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Efficient microwave enhanced regioselective synthesis of a series of benzimidazolyl/triazolyl spiro [indole-thiazolidinones] as potent antifungal agents and crystal structure of spiro[3*H*-indole-3,2′-thiazolidine]-3′(1,2,4-triazol-3-yl)-2,4′(1*H*)-dione

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Abstract—A microwave-assisted three-component, regioselective one-pot cyclocondensation method has been developed for the synthesis of a series of novel spiro[indole-thiazolidinones] (**6a**–**l**) using an environmentally benign procedure at atmospheric pressure in open vessel. This rapid method produces pure products in high yields within few minutes in comparison to a conventional two-step procedure. The crystal structure of one representative compound has been determined by X-ray diffraction. The synthesized compounds have been screened 'in vitro' for antifungal activity against *Rhizoctonia solani*, *Fusarium oxysporum* and *Collectotrichum capsici*. All compounds have shown good activity against these pathogens.
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1. Introduction

Microwave (MW) irradiation is nowadays currently used to carry out a wide range of reactions in short reaction times, producing compound in high yields and stereoselectivity. In the developing area of green-chemistry, the aim is to perform organic reactions under solvent-free, dry media conditions[1] for reducing the use of toxic solvents, thus preventing pollution. The MW reaction technique[2] is most convenient, since reactions performed by this method are clean and economical. Equally, multi-component reactions (MCRs) are gaining increasing importance in organic and medicinal chemistry.[3] In the context where a premium input on speed, diversity and efficiency in the drug discovery process,[4] MCR strategies offer significant advantages over conventional linear-type synthesis.[5] In such reactions, three or more reactants are employed in a single reaction vessel to obtain new products constitutive of all components.[6]

The indole moiety is probably the most well-known heterocycle, a common and important feature of a variety of natural products and medicinal agents.[7] Compounds carrying the indole residue, exhibiting antibacterial and antifungal activities, have been extensively reported.[8] Mitomycins are natural indole antibiotics that are also anticancer compounds acting as DNA crosslinking agents.[9] Thia-azaheterocycles have attracted considerable attention because of their wide

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biological and pharmacological activities[10] further, spiro[indole-thiazolidinones] are one of the most studied classes of 3-spiroindoline derivatives due to a wide variety of bioactivity associated with them and are used in pharmaceuticals because of their anti-inflammatory,[11] fungistatic,[12] bacteriostatic[13] and anticonvulsant activities.[14] Azole-containing antifungals attract much attention thanks to their clinical usage and represent an important antifungal drug group, acting via the aromatase inhibition pathway. Important examples are ketoconazole, clotrimazole, miconazole, and tioconazole.[15]

As part of our endeavour to discover new thia-azaheterocycles[16] of biocidal interest and guided by the observation that the presence of two or more different heterocyclic moieties in a single molecule often enhances the biocidal profile remarkably, we investigated a three-component reaction involving isatins (**1**) with heterocyclic amines, that is, 3-amino-1,2,4-triazole/2-aminobenzimidazole (**2**) and thioacid (**3**) under MW irradiation (Scheme 1). Three types of conditions were explored: (i) in dry media using various solid supports (KSF montmorillonite, silica gel, acidic or neutral alumina), (ii) neat reaction without solvent and (iii) conventional methods using different solvents. The main results are given in Table 1.

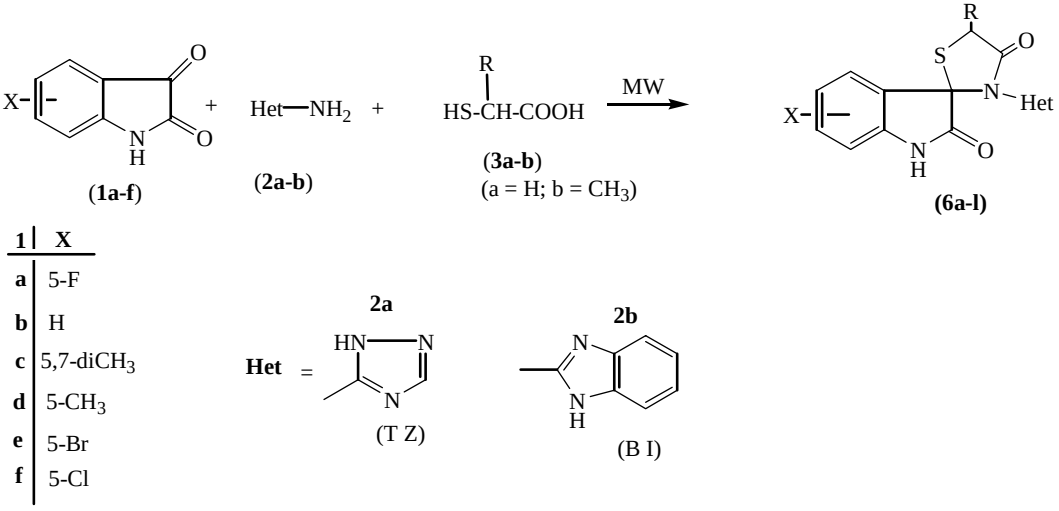
The exclusive formation of spiro[indole-thiazolidinones] (**6**) was observed as confirmed by spectral studies and X-ray diffraction under all conditions employed, while no formation of other possible system spiro[indole-thiadiazepinones] (**7**) was observed (Scheme 2). This constitutes a striking example of solvent-free regioselective synthesis of thiazolidinones greatly improving under MW irradiation. In solution-phase reaction, a literature survey shows that most of the reported methods for the synthesis of thiazolidinone involve the use of high boiling hydrocarbons like toluene or benzene with continuous removal of water[17] or requiring desiccants like anhydrous $ZnCl_2$[18] sodium sulfate[19] or molecular sieves and the use of stoichiometric amount of DCC[20] and Hünig base[21] in solution-phase reactions.

