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RESEARCH ARTICLE

Synthesis and antimicrobial evaluation of some pyrazolo-thiazolyl alkoxy-1H-isoindole-1, 3(2H)-dione derivatives

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1,3-Thiazolidine-2,4-dione **2** has been synthesized by the cyclisation reaction of thiourea and chloroacetic acid in the presence of ethanol. The reaction of compound **2** with substituted aromatic aldehyde afforded the corresponding derivatives of substituted 5-benzylidene-1,3-thiazolidinone-2,4-dione **3a–d**, which upon reflux with ω-bromoalkoxyphthalimide gave 2-{[-5-(substituted benzylidine)-2,4-dioxo-1,3-thiazolidine-3-yl]alkoxy}-1H-isoindole-1,3(2H)-dione **4a–i**. Further, compounds **4a–i** were treated with phenyl hydrazine and 2,4 dinitro phenyl hydrazine in the DMF to yield the title compound 2-[5-oxo-2,3-substituted diphenyl-2H-pyrazolo[3,4-d][1,3]thiazol-6(5H)-yl)alkoxy]-1H-isoindole-1,3(2H)-dione **5a–r**. Structures of newly synthesized compounds were established based on elemental analysis, IR, ^{1}H NMR and mass spectral data. Synthesized compounds have been assayed for their antibacterial activities against *B. subtilis, K. pneumoniae, P. aeruginosa* and *S. aureus* and antifungal activities against *A. fumigatus* and *C. albicans*.

Keywords: 2-Iminothiazolidinones; 5-Benzylidine-1,3-thiazolidinone-2,4-dione; Pyrazolo[3,4-d][1,3]thiazol; Alkoxyphthalimides; Bio-assay

1. Introduction

Heterocyclic bearing nitrogen and sulfur atoms constitute the core structure of a number of biologically interesting compounds. Thiazolidinones and thiazolidinediones were the first parent compounds in which thiazole ring was recognized [1]. A large number of thiazolidinones are reported in literature for their biological activities such as anticonvulsant [2] anti-inflammatory [3, 4], hypnotic [5], amoebicidal [6], analgesic [7], anti AIDS [8], etc. 4-Thiazolidinone derivatives substituted at 2, 3, 4 or 5 positions are antidiabetic drugs [9]. Pyrazole derivatives are also reported to possess antifungal [10], antidiabetic [11], herbicidal [12], antifertility [13], sedative [14] and antimicrobial activities [15], etc. Phthalimidoxy and other aminoxy compounds are known to possess wide range of biological activities like antimalarial, CNS depressant, antihypertensive and antimicrobial [16–19], etc.

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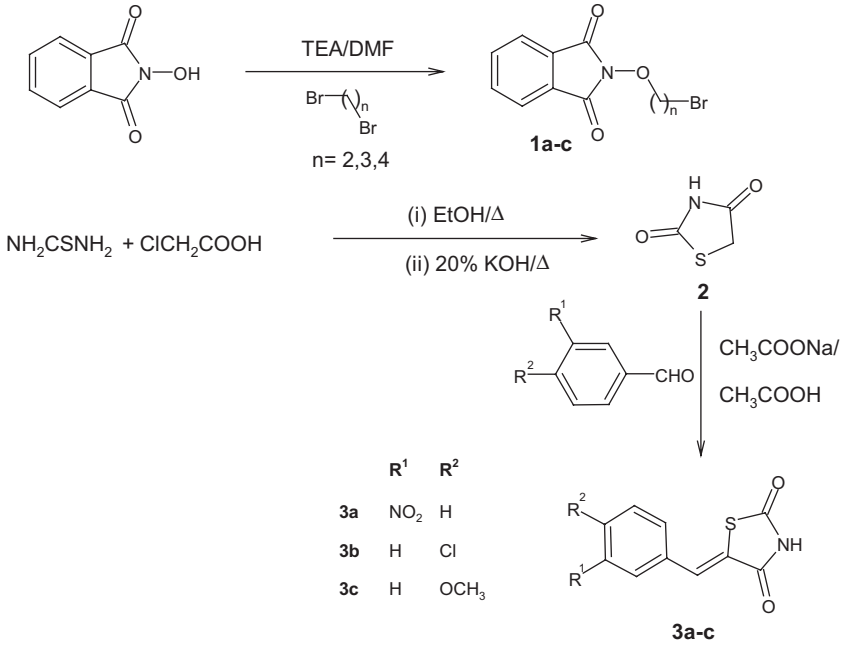
Recently some substituted 1H-pyrazole-thiazolidine as anti-inflammatory and antimicrobial agent have been recognized [20]. Study of various pyrazole and substituted thiazole has shown a direct correlation between compound structure and antimicrobial activity. In continuation of our interest in the synthesis of novel aminooxy containing heterocyclic framework, the plan was to design and synthesize a new class of combinational molecule in which all of these moieties are present, with the hope to achieve enhanced biological activity.

