88 %; M.P. 263–265 °C; IR (KBr υ_{max} cm^{-1}): 3,351 (N–H), 1731, 1,693 (C=O), 1,607 (C=N), 1,558 (C=C), 1,081 (C–S); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.46 (s, 2H), 3.94 (s, 3H), 7.32–7.38 (m, 3H), 7.61 (t, $J = 7.2$ Hz, 1H), 7.75–7.84 (m, 3H), 7.94 (d, $J = 7.6$ Hz, 1H), 8.54 (s, 1H), 11.71 (s, 1H); MS (ESI) *m/z*: 418 [M+H]+; Anal. calcd. for $C_{22}H_{15}N_3O_4S$: C, 63.30; H, 3.62; N, 10.07. Found: C, 63.19; H, 3.79; N, 10.29.

*6-Chloro-3-(2-(2-(3-oxo-2,3-dihydro-1H-inden-1-ylidene)hydrazinyl)thiazol-4-yl)-2H-chromen-2-one (**4c**)* Yellow solid, Yield 86 %; M.P. 268–270 °C; IR (KBr υ_{max} cm^{-1}): 3,394 (N–H), 1,723, 1,712 (C=O), 1,605 (C=N), 1,552 (C=C), 1,282 (C–O–C), 1,110 (C–S), 724 (C–Cl); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.52 (s, 2H), 7.50 (d, $J = 8.8$ Hz, 1H), 7.59–7.67 (m, 2H), 7.75 (d, $J = 7.6$ Hz, 1H), 7.79–7.99 (m, 4H), 8.49 (s, 1H), 11.74 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 112.09, 117.86, 120.58, 121.09, 121.57, 122.94, 127.61, 128.51, 130.57, 131.16, 135.46, 136.70, 137.71, 143.84, 145.72, 146.31, 150.88, 158.28, 168.36, 198.39; MS (ESI) *m/z*: 422 [M+H]+; Anal. calcd. for $C_{21}H_{12}ClN_3O_3S$: C, 59.79; H, 2.87; N, 9.96. Found: C, 59.61; H, 2.99; N, 9.81.

*6-Bromo-3-(2-(2-(3-oxo-2,3-dihydro-1H-inden-1-ylidene)hydrazinyl)thiazol-4-yl)2H-chromen-2-one (**4d**)* Green solid, Yield 90 %; M.P. 275–277 °C; IR (KBr υ_{max} cm^{-1}): 3,424 (N–H), 1,732, 1,702 (C=O), 1,592 (C=N), 1,558 (C=C), 1,010 (C–S), 599 (C–Br); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.53 (s, 2H), 7.43 (d, $J = 8.8$ Hz, 1H), 7.61 (t, $J = 7.6$ Hz, 1H), 7.75–7.95 (m, 5H), 8.11 (s, 1H), 8.48 (s, 1H), 11.74 (s, 1H); MS (ESI) *m/z*: 467 [M+H]+; Anal. calcd. for $C_{21}H_{12}BrN_3O_3S$: C, 54.09; H, 2.59; N, 9.01. Found: C, 54.20; H, 2.41; N, 9.17.

*6,8-Dinitro-3-(2-(2-(3-oxo-2,3-dihydro-1H-inden-1-ylidene)hydrazinyl)thiazol-4-yl)2H-chromen-2-one (**4e**)* Yellow solid, Yield 82 %; M.P. 292–294 °C; IR (KBr υ_{max}

cm^{-1}): 3,287 (N–H), 1,726 (C=O), 1,608 (C=N), 1,575 (C=C), 1,522, 1,338 (NO_2), 1,089 (C–S); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.54 (s, 2H), 7.61 (t, $J = 7.2$ Hz, 1H), 7.68 (d, $J = 9.2$ Hz, 1H), 7.75–7.83 (m, 2H), 7.93 (t, $J = 8.0$ Hz, 1H), 8.39–8.43 (m, 1H), 8.65 (s, 1H), 8.83 (s, 1H), 11.73 (s, 1H); MS (ESI) *m/z*: 478 [M+H]+; Anal. calcd. for $C_{21}H_{11}N_5O_7S$: C, 52.83; H, 2.32; N, 14.67. Found: C, 52.69; H, 2.21; N, 14.53.

