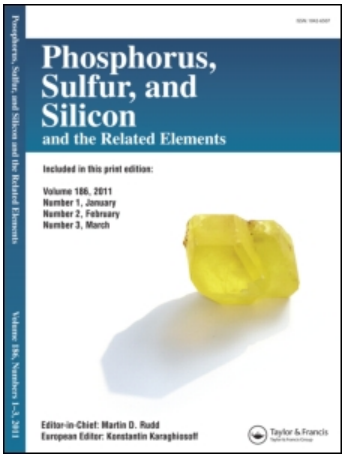

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MICROWAVE INDUCED DRY-MEDIA SYNTHESIS OF SPIRO[INDOLE-THIAZOLIDINONES/ THIAZINONES] AS POTENTIAL ANTIFUNGAL AND ANTITUBERCULAR AGENTS AND STUDY OF THEIR REACTIONS

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MICROWAVE INDUCED DRY-MEDIA SYNTHESIS OF SPIRO[INDOLE-THIAZOLIDINONES/ THIAZINONES] AS POTENTIAL ANTIFUNGAL AND ANTITUBERCULAR AGENTS AND STUDY OF THEIR REACTIONS

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*A series of new spiro[3*H*-indole-3,2′-thiazolidine]-2,4′(1*H*)-diones (IV) and spiro[3*H*-indole-3,2′-tetrahydro-1,3-thiazine]-2,4′(1*H*)-diones (V) have been synthesized in 85–93% yield by the one-pot environmentally benign microwave induced technique involving the cyclocondensation of 3-arylimino-2*H*-indol-2-ones (III) with thioacids viz. mercapto acetic-acid (a)/3-mercapto propionicacid (b) using montmorillonite KSF as inorganic solid support. Intermediates (III) were synthesized in situ by the reaction of indole-2,3-diones (I) and substituted anilines (II). The spiro compounds have been further subjected to solvent-free acetylation, aminoalkylation and thiation under microwave irradiation using solid supports. The synthesized compounds have been screened in vitro for antifungal activity against Rhizoctonia solani, Fusarium oxysporum, and Collectotrichum capsici, and antitubercular acivity against Mycobacterium tuberculosis.*

Keywords: Dry media; microwave irradiation; montmorillonite KSF; spiro-indoles; thiazinone; thiazolidinone

Microwave heating has already gained importance in synthetic organic chemistry in a short span of only a decade.[1–3] However, the use of solvents in microwave ovens gives rise to elevated temperatures and consequently high pressures. These problems have been overcome to a large extent by carrying out the reactions in dry conditions using

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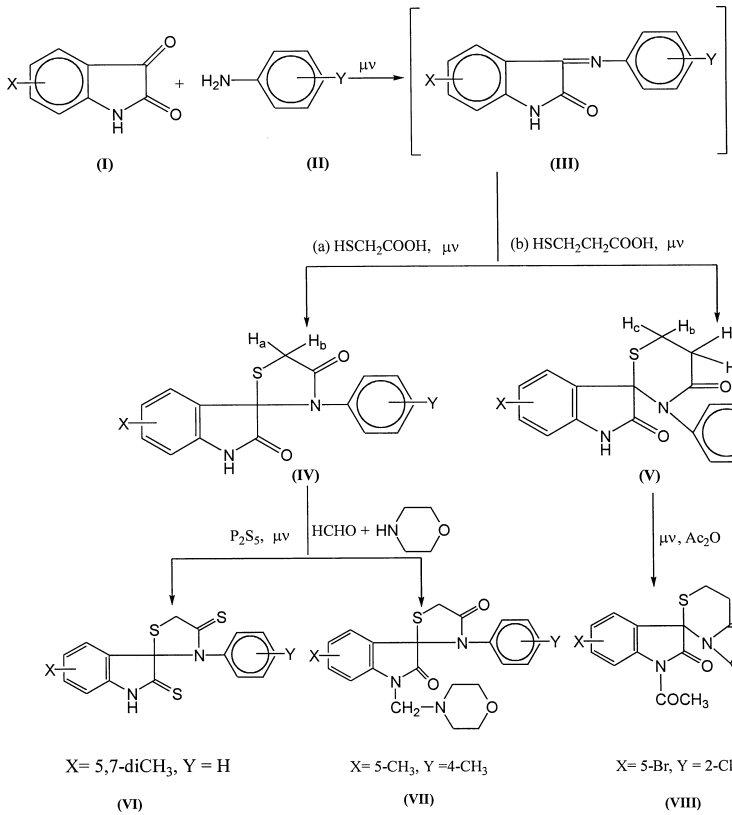


Compd.	X	Y
IVa	5,7-di CH_3	H
IVb	5,7-di CH_3	4-COOH
IVc	5,7-di CH_3	2-COOH
IVd	5,7-di CH_3	3-Cl
IVe	5-Br	4-COOH
IVf	5-Br	2-COOH
IVg	5-Br	2-Cl
IVh	5-CH_3	4-CH_3

Compd.	X	Y
Va	H	4-Cl
Vb	H	3-Cl
Vc	H	2-Cl
Vd	H	4-COOH
Ve	5,7-di CH_3	4-Cl
Vf	5,7-di CH_3	3-Cl
Vg	5,7-di CH_3	4-COOH
Vh	5,7-di CH_3	2-COOH
Vi	5-Br	3-Cl
Vj	5-Br	2-Cl
Vk	5-Br	4-COOH
V_l	5-Br	2-COOH
Vm	5-NO_2	4-F

SCHEME 1

solid supports. Microwave enhanced chemical reactions on inorganic solid supports under solvent-free conditions have attracted attention recently.[4–6] The advantages of this method are enhanced reaction rates, less or no formation of side products, higher yields of pure products, and reactions can be carried on a preparative scale in open vessels.

