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Synthesis and antimicrobial evaluation of some new fluorinated spiro[[1,5]-benzothiazepin-2,3′[3′*H*]-indol]-2′(1′*H*)-ones

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Abstract

A series of fluorinated spiro[1,5-benzothiazepin-2,3′[3′*H*]-indol]-2′(1′*H*)-ones have been prepared by the reaction of 2-aminobenzenethiols with 1,3-dihydro-3-[2-phenyl/(4-fluorophenyl)-2-oxoethylidene)-indol-2(1*H*)-ones (**I**) under microwave irradiation in open vessels using ethylene glycol as energy transfer medium and thermally in absolute ethanol saturated with hydrogen chloride gas. The comparative studies indicated that the microwave assisted organic synthesis has advantages of significantly reduced reaction time, improved yields and cleaner reactions as compared to the conventional method. All synthesized compounds have been characterized by analytical and spectral data and were screened for their antifungal activity against *Alternaria alternata* and *Fusarium oxysporium* and antitubercular activity against *Mycobacterium tuberculosis* **IVb** (R=F, X=F) and **IVe** (R=F, X=CH_3) have shown above 90% inhibition in reducing fungal growth of *A. alternata* while **IVa** (R=H, X=F) has shown 98% antitubercular activity on primary screening.

Keywords: 1,5-Benzothiazipine; Antimicrobial activity; 3-Spiro indole; Microwave-irradiation

1. Introduction

The syntheses of 1,5-benzothiazepine derivatives constitute an important area of research with a large member of 1,5-benzothiazepines exhibiting a variety of pharmacological activities. Diltiazem, Clentiazem and Siratiazem are important cardiovascular drugs of this family, which have been introduced for the treatment of a variety of cardiac ailments. Recently, reports have appeared that benzazepine analogue of diltiazem with a trifluoromethyl group at C-6 shows excellent potency in vitro and demonstrates pronounced and long lasting antihypertensive effects in spontaneously hypertensive rats [1].

It has been observed that introduction of a fluorine atom or CF_3 group to heterocycles may act as a pharmacophore, enhancing pharmacological properties of the compounds as compared to their nonfluorinated analogues [2]. Incorporation of fluorine atoms into the indole ring tends to increase drug persistence by increasing its solubility in lipoid material and fat deposits in the body [3]. Though fluorinated benzodiazepines, e.g., fluordiazepam [4], tifluadam [5,6], flurazepam [7,8], flunitrazepam [9,10], fletazepam [11] and triflubazam [12] are in clinical use, a literature survey has revealed scanty information on the fluorinated 1,5-benzothiazepines. A series of 1,5-benzothiazepines having fluorine and 4-fluorophenyl groups have been found effective in treating cancer metastasis [13–15]. 8-Fluoro-2-carboxy-4-(4-fluorophenyl)-2,3-dihydro-1,5-benzothiazepine, recently reported from our laboratory was found to be a promising anti-AIDS agent in preliminary screening [16]. Chemotherapeutic applications are also associated with fluorine-containing spiro-3-indole derivatives bearing a sulphur and nitrogen containing heterocyclic ring at the C-3 position through a spiro carbon atom [17,18] [19–27]. However, there are scanty reports about 3-spiroindolines incorporating a 1,5-benzothiazepine moiety except from this laboratory [28,29].

Further utilization of 'Microwave-Oven Induced Reaction Enhancement' (MORE) chemistry' for highly accelerated synthesis of divergent types of heterocycles, is of current interest due to the rapid heating associated with microwave technology [30]. A literature survey has revealed that there is only one report about the synthesis of indole derivatives under microwave conditions [31].

As an extension of our research work on the synthesis of fluorine containing bioactive heterocycles [16–19,32–37]

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Table 1
Analytical and physical data

Compound	R	X	Time		Yield (%)		MP (°C)	Molecular formula	Elemental/analysis [a] for nitrogen
			Classical method (h)	Microwave method (min)	Classical method	Microwave method			Found (calculated) (%)
IVa	H	F	6	12	60	62.4	145	$C_{22}H_{15}N_2SOF$	7.51 (7.48)
IVb	F	F	5	10	49	53.1	191	$C_{22}H_{14}N_2SOF_2$	7.20 (7.14)
IVc	F	Cl	4	8	58	65.0	198	$C_{22}H_{14}N_2SOFCl$	6.90 (6.86)
IVd	F	Br	4	8	51.2	56.0	164	$C_{22}H_{14}N_2SOFBr$	6.22 (6.18)
IVe	F	CH_3	4	10	54.0	60.0	132	$C_{23}H_{17}N_2SOF$	7.27 (7.21)

[a] Satisfactory microanalysis were obtained for **IVa–e**: C ± 0.05%, H ± 0.03%.