2. Results and discussion

From the comparative results shown in Table 1 for the synthesis of **6a** by varying methods, it is clear that KSF montmorillonite is the most suitable support since higher yields with reasonable purity were achieved in a shorter reaction time by this method as already observed earlier in clay supported reactions.

The reaction was also carried out without adding support or solvent (neat reaction). Although the reaction proceeded efficiently with respect to the starting material consumed (100% conversion, indicated by TLC), the yields in isolated products were lower due to formation of a side product, requiring further crystallization after trituration with light petroleum ether, thus involving a tedious work-up process. The reaction was facile also when carried out using a minimum amount of the environmentally benign solvent ethanol. The conventional synthesis of spiro[indole-thiazolidinone] (**6a**) involves a tedious two-step procedure and the reaction requires extended heating (8–12 h), providing the product in a lower yield and needs further purification of the product by column chromatography, with further need of solvent.

In the MW-assisted reaction, indole-2,3-dione (**1a**–**f**), 3-amino-1,2,4-triazole/benzimidazole (**2a**, **b**) and thioacids (**3a**, **b**) were mixed together and irradiated inside the MW oven. The reaction pathway of **1b**, **2a** and **3b** is depicted as a representative in Scheme 2, involving first the in situ formation of intermediate 3-indolylimines (**4**) by condensation of **1** and **2**. The next step involves the nucleophilic attack of the thiol group on the imine carbon–nitrogen double bond giving the intermediate **5**,[22] which has two possible nucleophilic

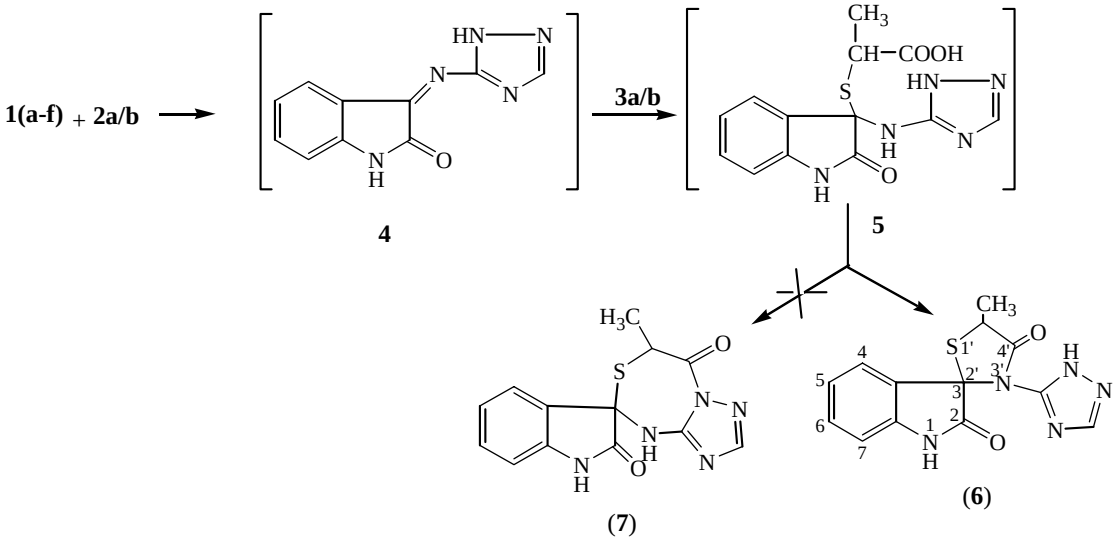


Scheme 1.