2. Result and discussion

In the present work an effort has been made to synthesize various substituted 5-benzylidine-1,3-thiazolidine-2,4-diones **3a–d** and their various alkoxy phthalimide derivatives 2-[5-oxo-2,3-substituted diphenyl-2H-pyrazolo[3,4-d][1,3]thiazol-6(5H)-yl) alkoxy]-1H-isoindole-1,3 (2H)-dione **5a–r** using a multistep process.

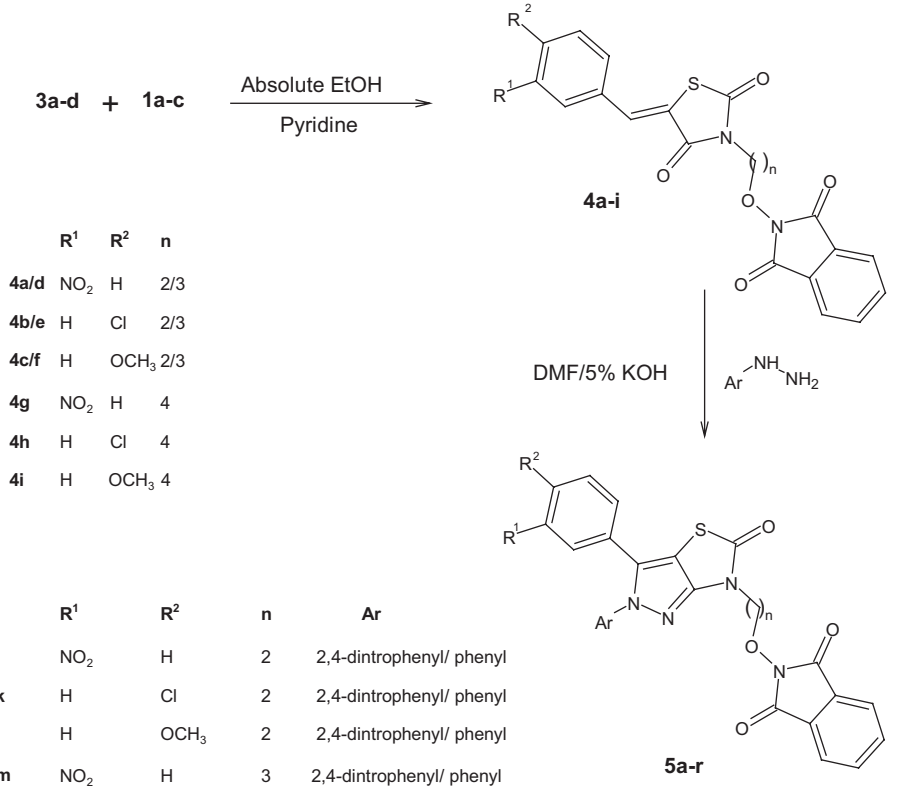
ω-Bromoalkoxy phthalimides (**1a–c**) were prepared by the reported method. In this method N-hydroxyphthalimide and ω, ω'-dibromoalkane were kept overnight (17–22 h) in dimethyl-formamide medium using triethylamine as base. Disappearance of the N-OH group resonance at 6.2 (singlet) along with new resonance for the alkyl side chain confirmed the reaction. Syntheses of **3a–d** are achieved by the chemoselective reaction of reactive methylene group of compound **2** with various aromatic aldehyde to form α-β unsaturated moiety in the presence of base. Compound **2** was prepared by the cyclization of thiourea with chloroacetic acid in ethanol media. Finally, treatment with 20% KOH achieved hydrolysis of the imino group (scheme 1).

Compounds **3a–d** were condensed with various ω-bromoalkoxyphthalimide in the presence of absolute alcohol and catalytic amount of pyridine to give 2-{[-5-(substituted benzylidine)-2,4-dioxo-1,3-thiazolidine-3-yl]alkoxy}-1H-isoindole-1,3(2H)-dione **4a–i**. In the present



SCHEME 1

investigation, we have used various organic bases like pyridine, piperidine, triethylamine, piperazine, trimethylamine and inorganic bases like NaOH, NaH, anh. K_2CO_3 or Na_2CO_3 were also tried for above reactions. Reaction gave poor yields when TEA was used and required longer refluxing time whereas piperidine and piperazine gave generally sticky product. Better yields were obtained when pyridine was used as a base. Inorganic bases gave decomposed product. Condensation of ω-bromoalkoxyphthalimide at the N-atom was confirmed by IR spectroscopy. The stretching vibration band for −NH group at 3300–3100 cm^{-1} disappeared and a strong band at 1300–1160 cm^{-1} appeared for the C−N stretching of the CH_2−N−CO group confirming the formation of a new C−N band. Compounds **4a–i** further refluxed with substituted phenyl hydrazine in DMF media gave the title compounds **5a–r** (scheme 2). Formation of these compounds were confirmed by the appearance of a new C=N stretching at 1602–1626 cm^{-1} in IR and disappearance of ^1H NMR signal at 6.2 δ for C=CH−Ar group. The structure of all the synthesized compounds have been assigned on the basis of their spectral data and elemental analysis which have been given in the tables 1 and 2, respectively.



