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RESEARCH ARTICLE

Synthesis and antimicrobial activity of some new indole containing isoxazolines and phthalimidoxy derivatives of thiazolidinone and thiohydantoin

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3-Thiazolidin-4-one-2-yl-methylene hydrazido-1H-indole **2** and 3-[2-thioxo-imidazolin-4-one-3-yl-imino methylene]-1H-indole **3** were obtained by condensation of indole-3-carbaldehyde thiosemicarbazone **1** with chloroacetic acid under different conditions. Compounds **2** and **3** on interaction with aromatic aldehydes afforded the corresponding 5-arylidene derivatives **4a–d** and 5-arylidene-thioxo-imidazolinon indoles **5a–d**, respectively. Upon refluxing the latter with phthalimidoxyethyl bromide furnished the corresponding 3-[(5-arylidene-3-N-ethoxyphthalimido-1,3-thiazolidin-4-one-2-yl)methylene hydrazide]-1H-indoles **6a–d** and 3-[5-arylidene-2-(2-N-ethoxyphthalimido-thiol)imidazolin-4-one-3-yl-imino methylene]-1H-indoles **7a–d**. Compounds **4a–d** were also cyclized with hydroxylamine hydrochloride to yield 3-[(3-aryl-[4,6]thiazolidino[4,5-c]isoxazolin-5(6H)-yl]methylene hydrazido-1H-indoles **8a–d**. All the synthesized compounds were characterized by their spectral and elemental analysis data. Antibacterial and antifungal activities of the final compounds have been evaluated and some of the compounds have shown significant inhibition on bacterial and fungal growth.

Keywords: Indole-3-carbaldehyde; Thiazolidinone; Thiohydatoin; Isoxazoline; Phthalimidoxy; Spectral analysis; Antimicrobial activity

1. Introduction

Thiourea is a versatile synthetic intermediate for the preparation of many heterocyclic entities. In the literature many researchers have reported the S/N regioselective nucleophilic completion in the synthesis of heterocyclic compounds by intermolecular and intramolecular cyclization reactions. Changes in reaction conditions can induce S-attack or N-attack to eventually afford different cyclic products from a single starting material. Thiourea has been used as intermediate for a great variety of heterocyclic products, such as thiohydantoins,

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thiazolidinones, thioxopyrimidindiones etc. The indole nucleus is present in an astonishing variety of natural products endowed with broadly potent biological activities [1]. Furthermore, synthetic indole derivatives represent a wide spectrum of biological activity [2–6]. It is reported that thiazolidinones exhibit anticonvulsant [7], anti-inflammatory [8], amoebicidal [9], analgesic [10], anti-HIV [11] activities and thiohydantoin derivatives possess potential biological and medicinal activities, such as antiviral [12], fungicidal [13] and anticonvulsant [14]. Moreover isoxazoline derivatives elicit were varieties of biological activities as bactericidal [15], fungicidal [16], pesticidal [17], analgesic [18] and antitumor [19]. Encouraged by these reports and also in continuation of our earlier work on synthesis of new aminoxy- and alkoxyphthalimides containing different heterocyclic systems [20–22], we planned to undertake the synthesis and characterization of some indole derivatives carrying the above biodynamic heterocyclic systems at position-3 linked through an imine bridge with the hope to achieve enhanced biological activity.

2. Results and discussion

The required 3-thiazolidin-4-one-2-yl-methylene hydrazido-1H-indole (**2**) was prepared by the condensation of indole-3-carbaldehyde thiosemicarbazone **1** with chloroacetic acid in ethanol containing anhydrous sodium acetate. The IR spectrum displayed an absorption at 1690 cm^{-1} due to imide carbonyl group. The structure was further supported by ^{1}H NMR spectrum exhibiting signals at δ 9.50 (NH thiazolidinone), 8.60 (NH indole), 6.77 (CH=N), and 4.30 ($CO-CH_2-S$). On the other hand, 3-[2-thioxo-imidazolin-4-one-3-yl-imino methylene]-1H-indole **3** was obtained by the condensation of indole-3-carbaldehyde thiosemicarbazone **1** with chloroacetic acid in the presence of pyridine. IR and ^{1}H NMR data established the structure of **3**. Its IR spectrum showed absorption bands at 1220 cm^{-1} and 1715 cm^{-1} attributed to C=S and C=O groups, respectively. ^{1}H NMR spectra showed the signals at 10.33 (NH thiazolidine), 8.98 (NH indole), 6.83 (CH=N) and 3.92 ($-CO-CH_2-$). When compounds **2** and **3** were condensed with aromatic aldehydes in acetic acid and sodium acetate the corresponding arylidene derivatives **4a–d** and **5a–d** were obtained. The ^{1}H NMR spectrum of both compounds **4a** and **5a** were devoid of the singlet at δ 4.30 and 3.92 exhibited by their precursors and appearance of the singlet at δ 6.33 and 6.34 for=CH−Ar. This clearly supports that the condensation took place between compounds **2/3** and aldehydes. Base catalyzed condensation of **4a–d** and **5a–d** with phthalimidoxy ethylbromide in DMF yielded 3-[(5-arylidene-3-N-ethoxyphthalimido-1,3-thiazolidin-4-one-2-yl)methylene hydrazide]-1H-indoles **6a–d** and 3-[5-arylidene-2-(2-ethoxyphthalimido-thiol)imidazolin-4-one-3-yl imino methylene]-1H-indoles **7a–d**. Absence of singlet at δ 9.60 (**4a**) and 10.32 (**5a**) for the proton of NH and appearance of two triplets corresponding to their phthalimidoxy group in the ^{1}H NMR spectrum (c.f. table 2) confirm the structure of **6a** and **7a**. Formation of compound **7a** was further supported by disappearance of the IR band at 1220 due to the C=S group and appearance of a new band at 688 due to the C−S bond. The phthalimidoxy group was not attached to NH proton of indole moiety because NH proton of thiazolidine is much more reactive so we get compounds **6a–d** instead of **9a–d**. In parallel, cyclocondensation of **4a–d** with hydroxylamine hydrochloride in presence of sodium acetate yielded 3-[(3-aryl-[4,6]thiazolidino[4,5-c]isoxazolin-5(6H)-yl]methylene hydrazido-1H-indoles **8a–d**. The IR, ^{1}H NMR and elemental analysis of this reaction product were found to be in a good agreement with the assigned structure (cf. tables 1 and 2). Moreover, the mass spectrum of **8a** gave m/z at 395, which corresponds to the molecular weight of $C_{19}H_{14}N_5OSCl$ of the assigned structure.