Table 1. Synthesis of **6a** (MW = microwave irradiation; Δ = conventional heating in an oil bath)

Exp.	Medium	Mode of activation	Time (min/h)	Temperature[a] (°C)	Yield[b] (%)
1	Neat	MW	5 min	135	82
2	EtOH	MW	15 min	78	85
3	Neutral alumina	MW	7 min	120	70
4	Acidic alumina	MW	8 min	122	78
5	Silica gel	MW	10 min	125	70
6	**KSF clay**	**MW**	**6 min**	**138**	**90**
7	Dry toluene[c]	Δ	4 + 8 h	Reflux	50
8	DMF + $ZnCl_2$[c]	Δ	4 + 6 h	Reflux	55

[a] Final temperature is measured at the end of MW irradiation by introducing a glass thermometer in the reaction mixture.
[b] Isolated yield.
[c] Conventionally, compound **6a** was synthesized in two steps, for example, 4 + 8 indicates first refluxing for 4 h to give intermediates **4** and then 8 h required for the formation of spiro compounds.



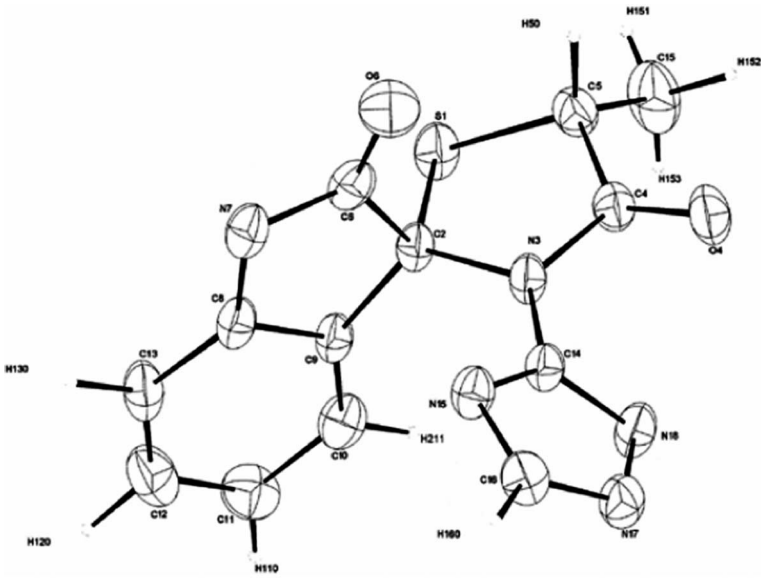
Scheme 2.

nitrogens for reaction with the thioacid carboxyl group. This would lead to the formation of either spiro[indole-thiazolidinone] (**6**) or spiro[indole-thiadiazepinone] (**7**). The X-ray crystal structure of compound (**6b**) confirmed the regioselective formation of **6** instead of the earlier reported formation of thiadiazepine **7** ring in an analogous reaction with 3-amino pyrazole.[23]

The structures of the synthesized compounds have been confirmed on the basis of analytical and spectral data. They were identified as spiro[indole-thiazolidinone] with various substituted isatins and thioacids. Spiro compounds (**6a**–**d**) where R = CH_3 contain two chiral centers, hence they exist in two diastereoisomeric forms, which is confirmed by the appearance of two sets of signals in ^{1}H NMR due to CH-CH_3, CH-CH_3 and NH protons. However, the signals of aromatic and other methyl protons of the two diastereoisomers could not be resolved due to complex multiplets. The detailed spectral data of synthesized compounds are given in Table 9. In the ^{13}C NMR spectrum of the compound **6a**, characteristic signals were observed at 41.91 (–CH_2–), 81.19 (spiro carbon), 111.25 (7-C), 123.20 (5-C), 126.21 (4-C), 132.29 (6-C), 142.42 (3a-C), 157.0 (C=N), 160.2 (C=N), 168.9 (C=O), and 174.5 (C=O).