Thiazolidin-4-ones have exhibited a long history of biological activity.[7,8] The presence of N—C—S linkage is believed to account for the fungicidal, antibacterial and antiviral activities.[9–11] They also are known to possess amoebicidal and anticonvulsant activities.

The recent literature survey reveals a wide range of pharmacological properties associated with spiro[indole-thiazolidine]-diones.[12–13] The significance of these compounds can be judged from the fact that most of the references of spiro-indoles in the literature are patents. Spiro[3*H*-indole-3,2′-tetrahydro-1,3-thiazines]-2(1*H*)-ones also are reported to possess anti-inflammatory, analgesic and anticonvulsant activities.[14]

The spiro[indole-thiazolidinone] system has been synthesized earlier conventionally by a two-step procedure in 40–60% yield using isatin-3-imines as key intermediate, which were synthesized from substituted isatins and aromatic amines. The classical methods involving either the azeotropic removal of water[15] or reaction in presence of dehydrating agent[16] and use of large amount of volatile and toxic solvents at elevated temperature for several hours heating were of some utility. Further, the products are generally purified by crystallization or column chromatography with further need of solvent. Spiro[indole-thiazinones] also have been synthesized thermally in two steps by the azeotropic removal of water.[17]

Keeping in view the various biological activities associated with spiro indolines and in continuation of our ongoing program to develop benign and expeditious methods for organic transformation under solvent-free conditions using microwave irradiation and the interest in "green chemistry" theme with growing emphasis on pollution prevention,[18] we report here in one-pot environmentally desirable dry media synthesis of a series of new spiro[indole-thiazolidinones] and spiro-[indole-thiazinones] under microwave irradiation, where in not only the reaction time has been brought down from hours to minutes in comparison to conventional heating but also with improved yield. Crystalline products in reasonable purity (TLC) were isolated with no need of further purification.

RESULTS AND DISCUSSION

The cyclocondensation of III with thioacids (a/b) yielding exclusively spiro compounds (IV/V) was studied using different types of inorganic solid supports, e.g., montmorillonite KSF, alumina (acidic, basic, neutral), and silica gel. Since, montmorillonite KSF efficiently catalyzed the reaction, giving maximum yield (85–93%) with shortest period (6–7 min) and easier work up, all compounds listed in Table I have been

TABLE I Physical and Structural Characteristics of Spiro Compounds

Cmpd	Time (min)	Yield (%)	m.p. (°C)	IR (cm^{-1})	^1H and ^{13}CNMR (δ, ppm)	MS : m/z (% relative intensity)	Molecular formula	Found (Calcd.) % C	N
IVa	1 + 5	91	222	3320 (NH), 1720, 1690 (2 × C=O)	δ_H2.15 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 4.02 (dd, 2H, H_a & H_b, J = 13.5 Hz), 6.81–7.42 (m, 7H, Ar–H), 9.01 (br, 1H, NH*) δc 13.01, 21.08 (two CH_3), 33.33 (S–CH_2), 73.12 (spiro carbon), 120.08–140.86 (12 aromatic carbons), 170.96, 177.12 (two C=O).	324 (M^+, 100), 296 (M^+–CO, 70), 250 (M^+–CH_5OS, 65), 222 (M^+–$C_3H_2O_2S$, 80)	$C_{18}H_{16}N_2O_2S$	66.48 (66.64)	8.61 (8.64)
IVb	1 + 5	92	175 (d)	3480 (OH), 3300 (NH), 1735, 1710, 1690 (3 × C=O)	δ_H2.14 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 4.05 (dd, 2H, H_a & H_b, J = 13.6 Hz), 6.73–7.45 (m, 6H, Ar–H), 9.05 (br, 1H, NH*), 9.55 (br, 1H, OH*)		$C_{19}H_{16}N_2O_4S$	61.76 (61.94)	7.57 (7.60)
IVc	1 + 5	93	188	3490 (OH), 3290 (NH), 1730, 1710, 1695 (3 × C=O)	δ_H2.15 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 4.06 (dd, 2H, H_a & H_b, J = 13.7 Hz), 6.75–7.47 (m, 6H, Ar–H), 9.02 (br, 1H, NH*), 9.58 (br, 1H, OH*)		$C_{19}H_{16}N_2O_4S$	61.75 (61.94)	7.62 (7.60)
IVd	1 + 6	90	168 (d)	3310 (NH), 1720, 1695 (2 × C=O), 740 (C–Cl)	δ_H2.13 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 3.99 (dd, 2H, H_a & H_b, J = 13.6 Hz), 6.70–7.51 (m, 6H, Ar–H), 9.04 (br, 1H, NH*)	358 (M^+, 100), 360 (M^+ + 2 , 40), 330 (M^+–CO, 75), 284 (M^+–CH_5OS, 50), 256 (M^+–$C_2H_5O_2S$, 55)	$C_{18}H_{15}ClN_2O_2S$	60.42 (60.25)	7.83 (7.81)
IVe	2 + 6	86	220	3480 (OH), 3290 (NH), 1725, 1705, 1690 (3 × C=O), 630 (C–Br)	δ_H 4.11 (dd, 2H, H_a & H_bJ = 13.7 Hz), 6.69–7.62 (m, 7H, Ar–H), 9.04 (br, 1H, NH*), 10.01 (br, 1H, OH*) δc 33.98 (S–CH_2), 74.01 (spiro carbon), 121.22–142.94 (12 aromatic carbons), 172.02, 176.32, 180.21 (three C=O).		$C_{17}H_{11}BrN_2O_4S$	48.55 (48.70)	6.66 (6.68)
IVf	2 + 6	88	237	3495 (OH), 3310 (NH), 1735, 1710, 1690 (3 × C=O), 650 (C–Cl)	δ_H 4.09 (dd, 2H, H_a & H_b, J = 13.9 Hz), 6.65–7.72 (m, 7H, Ar–H), 9.06 (br, 1H, NH*), 10.03 (br, 1H, OH*)		$C_{17}H_{11}BrN_2O_4S$	48.56 (48.70)	6.70 (6.68)
IVg	1 + 6	89	198 (d)	3320 (NH), 1715, 1695 (2 × C=O), 640 (C–Br), 760 (C–Cl)	δ_H 4.06 (dd, 2H, H_a & H_b, J = 13.8 Hz), 6.71–7.73 (m, 7H, Ar–H), 9.06 (br, 1H, NH*)		$C_{16}H_{11}BrClN_2O_2S$	46.77 (46.91)	6.82 (6.84)