	R^1	R^2	n
4a/d	NO_2	H	2/3
4b/e	H	Cl	2/3
4c/f	H	OCH_3	2/3
4g	NO_2	H	4
4h	H	Cl	4
4i	H	OCH_3	4

	R^1	R^2	n	Ar
5a/5j	NO_2	H	2	2,4-dintrophenyl/ phenyl
5b/5k	H	Cl	2	2,4-dintrophenyl/ phenyl
5c/5l	H	OCH_3	2	2,4-dintrophenyl/ phenyl
5d/5m	NO_2	H	3	2,4-dintrophenyl/ phenyl
5e/5n	H	Cl	3	2,4-dintrophenyl/ phenyl
5f/5o	H	OCH_3	3	2,4-dintrophenyl/ phenyl
5g/5p	NO_2	H	4	2,4-dintrophenyl/ phenyl
5h/5q	H	Cl	4	2,4-dintrophenyl/ phenyl
5i/5r	H	OCH_3	4	2,4-dintrophenyl/ phenyl

SCHEME 2

Table 1. Characterization data of the newly synthesized compounds.

Compounds	m.p./°C (solvent)	Colour yield (%)	Mol. Formula (Mol. Wt.)	Elemental analysis [calcd/found (%)]			
				C	H	N	S
4a	270 EtOH	Yellow 72	$C_{20}H_{13}N_3O_7S$ 439.39	54.67 54.60	2.98 2.91	9.56 9.51	7.30 7.26
4b	205 EtOH	Dark yellow 70	$C_{20}H_{13}ClN_2O_5S$ 428.84	56.01 55.80	3.06 3.01	6.53 6.50	7.48 7.44
4c	192 EtOH	Yellow 71	$C_{21}H_{16}N_2O_6S$ 424.42	59.43 59.28	3.80 3.72	6.60 6.58	7.55 7.51
4d	230 EtOH	Pale yellow 68	$C_{21}H_{15}N_3O_7S$ 453.42	55.63 55.40	3.33 3.30	9.27 9.96	7.07 7.00
4e	209 EtOH	Yellow 65	$C_{21}H_{15}ClN_2O_5S$ 442.87	56.95 56.70	3.41 3.37	6.33 6.31	7.24 7.17
4f	216 EtOH	Orange yellow 67	$C_{22}H_{18}N_2O_6S$ 438.45	60.27 60.08	4.14 4.11	6.39 6.37	7.31 7.26
4g	202 EtOH	Yellow 66	$C_{22}H_{17}N_3O_7S$ 467.45	56.53 56.32	3.67 3.63	8.99 8.98	6.86 6.83
4h	242 EtOH	Yellow 70	$C_{22}H_{17}ClN_2O_5S$ 456.89	57.83 57.72	3.75 3.70	6.13 6.11	7.02 7.00
4i	189 EtOH	Yellow 60	$C_{23}H_{20}N_2O_6S$ 452.47	61.05 60.85	4.46 4.39	6.19 6.18	7.09 7.02
5a	268 CH_3COOH	Dark Brown 58	$C_{26}H_{15}N_7O_{10}S$ 617.50	50.57 50.42	2.45 2.40	15.88 15.70	5.19 5.12
5b	240 CH_3COOH	Brown 55	$C_{26}H_{15}ClN_6O_8S$ 606.95	51.45 51.38	2.49 2.43	13.85 13.79	5.28 5.22
5c	291 CH_3COOH	Brown 52	$C_{27}H_{18}N_6O_9S$ 602.53	53.82 53.40	3.01 2.98	13.95 13.85	5.32 5.26
5d	253 CH_3COOH	Brown 59	$C_{27}H_{17}N_7O_{10}S$ 631.58	51.35 51.22	2.17 2.11	15.53 15.48	5.08 5.01
5e	278 CH_3COOH	White 63	$C_{27}H_{17}ClN_6O_8S$ 620.97	52.22 52.12	2.76 2.71	13.53 13.49	5.16 5.11
5f	294 CH_3COOH	White 62	$C_{28}H_{20}N_6O_9S$ 616.55	54.54 54.48	3.27 3.22	13.63 13.60	5.20 5.16
5g	>300 CH_3COOH	White 65	$C_{28}H_{19}N_7O_{10}S$ 645.55	52.09 52.01	2.97 2.92	15.19 15.17	4.57 4.53
5h	290 CH_3COOH	White 67	$C_{28}H_{19}ClN_6O_8S$ 635	52.96 52.89	3.02 3.01	13.23 13.19	5.05 5.02
5i	>300 CH_3COOH	Light brown 65	$C_{29}H_{22}N_6O_9S$ 630.58	55.24 55.08	3.52 3.48	13.33 13.29	5.05 5.00
5j	240 CH_3COOH	Light brown 67	$C_{26}H_{17}N_5O_6S$ 527.50	59.20 59.09	3.28 3.22	13.28 13.24	6.08 6.03
5k	227 CH_3COOH	Brown 53	$C_{26}H_{17}ClN_4O_4S$ 516.95	60.41 60.38	3.31 3.26	10.82 10.79	6.20 6.18
5l	276 CH_3COOH	Brown 54	$C_{27}H_{20}N_4O_5S$ 512.53	63.27 63.21	3.93 3.89	10.93 10.88	6.26 6.21
5m	253 CH_3COOH	Brown 59	$C_{27}H_{19}N_5O_6S$ 541.53	59.88 59.72	3.54 3.51	12.93 12.90	5.92 5.90
5n	270 CH_3COOH	Dark brown 61	$C_{27}H_{19}ClN_4O_4S$ 530.98	61.07 60.95	3.61 3.58	10.55 10.51	6.04 6.01
5o	278 CH_3COOH	Dark brown 65	$C_{28}H_{22}N_4O_5S$ 526.56	63.87 63.77	4.21 4.19	10.64 10.49	6.09 6.07
5p	273 CH_3COOH	Dark brown 59	$C_{28}H_{21}N_5O_6S$ 555.56	60.53 60.42	3.81 3.79	12.61 12.58	5.77 5.75
5q	260 CH_3COOH	Dark brown 62	$C_{28}H_{21}ClN_4O_4S$ 545.56	61.71 61.68	3.88 3.86	10.28 10.26	5.88 5.86
5r	283 CH_3COOH	Dark brown 58	$C_{28}H_{24}N_4O_5S$ 540.58	64.43 64.39	4.47 4.46	10.36 10.31	5.93 5.91