Finally, to explore the possible intervention of specific (non-purely thermal) microwave effects,[24] the best results obtained under MW irradiation were compared to conventional heating. The reaction, in the case of compound **6a**, was carried out using a preheated oil bath, under similar reaction conditions as under MW (time, temperature, pressure and vessel) and using the two better methods (neat and KSF clay). It should be noted that under conventional conditions only traces of product were obtained. Although the reaction was complete within 45 min. under neat conditions, only 40% isolated yield was achieved (due to the formation of a mixture of products), while using KSF clay, the reaction occurred in 80 min with 61% yield (Table 2). This indicates that the microwave effect is not purely thermal.[25]

The specific non-thermal MW effect observed here may be interpreted by considering the mechanism concerned.[26] The rate-determining step consists of the nucleophilic attack of the thiol group on the imine carbon–nitrogen double bond (Scheme 3). As the transition state



X-ray picture of compound **6b**

Table 2. Comparative study for the synthesis of **6a**

Exp.	Medium	Mode of heating	Time (min)	Temperature[a] (°C)	Yield[b] (%)
1	Neat	MW	5	135	82
2	Neat	Δ	5	135	Traces
3	Neat	Δ	45	135	40
4	KSF clay	MW	6	138	90
5	KSF clay	Δ	6	138	Traces
6	KSF clay	Δ	80	138	61

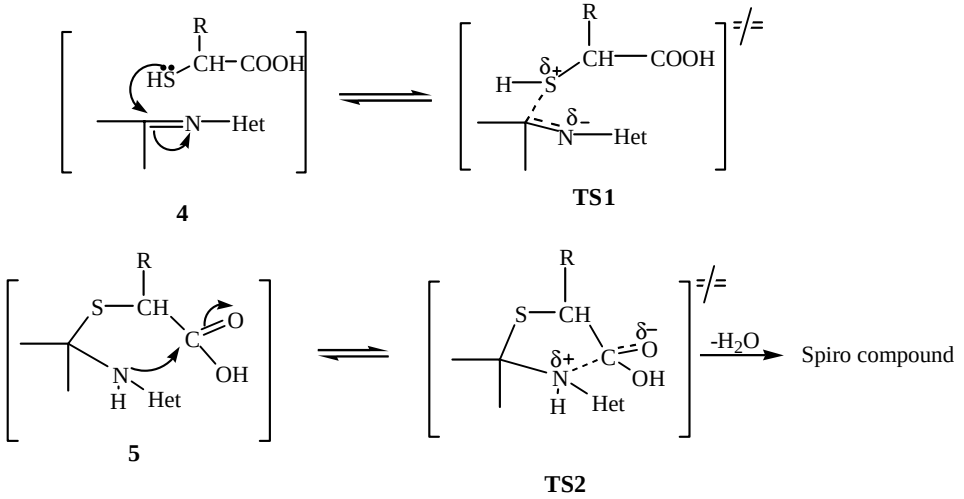
[a] Final temperature is measured at the end of MW irradiation by introducing a glass thermometer in the reaction mixture.
[b] Isolated yield.

(TS1) is more polar than the ground state, due to the development of a dipole, a greater stabilization of the transition state results in a MW as the dipole–dipole coulombic-type interactions are increased, leading to a decrease in the activation energy. Additionally, the specific positive MW effect can also be foreseen when considering the second step in the mechanism, where the cyclization of **5** occurs also via a dipolar transition state (TS2), prone to the development of favourable interactions with the electric field.

In conclusion, the three-component one-pot procedure described in this paper is a very regioselective, facile and practical method for the synthesis of spiro-indolines. The ease of the reaction procedure and work-up, the high yields and significantly very short reaction times can prove this procedure to be a useful and attractive alternative to the currently available methods.

3. Evaluation of antifungal activity

The synthesized compounds were screened for antifungal activity against three pathogenic fungi, namely *Rhizoctonia solani*, causing root rot of okra, *Fusarium oxysporum*, causing wilt of mustard and *Colletotrichum capsici* causing leaf spot and it has been found that all compounds show good activity against these pathogens,



Scheme 3.

Table 3. Effect of concentrations of different chemicals on the mean radial growth (cms) of different fungi in vitro

Compound	*Rhizoctonia solani*		*Fusarium oxysporum*		*Colletotrichum capsici*	
	1000 ppm	500 ppm	1000 ppm	500 ppm	1000 ppm	500 ppm
6a	1.87[b]	2.56[a]	2.98	3.12	2.08	5.66
6b	2.68	3.16	1.96[b]	2.76	3.67	5.29
6c	1.98[b]	3.25	2.19	3.68	1.37[b]	3.62[b]
6d	2.33	4.26	1.28[a]	2.52[a]	2.54	4.78
6e	4.29	5.50	2.59	3.56	1.08[a]	3.34
6f	4.02	5.23	3.36	4.90	2.17	2.99[a]
6g	3.58	4.68	2.69	5.02	3.21	4.51
6h	1.75[a]	3.33	1.68[b]	2.63[b]	1.67[b]	3.79
6i	1.80[b]	2.93[b]	1.79[b]	2.74	2.08	4.00
6j	5.25	5.92	4.23	5.06	3.75	4.67
6k	4.68	5.51	4.09	5.57	4.09	5.28
6l	5.75	6.69	3.92	4.68	3.99	5.17
Check	9.00	9.00	8.17	8.17	7.33	7.33
CD%	0.74	1.22	0.77	1.14	1.08	1.25

[a] Min value.
[b] At par with min values.