IVh	1 + 6	91	>360	3310 (NH), 1720, 1690 (2 × C=O)	δ_H2.03 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 4.03 (dd, 2H, H_a & H_b, J = 13.6 Hz), 6.74–7.83 (m, 7H, Ar–H), 9.08 (br, 1H, NH*)	324 (M^+, 100)	$C_{18}H_{16}N_2O_2S$	66.50 (66.64)	6.61 (6.64)
Va	1 + 5	90	205	3290 (NH), 1715, 1695 (2 × C=O), 760 (C–Cl)	δ_H 2.69 (dt,1H, H_a), 3.26 (dd, 2H, 2 × H_b), 4.15 (dt, 1H, H_c), 6.75–7.38 (m, 8H, Ar–H), 8.97 (br, 1H, NH*) δc 26.2 (S–CH_2), 31.3 (CH_2C=O), 72.04 (spiro carbon), 117.01–139.65 (12 aromatic carbons), 168.93, 172.11 (two C=O)		$C_{17}H_{13}ClN_2O_2S$	59.04 (59.21)	8.09 (8.12)
Vb	1 + 6	88	145	3305 (NH), 1718, 1695 (2 × C=O), 750 (C–Cl)	δ_H 2.68 (dt,1H, H_a), 3.25 (dd, 2H, 2 × H_b), 4.18 (dt, 1H, H_c), 6.71–7.39 (m, 8H, Ar–H), 8.99 (br, 1H, NH*)		$C_{17}H_{13}ClN_2O_2S$	59.03 (59.21)	8.15 (8.12)
Vc	1 + 5	91	165	3265 (NH), 1715, 1690 (2 × C=O), 765 (C–Cl)	δ_H 2.66 (dt,1H, H_a), 3.26 (dd, 2H, 2 × H_b), 4.19 (dt, 1H, H_c), 6.72–7.38 (m, 8H, Ar–H), 9.01 (br, 1H, NH*)		$C_{17}H_{13}ClN_2O_2S$	59.37 (59.21)	8.10 (8.12)
Vd	1 + 5	87	265	3470 (OH), 3280 (NH), 1735, 1715, 1690 (2 × C=O), 750 (C–Cl)	δ_H 2.71(dt, 1H, H_a), 3.29 (dd, 2H, 2 × H_b), 4.21 (dt, 1H, H_c), 6.70–7.39 (m, 8H, Ar–H), 8.99 (br, 1H, NH), 9.66 (br, 1H, OH*)		$C_{18}H_{17}N_2O_4S$	61.19 (61.01)	7.92 (7.90)
Ve	2 + 6	92	202	3290 (NH), 1720, 1695 (2 × C=O), 760 (C–Cl)	δ_H 2.19 (bs, 6H, 2 × CH_3), 2.73 (dt,1H, H_a), 3.30 (dd, 2H, 2 × H_b), 4.20 (dt, 1H, H_c), 6.76–7.41 (m, 6H, Ar–H),9.01 (br, 1H, NH*)		$C_{19}H_{17}ClN_2O_2S$	61.02 (61.20)	7.53 (7.51)
Vf	2 + 6	91	176	3305 (NH), 1710, 1690 (2 × C=O), 750 (C–Cl)	δ_H 2.21 (bs, 6H, 2 × CH_3), 2.70 (dt,1H, H_a), 3.28 (dd, 2H, 2 × H_b), 4.23 (dt, 1H, H_c), 6.74–7.38 (m, 6H, Ar–H), 8.99 (br, 1H, NH*) δc 18.95, 29.08 (two CH_3) 27.01 (S–CH_2), 32.11 (CH_2C=O), 72.98 (spiro carbon), 119.13–140.02 (12 aromatic carbons), 169.11, 173.69 (two C=O)		$C_{18}H_{17}ClN_2O_2S$	61.38 (61.20)	7.49 (7.51)
Vg	1 + 5	89	240	3490 (OH), 3310 (NH), 1730, 1710, 1680 (3 × C=O)	δ_H 2.20 (bs, 6H, 2 × CH_3), 2.69 (dt,1H, H_a), 3.29 (dd, 2H, 2 × H_b), 4.18 (dt, 1H, H_c), 6.73–7.37 (m, 6H, Ar–H), 9.01 (br, 1H, NH*), 9.71 (br, 1H, OH*)		$C_{20}H_{18}N_2O_4S$	62.62 (62.81)	7.30 (7.33)