Table 1. Characterization data of the newly synthesized compounds.

Compds	m.p./°C (Solvent)	Colour yield (%)	Mol. Formula (Mol. Wt.)	Elemental Analysis [Calcd./Found (%)]			
				C	H	N	S
2	260	Pale Yellow	$C_{12}H_{10}N_4OS$	55.80	3.90	21.69	12.41
	(EtOH)	87	(258.30)	55.73	3.85	21.62	12.37
3	200–204	Yellow	$C_{12}H_{10}N_4OS$	55.80	3.90	21.69	12.41
	(EtOH)	74	(258.30)	55.71	3.85	21.60	12.36
4a	225	Dark Yellow	$C_{19}H_{13}N_4OSCl$	59.92	3.44	14.71	8.42
	(EtOH)	82	(380.85)	59.83	3.39	14.69	8.35
4b	215	Yellow	$C_{19}H_{13}N_4OSF$	62.62	3.60	15.38	8.80
	(EtOH)	78	(364.40)	62.56	3.54	14.98	8.72
4c	245	Yellow	$C_{20}H_{16}N_4O_2S$	63.81	4.28	14.88	8.52
	(EtOH)	72	(376.43)	63.76	4.19	14.76	8.47
4d	211	Yellow	$C_{19}H_{14}N_4OS$	65.88	4.07	16.17	9.26
	(EtOH)	77	(346.40)	65.78	3.97	16.09	9.17
5a	187	Yellow	$C_{19}H_{13}N_4OSCl$	59.92	3.44	14.71	8.42
	(AcOH)	78	(380.85)	59.87	3.40	14.65	8.37
5b	198	Yellow	$C_{19}H_{13}N_4OSF$	62.62	3.60	15.38	8.80
	(AcOH)	73	(364.40)	62.56	3.57	15.27	8.74
5c	222	Yellow white	$C_{20}H_{16}N_4O_2S$	63.81	4.28	14.88	8.52
	(AcOH)	71	(376.43)	63.77	4.15	14.82	8.46
5d	238	Off white	$C_{19}H_{14}N_4OS$	65.88	4.07	16.17	9.26
	(AcOH)	82	(346.40)	65.74	3.99	16.11	9.19
6a	242	Dark yellow	$C_{29}H_{20}N_5O_4SCl$	61.11	3.54	12.29	5.63
	(EtOH)	75	(570.01)	61.02	3.49	12.12	5.61
6b	264	Yellow	$C_{29}H_{20}N_5O_4SF$	62.92	3.64	12.65	5.79
	(EtOH)	78	(553.56)	62.87	3.59	12.52	5.72
6c	>360	Pale yellow	$C_{30}H_{23}N_5O_5S$	63.71	4.10	12.38	5.67
	(EtOH)	72	(565.60)	63.61	4.17	12.26	5.61
6d	229	Yellow	$C_{29}H_{21}N_5O_4S$	65.03	3.95	13.08	5.99
	(EtOH)	77	(535.57)	65.00	3.87	12.98	5.87
7a	220	Yellow	$C_{29}H_{20}N_5O_4SCl$	61.11	3.54	12.29	5.63
	(EtOH)	78	(570.01)	60.93	3.47	12.26	5.59
7b	267	Yellow	$C_{29}H_{20}N_5O_4SF$	62.92	3.64	12.65	5.79
	(EtOH)	73	(553.56)	62.86	3.57	12.59	5.74
7c	320	Yellow white	$C_{30}H_{23}N_5O_5S$	63.71	4.10	12.38	5.67
	(EtOH)	75	(565.60)	63.64	4.02	12.29	5.58
7d	277	Yellow	$C_{29}H_{21}N_5O_4S$	65.03	3.95	13.08	5.99
	(EtOH)	71	(535.57)	64.97	3.86	13.01	5.92
8a	205	Brown	$C_{19}H_{14}N_5OSCl$	57.65	3.56	17.69	8.10
	(EtOH)	76	(395.86)	57.54	3.49	17.52	7.99
8b	228	Light Brown	$C_{19}H_{14}N_5OSF$	60.15	3.72	18.46	8.45
	(EtOH)	71	(379.41)	60.01	3.69	17.92	8.38
8c	167	Brown	$C_{20}H_{17}N_5O_2S$	61.37	4.38	17.89	8.19
	(EtOH)	65	(391.44)	61.29	4.31	17.80	8.11
8d	185	Brown	$C_{19}H_{15}N_5OS$	63.14	4.08	19.38	8.87
	(EtOH)	72	(361.42)	63.04	4.12	19.29	8.81