Table 4. Evaluation of spiro[indole-thiazolidine]-dione (**6a–l**) as seed dressers against *Rhizoctonia solani* causing root rot of okra (in pot trial)

Compound	Percent germination	Plant stand 25 DAS
4a	74.00	61.00
4b	69.00	43.00
4c	68.00	32.00
4d	61.00	50.00
4e	70.00	38.00
4f	41.00	56.00
4g	47.00	59.00
4h	45.00	62.00
4i	48.00	60.00
4j	29.00	19.00
4k	37.00	21.00
4l	33.00	28.00
Baynate (0.2%)	98.00	64.00
Thiram (0.3%)	79.00	68.00
Check with inoculum	10.00	6.00

DAS, days after sowing.

Table 5. Crystal data and structure refinement parameters of spiro[indole-thiazolidine]-dione

Crystal morphology	White parallelepipede
Crystal size	$0.20 \times 0.24 \times 0.30$
Chemical formula	$C_{13}H_{11}N_5O_2S$
Molecular weight	301.33
Crystal system	Monoclinic
Space group	C12/c1
Cell constants	$a = 23.397(5)$ Å, $b = 8.661(5)$ Å and $c = 14.299(5)$ Å, $\alpha = 90°$, $\beta = 114.810(5°)$, $\gamma = 90°$
Volume	2630.1(19) Å
Absorption coefficient	0.259 mm^{-1}
Density	1.522 mg m^{-3}
Temperature	293 K
Range for data collection	1.918–30.123
Index range	$h = -31 \rightarrow 28$, $k = 0 \rightarrow 12$, $l = 0 \rightarrow 18$
R	0.0642
R_w	0.0520
Threshold expression	$I > 2.00$ u (I)
Diffraction radiation	$M_0K\alpha$
λ	0.71070 Å

Table 6. Selected bond distances

Atom	Bond length (Å)
S1–C2	1.8219(14)
S1–C5	1.8065(17)
N3–C2	1.4648(18)
N3–C4	1.373(2)
N3–C14	1.4039(18)
N18–N17	1.3515(19)
N18–C14	1.3103(19)
N15–C14	1.3561(19)
N15–C16	1.328(2)
N17–C16	1.317(2)
N7–C6	1.360(2)
N7–C8	1.403(2)
O4–C4	1.213(2)
O6–C6	1.199(2)
C2–C6	1.549(2)
C2–C6	1.549(2)
C2–C9	1.496(2)
C4–C5	1.517(2)
C5–C15	1.517(3)
C8–C9	1.391(2)

indicating that the incorporation of triazole ring enhances the antifungal activity of compounds (**6a–i**) as compared to parent skeleton spiro[indole-thiazolidinone] ring as observed in our earlier report.[12b,c] In the pot trial experiment, all the synthesized compounds also showed better germination, indicating that, these are most effective in controlling the growth of pathogen. 'Baynate' and 'Thiram' recommended as standard fungicides as seed dressers to control this disease are also having a –N-C-S linkage, similar to the synthesized compounds, which is responsible for their antifungal activity. It was done by two methods.

(i) *Poison plate technique*:[27] The compounds synthesized were dissolved in acetone and compounds were prepared in 1000 and 500 ppm concentrations. Potato-dextrose-agar medium was prepared in flasks and sterilized. To this medium, a requisite quantity of solution was added and then the medium was poured into petri plates in three replica-

Table 7. Selected bond angles

Atom	Bond angle
C2–S1–C5	92.91(7)
C2–N3–C4	117.21(12)
C2–N3–C14	120.34(12)
C4–N3–C14	121.49(12)
N17–N18–C14	101.99(13)
C14–N15–C16	101.18(13)
N18–N17–C16	109.96(13)
N18–N17–H170	120.645
C6–N7–C8	111.80(18)
C6–N7–H70	121.368
S1–C2–N3	104.25(9)
S1–C2–C6	109.8(1)
N3–C2–C6	111.50(12)
S1–C2–C9	109.8(1)
N3–C2–C9	118.29(13)
C6–C2–C9	103.23(12)
N3–C4–O4	124.89(15)
N3–C4–C5	112.41(13)
O4–C4–C5	122.69(15)
S1–C5–C4	106.16(11)
S1–C5–C15	111.59(13)
C4–C5–H50	107.088
N7–C6–O6	127.77(16)
N7–C6–C2	106.59(14)
O6–C6–C2	125.61(15)
N7–C8–C9	110.08(14)
N7–C8–C13	128.41(16)
C9–C8–C13	121.49(17)
C8–C13–C12	117.3617()
N3–C14–N18	120.91(13)
N3–C14–N15	123.38(13)
N18–C14–N15	111.15(14)
N15–C16–N17	123.420
N15–C16–H160	

tions. A culture of test fungus was grown on PDA for 6–7 days. A small disc (4 mm) of the fungus culture was cut with a sterile corkborer and transferred aseptically, upside-down to centre of petri dishes containing the medium and fungicides. Plates was incubated at 25 ± 1 °C for 6 days. Colony diameter was measured and data were statistically analysed (Table 3).