Table 2. Characterization data of the newly synthesized compounds.

Compound number	Spectra
4a	ν (cm^{-1}): 3040 (C−H, ArH), 2892 (C−H, CH_2), 1695 (C−O str.,C=O),1725 (C=O str, thiazolidinone ring), 1535–1342 (N−O str, NO_2), 1751 (C=O str., CO−N−CO), 1208 (C−N), 1188 (C−O), 790 (disub. benzene), 685 (C−S−C) δ_H (ppm): 7.44–7.64 (m, 4H, ArH, $J = 2$ Hz, $J = 9$ Hz), 7.0–7.33 [m, 4H, ArH(NO_2), $J = 8.5$ Hz], 6.63 (s, 1H, C=CH−Ar), 3.32 (t, 2H, OCH_2, $J = 6$ Hz), 2.96 (t, 2H, NCH_2)
4b	ν (cm^{-1}):3045 (C−H, ArH), 2894 (C−H, CH_2), 1696 (C−O str., C=O), 1728 (C=O str, thiazolidinone ring), 1748 (CO−N−CO), 1216 (C−N), 1186 (C−O), 854 (disubs. benzene), 682 (C−S−C) δ_H (ppm): 7.10–7.67 (m, 8H, ArH, $J = 8.7$ Hz), 6.58 (s, 1H, C=CH−Ar), 3.43 (t, 2H, OCH_2, $J = 6.8$ Hz), 3.07 (t, 2H, NCH_2)
4c	ν (cm^{-1}): 3038 (C−H, ArH), 2887 (C−H, CH_2), 2928 (C−H, CH_3), 1694 (C−O str., C=O), 1746 (CO−N−CO), 1722 (C=O str, thiazolidinone ring), 1222 (C−N), 1181 (C−O), 860, 680 (C−S−C). δ_H (ppm): 7.09–7.66 (m, 8H, ArH, $J = 9$ Hz, $J = 1.5$ Hz), 6.38 (s, 1H, C=CHAr), 3.33 (t, 2H, O−CH_2, $J = 6.5$ Hz), 3.13 (t, 2H, NCH_2), 3.67 (s, 3H, OCH_3)
4d	ν (cm^{-1}): 3044 (C−H, ArH), 2886 (C−H, CH_2), 1698 (C=O), 1724 (C=O str, thiazolidinone ring), 1538–1332 (NO_2), 1750 (CO−N−CO), 1208 (C−N), 1192 (C−O), 792, 689 (C−S−C). δ_H (ppm): 7.2–7.76 (m, 8H, ArH, $J = 8.4$ Hz), 6.62 (s, 1H, C=CH Ar), 3.36 (t, 2H, OCH_2, $J = 6.6$ Hz), 2.64 (q, 2H, OCH_2−**CH_2**−CH_2−N), 3.09 (t, 2H, NCH_2).
4e	ν (cm^{-1}): 3045 (C−H, ArH), 2891 (C−H, CH_2), 1693 (C=O), 1744 (CO−N−CO), 1724 (C=O str, thiazolidinone ring), 1220 (C−N), 1180 (C−O), 852 (ArH), 683 (C−S−C). δ_H (ppm): 7.16–7.70 (m, 8H, ArH, $J = 9.8$ Hz), 6.52 (s, 1H, C=CH Ar), 3.44 (t, 3H, OCH_2, $J = 6.7$ Hz), 3.12 (t, 2H, CH_2−N), 2.66 (q, 2H, OCH_2−**CH_2**−CH_2−N).
4f	ν (cm^{-1}): 3038 (C−H, ArH), 2886 (C−H, CH_2), 2936 (C−H, CH_3), 1683 (C=O), 1751 (CO−N−CO), 1729 (C=O str, thiazolidinone ring), 1215 (C−N), 1187 (C−O), 847 (ArH), 687 (C−S−C). δ_H (ppm): 7.07–7.76 (m, 8H, ArH, $J = 7$ Hz), 6.44 (s, 1H, C=CH Ar), 3.67 (s, 3H, OCH_3), 3.42 (t, 2H, OCH_2), 2.92 (t, 2H, CH_2N), 2.67 (q, 2H, OCH_2−**CH_2**−CH_2−N)