3. Antimicrobial activity

All the newly synthesized heterocycles were screened for their antibacterial and antifungal activities using the cup and well method [23, 24]. Antibacterial activity of compounds (1000 ppm.) have been evaluated against three bacterial strain viz. *K. pneumoniae*, *E. coli* and *S. aureus* using flucanazole as standard. Compounds **6a**, **6b**, **7a**, **7b**, and **8b** were highly active against all the pathogenic bacteria, whereas the rest of the compounds showed moderate activity as compared to the standard drug (flucanazole). Antifungal activity of the synthesized compounds was evaluated against *C. albicans* and *A. fumigatus* using Attraconazole as the standard at 1000 ppm. Compounds **6a**, **6b**, **7a**, and **7b** show good activity against both fungal

Table 2. Spectra of the newly synthesized compounds.

Comp. No.	Spectra
2	$\nu(cm^{-1})$: 3421 (NH), 1690 (C=O), 1638 (C=N), 698 (C−S−C) δ_H (ppm): 9.50 (s, 1H, NH thiazolidinone), 8.60 (s, 1H, NH indole), 6.97–7.42 (m, 5H, Ar−H), 6.77 (s, 1H, CH=N), 4.30 (s, 2H, CH_2)
3	$\nu(cm^{-1})$: 3321 (NH), 1715 (C=O), 1630 (C=N), 1220 (C=S) δ_H (ppm): 10.33 (s, 1H, NH thiohydantoin), 8.98 (s, 1H, NH indole), 6.91–8.16 (m, 5H, Ar−H), 6.83 (s, 1H, CH=N), 3.92 (s, 2H, CH_2)
4a	$\nu(cm^{-1})$: 3340 (NH),1685 (C=O), 1632 (C=N), 748 (C−Cl), 690 (C−S−C) δ_H (ppm): 9.60 (s, 1H, NH thiazolidinone), 8.63 (s, 1H, NH indole), 6.77–7.41 (m, 9H, Ar−H), 6.73 (s, 1H, CH=N), 6.33 (s, 1H, Ar−CH=)
4b	$\nu(cm^{-1})$: 3336 (NH), 1681 (C=O), 1628 (C=N), 1110 (C−F), 684 (C−S−C) δ_H (ppm): 9.56 (s, 1H, NH thiazolidinone), 8.58 (s, 1H, NH indole), 6.74–7.39 (m, 9H, Ar−H), 6.68 (s, 1H, CH=N), 6.28 (s, 1H, Ar−CH=)
4c	$\nu(cm^{-1})$: 3340 (NH), 1694 (C=O), 1632 (C=N), 1075 (C−O), 688 (C−S−C) δ_H (ppm): 9.54 (s, 1H, NH thiazolidinone), 8.56 (s, 1H, NH indole), 6.73–7.97 (m, 9H, Ar−H), 6.63 (s, 1H, CH=N), 6.38 (s, 1H, Ar−CH=)
4d	$\nu(cm^{-1})$: 3337(NH), 1698 (C=O), 1627 (C=N), 683 (C−S−C) δ_H (ppm): 9.59 (s, 1H, NH thiazolidinone), 8.53 (s, 1H, NH indole), 6.70–7.87 (m, 9H, Ar−H), 6.64 (s, 1H, CH=N), 6.34 (s, 1H, Ar−CH=)
5a	$\nu(cm^{-1})$: 3280 (NH), 1705 (C=O), 1618 (C=N), 1215 (C=S), 745 (C−Cl) δ_H (ppm): 10.32 (s, 1H, NH thiohydantoin), 8.78 (s, 1H, NH indole), 6.87–8.16 (m, 9H, Ar−H), 6.80 (s, 1H, CH=N), 6.34 (s, 1H, Ar−CH=)
5b	$\nu(cm^{-1})$: 3276 (NH), 1702 (C=O), 1618 (C=N), 1210 (C=S), 1106 (C−F) δ_H (ppm): 10.24 (s, 1H, NH thiohydantoin), 8.71 (s, 1H, NH indole), 6.84–8.10 (m, 9H, Ar−H), 6.76 (s, 1H, CH=N), 6.29 (s, 1H, Ar−CH=)
5c	$\nu(cm^{-1})$: 3274 (NH), 1700 (C=O), 1624 (C=N), 1211 (C=S), 1070 (C−O) δ_H (ppm): 10.27 (s, 1H, NH thiohydantoin), 8.74 (s, 1H, NH indole), 6.81–8.14 (m, 9H, Ar−H), 6.71 (s, 1H, CH=N), 6.22 (s, 1H, Ar−CH=)