(ii) *Pot trial method*:[28] White seeded sorghum grains were soaked in water for about 12 h, 160 g of the soaked kernels was placed in 500 ml flasks and 20 ml water was added to each. The material was autoclaved twice on successive days before inoculation. After sterilization, fungus bits were inoculated in each flask and flasks were kept for 10 days at 25–27 °C. Hundred seeds of okra were taken for one treatment of each compound. Inoculum was added at 2 g/kg of soil, 3-days prior to sowing. Sowing was done after 3-days and germination data were recorded after 7, 15 and 25 days of sowing. Suitable checks were maintained and the data were statistically analysed (Table 4).

4. Experimental section

Colourless needle-like single crystals suitable for X-ray diffraction were grown from methanol using the slow evaporation technique and ^{1}H NMR spectrum showed the presence of only single major isomer. X-ray intensity data were collected on an Enraf–Nonius CAD4 diffractometer. The additional material available from the Cambridge Crystallographic Data Centre (CCDC No. 287191) comprises the final atomic coordinates for all

Table 8. Physical data of spiro[indole-thiazolidinones] (**6a–l**)

Compound	X	R	Het	Time	Mp (°C)	Yield (%)	Molecular formula	Analysis found (Calcd)%	
								C	N
6a	5-F	CH_3	TZ	5	280	87	$C_{13}H_{10}FN_5O_2S$	48.76 (48.90)	21.87 (21.93)
6b	H	CH_3	TZ	4	272	84	$C_{13}H_{11}N_5O_2S$	51.68 (51.82)	23.32 (23.24)
6c	5,7-diCH_3	CH_3	TZ	5	278	88	$C_{15}H_{15}N_5O_2S$	54.55 (54.70)	21.32 (21.26)
6d	5-CH_3	CH_3	TZ	6	270	86	$C_{14}H_{13}N_5O_2S$	53.47 (53.32)	22.27 (22.21)
6e	5,7-diCH_3	H	TZ	5	150	89	$C_{14}H_{13}N_5O_2S$	53.15 (53.32)	22.16 (22.21)
6f	H	H	TZ	6	295	90	$C_{12}H_9N_5O_2S$	50.01 (50.17)	24.29 (24.38)
6g	5-CH_3	H	TZ	7	268	86	$C_{13}H_{11}N_5O_2S$	51.68 (51.82)	23.18 (23.24)
6h	5-Br	H	TZ	5	360	84	$C_{12}H_8BrN_5O_2S$	39.48 (39.36)	21.76 (21.82)
6i	5-Cl	H	TZ	6	268	85	$C_{12}H_8ClN_5O_2S$	44.39 (44.50)	21.84 (21.77)
6j	H	H	BI	5	232	83	$C_{17}H_{12}N_4O_2S$	60.85 (60.70)	16.71 (16.66)
6k	5,7-diCH_3	H	BI	6	260	85	$C_{19}H_{16}N_4O_2S$	62.79 (62.62)	15.32 (15.37)
6l	5-CH_3	H	BI	6	258	82	$C_{18}H_{14}N_4O_2S$	61.52 (61.70)	15.94 (15.99)

Table 9. Spectral data of spiro[indole-thiazolidinones]