4g	ν (cm^{-1}): 3042 (C−H, ArH), 2896 (C−H, CH_2), 1693 (C=O), 1746 (CO−N−CO), 1727 (C=O str, thiazolidinone ring), 1226 (C−N), 1193 (C−O), 794 (ArH), 685 (C−S−C). δ_H (ppm): 7.0–7.78 (m, 8H, ArH, $J = 8.5$ Hz), 6.68 (s, 1H, C=CHAr), 3.46 (t, 2H, OCH_2, $J = 7$ Hz), 2.95 (t, 2H, NCH_2), 2.86 (q, 2H, OCH_2−**CH_2**−CH_2−CH_2−N), 2.59 (q, 2H, OCH_2−CH_2−**CH_2**−CH_2−N),
4h	ν (cm^{-1}): 3047 (C−H, ArH), 2893 (C−H, CH_2), 1683 (C=O), 1749 (CO−N−CO), 1724 (C=O str, thiazolidinone ring), 1211 (C−N), 1186 (C−O), 854 (ArH), 682 (C−S−C). δ_H (ppm): 7.0–7.78 (m, 8H, ArH, $J = 8.0$ Hz), 6.54 (s, 1H, C=CHAr), 3.42 (t, 2H, O−CH_2, $J = 6.9$ Hz), 2.97 (t, 2H, CH_2−N), 2.81 (q, 2H, O−CH_2−**CH_2**−CH_2CH_2−N), 2.62 (q, 2H, O−CH_2−CH_2−**CH_2**−CH_2−N)
4i	ν (cm^{-1}): 3037 (C−H, ArH), 2893 (C−H, CH_2), 2933 (C−H, CH_2), 1693 (C=O), 1746 (CO−N−CO), 1727 (C=O str, thiazolidinone ring), 1219 (C−N), 1181 (C−O), 858 (ArH), 684 (C−S−C). δ_H (ppm): 7.0–7.52 (m, 8H, ArH, $J = 7$ Hz), 6.48 (s, 1H, C=CHAr), 3.66 (s, 3H, OCH_3), 3.40 (t, 2H, OCH_2, $J = 6.6$ Hz), 2.90 (t, 2H, −CH_2N), 2.74 (q, 2H, OCH_2−**CH_2**−CH_2−CH_2−N), 2.65 (q, 2H, OCH_2−CH_2−**CH_2**−CH_2−N).
5a	ν (cm^{-1}): 3052 (CH, ArH), 2898 (C−H str, CH_2), 1724 (C=O str, thiazolidinone ring), 1550–1348 (N−O str, NO_2), 1748 (CO−N−CO), 1208 (C−N), 1189 (C−O), 1605 (C=N), 1176 (N−N str), 740 (disub. benz), 689 (C−S−C str), δ_H (ppm): 7.23–7.59 (m, 8H, ArH, $J = 8$ Hz), 7.6–7.77 (m, 3H, dinitro benz, $J = 1.7$ Hz, $J = 8.5$ Hz), 3.51 (t, 2H, OCH_2, $J = 6$ Hz), 2.92 (t, 2H, CH_2N) Mass m/z: 617 (3), 427 (77), 399 (72), 231 (42), 203 (11), 190 (100), 162 (11)
5c	ν (cm^{-1}): 3062 (CH, ArH), 2893 (C−H str, CH_2), 1723 (C=O str, thiazolidinone ring), 1549–1346 (N−O str, NO_2), 1748 (CO−N−CO), 1216 (C−N), 1189 (C−O), 1609 (C=N), 1178 (N−N str), 840 (disub. benz), 689 (C−S−C str) δ_H (ppm): 7.1–7.68 (m, 8H, ArH, $J = 8.8$ Hz), 7.69–781 (m, 3H, dintro benz, $J = 1.9$ Hz, $J = 9.3$ Hz), 3.52 (t, 2H, OCH_2, $J = 6.6$ Hz), 2.91 (t, 2H, CH_2N). Mass m/z: 602 (4), 412 (75), 384 (68), 217 (40), 189 (13), 190 (100), 162 (10), 146 (18), 132 (80), 104 (8), 76 (12)

(*continued*)

Table 2. Continued.