*6-Bromo-8-methoxy-3-(2-(2-(3-oxo-2,3-dihydro-1H-inden-1-ylidene)hydrazinyl)thiazol-4-yl)2H-chromen-2-one (**4f**)* Yellow solid, Yield 91 %; M.P. 285–287 °C; IR (KBr υ_{max} cm^{-1}): 3,231 (N–H), 1,737, 1,703 (C=O), 1,594 (C=N), 1,564 (C=C), 1,267 (C–O–C), 1,089 (C–S), 573 (C–Br); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.52 (s, 2H), 3.96 (s, 3H), 7.47 (s, 1H), 7.61–7.65 (m, 2H), 7.75–7.88 (m, 3H), 7.94 (d, $J = 7.6$ Hz, 1H), 8.45 (s, 1H), 11.73 (s, 1H); MS (ESI) *m/z*: 497 [M+H]+; Anal. calcd. for $C_{22}H_{14}BrN_3O_4S$: C, 53.24; H, 2.84; N, 8.47. Found: C, 53.07; H, 2.69; N, 8.59.

*General procedure for the synthesis of substituted thiazolylhydrazones (**6a–f**)*

To a mixture of 1,3-indandione (**1**, 1 mmol), thiosemicarbazide (**2**, 1 mmol) and 2-bromo-1-(4-substituted-phenyl)ethanone (**5a–f**, 1 mmol) in 10 ml ethanol, a catalytic amount of acetic acid was added and refluxed for 2–4 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the solid separated out was filtered and washed with hot ethanol, which afforded an analytically pure product without recrystallization.

*3-(2-(4-(4-Bromophenyl)thiazol-2-yl)hydrazono)-2,3-dihydro-1H-inden-1-one (**6a**)* Brown solid, Yield 88 %; M.P. 265–267 °C; IR (KBr υ_{max} cm^{-1}): 3,069 (N–H), 1,722 (C=O), 1,614 (C=N), 1,501 (C=C), 1,068 (C–S), 510 (C–Br); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.51 (s, 2H), 7.47 (s, 1H), 7.58–7.63 (m, 3H), 7.74–7.84 (m, 4H), 7.93 (d, $J = 8.0$ Hz, 1H), 11.61 (s, 1H); MS (ESI) *m/z*: 399 [M+H]+; Anal. calcd. for $C_{18}H_{12}BrN_3OS$: C, 54.28; H, 3.04; N, 10.55. Found: C, 54.07; H, 3.19; N, 10.71.

*3-(2-(4-(4-Chlorophenyl)thiazol-2-yl)hydrazono)-2,3-dihydro-1H-inden-1-one (**6b**)* Brown solid, Yield 86 %; M.P. 271–273 °C; IR (KBr υ_{max} cm^{-1}): 3,045 (N–H), 1,720 (C=O), 1,614 (C=N), 1,498 (C=C), 1,045 (C–S), 758 (C–Cl); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.51 (s, 2H), 7.46–7.58 (m, 3H), 7.60 (t, $J = 7.2$ Hz, 1H), 7.74–7.83 (m, 2H), 7.89–7.94 (m, 3H), 11.62 (s, 1H); MS (ESI) *m/z*: 354 [M+H]+; Anal. calcd. for $C_{18}H_{12}ClN_3OS$: C, 61.10; H, 3.42; N, 11.88. Found: C, 61.21; H, 3.31; N, 11.69.

*3-(2-(4-(4-methoxyphenyl)thiazol-2-yl)hydrazono)-2,3-dihydro-1H-inden-1-one (**6c**)* Brown solid, Yield 83 %; M.P. 259–261 °C; IR (KBr υ_{max} cm^{-1}): 3,140 (N–H), 1,716 (C=O), 1,614 (C=N), 1,503 (C=C), 1,254 (C–O–C), 1,037 (C–S); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.51 (s, 2H), 3.79 (s, 3H), 6.98 (d, $J = 9.2$ Hz, 2H), 7.21 (s, 1H), 7.59 (t, $J = 7.2$ Hz, 1H), 7.75 (d, $J = 7.6$ Hz, 1H), 7.78–7.82 (m, 3H), 7.93 (d, $J = 7.6$ Hz, 1H), 11.63 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.77, 55.13, 102.16, 114.00, 121.13, 122.94, 126.92, 127.09, 130.46, 135.45, 137.67, 145.45,

146.43, 158.89, 168.68, 198.48; MS (ESI) *m/z*: 350 [M+H]+; Anal. calcd. for $C_{19}H_{15}N_3O_2S$: C, 65.31; H, 4.33; N, 12.03. Found: C, 65.43; H, 4.15; N, 12.27.