Compound	IR (cm^{-1})	^1H NMR (δ, ppm)	Mass (M^+)
6a	3350–3250 (two NH), 2940, 2880 (C-H), 1727, 1700 (two C=O), 1610 (C=N), 1540, 1480, 1240, 800, 705, 650	Diastereomeric ratio (3:1) δ 1.66–1.88 (d, 3H, CH–*CH*$_3$, *J* = 4.8 Hz) 4.56–4.27 (q, 1H, *CH*–CH$_3$), 6.86/7.93 (m, 4H, Ar-H & N=CH), 10.44–10.59 (br s, 1H, NH), 13.71–13.99 (br s, 1H, NH)	
6b	3360–3270 (two NH), 2945, 2890 (C-H) 1735, 1700 (two C=O), 1605 (C=N), 1560, 1490, 1250, 810, 720,640	Diastereomeric ratio (3:1) δ 1.68–1.89 (d, 3H, CH–*CH*$_3$) 4.62–4.42 (q, 1H, *CH*–CH$_3$), 6.89–7.52 (m, 5H, Ar-H and N=CH), 10.46–10.62 (br s, 1H, NH), 13.71–13.98 (br s, 1H, NH)	301 [M^+, (77.5%)], 302 [M^+ + 1(100%)] 262 (32%), 214 (30%), 148 (40%)
6c	3350–3260 (two NH), 2920, 2880 (C-H) 1730, 1690 (two C=O), 1620 (C=N), 1530, 1480, 1350,1200, 750, 610	Diastereomeric ratio (3:1) δ 1.64–1.85 (d, 3H, CH–*CH*$_3$) 2.16–2.38 (br s, 6H, two CH$_3$), 4.53–4.24 (q, 1H, *CH*–CH$_3$), 6.82–7.90 (m 3H, Ar-H and N=CH), 10.41–10.60 (br s, 1H, NH), 13.69–13.90 (br s, 1H, NH)	
6d	3360–3250 (two NH), 2910, 2890 (C-H) 1735, 1700 (two C=O), 1610 (C=N), 1540, 1470, 1250, 740, 640	Diastereomeric ratio (3:1) δ 1.65–1.86 (d, 3H, CH–*CH*$_3$), 2.19 (s, 3H, CH$_3$), 4.58–4.26 (q, 1H, *CH*–CH$_3$), 6.84–7.92 (m, 4H, Ar-H and N=CH), 10.51–10.68 (br s, 1H, NH), 13.75–13.97 (br s, 1H, NH)	
6e	3370–3245 (two NH), 2930, 2880 (C-H), 1730, 1690 (two C=O), 1610 (C=N) 1550, 1460, 1240, 730, 660,	δ 2.12–2.29 (br s, 6H, two-CH$_3$), 3.95–4.68 (dd, 2H, –CH$_2$–, *J* = 13.1 Hz), 6.70–7.95 (m, 3H, Ar-H & N=CH), 10.68 (br s, 1H, NH), 13.60 (br s, 1H, NH)	
6f	3370–3240 (two NH), 1725, 1690 (two C=O), 1605 (C=N), 1530, 1420, 1290, 740, 620	δ 3.88–4.58 (dd, 2H, –CH$_2$–, *J* = 13.0 Hz), 6.70–7.98 (m, 5H N=CH and Ar-H), 10.58 (br s, 1H, NH), 13.56 (br s, 1H, NH)	
6g	3380–3260 (two NH), 2900, 2860 (C-H) 1728, 1693 (two C=O), 1605 (C=N), 1530, 1460, 1220, 750, 620	δ 2.14 (br s, 3H, CH$_3$), 3.92–4. 63 (dd, 2H, CH$_2$–, *J* = 12.9 Hz) 6.75–7.92 (m, 4H, Ar-H and N=CH), 10.61 (br s, 1H, NH), 13.62 (br s, 1H, NH)	
6h	3350–3260 (two NH), 1730, 1695 (two C=O), 1610 (C=N), 1570 1450, 1230, 760, 610	δ 3.94–4.65 (dd, 2H –CH$_2$–, *J* = 13.3 Hz), 6.71–7.93 (m, 4H, Ar-H & N=CH), 10.65 (br s, 1H, NH), 13.59 (br s, 1H, NH)	
6i	3360–3270 (two NH), 1728, 1698 (two C=O), 1610 (C=N), 1560, 1470, 1260, 780, 630	δ 3.91–4.60 (dd, 2H, CH$_2$–, *J* = 13.5 Hz), 6.76–7.81 (m, 4H, Ar-H and N=CH), 10.68 (br s, 1H,NH), 13.71–13.61 (br s, 1H, NH)	
6j	3370–3240 (two NH), 1725, 1690 (two C=O), 1605 (C=N), 1530, 1420, 1290, 740, 620	δ 3.81–4.50 (dd, 2H, –CH$_2$–, *J* = 13.4 Hz), 6.72–7.78 (m, 8H, Ar-H), 10.12 (br s, 1H, NH), 12.89 (br s, 1H, NH)	336 [M^+]
6k	3370–3245 (two NH), 2930, 2880 (C-H), 1728, 1700 (two C=O), 1610 (C=N) 1560, 1470, 1230, 730, 660	δ 2.14–2.32 (br s, 6H, two-CH$_3$), 3.83–4.58 (dd, 2H, –CH$_2$–, *J* = 13.3 Hz), 6.70–7.75 (m, 6H, Ar-H), 10.18 (br s, 1H, NH), 12.85 (br s, 1H, NH)	
6l	3370–3245 (two NH), 2930, 2880 (C-H), 1730, 1700 (two C=O), 1610 (C=N) 1550, 1460, 1240, 730, 660	δ 2.18 (s, 3H, CH$_3$), 3.82–4.56 (dd, 2H, CH$_2$–, *J* = 13.2 Hz), 6.70–7.77 (m, 7H, Ar-H), 10.18 (br s, 1H, NH), 12.58 (br s, 1H, NH)	

atoms, thermal parameters and a complete listing of bond distances and angles (Tables 5–7).