(Continued on next page)

TABLE I Physical and Structural Characteristics of Spiro Compounds (*Continued*)

Cmpd	Time (min)	Yield (%)	m.p. (°C)	IR (cm^{-1})	^1H and ^{13}CNMR (δ, ppm)	MS : m/z (% relative intensity)	Molecular formula	Found (Calcd.) % C	Found (Calcd.) % N
Vh	1 + 6	90	216	3500 (OH), 3300 (NH), 1735, 1715, 1695 (3 × C=O)	δ_H 2.19 (bs, 6H, 2 × CH_3), 2.66 (dt,1H, H_a), 3.27 (dd, 2H, 2 × H_b), 4.17 (dt, 1H, H_c), 6.77–7.48 (m, 6H, Ar–H), 8.99 (br, 1H, NH*), 9.69 (br, 1H, OH*).		$C_{20}H_{18}N_2O_4S$	62.63 (62.81)	7.35 (7.33)
Vi	2 + 6	87	180	3280 (NH), 1720, 1690 (2 × C=O), 670 (C–Br) 740 (C–Cl)	δ_H 2.71 (dt,1H, H_a), 3.26 (dd, 2H, 2 × H_b), 4.16 (dt, 1H, H_c), 6.76–7.39 (m, 7H, Ar–H), 9.02 (br, 1H, NH*).		$C_{17}H_{12}BrClN_2O_2S$	48.03 (48.19)	6.63 (6.61)
Vj	2 + 6	89	190	3290 (NH),1715, 1685 (2 × C=O), 650 (C–Br) 760 (C–Cl)	δ_H 2.72 (dt,1H, H_a), 3.28 (dd, 2H, 2 × H_b), 4.18 (dt, 1H, H_c), 6.72–7.35 (m, 7H, Ar–H), 9.04 (br, 1H, NH*).		$C_{17}H_{12}BrClN_2O_2S$	48.01 (48.19)	6.58 (6.61)
Vk	2 + 6	85	198	3490 (OH), 3280 (NH), 1735, 1720, 1695 (3 × C=O), 640 (C–Br)	δ_H 2.70 (dt,1H, H_a), 3.28 (dd, 2H, 2 × H_b), 4.18 (dt, 1H, H_c), 6.72–7.35 (m, 7H, Ar–H), 8.99 (br, 1H, NH*), 9.71 (br, 1H, OH*).		$C_{18}H_{13}BrN_2O_4S$	49.75 (49.90)	6.49 (6.47)
V_l	2 + 5	86	225	3495 (OH), 3295 (NH), 1730, 1718, 1698 (3 × C=O), 650 (C–Br)	δ_H 2.69 (dt,1H, H_a), 3.27 (dd, 2H, 2 × H_b), 4.19 (dt, 1H, H_c), 6.75–7.36 (m, 7H, Ar–H),.9.01 (br, 1H, NH*), 9.69 (br, 1H, OH*).		$C_{18}H_{13}BrN_2O_4S$	50.03 (49.90)	6.45 (6.47)
Vm	2 + 6	85	238	3290 (NH), 1720, 1690 (2 × C=O), 1450, 1510 (NO_2), 1200	δ_H 2.74 (dt,1H, H_a), 3.31 (dd, 2H, 2 × H_b), 4.23 (dt, 1H, H_c), 6.73–7.35 (m, 7H, Ar–H), 9.05 (br, 1H, NH*), 9.75 (br, 1H, OH*).	372 (M^+, 100), 353 (51), 325 (35), 279 (21), 248 (20), 121(18)	$C_{17}H_{12}FN_3O_4S$	54.82 (54.69)	11.28 (11.25)
VI	7	75	>360	3310 (NH), 2920, 2870 (C–H str), 1250–1230 (C=S), 1160	δ_H 2.20 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 3.96 (dd, 2H, $-CH_2$), 6.84–7.84 (m, 7H, Ar–H), 8.99 (br, 1H, NH*).		$C_{18}H_{16}N_2S_3$	60.50 (60.54)	7.84 (7.86)
VII	6	89	165	2850–2900 (C–H str), 1720, 1680 (2 × C=O), 1120, 1200 (C–O–C)	δ_H 2.01(s, 3H, CH_3), 2.32–2.78 (m, 7H, $O(CH_2)_2$ and CH_3), 3.91 (t, 4H, N $(CH_2)_2$, 4.08 (dd, 2H, S–CH_2), 5.01 (s, 2H, N–CH_2-N), 6.89–7.54 (m, 7H, Ar–H).		$C_{23}H_{25}N_3O_3S$	65.04 (65.22)	9.90 (9.92)
VIII	7	85	155	2910, 2880 (C–H str), 1720, 1700 1680 (3 × C=O), 655 (C–Br), 765 (C–Cl)	δ_H 2.38 (s, 3H, CH_3), 2.76 (dt, 1H, H_a), 3.31 (dd, 2H, 2 × H_c), 6.74–7.39 (m, 7H, Ar–H).		$C_{19}H_{14}BrClN_2O_3S$	50.11 (49.00)	5.99 (6.01)