Compound number	Spectra
5e	ν (cm^{-1}): 3064 (CH, ArH), 2896 (C−H str, CH_2), 1728 (C=O str, thiazolidinone ring), 1545–1340 (N−O str, NO_2), 1748 (CO−N−CO), 1213 (C−N), 1189 (C−O), 1619 (C=N), 1179 (N−N str), 850 (disub. benz), 686 (C−S−C str). δ_H (ppm): 7.15–7.68 (m, 8H, ArH, $J = 7$ Hz), 7.78 (m, 3H, $J = 8$ Hz), 3.58 (t, 2H, OCH_2, $J = 7.0$ Hz), 2.88 (t, 2H, OCH_2), 2.65 (q, 2H, $OCH_2\mathbf{CH_2}$ CH_2N). Mass m/z: 620 $[M]^+$, 622 [M+2] (3), 418 (73), 390 (65), 223 (37), 204 (100), 162 (12), 146 (17), 132 (78), 104 (9.5), 76 (14)
5f	ν (cm^{-1}): 3054 (CH, ArH), 2892 (C−H str, CH_2), 2924 (C−H, OCH_3), 1725 (C=O str, thiazolidinone ring), 1542–1336 (N−O str, NO_2), 1744 (CO−N−CO), 1217 (C−N),1184 (C−O), 1614 (C=N), 1173 (N−N str), 854 (disub. benz), 684 (C−S−C str), δ_H (ppm): 7.13–7.60 (m, 8H, ArH, $J = 9$ Hz), 7.77 (m, 3H, ArH, $J = 8$ Hz), 3.33 (t, 2H, OCH_2, $J = 6.9$ Hz), 2.94 (t, 2H, CH_2N), 2.73 (q, 2H, O $CH_2\mathbf{CH}_2CH_2N$), 3.63 (s, 3H, OCH_3) Mass m/z: 616 (2.5), 412 (72), 384 (63), 217 (36), 204 (100), 162 (13), 146 (17.5), 132 (78), 104 (9), 76 (13)
5i	ν (cm^{-1}): 3064 (CH, ArH), 2895 (C−H str, CH_2), 2935 (C−H, OCH_3), 1727 (C=O str, thiazolidinone ring), 1744 (CO−N−CO), 1210 (C−N), 1188 (C−O), 1610 (C=N), 1176 (N−N str), 844 (disub. benz), 688 (C−S−C str). δ_H (ppm): 7.07–7.59 (m, 8H, ArH, $J = 8.5$ Hz), 7.64 (m, 3H, ArH, $J = 7.6$ Hz), 3.56 (s, 3H, OCH_3), 3.32 (t, 2H, OCH_2, $J = 6.7$ Hz), 2.86 (t, 2H, CH_2N), 2.70 (q, 2H, O $CH_2\mathbf{CH_2}CH_2CH_2N$), 2.52 (q, 2H, $OCH_2CH_2\mathbf{CH_2}CH_2N$) Mass m/z: 630 (1.8), 412 (77), 384 (67), 217 (44), 189 (12), 218 (100), 162 (12), 146 (18.8), 132 (77), 104 (10), 76 (12)
5k	ν (cm^{-1}): 3058 (CH, ArH), 2888 (C−H str, CH_2), 1729 (C=O str, thiazolidinone ring), 1749 (CO−N−CO), 1214 (C−N), 1181 (C−O), 1609 (C=N), 1177 (N−N str) 842 (disub. benz), 682 (C−S−C str). δ_H (ppm): 7.4–7.69 (m, 8H, ArH, $J = 8$ Hz), 7.0–7.35 (m, 5H, ArH, $J = 7$ Hz, $J = 2$ Hz), 3.51 (t, 2H, OCH_2, $J = 6.8$ Hz), 2.89 (t, 2H, CH_2N) Mass m/z: 516 $[M]^+$, 518[M+2] (2), 328 (75), 300 (66), 189 (42), 161 (13), 190 (100), 162 (10), 146 (16), 132 (80), 104 (9), 76 (13), 51 (14)
5m	ν (cm^{-1}): 3054 (CH, ArH), 2898 (C−H str, CH_2), 1722 (C=O str, thiazolidinone ring), 1547–1338 (N−O str, NO_2), 1748 (CO−N−CO), 1216 (C−N), 1187 (C−O), 1606 (C=N), 1179 (N−N str),754 (disub. benz), 684 (C−S−C str), δ_H (ppm): 7.48–7.69 (m, 8H, ArH, $J = 7.8$ Hz), 7.0–7.18 (m, 5H, ArH, $J = 7.5$ Hz, $J = 2.4$ Hz), 3.55 (t, 2H, OCH_2, $J = 6.7$ Hz), 2.68 (q, 2H, $OCH_2\mathbf{CH_2}CH_2N$), 2.92 (t, 2H, CH_2N) Mass m/z: 541 (3), 337 (75), 309 (63), 187 (42), 159 (13), 204 (100), 162 (11), 146 (15), 132 (78), 104 (10), 76 (14)
5o	ν (cm^{-1}): 3056 (CH, ArH), 2882 (C−H str, CH_2), 2928 (C−H, OCH_3), 1725 (C=O str, thiazolidinone ring), 1749 (CO−N−CO), 1219 (C−N), 1179 (C−O), 1611 (C=N), 1174 (N−N str), 860 (disub. benz), 687 (C−S−C str). δ_H (ppm): 7.3–7.77 (m, 8H, ArH, $J = 8.5$ Hz), 7.14–7.29 (m, 5H, ArH, $J = 9.7$ Hz, $J = 2.2$ Hz), 3.58 (s, 3H, OCH_3, $J = 6.9$ Hz), 3.35 (t, 2H, OCH_2), 2.88 (t, 2H, CH_2N), 2.70 (q, 2H, $OCH_2\mathbf{CH_2}CH_2N$) Mass m/z: 526 (3), 322 (74), 294 (65), 187 (45), 159 (10), 204 (100), 162 (115), 146 (19), 132 (78), 104 (9), 76 (13), 51 (15.5)
5p	ν (cm^{-1}):3051 (CH, ArH), 2892 (C−H str, CH_2), 1728 (C=O str, thiazolidinone ring), 1548–1335 (N−O str, NO_2), 1741 (CO−N−CO), 1209 (C−N), 1187 (C−O), 1618 (C=N), 1174 (N−N str), 758 (disub. benz), 684 (C−S−C str). δ_H (ppm): 7.41–7.64, (m, 8H, ArH, $J = 8$ Hz), 7.12–7.29 (m, 5H, ArH, $J = 9$ Hz), 3.19 (t, 2H, OCH_2, $J = 7$ Hz), 2.86 (t, 2H, CH_2N), 2.69 (q, 2H, $OCH_2\mathbf{CH}_2CH_2CH_2N$), 2.54 (q, 2H, $OCH_2CH_2\mathbf{CH}_2CH_2N$) Mass m/z: 555 (2), 337 (76), 309 (62), 187 (46), 159 (12), 218 (100), 162 (12), 146 (20), 132 (78), 104 (10), 76 (13), 51 (15)
5r	ν (cm^{-1}): 3058 (CH, ArH), 2890 (C−H str, CH_2), 2929 (C−H, OCH_3), 1729 (C=O str, thiazolidinone ring), 1549–1336 (N−O str, NO_2), 1743 (CO−N−CO), 1217 (C−N), 1185 (C−O), 1619 (C=N), 1178 (N−N str), 858 (disub. benz), 688 (C−S−C str). δ_H (ppm): 7.34–7.72 (m, 8H, ArH, $J = 9.5$ Hz), 7.27 (m, 5H, ArH, $J = 8$ Hz), 3.64 (s, 3H, OCH_3, $J = 6$ Hz), 3.28 (t, 2H, OCH_2), 2.84 (t, 2H, CH_2N), 2.71 (q, 2H, $OCH_2\mathbf{CH_2}CH_2CH_2N$), 2.63 (t, 2H, $OCH_2CH_2\mathbf{CH_2}CH_2N$) Mass m/z: 540 (3), 322 (76), 294 (66), 187 (46), 159 (15), 218 (100), 162 (13), 146 (20), 132 (82), 104 (12), 76 (13), 51 (15)