5d	$\nu(cm^{-1})$: 3280 (NH), 1698 (C=O), 1614 (C=N), 1211 (C=S) δ_H (ppm): 10.11 (s, 1H, NH thiohydantoin), 8.77 (s, 1H, NH indole), 6.84–8.04 (m, 9H, Ar−H), 6.77 (s, 1H, CH=N), 6.16 (s, 1H, Ar−CH=)
6a	$\nu(cm^{-1})$: 3321 (NH),1720 (CO−N−CO), 1690 (C=O), 1636 (C=N), 752 (C−Cl), 695 (C−S−C) δ_H (ppm): 8.61 (s, 1H, NH indole), 6.97–7.42 (m, 13H, Ar−H, $J = 8.0$ Hz, $J = 2.0$ Hz), 6.68 (s, 1H, CH=N), 6.29 (s, 1H, Ar−CH=), 4.19 (t, 2H, O−**CH**$_2$−CH_2−N, $J = 6.1$ Hz), 3.87 (t, 2H, O−CH_2−**CH**$_2$−N) Mass m/z (%): 569 (82), 541 (88), 427 (100), 368 (51), 340 (68), 162 (48), 142 (42), 132 (36), 115 (32)
6b	$\nu(cm^{-1})$: 3336 (NH), 1716 (CO−N−CO), 1681 (C=O), 1629 (C=N), 1110 (C−F), 684 (C−S−C) δ_H (ppm): 8.57 (s, 1H, NH indole), 6.94–7.42 (m, 13H, Ar−H, $J = 9.1$ Hz, $J = 5.0$ Hz), 6.61 (s, 1H, CH=N), 6.23 (s, 1H, Ar−CH=), 4.11 (t, 2H, O−**CH**$_2$−CH_2−N, $J = 6.6$ Hz), 3.85 (t, 2H, O−CH_2−**CH**$_2$−N) Mass m/z (%): 553 (81), 525 (85), 411 (100), 352 (52), 324 (71), 190 (54), 162 (47), 142 (44), 115 (43)
6c	$\nu(cm^{-1})$: 3329 (NH), 1714 (CO−N−CO), 1684 (C=O), 1632 (C=N), 1075 (C−O), 678 (C−S−C) δ_H (ppm): 8.56 (s, 1H, NH indole), 6.94–7.97 (m, 13H, Ar−H, $J = 7.5$ Hz, $J = 2.2$ Hz), 6.64 (s, 1H, CH=N), 6.28 (s, 1H, Ar−CH=), 4.09 (t, 2H, O−**CH**$_2$−CH_2−N, $J = 6.8$ Hz), 3.78 (t, 2H, O−CH_2−**CH**$_2$−N) Mass m/z (%): 565 (79), 537 (89), 423 (100), 364 (50), 336 (66), 190 (54), 162 (49), 142 (42), 115 (30), 104 (20)
6d	$\nu(cm^{-1})$: 3337(NH), 1715 (CO−N−CO), 1680 (C=O), 1627 (C=N), 680 (C−S−C) δ_H (ppm): 8.53 (s, 1H, NH indole), 6.70–7.87 (m, 13H, Ar−H, $J = 7.6$ Hz, $J = 2.1$ Hz), 6.59 (s, 1H, CH=N), 6.19 (1H, Ar−CH=), 4.14 (t, 2H, O−**CH**$_2$−CH_2−N, $J = 6.3$ Hz), 3.80 (t, 2H, O−CH_2−**CH**$_2$−N) Mass m/z (%): 535 (80), 507 (84), 393 (100), 334 (51), 306 (73), 190 (52), 162 (53), 142 (31), 115 (28)
7a	$\nu(cm^{-1})$: 3322 (NH), 1728 (CO−N−CO), 1695 (C=O), 1622 (C=N), 688 (C−S), 742 (C−Cl) δ_H (ppm): 8.74 (s, 1H, NH indole), 6.91–8.18 (m, 13H, Ar−H, $J = 8$ Hz, $J = 2.4$ Hz), 6.85 (s, 1H, CH=N), 6.39 (s, 1H, Ar−CH=), 4.20 (t, 2H, O−**CH**$_2$−CH_2−N, $J = 6.3$ Hz), 2.87 (t, 2H, O−CH_2−**CH**$_2$−N) Mass m/z (%): 569 (82), 541 (87), 511 (36), 483 (57), 427 (100), 345 (69), 222 (53), 190 (56), 162 (48), 132 (36), 115 (30).
7b	$\nu(cm^{-1})$: 3306 (NH), 1723 (CO−N−CO), 1688 (C=O), 1618 (C=N), 678 (C−S), 1100 (C−F) δ_H (ppm): 8.71 (s, 1H, NH indole), 6.84–8.15 (m, 9H, Ar−H, $J = 9.7$ Hz, $J = 5.3$ Hz), 6.79 (s, 1H, CH=N), 6.35 (s, 1H, Ar−CH=), 4.16 (t, 2H, O−**CH**$_2$−CH_2−N, $J = 6.9$ Hz), 2.81 (t, 2H, O−CH_2−**CH**$_2$−N) Mass m/z (%): 553 (80), 525 (84), 495 (33), 467 (54), 412 (100), 331 (44), 329 (67), 222 (51), 190 (57), 162 (47), 132 (34), 115 (28)

(*continued*)

Table 2. Continued.