Table 2
IR, ^{1}H NMR and ^{19}F NMR spectral data of new spiro[[1,5]-benzothiazepin-2,3′-[3′*H*]-indol]-2′(1′*H*)-ones (**IV**)

Compound	IR (cm^{-1})	^{1}H NMR (δ ppm)				^{19}F NMR (δ ppm)
		=CH	Ar–H	NH	NH	
IVa	3145, 3060, 2945, 1693, 1458, 1375, 1172	6.8	6.85–7.81 (m, 12H)	8.09	8.32	−119.83
IVb	3130, 3070, 2910, 1710, 1600, 1500, 1460, 1375, 1220, 1160, 1105	7.02	6.80–7.67 (m, 11H)	8.09	8.27	−119.42, −120.23
IVc	3136, 3080, 2970, 1715, 1600, 1480, 1475, 1380, 1180, 1100	7.05	6.9–7.45 (m, 11H)	8.2	8.4	−119.31
IVd	3135, 3065, 2965, 1710, 1595, 1485, 1450, 1385, 1175, 1102	6.98	6.89–7.81 (m, 11H)	8.08	8.36	−118.61
IVe	3142, 3035, 2970, 1712, 1600, 1505, 1450, 1375, 1165, 1095	6.92	6.95–7.6 (m, 11H)	8.17	8.33	−118.45

and our interest on the reactions of 2-aminobenzenethiols with α,β-unsaturated ketones and analogous compounds [16,38,39], we wish to report herein, the synthesis of new fluorinated 2,5-dihydro-4-aryl spiro [1,5-benzothiazepin-2,3′[3′*H*]-indole]-2′(1′*H*)-ones, by thermal methods and under microwave irradiation.

A comparative study of the two synthetic approaches indicates the versatility of the microwave heating technique, as the reaction time is decreased to a few minutes besides giving improved yields and cleaner reactions.

2. Results and discussion

We have investigated the synthesis of a series of new fluorinated spiro[1,5]-benzothiazepine indol]-ones, under thermal and microwave reaction conditions (Table 1). IR spectra of the final products showed characteristic IR absorptions, 3130–3145 (NH), 1693–1715 (NHCO) and 1160–1186 (C–N) cm^{-1}. ^{1}H NMR spectra displayed signals at δ 6.8–7.02 (S, 1H, =C–**H**), 6.8–7.81 (m, aromatic protons), 8.08–8.15 (S, 1H, N**H**) and 8.27–8.4 (S, 1H, N**H**) ppm (Table 2) and deuteration further confirmed the presence of NH peaks. Disappearance of exocyclic C=C at 1620, C=O absorptions at 1670 cm^{-1} and retention of NHCO band at 1693–1715 cm^{-1} indicated the participation of α, β-unsaturated carbonyl system of side chain of **I** resulting in the formation of a spiro heterocycle at the position-3 of 2-indolinone. Further, the absence of primary amino group absorptions at 3450 and 3350 cm^{-1} affirmed the formation of 1,5-benzothiazepine ring systems.

Presence and position of fluorine was confirmed by ^{19}F NMR spectra (Table 3). Single fluorine attached to the 4-position of the phenyl ring (**IVb–e**) and 8-position of the benzothizepine ring (**IVa,b**) appeared at δ −118.95 to 120.23 ppm. Structure assigned to the spiro compounds was further corroborated by mass spectra. In the mass spectra of **IVa, IVe**, the molecular ion peaks were observed at *m/z* 374 (1.7%) and 388 (3.9%) corresponding to the molecular weights of the compounds.

3. Evaluation of antifungal activity

The synthesized compounds were screened for antifungal activity against *Alternaria alternata* and *Fusarium oxysporium* in three replications by 'Food poison technique' [40]. Each of the compounds was dissolved in 20% acetone at 1000 ml 500 ppm concentrations, which was then added in required quantities to Potato–Dextrose–Agar (PDA) medium, before dispersing into petri-plates. Standard checks were also prepared by inoculating fungi in a PDA medium for comparison. After 7 days of incubation at 25°C, radial growth of the colony was measured in cm. The results obtained are given in Table 3.

Table 3
Effect of synthesized compounds (**IVa–e**) on the radial growth of different fungi

Compound no.	R	X	Radial growth [a] (in cm) and percent inhibition of *Alternaria alternata*					Radial growth [a] (in cm) and percent inhibition [b] of *Fusarium oxysporium*				
			Control (0 ppm)	500 ppm	Percent inhibition	1000 ppm	Percent inhibition	Control (0 ppm)	500 ppm	Percent inhibition	1000 ppm	Percent inhibition
IVa	H	F	3.3	1.0	69.7	0.5	84.9	3.6	1.0	71.4	0.5	85.8
IVb	F	F	5.1	1.7	67.4	0.4	92.1	4.6	2.1	53.3	1.0	77.8
IVc	F	Cl	5.1	1.9	64.8	1.4	72.6	4.6	2.0	55.6	1.3	71.1
IVd	F	Br	5.1	1.2	76.4	1.0	80.3	4.6	2.2	51.1	1.2	73.3
IVe	F	CH_3	5.1	1.3	74.6	0.5	90.1	4.6	2.4	46.7	1.4	67.6

[a] Each observation an average of three replications.
[b] Percent inhibition = (radial growth in control (cm) − radial growth in treatment (cm))/(radial growth in control (cm)) × 100.