Table 3. Response of various microorganisms to some synthesized compounds *in vitro* culture.

	Antibacterial activity				Antifungal activity	
Compound	*K. pneumoniae*	*P. aeruginosa*	*S. aureus*	*B. subtilis*	*A. fumigatus*	*C. albicans*
5a	+++	++	++	+	+++	+
5b	++	++	−	++	+	+++
5c	++	++	++	+	+	++
5d	+++	++	++	−	++	+
5e	++	−	+	−	+	++
5f	++	+	++	+	++++	+
5g	+	+	−	−	++	+
5h	+	−	−	−	++++	++
5i	+	+	+	−	++	+
5j	++	++	+	+	+++	++
5k	++	+	++	+	++	+
5l	−	++	+	−	+++	+
5m	++	−	−	−	++	+
5n	+	−	+	−	+	++
5o	++	+	+	+	+	+++
5p	+	−	−	+	+	+
5q	+	+	+	−	+	++
5r	+	−	−	+	+	+
C_1	++++	++++	++++	++++	−	−
C_2	−	−	−	−	++++	++++

Zone of inhibition: − = <3 (no activity), + = 3–5 (weak activity), ++ = 5–10 (moderate activity), +++ = 10–15 (strong activity), ++++ = >15. (Standard): C_1 = Ciprofloxacin (Zone of inhibition = 18 mm) for antibacterial activity; C_2 = Fluconazole (Zone of inhibition = 15 mm) for antifungal activity.