Comp. No.	Spectra
7c	ν(cm^{-1}): 3284 (NH), 1720 (CO−N−CO), 1682 (C=O), 1619 (C=N), 679 (C−S), 1064 (C−O) δ_H (ppm): 8.68 (s, 1H, NH indole), 6.87–8.14 (m, 13H, Ar−H, J = 8.0 Hz, J = 3.1 Hz), 6.82 (s, 1H, CH=N), 6.31 (s, 1H, Ar−CH=), 4.09 (t, 2H, O−**CH**$_2$−CH$_2$−N, J = 6.6 Hz), 2.84 (t, 2H, O−CH$_2$−**CH**$_2$−N) Mass m/z (%): 565 (79), 537 (82), 507 (38), 479 (53), 424 (100), 343 (43), 341 (65), 190 (51), 162 (44), 132 (31), 104 (18)
7d	ν(cm^{-1}): 3287 (NH), 1717 (CO−N−CO), 1688 (C=O), 1613 (C=N), 684 (C−S) δ_H (ppm): 8.70 (s, 1H, NH indole), 6.84–8.08 (m, 14H, Ar−H, J = 7.0 Hz, J = 2.0 Hz), 6.77 (s, 1H, CH=N), 6.26 (s, 1H, Ar−CH=), 4.13 (t, 2H, O−**CH**$_2$−CH$_2$−N, J = 6.4 Hz), 3.83 (t, 2H, O−CH$_2$−**CH**$_2$−N) Mass m/z (%): 535 (81), 507 (89), 477 (33), 449 (54), 313 (43), 311(100), 222 (49), 190 (57), 162 (47), 132 (34), 104 (19)
8a	ν(cm^{-1}): 3266 (NH), 1642 (C=N), 1136 (C−O), 939 (N−O), 744 (C−Cl), 687 (C−S−C) δ_H (ppm): 9.70 (s, 1H, NH thiazolidinone), 8.60 (s, 1H, NH indole), 7.25–7.52 (m, 9H, Ar-H, J = 8.0 Hz, J = 5.1 Hz), 6.82 (s, 1H, CH=N), 4.49–4.51 (d, 1H, CH−O), 3.78–3.84 (d, 1H, CH−S) Mass m/z (%): 395 (81), 369 (60), 311 (52), 255 (69), 253 (100), 142 (72), 115 (46), 111 (32)
8b	ν(cm^{-1}): 3242 (NH), 1636 (C=N), 1129 (C−O), 1107 (C−F), 935 (N−O), 682 (C−S−C) δ_H (ppm): 9.66 (s, 1H, NH thiazolidinone), 8.58 (s, 1H, NH indole), 7.18–7.49 (m, 9H, Ar-H, J = 10 Hz, J = 5.4 Hz), 6.76 (s, 1H, CH=N), 4.46–4.48 (d, 1H, CH−O), 3.75–3.83 (d,1H, CH−S) Mass m/z (%): 379 (79), 353 (58), 295 (53), 255 (68), 237 (100), 142 (71), 115 (43), 95 (30)
8c	ν(cm^{-1}): 3240 (NH), 1632 (C=N), 1075 (C−O), 928 (N−O), 680 (C−S−C) δ_H (ppm): 9.62 (s, 1H, NH thiazolidinone), 8.55 (s, 1H, NH indole), 7.02–7.47 (m, 9H, Ar−H, J = 7.6 Hz, J = 5.5 Hz), 6.77 (s, 1H, CH=N), 4.45–4.48 (d, 1H, CH−O), 3.73–3.78 (d, 1H, CH−S) Mass m/z (%): 391 (80), 365 (59), 307 (53), 255 (62), 249 (100), 142 (70), 115 (45), 107 (30)
8d	ν(cm^{-1}): 3237(NH), 1626 (C=N), 1026 (C−O), 925 (N−O), 683 (C−S−C) δ_H (ppm): 9.58 (s, 1H, NH thiazolidinone), 8.56 (s, 1H, NH indole), 6.97–7.48 (m, 10H, Ar−H, J = 7.7 Hz, J = 3.0 Hz), 6.74 (s, 1H, CH=N), 4.39–4.42 (d, 1H, CH−O), 3.76–3.81 (d, 1H, CH–S) Mass m/z (%): 361 (83), 335 (56), 277 (49), 255 (71), 219 (100), 142 (69), 115 (43), 77 (30), 65 (25)

Table 3. Antimicrobial activity of some synthesized compounds. Zone of inhibition (mm) (activity index).*