*Both –NH and –OH are D_2O exchangeable.

synthesized in one pot using montmorillonite KSF as inorganic solid support. Intermediate (III) were synthesized in situ by the reaction indole-2,3-diones (I) with substituted anilines (II). One hundred percent conversion was observed on TLC which also showed a formation of single product.

The structure of the both spiro systems IV/V were assigned on the basis of their elemental analyses, ^{1}H NMR, ^{13}C NMR and mass spectral data (see Table I).

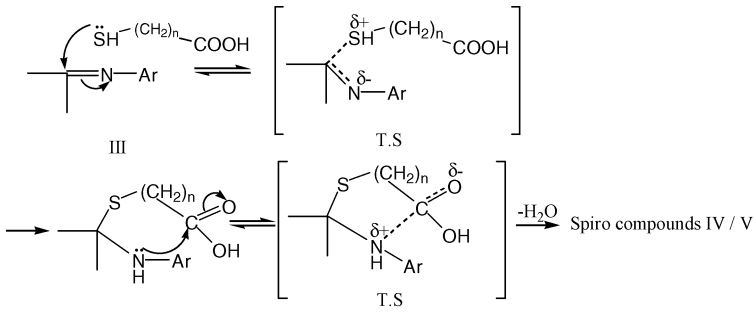
Finally, to check the possible intervention of specific (non-thermal) microwave effects on reactivity, the reactions (in case of compounds IVa, IVb, and Va, Table II) have been carried out using preheated oil-both at the same time and at the same final temperature (134–138°C) as measured at the end of exposure during the microwave experiment. It has been found that only traces of products (8–10%) were detected on TLC. Lower yields were obtained under conventional heating, even after one hour, indicating that effect of microwave irradiation is not purely thermal.[19]

The noticeable rate enhancement due to a specific microwave effect is consistent with the reaction mechanism,[20] if we admit that the kinetic rate determining step consists the nucleophilic attack of thiol group on carbon-nitrogen double bond of imines (III). As the transition state is more polar than the ground state due to development of a dipole, a greater stabilization results with microwave as dipole-dipole interactions are increased and favoured.

TABLE II Comparative Results for the Synthesis of Spiro Compounds Using Microwave Activation (A) and Conventional Heating (B) Indicating Existence of Specific Microwave Effect

Compd no.	Method		Reaction time (min)	Final* temp (°C)	Isolated yield (%)
IVa	A	MW	1 + 5	134–136	91
	B (i)	Δ	1 + 5	134–136	traces
	B (ii)	Δ	5 + 5	134–136	traces
	B (iii)	Δ	5 + 60	134–136	61
IVb	A	MW	1 + 6	136–138	92
	(i) B	Δ	1 + 6	136–138	traces
	(ii) B	Δ	7 + 6	136–138	traces
	(iii) B	Δ	7 + 60	136–138	58
Va	A	MW	1 + 5	136–138	90
	B (i)	Δ	1 + 5	136–138	traces
	B (ii)	Δ	6 + 5	136–138	traces
	B (iii)	Δ	6 + 60	136–138	60

*Final temperature is measured by introducing a glass thermometer in the reaction mixture at the end of exposure to microwave irradiation.



Further, in view to improve bioactivity, certain pharmacophores are introduced in to spiro system and acetylation, thiation and amino alkylation of these compounds were carried out using solvent-free conditions under microwave irradiation.

Thiation of heterocycles for the conversion of oxo group to thio group provides precursors for fused heterocyclic systems.[21] In these conversions usually use of larger amounts of P_2S_5 in toxic pyridine[22] and benzene[23] is required, the time of reaction is long and the yields are moderate to low especially in an scale up.[24] Amino alkylation and acetylation of organic compounds also requires several hours heating using toxic and environmentally hazardous organic solvents. Faced with this dilemma, we explored more effective and much faster routes for the implementation of thiation, acetylation and aminoalkylation of the spiro compounds in solvent free conditions using different types of inorganic solid supports under microwave irradiation in few minutes. Acetylation of spiro compound was tried using different types of inorganic solid supports, i.e., aluminas (neutral or basic) and montmorillonite KSF. It has been observed that reaction did not occur using neutral alumina or montmorillonite KSF. However, acetylation of spiro compound occurred successfully when two or three drops of piperidine and neutral alumina were used. Further, for the aminoalkylation, also different types of inorganic solid supports were tried such as aluminas (basic, acidic, neutral), montmorillonite KSF, silica gel. Acidic alumina was found to be the best solid support for this conversion giving maximum yield with shorter time as shown in Table III. Successful thiation of spiro compound was carried out using silica gel.