3-(2-(4-(p-Tolyl)thiazol-2-yl)hydrazono)-2,3-dihydro-1H-inden-1-one ***(6d)*** Brown solid, Yield 85 %; M.P. 261–263 °C; IR (KBr υ_{max} cm^{-1}): 3,069 (N–H), 1,728 (C=O), 1,614 (C=N), 1,503 (C=C), 1,070 (C–S); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.33 (s, 2H), 3.51 (s, 3H), 7.23 (d, $J = 8.0$ Hz, 2H), 7.31 (s, 1H), 7.60 (t, $J = 7.6$ Hz, 1H), 7.74–7.83 (m, 4H), 7.93 (d, $J = 7.6$ Hz, 1H), 11.73 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.82, 103.46, 121.19, 122.97, 125.57, 129.23, 130.53, 131.53, 135.49, 137.04, 137.71, 145.64, 146.41, 149.82, 168.71, 198.49; MS (ESI) *m/z*: 334 [M+H]+; Anal. calcd. for $C_{19}H_{15}N_3OS$: C, 68.45; H, 4.53; N, 12.60. Found: C, 68.31; H, 4.41; N, 12.49.

3-(2-(4-([1,1′-Biphenyl]-4-yl)thiazol-2-yl)hydrazono)-2,3-dihydro-1H-inden-1-one ***(6e)*** Brown solid, Yield 89 %; M.P. 256–258 °C; IR (KBr υ_{max} cm^{-1}): 3,070 (N–H), 1,722 (C=O), 1,614 (C=N), 1,503 (C=C), 1,011 (C–S); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.53 (s, 2H), 7.38 (t, $J = 7.6$ Hz, 1H), 7.48 (t, $J = 8.0$ Hz, 3H), 7.61 (d, $J = 7.6$ Hz, 1H), 7.72–7.77 (m, 5H), 7.82 (d, $J = 7.6$ Hz, 1H), 7.94–7.99 (m, 3H), 11.48 (s, 1H); MS (ESI) *m/z*: 396 [M+H]+; Anal. calcd. for $C_{24}H_{17}N_3OS$: C, 72.89; H, 4.33; N, 10.63. Found: C, 72.71; H, 4.51; N, 10.51.

3-(2-(4-Phenylthiazol-2-yl)hydrazono)-2,3-dihydro-1H-inden-1-one ***(6f)*** Yellow solid, Yield 87 %; M.P. 250–252 °C; IR (KBr υ_{max} cm^{-1}): 3,418 (N–H), 1,716 (C=O), 1,607 (C=N), 1,504 (C=C), 1,064 (C–S); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.52 (s, 2H), 7.33 (t, $J = 7.2$ Hz, 1H), 7.39–7.44 (m, 3H), 7.58–7.62 (m, 1H), 7.75–7.95 (m, 5H), 11.58 (s, 1H); MS (ESI) *m/z*: 320 [M+H]+; Anal. calcd. for $C_{18}H_{13}N_3OS$: C, 67.69; H, 4.10; N, 13.16. Found: C, 67.47; H, 4.29; N, 13.03.

Biological assay

Antibacterial activity

In vitro antibacterial activity was carried out against four pathogenic bacteria, Gram-positive bacteria: *Staphylococcus aureus* (MTCC 96) and *Streptococcus pyogenes* (MTCC 1926) Gram-negative bacteria: *Klebsiella pneumonia* (MTCC 109) and *Pseudomonas aeruginosa* (MTCC 4673) by means of agar well diffusion method [32, 33]. Streptomycin (30 μg/ml) was used as standard drug. Cell suspension containing 10^8 CFU/ml were prepared and evenly spread on the surface of the agar plates of Mueller–Hinton agar medium using sterile swab sticks. Once the plates had been aseptically dried, 10-mm wells were bored using a sterile cork borer. The samples were first dissolved in dimethyl sulfoxide. The sets of five dilutions (25, 50, 100, and 200 μg) of samples were prepared in dimethyl sulfoxide using nutrient agar tubes for calculating MIC values. The samples were tested at a concentration of 150 μg/ml for calculating ZOI. The samples were placed into the wells and the plates were incubated at 37 °C for 24 h for bacterial strains. The experiments were done in triplicates for each sample. Antibacterial activity was evaluated by measuring the zone of inhibition (mm) and MIC (the lowest

concentration of compounds required to inhibit the growth of the tested microorganisms) values.

Antifungal activity

In vitro antifungal activity was carried out against four pathogenic fungi (*Candida albicans* (MTCC 183), *Candida glabrata* (MTCC3019), *Aspergillus niger* (MTCC 282), and *Aspergillus parasiticus* (MTCC 8850) by means of agar well diffusion method [32, 33]. Clotrimazole was used as standard drug. Cell suspension containing 10^5 spore/ml were prepared and evenly spread on the surface of agar plates of Sabouraud dextrose agar medium using sterile swab sticks. Once the plates had been aseptically dried, 10-mm wells were bored using a sterile cork borer. The samples were first dissolved in dimethyl sulfoxide. The samples (150 μg/ml) were placed into the wells and the plates were incubated at 28 °C for 48 h and the resulting zones of inhibitions were measured. The experiments were done in triplicates for each sample.

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