	Antibacterial activity			Antifungal activity	
Compound	*K. pneumoniae*	*E. coli*	*S. aureus*	*C. albicans*	*A. fumigatus*
6a	17 (0.85)	17 (0.94)	19 (0.90)	20 (0.86)	18 (0.72)
6b	19 (0.95)	18 (1.0)	21 (1.0)	22 (0.95)	21 (0.84)
6c	14 (0.70)	15 (0.83)	16 (0.76)	16 (0.69)	16 (0.64)
6d	13 (0.65)	10 (0.55)	14 (0.66)	15 (0.65)	13 (0.52)
7a	18 (0.90)	16 (0.88)	16 (0.76)	18 (0.78)	17 (0.68)
7b	20 (1.0)	17 (0.94)	18 (0.85)	21 (0.91)	23 (0.92)
7c	15 (0.75)	12 (0.66)	17 (0.80)	12 (0.52)	17 (0.68)
7d	11 (0.55)	9 (0.50)	13 (0.62)	10 (0.43)	12 (0.48)
8a	16 (0.80)	16 (0.88)	15 (0.71)	14 (0.60)	20 (0.80)
8b	18 (0.90)	17 (0.94)	18 (0.85)	17 (0.73)	22 (0.88)
8c	13 (0.65)	11 (0.61)	12 (0.57)	10 (0.43)	15 (0.60)
8d	11 (0.55)	12 (0.66)	10 (0.47)	9 (0.39)	13 (0.52)
C$_1$	20	18	21	–	–
C$_2$	–	–	–	23	25

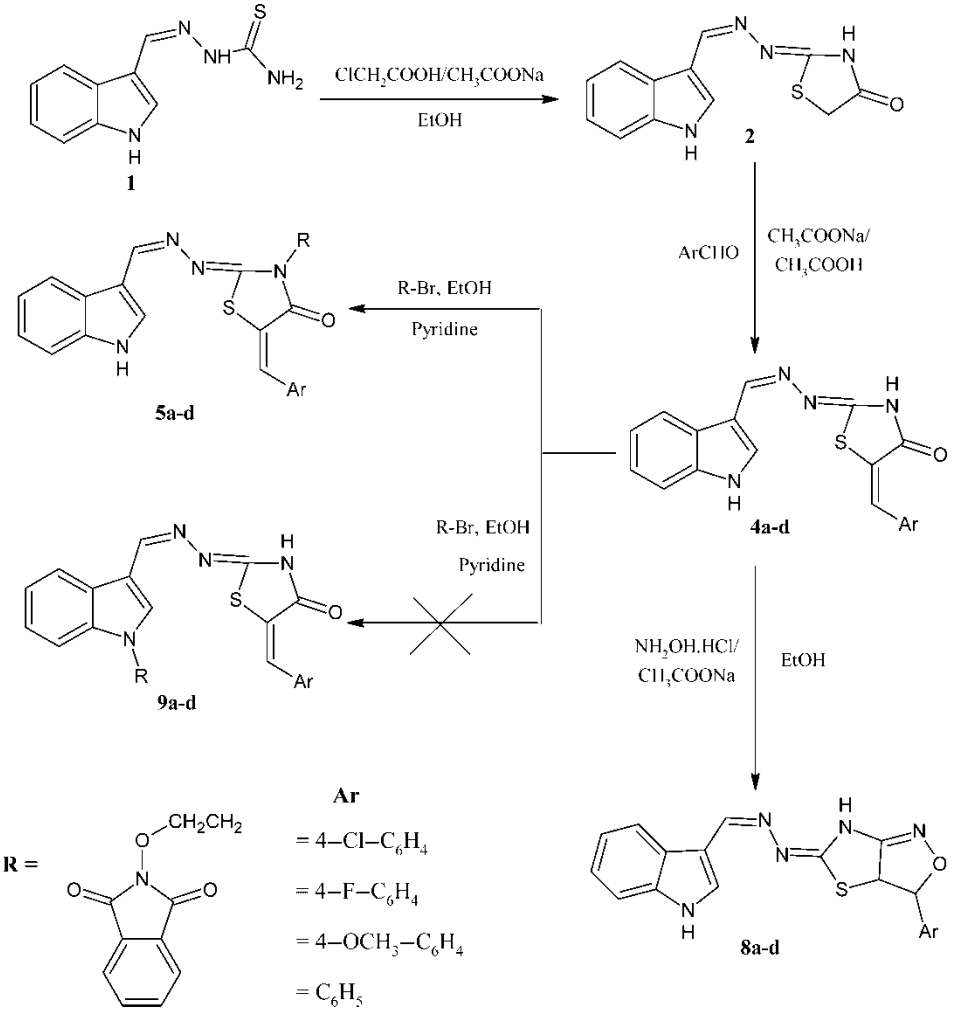
*Activity index = Inhibition area of the sample/inhibition area of the standard.
C$_1$ = Flucanazole; C$_2$ = Attraconazole. Diameter of disc in 5 mm.

pathogens but compounds **8a** and **8b** exhibited promising activity towards *A. fumigatus*. The remaining compounds did not show any remarkable antifungal activity. All the fluoro derivatives showed strong activity, although no specific correlation could be established between various substituents and activity (table 3).