It is noteworthy to mention here that the thiation occur at both carbonyl groups when spiro compound and P_2S_5 in 1:2 molar ratio adsorbed on silica gel has been irradiated. Dithiation of the spiro compound has been confirmed by the disappearance of both carbonyl groups in the IR spectrum. Acetylation and aminoalkylation occur exclusively at indole nitrogen. The formation of N-acetylated spiro compound has been

TABLE III Effect of Solid Supports in Dry Media Aminoalkylation of Spiro[indole-thiazolidinone] (IVh, Table IIIa) and Acetylation of Spiro[indole-thiazine] (Vj, Table IIIb) Under Microwave Irradiation

IIIA

Support	Basic alumina	Neutral alumina	Acidic alumina	Montmorillonite KSF	Silica gel
Yield (%)	76	74	92	72	67
Time (min)	11	9	6	10	9

IIIB

Support	Basic alumina	Montmorillonite KSF	Neutral alumina + piperidine
Yield (%)	Nil	Nil	85
Time (min)	15	12	7

confirmed on the basis of complete disappearance of NH absorption in IR and ^{1}H NMR spectrum and the appearance of a new C=O absorption band in IR spectrum and additional signals at δ 2.38 (s, 3H, $COCH_3$) in ^{1}H NMR spectrum. Formation of Mannich base from the corresponding spiro compound has been confirmed by complete disappearance of NH absorption in IR and ^{1}H NMR spectrum and by the appearance of new resonance signals centered at δ 2.78, 3.91, and 5.01 ppm in ^{1}H NMR spectrum due to morpholino group.

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 fruit rot of chilli. It was done by two methods.

(i) Poison Plate Technique[25]

The compounds synthesized were dissolved in acetone and compounds were prepared in 1000 and 500 ppm concentrations. Potato dextrose-agar (PDA) medium was prepared in flasks and sterilized. To this medium, a requisite quantity of solution was added and then the medium was poured into petriplates in three replication. A culture of test fungus was grown on PDA for 6–7 days. Small disc (4 mm) of the fungus culture was cut with a sterile corkborer and transferred asceptically, upside-down in the center of petridishes containing the medium and fungicides. Plates were incubated at 25°C ± 1°C for 6 days. Colony diameter were measured and data was statistically analysed.

TABLE IV Effect of Concentration of Different Chemicals on the Mean Radial Growth (cms) of Fungus in vitro (Poison Plate Technique)

Compd. no.	*Rhizoctonia solani*		*Fusarium oxysporum*		*Colletorichum capsici*	
	1000 ppm	500 ppm	1000 ppm	500 ppm	1000 ppm	500 ppm
IVa	3.52	3.91	4.72	4.50	4.77	6.77
IVb	3.10	4.58	3.75	5.17	4.07	6.46
IVc	5.98	8.43	1.54	3.50	3.77	4.21
IVd	6.92	7.35	2.16	4.17	3.25	4.58
IVe	8.58	8.30	4.00	5.17	1.83	2.92
IVf	4.55	9.00	3.67	3.67	2.31	3.56
IVg	5.10	7.25	3.68	5.28	3.58	5.98
IVh	7.92	9.00	1.98	2.83	3.58	5.51
Va	9.00	9.00	2.10	4.17	3.42	5.00
Vb	9.01	7.92	1.83	2.75	1.87	3.65
Vc	6.15	8.64	1.40	2.67	2.67	3.25
Vd	1.38	2.25	3.42	5.37	3.83	6.43
Ve	7.02	9.00	3.58	5.58	3.00	4.95
Vf	7.92	8.68	3.25	4.33	3.25	4.35
Vg	6.52	6.54	3.17	3.58	1.55	2.95
Vh	8.30	9.00	3.00	4.00	3.00	4.81
Vi	9.00	9.00	3.75	4.25	2.67	3.79
Vj	1.75	2.75	4.25	4.33	1.35	2.08
Vk	7.33	8.02	2.50	4.25	2.83	4.33
V_l	9.00	9.00	3.08	3.75	4.17	4.25
Vm	1.92	9.00	3.25	4.58	1.67	3.00
VI	3.33	8.74	1.33	6.50	3.50	6.33
VII	5.08	5.08	2.50	2.88	1.83	3.67
Check	9.00	9.00	8.67	8.67	7.67	7.67
CD%	0.78	1.21	0.91	0.92	1.06	1.28

☐ Min value.
__ At par with min value.

The fungicidal data (Table IV) indicates that some of the compounds were found significantly superior over check (9.0 cm) in controlling the radial growth (1.30–6.00 cm) of all the there pathogens. Rest were at par with check.

It was found that the compound V_d (X = H, Y = 4-COOH), Vj (X = 5-Br, Y = 2-Cl), Vm (X = 5-NO_2, Y = 4-F) were most effective against *R. Solani* (1.38–1.92 cm), compound IVc (X = 5,7-diCH_3, Y = 2-COOH), IVd (X = 5,7-diCH_3, Y = 3-Cl), IV_h (X = 5-CH_3, Y = 4-CH_3), Va (X = H, Y = 4-Cl), Vb (X = H, Y = 3-Cl), Vc (X = H, Y = 2-Cl) and VI (X = 5,7-diCH_3, Y = H) were most effective against *F. oxysporum* (1.33–2.16 cm) and the IVe (X = 5-Br, Y = 4-COOH), Vb (X = 4, X = 3-Cl), Vg (X = 5,7-diCH_3, Y = 4-COOH), Vj (X = 5-Br, Y = 2-Cl) and VII

(X = 5-CH_3, Y = 4-CH_3) were also found to be most effective against *C. capsici* (1.25–1.87 cm). Compound IVa, IVb, IVg, Ve, Vf, Vh, Vi, and Ve have shown moderate activity (2.50–3.92 cm) against these pathogens.