MW experiments were carried out in a domestic oven operating at a frequency of 2450 MHz. After a careful determination of the higher density electric spot using an aqueous solution of cobalt chloride,[29] reactions were performed in this point at the maximum continuous power output of 700 Watts.

KSF montmorillonite (clay), 3-amino-1,2,4-triazole and 2-aminobenzimidazole were purchased from Aldrich and were used as received.

4.1. Spiro[3*H*-indole-3,2′-thiazolidine]-3′(1,2,4-triazol-3-yl)- 2,4′(1*H*)-dione (6a)

This compound was synthesized using two activation modes:

4.1.1. Microwave-assisted syntheses (three-component synthesis)

(a) An equimolar mixture of **1a**, **2a** and **3a** (0.01 mol) was irradiated in the MW oven until completion of the reaction (TLC). A solid mass was obtained, which was triturated with light petroleum ether and recrystallized from methanol.
(b) The same mixture was dissolved in the minimum quantity of ethanol required to form a slurry and irradiated in the MW oven until the completion of reaction (followed by TLC). On cooling, crystals were separated out by filtration.
(c) An equimolar mixture of **1a** and **2a** (0.01 mol) was adsorbed onto the inorganic solid support (6 g of KSF clay, alumina or silica gel) with the help of methanol. The acid (**3a**) (0.01 mol) was then added and the reaction mixture was placed inside the MW oven and then irradiated until the completion of reaction (TLC). The mixture was cooled and the product was extracted into methanol and subsequent solvent removal under reduced pressure gave compound **6a**.

4.1.2. Conventional synthesis (two-step synthesis)

(a) Synthesis of (4a). An equimolar mixture of **1a** and **2a** (0.01 mol.) in ethanol was refluxed for 3 h. On cooling, crystals separated out, which were filtered and recrystallized from ethanol.

(b) Synthesis of spiro compound (6a). The synthesis of spiro compound **6a** was carried out using two different methods:

(i) A mixture of the intermediate **4a** (0.01 mol) and mercaptoacetic acid **3a** (0.025 mol) was taken up in dry toluene (30 ml) and refluxed for 8 h with azeotropical removal of water. The solvent was removed under reduced pressure and the residue was diluted with $CHCl_3$ (75 mL), sequentially washed with satd $NaHCO_3$, H_2O, brine and then dried over Na_2CO_3. Solvent was removed under reduced pressure to provide a crude product, which was purified by column chromatography (silica gel, hexane-EtOAc) to afford pure **6a**.
(ii) A mixture of the intermediate **4a** (0.01 mol) and mercaptoacetic acid **3a** (0.015 mol) in DMF (25 mL) containing a catalytic amount of anhydrous $ZnCl_2$ was refluxed for 6 h. After this time, the mixture was cooled and poured onto crushed ice. The precipitate thus obtained was filtered, washed with water and recrystallized from DMF to furnish **6a**.

4.2. Synthesis of spiro compound (6b)

An equimolar mixture of **1b** and **2a** (0.01 mol) was adsorbed onto montmorillonite KSF (6 g) with the help of methanol. The acid (**3b**) (0.01 mol) was then added and the reaction mixture was placed inside the MW oven and then irradiated until the completion of reaction (TLC). The mixture was cooled and the product was extracted into methanol and subsequent solvent removal under reduced pressure gave crystalline compound **6b**. ^{1}H NMR spectrum of the product showed the presence of two diastereomers in the ratio 3:1 (Tables 8 and 9).

The crystals suitable for X-ray diffraction were grown from methanol using the slow evaporation technique and crystal separated after 3 days was found as single isomer by ^{1}H NMR studies showing peaks at δ 1.68 (d, 3H, CH–CH_3) 4.62 (q, 1H, CH–CH_3), 6.89 (m, 5H, Ar-H and N=CH), 10.46 (br s, 1H, NH) and 13.71 (br s, 1H, NH).

The remaining compounds listed in Tables were similarly synthesized in one step using KSF montmorillonite as inorganic solid support.

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