The results indicate that the incorporation of fluorine in a compound increases the antifungal activity against *A. alternata*. Compounds (**IVa–e**) are more effective against *A. alternata* than *F. oxysporium* (Table 3). For the given compounds, concentration at 1000 ppm was superior to 500 ppm. **IVb** and **IVe** are the most effective compounds against *A. alternata* showing above 90% inhibition.

4. Evaluation of antitubercular activity

IVa was tested for antitubercular activity against *Mycobacterium tuberculosis* [41,42]. Primary screening was conducted at 12.5 μg/ml against *M. tuberculosis* H 37 Rv in BACTEC 12B medium using the BACTEC 460 radiometric system. Controls received 50 μl DMSO Rifampin was included as a positive drug control. It was used for comparison at minimum inhibitory concentration, MIC RMP = 0.25 μg/ml, 98% inhibition vs. *M. tuberculosis*. **IVa** was found to possess 98% antibacterial activity against *M. tuberculosis* and its advanced screening is under progress. Primary screening of remaining compounds is under progress.

5. Experimental

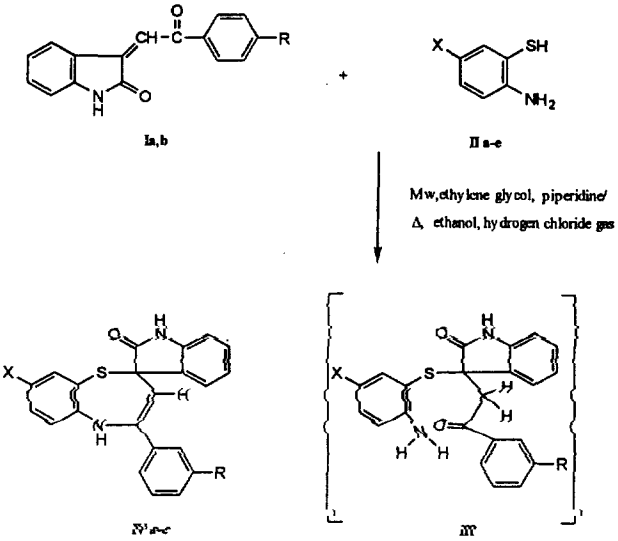
Melting points were determined in open glass capillaries and were uncorrected. IR spectra (KBr) were recorded on a Magna IR-550 spectrophotometer. ^1H and ^{19}F NMR were recorded on a Jeol (model-FX90 Q) using $CDCl_3$ as solvent at 89.55 and 84.25 MHz, respectively. TMS was used as internal reference for ^1H NMR and hexafluorobenzene as external reference for ^{19}F NMR. Mass spectra were recorded on a *Jeol D-300 mass spectrometer at an ionisation potential of 70 eV. All compounds were tested for purity, carried out* in silica gel 'G' coated glass plates using solvent system, benzene:ethanol:ammonia (7:2:1), homogenous on TLC. The microwave accelerated reactions were carried out using induced microwave convection system operating at 1200 W generating 2450 MHz frequency. 5-Fluoro/chloro/bromo/methyl-2-aminobenzene-thiols (**IIb–e**) were prepared by literature methods from *p*-substituted aniline by carrying out thiocyanation with ammonium thiocyanate/copper thiocyanate to give 6-substituted-2-aminobenzothiazoles, which on hydrolysis with KOH and subsequent acidification gave 5-substituted-2-aminobenzenethiols [43]. **Ia,b** was synthesized by the Knoevenagel reaction of indole-2,3-dione with the appropriate acetophenone in the presence of diethylamine as basic catalyst followed by dehydration in concentrated hydrochloric acid and glacial acetic acid medium [44].

5.1. 8-Substituted-2,5-dihydro-4-aryl spiro[1,5-benzothiazepin-2,3'-[3'H]-indol]-2'(1'H)-ones (IVa–e)

Compounds **IVa–e** (Scheme 1) were prepared by two methods: (i) Thermal and (ii) microwave irradiation.

5.1.1. Thermal method

A solution of 1,3-dihydro-3-[2-aryl-2-oxoethylidene]-indol-2(*H*)-one (1 mmol) in ethanol (15 ml) was saturated with hydrogen chloride gas. When the red coloured solution



Scheme 1.

turned brown, a solution of 5-substituted-2-aminobenzenethiol (1 mmol) in absolute ethanol (5–10 ml) was added dropwise with continuous stirring and the reaction mixture was then refluxed on a steam bath for 4–6 h. Progress of the reaction was monitored by TLC. Solid obtained on cooling was filtered, washed with saturated $NaHCO_3$ and crystallized from methanol to obtain the title compounds (**IVa–e**).

5.1.2. Microwave method

A mixture of **I** (1 mmol) and 5-substituted-2-aminobenzenethiol (1 mmol) in ethylene glycol (10 ml) containing a catalytic amount of piperidine was placed in a microwave oven (1200 W, 2450 MHz using 20% power) and irradiated for 8–12 min. The irradiation was completed with a short interruption of 1 min to avoid overheating of the solvent. Progress of the reaction was monitored by TLC. Reaction mixture was cooled and poured over crushed ice, and the solid thus separated was filtered, washed with water, dried and crystallised from methanol to obtain the title compounds (**IVa–e**).

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