(ii) Pot Trial Method[26]

White seeded sorghum grains were soaked in water for about 12 h. Of the soaked kernels 160 gm were placed in 500 ml flasks and 20 ml of 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. One hundred seeds of okra were taken for one treatment of each compound. Inoculum was added @ 2g/kg of soil, 3-days prior to sowing. Sowing was done after 3 days, and germination data were recorded after 7,15,25 days of sowing. Suitable checks were maintained and the data was statistically analysed (Table V). It was found that IVb having two-CH_3 and COOH groups showed maximum germination (63%). "Baynate" and "Thiram," standard fungicides also are having —N—C—S linkage, similar to the synthesized compounds. "Baynate" was found best in reducing the plant mortality.

Evaluation of Antitubercular Activity

The antitubercular evaluation of the compunds was carried out at "Tuberculosis Antimicrobial Acquisition and Coordinating Facility" (TAACF) USA. Primary screening of the compounds for antitubercular

TABLE V Evaluation of Spiro[indole-thiazolidinone/thiazinone] Derivatives as Seed Dressers Against *Rhizoctonia solani* Causing Root Rot of Okra (in Pot Trial)

Compd no.	Percent germination 7 DAS	Plant stand 25 DAS
IVa	61.00	48.00
IVb	63.00	45.00
IVe	55.00	42.00
IVh	58.00	41.00
Va	28.00	21.00
Vf	59.00	40.00
V_I	51.00	39.00
Vm	29.00	19.00
Baynate (0.2%)	98.00	64.00
Thiram (0.3%)	79.00	68.00
Check with inoculum	12.00	4.00
Check without inoculum	95.00	90.00

DAS—Days after sowing.

TABLE VI In vitro Evaluation of Anti Tuberculosis Activity Against *Mycobacterium tuberculosis*

Compd no.	Antitubercular activity ($H_{37}Rv$) MIC (μg/ml)	% Inhibition
IVa	<12.5	93
IVb	<12.5	94
IVc	<12.5	95
IVd	<12.5	92
IVe	>12.5	72
IVf	>12.5	45
IVg	>12.5	68
IVh	<12.5	95
Va	>12.5	32
Vb	>12.5	50
Vd	>12.5	35
Ve	>12.5	88
Vh	<12.5	94
V_I	>12.5	25
VI	<12.5	93
VII	<12.5	90

MIC—Minimum inhibition concentration in μg/ml.

activity has been conducted at 12.5 μg/ml against mycobacterium tuberculosis $H_{37}Rv$, in BACTEC 12B medium using BACTEC 460 radiometric system. Antitubercular activity data were compared with standard drug Rifampin at 0.25 μg/ml concentrations, which showed 98% inhibition. The results are presented in Table VI compounds IVa, IVb, IVc, IVd, IVh, Vh, Vl, and VII were must effective against *M. tuberculosis* at 12.5 μg/ml concentration and showed 90–95% inhibition while the other compounds showed moderate activity against *Mycobacterium tuberculosis*.

EXPERIMENTAL

Melting points were determined in open glass capillaries and were uncorrected. IR spectra were recorded on a Perkin-Elmer (model 577) in KBr pellets. ^1H NMR and ^{13}C NMR were recorded on a Jeol model FX90Q, using $CDCl_3$ and TFA as solvent at 89.55 and 22.4 MHz, respectively using TMS as internal reference. All compounds were found homogenous on TLC in various solvent systems. The induced microwave convection system used has microwave generated at a frequency of 2450 MHz. The oven has a range of microwave output energy of 700 watts. Montmorillonite KSF and anilines were Aldrich products and were used as received.

*Spiro[indole-3,2′-thiazolidine]-2,4′(1*H*)-diones (IVa–h) and Spiro[3*H*-indole-3,2′-tetrahydro-1,3-thiazine]-2,4′(1*H*)-diones (Va–m)*

Spiro compounds IV/V have been synthesized in one-step without isolating the intermediate anil (III) using montmorillonite KSF under microwave irradiation.

An equimolar mixture of appropriate indole-2,3-dione (I) and substituted aniline (II) (0.005 mmol) was adsorbed on montmorillonite KSF (4 gm) and irradiated for 30–90 s at 640 watt under microwave irradiation. As the reactants disappeared (TLC) thioacids (a/b) (0.005 mmol) was added to the reaction mixture, mixed thoroughly and again irradiation at 640 watt for the specificed time (Table I). The product was obtained by desorption with methanol and found to be pure by TLC.