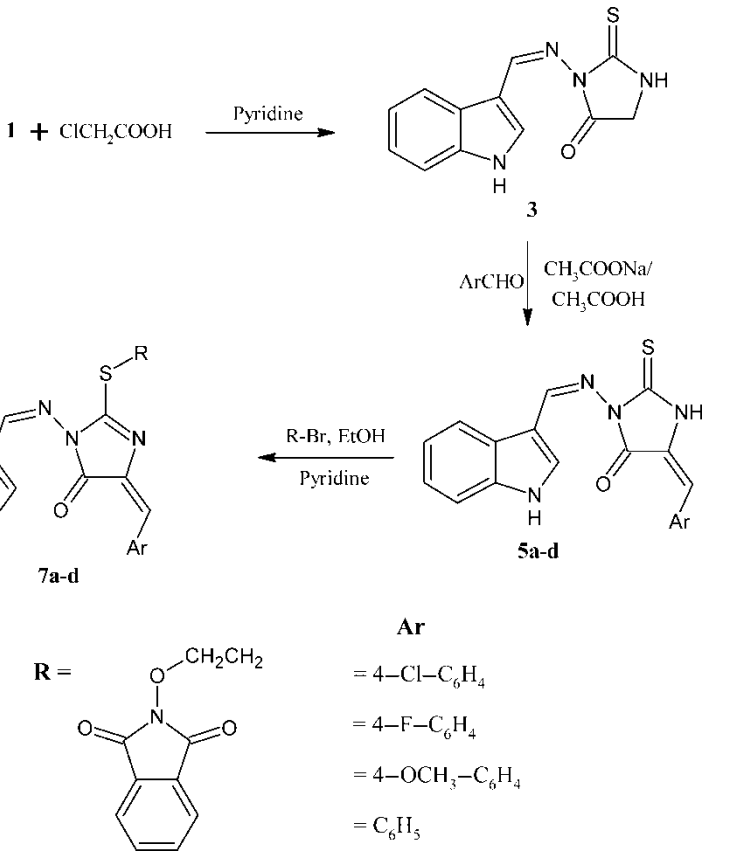
4. Experimental section

4.1 *General procedures*

All melting points were determined in open capillary tube and are uncorrected. The IR spectra were recorded on Perkin-Elmer spectrometer. The ^{1}H NMR spectra were scanned on a DRX-300 MHz. spectrometer (300 MHz) in CDCl3/DMSO-d6 using TMS as internal standard and chemical shifts are expressed in δ ppm. The mass spectra were recorded on Jeol SX-102 (FAB). m-Nitrobenzyl alcohol (NBA) was used as a matrix. TLC using silica gel-G confirmed the



SCHEME 1 Synthesis of Isoxazolinyl indole and exthoxyphthalimido-thiazolidinoyl indole.



SCHEME 2 Synthesis of ethoxyphthalimidothiolimidazolidinyl indole.

purity of synthesized compounds. Spots were exposed in an iodine chamber. Compound **1** was synthesized by a literature method [25].

4.2 *Synthesis of 3-thiazolidin-4-one-2-yl-methylene hydrazido-1H-indole (2)*

A mixture of indole-3-carbaldehyde thiosemicarbazone **1** (0.01 mol), chloroacetic acid (0.01 mol) and anhydrous sodium acetate (0.02 mol) in ethanol (70 mL) were heated under reflux for 7–8 hrs. on a water bath with occasional shaking. The solvent was removed and the reaction mixture was poured into ice water and filtered. The crude product was crystallized from ethanol to give **2**.

4.3 *Synthesis of 3-[2-thioxo-imidazolin-4-one-3-yl-imino methylene]-1H-indole(3)*

An equimolar mixture of indole-3-carbaldehyde thiosemicarbazone **1** (0.01 mol) and monochloroacetic acid (0.01 mol) in pyridine (15 mL) was warmed gently till the exothermic reaction started. After cooling the reaction mixture was treated with ethanol (10 mL) and refluxed for 7 hrs, poured into ice water, filtered and dried. The crude product recrystallized from ethanol, giving yellowish crystals of **3**.

4.4 *Synthesis of 3-[5-arylidene-1,3-thiazolidin-4-one-2-yl-methylene hydrazido]-1H-indole (4a–d)*

To a solution of **2** (0.01 mol) in acetic acid were added appropriate aromatic aldehydes (0.01 mol) and sodium acetate (0.01 mol). The reaction mixture was refluxed for 5 hrs, cooled, poured on crushed ice. The separated solid was filtered, washed thoroughly with water, dried and crystallized from a suitable solvent to yield **4a–d**.

4.5 *Synthesis of 3-[5-arylidene-2-thioxo-imidazolin-4-one-3-yl-imino methylene]-1H-indole (5a–d)*

A mixture of **3** (0.01 mol), appropriate aromatic aldehydes (0.01 mol) and sodium acetate (0.01 mol) in acetic acid (40 mL) was refluxed for 5 hrs, cooled and poured onto crushed ice. The yellow solid thus obtained was filtered, washed several times with water and crystallized from acetic acid.