3. Antimicrobial activity

The title compounds (**5a–r**) were screened for their antibacterial and antifungal activities using cup and well method [21, 22]. Antibacterial activity of compounds (500 μg/ml) have been evaluated against four bacterial strain viz. *K. pneumoniae, P. aeruginosa, S. aureus* and *B. subtilis*. Almost all the compounds showed low to moderate activity against *K. pneumoniae, P. aeruginosa* and *S. aureus*. Majority of the compounds were inactive against *B. subtilis as* compared to the standard drug (Ciprofloxacin) used. Screening of the title compounds (500 μg/ml) for antifungal activity was carried out against two fungal strain viz. *A. fumigatus* and *C. albicans* using flucanazole as a standard drug. Compounds **5a**, **5f**, **5h**, **5l** and **5j** were highly active against *A. fumigatus* and other were good active. While compounds **5b**, **5c**, **5e**, **5o, 5q**, and **5r** have not exhibited appreciable activity against *A. fumigatus* but these were found to be moderately active against *C. albicans* (table 3). Although the antibacterial and antifungal activity could not be directly related to the structure, yet some conclusions can be drawn that all the compounds showed good antifungal activity and increased antimicrobial activity was observed when an electron withdrawing group attached to phenyl ring but activity was found to decrease when an electron donating group was present in phenyl ring.

4. Experimental

Melting points of all synthesized compounds were determined in open capillary tube and are uncorrected. IR spectra (KBr) and ^{1}H NMR spectra (DMSO-d_6) were recorded on FTIR RXI Perkin-Elmer 1800 spectrophotometer and DRX-300 (300 MHz) spectrophotometer using TMS as internal standard, respectively and mass spectra were recorded on a Jeol SX-102

(FAB) spectrometer. The purity of compounds was checked by elemental analysis and also by TLC using silica gel "G", as adsorbent and visualization was accomplished by Iodine.

Compounds **1a–c** were synthesized by literature methods [23]. Physical and analytical data of the synthesized compounds are given in table 1.

4.1 *Synthesis of 1,3-thiazolidin-2,4-dione: (2)*

A mixture of thiourea (0.5 mole), in ethanol and chloroacetic acid (0.6 mole) was refluxed for 5 hours. It was allowed to cool; separated solid was filtered and washed with ethanol. The crude hydrochloride obtained was dissolved in boiling water (75 ml) after 24 hours the separated crystal was filtered and refluxed for 2 hours in aqueous KOH (20%, 15 ml). The reaction mixture was cooled and poured into dilute acetic acid (1:1, 50 ml). The precipitated solid was filtered and recrystallised from ethanol.

4.2 *Synthesis of substituted 5-benzylidene-1, 3-thiazolidine-2, 4-Dione: (3a–c)*

Compound **2** (0.05 mole), glacial acetic acid 30 ml, fused sodium acetate (0.05 mole) and arylaldehyde (0.05 mole) were refluxed for 6 hours. After cooling, reaction mixture was slowly poured into crushed ice and yellow solid obtained was filtered and washed with ethanol. The crude solid mass was recrystallised from glacial acetic acid.

4.3 *Synthesis of 2-{[-5-(substituted benzylidine)-2,4-dioxo-1,3-thiazolidine-3-yl]alkoxy}-1H-isoindole-1,3(2H)-dione: (4a–i)*

To a three necked flask, provided with a reflux condenser, a dropping funnel and a mechanical stirrer, a solution of compound **3a–d** (0.01 mole), ω-bromoalkoxypthalimide (0.01 mole) in absolute alcohol were charged. To this stirred solution pyridine (4 ml). was added dropwise and the mixture was refluxed for 15–18 hrs. After cooling, excess of solvent was removed under reduced pressure. The separated solid was filtered, dried and recrystallised from ethanol (tables 1 and 2).

4.4 *Synthesis of 2-[5-oxo-2,3-disubstituted diphenyl-2H-pyrazolo[3,4-d][1,3]thiazol-6 (5H)-yl) alkoxy]-1H-isoindole-1,3(2H)-dione: (5a–r)*

In a three necked flask., an equimolar amount of compound **4a–i** (0.05 mole) and substituted phenyl hydrazine (0.05 mole) were dissolved in DMF (15 ml). To this stirred solution, 5% KOH (4–6 ml) was added dropwise during 30–40 min and reaction mixture was refluxed for 5–8 hr. After cooling, the reaction mixture was poured slowly onto crushed ice with stirring. The solid product so obtained was filtered, washed, dried and crystallised from glacial acetic acid to yield compounds **5a–r** (tables 1 and 2).

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