*Synthesis of 5,7-Dimethyl-3′-phenyl-spiro[3*H*-indole-3,2′-thiazolidine]-2,4′-(1*H*)-dithione (VI)*

Spiro compound IVa and P_2S_5 in 1:2 molar ratio was adsorbed on silica gel with the help of methanol. After removal of methanol, the dry reaction mixture thus obtained was irradiated at 640 watt until the completion of reaction (7 min, monitored by TLC). The product was extracted into ethylacetate and further purified by methanol.

*Synthesis of 1-Morpholinomethyl-5-methyl-3′-(4-methylphenyl) spiro [3*H*-indole-3,2′-tetrahydro]-1,3-thiazine]-2,4′ (1*H*)-dione (VII)*

A mixture of spiro compound IVh (1 mmol), formaldehyde solution (1.5 mmol, 40%, aqueous solution) and morpholine (1 mmol) were mixed and ground with acidic alumina (3 g) in a mortar. The dry powder thus obtained was irradiated in a microwave oven at 640 watt for (6 min). The inorganic support was separated by filtration after eluting the product with ethyl acetate and product obtained after removal of solvent was found to be pure by TLC.

*1-Acetyl-5-bromo-3′-(2-chlorophenyl)-spiro[3*H*-indole-3,2′-tetrahydro-1,3-thiazine)-2,4′-(1*H*)-diones (VIII)*

A mixture of spiro compound Vj (1 mmol) and acetic anhydride (1.5 mmol) was adsorbed on neutral alumina (3 g). To this mixture two drops of piperidine was added, mixed thoroughly and irradiated at 640 watt for 6 min (monitored by TLC). The product was extracted into ethylacetate and found to be pure by TLC.

REFERENCES

[1] D. M. P. Mingos and D. R. Baghurst, *Chem. Soc. Rev*., **1,** 20 (1991).
[2] S. Caddick, *Tetrahedron*, **51,** 10403 (1995).
[3] C. R. Strauss and R. W. Trainor, *Aust. J. Chem*., **48,** 1665 (1995).
[4] A. Loupy, A. Petit, J. Hamelin, F. T. Boullet, P. Jacquault, and D. Mathe, *Synthesis*, 1213 (1998).
[5] R. S. Varma, *Green Chemistry*, **1,** 43 (1999).
[6] R. S. Varma, *Ceramic Transactions*, **80,** 35 (1997).
[7] S. P. Singh, S. S. Parmar, K. Raman, and I. Stenberg, *Chem. Rev*., **81,** 175 (1981).
[8] R. S. Lodhi, S. S. Srivastava, and S. K. Srivastava, *Indian J. Chem*., **37B,** 899 (1998).
[9] H. D. Joshi, P. S. Upadhyay, and A. J. Baxi, *Indian J. Chem*., **39B,** 967 (2000).
[10] S. K. Srivastava, R. B. Pathak, and S. C. Bahel, *Indian J. Chem*., **30B,** 620 (1991).
[11] H. A. Al-Khamees, S. M. Bayomi, H. A. Kandil, and K. E. H. Tahir *Eur. J. Med. Chem*., **25,** 103 (1990).
[12] M. H. Khan, S. Tewari, K. Begum, and Nizamuddin, *Indian J. Chem.,* **37B,** 1075 (1998).
[13] K. C. Joshi and R. Joshi, *J. Indian Chem. Soc.*, **76,** 515 (1999).
[14] M. Molf, US Patent 3314 951 (1967); (*Chem. Abstr.*, **67,** 90819i (1967).
[15] M. Rajopadhye and F. D. Popp, *J. Heterocycle Chem*., **21,** 289 (1984).
[16] K. Mogilaiah and R. Babu Rao, *Indian J. Chem.*, **37B,** 894 (1998).
[17] M. Rajopadhye and F. D. Popp, *J. Heterocycl Chem*., **22,** 93 (1985).
[18] a) A. Dandia, H. Taneja, and R. Singh, *J. Chem. Res. (S)*, **272** (2000); b) A. Dandia, H. Sachdheva, and R. Singh, *Synth. Commun*., **31**(12), 1879 (2001); c) A. Dandia, R. Singh, H. Sachdeva, and K. Arya, *J. Fluorine Chem.*, **111,** 61 (2001).
[19] a) M. Suarez, A. Loupy, E. Perez, et al., *Heterocyclic Commum*., **2,** 275 (1996); b) A. Loupy, P. Pigeon, and M. Ramdani, *Tetrahedron*, **52,** 6705 (1996); c) A. R. Hajipour, S. E. Mallakpour, and A. Afroushen, *Tetrahedron,* **55,** 2311 (1999).
[20] A. Loupy and L. Perruex, *Tetrahedron*, **57,** 9199 (2001).
[21] Ch Chyi Tzang, N. C. Motola, and R. P. Panzica, *J. Org. Chem*., **48,** 1271 (1983).
[22] Y. Mizuno, M. Ikehara, and K. A. Matanahe, *Chem. Pharm. Bull*., **10,** 647 (1962).
[23] K. R. Heneray-logan, H. P. Konepfel, and J. Rodricks, *J. Heterocycl Chem*., **5,** 433 (1965).
[24] E. C. Taylor and E. E. Garcia, *J. Org. Chem*., **29,** 2121 (1964).
[25] Y. L. Nene, P. N. T. Hapliyal, *Fungicides in Plant Disease Control* (Oxyord, New Delhi, 1993).
[26] M. D. Whitehead, *Phytopath*., **47,** 450 (1952).