4.6 *Synthesis of 3-[(5-arylidene-3-N-ethoxyphthalimido-1,3-thiazolidin-4-one-2-yl) methylene hydrazido]-1H-indole (6a–d)*

A mixture of **4a–d** (0.01 mol) and phthalimidoxyethylbromide (0.01 mol) were dissolved in absolute alcohol, pyridine (0.02 mol) was added to this reaction mixture as a base. The reaction mixture was refluxed for 8–9 hrs, subsequently, ethanol was distilled off and the crystals were filtered, dried and crystallized from ethanol.

4.7 *Synthesis of 3-[5-arylidene-2-(2-N-ethoxyphthalimido-thiol)imidazolin-4-one-3-yl imino methylene]-1H-indole (7a–d)*

A mixture of compound **5a-d** (0.01 mol), phthalimidoxyethylbromide (0.01 mol) and pyridine (2 mL) were refluxed in absolute alcohol (30 mL) for 10 hrs. Excess of solvent from the filtrate was removed under pressure, on cooling; the solid separated was crystallized from ethanol.

4.8 *Synthesis of 3-[(3-aryl-[4,6]-thiazolidino[4,5-c]isoxazolin-5(6H)-yl]methylene hydrazido-1H-indole (8a–d)*

Solution of sodium acetate (0.012 mol) in acetic acid (5 mL) was added in a mixture of **4a–d** (0.01 mol) and hydroxylamine hydrochloride (0.012 mol) in absolute ethanol. The reaction mixture was refluxed for 10 hrs and kept overnight. Excess of solvent was distilled off under reduced pressure and the remainder was then poured into water. The solid thus obtained was crystallized from EtOH to give **8a–d**.

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References

[1] K.C. Joshi, P. Chand. *Pharmazie*, **1**, 37 (1982).
[2] D.L. Germisk, G.Y. Parks, N.P. Plotnikof. *US Pat*, 3, 705902 (1971).
[3] S. Kakimoto, J. Nishie. *Jpn. J. Tubere*, **2**, 334 (1954).
[4] A.L. Berry. *The antibiotics susceptibility test: Principle and Practices*, 180–193 (1976).
[5] P. Kumar, S.K. Agarwal, S.D. Bakunni. *Ind. J. Chem*., **29B**, 1077 (1990).
[6] A.C. Bajji, K.P. Channabasavaraj, K.M.K. Swamy. *Indian Drugs*, **31**, 269 (1994).
[7] R. Lesyk, O. Vladzimirska, B. Zimenkovsky, S. Golota, I. Nektegagayev, O. Cherpark, M. Leb'yak, O. Kozak. *Boll. Chim. Farm.*, **144**, 197 (2002).
[8] P.K. Sharma, S.N. Sawhney. *Bioorg*. *Med. Chem. Lett*., **7**, 2427 (1997).
[9] S.P. Sachchar, A.K. Singh. *J. Indian Chem. Soc*., **61**, 239 (1985).
[10] K.D. Patel, B.D. Mistry, K.R. Desai. *J. Indian Chem. Soc.*, **18**, 783 (2004).
[11] N.C. Desai, H.K. Shukla, K.A. Thaker. *J. Indian Chem. Soc.*, **62**, 242 (1984).
[12] A.A. El-Barbary, A.I. Khodiair, E.B. Pederson, C. Nielsen. *Monatsh. Chem.*, **125**, 593 (1994).
[13] V. Shah, C.K. Pant, P.C. Joshi. *Asian J. Chem.*, **5**, 82 (1993).
[14] H.C. Chiang, J.R. Ko. *Heterocycles*, **19**, 529 (1982).
[15] F. Vittorio, G. Ronsisvalle, M.S. Pappalardo, G. Blandino. *Farmaco*, **40**, 359 (1985).
[16] J.D. Davenport. *US Pat*, **4**, 283 (1981).
[17] El-Bayouki, A.M. Khairy, J.H. Ibrahim, N. Lalit. *Egypt J. Chem*., **29**, 107 (1986).
[18] M. Stamper, B.F. Aycock. *J. Am. Chem. Soc.*, **76**, 2786 (1954).
[19] J.S. Sebolt, T. Aoki, J.N. Eble, J.L. Glover, G. Weber. *Biochem. Pharmacol*, **34**, 97 (1985).
[20] S. Jain, D.P. Nagda, G.L. Talesara. *Phosphorous Sulfur Silicon Related Elem.*, **181**, 1665 (2006).
[21] R. Sharma, M. Ahmed, K. Sharma, G.L. Talesara. *Ind. J. Pharm. Sci.*, **67**, 462 (2005).
[22] U. Ameta, S. Ojha, D. Bhambi, G.L. Talesara. *ARKIVOC*, **xiii**, 83 (2006).
[23] P.S. Bisen, K. Verma, *Hand Book of Microbiology*, 1st Edition, CBS Publications and Distributors, New Delhi (1998).
[24] S.E. Joon. *Clinical Becteria*, 4th Edition, p. 226, Edward Arnold, London (1975).
[25] P.M.S. Chauhan, R.K. Chatterjee. *Indian J. Chem.*, **33B**, 32 (1994).