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Short communication

Brønsted acidic ionic liquids: Green, efficient and reusable catalyst for synthesis of fluorinated spiro [indole-thiazinones/thiazolidinones] as antihistamic agents

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ABSTRACT

Brønsted acidic ionic liquid containing nitrogen-based organic cations 1-methylimidazolium and 1-butyl-3-methylimidazolium and inorganic anions such as BF_4^-, PF_6^- and $PTSA^-$ used as catalysts and reaction medium for synthesis of fluorinated spiro[3H-indole-3,2′-tetrahydro-1,3-thiazine]-2,4′(1H)-diones (4a-f), fluorinated spiro[3H-indole-3,2′-thiazolidine]-2,4′ (1H)-diones (**5a-f**) in 90–97% yield by one-pot environmentally benign microwave induced technique. Synthesized compounds have been evaluated for their ability to inhibit the contractions induced by histamine on guinea pig ileum. The measurement of pA_2 values suggested that the reported compounds showed H1-antagonism.

1. Introduction

Room temperature ionic liquids (RTILs) have attracted extensive research interest as environmentally benign solvents due to their favorable properties such as non-inflammability, negligible vapour pressure, reusability and high thermal stability [1,2]. They have also been referred to as 'designer solvents' as their physical and chemical properties could be adjusted by a careful choice of cation and anion. Apart from this, they exhibit acidic properties. Combining these unique properties of ionic liquids they are emerging as a 'green reaction media' (catalyst + solvent). The use of ionic liquids as reaction medium may offer a convenient solution to both the solvent emission and catalytic recycling problem [3–5]. Multi-component reactions (MCRs) have been frequently used by synthetic chemists as a facile means to generate molecular diversity from bifunctional substrates that react sequentially in an intramolecular fashion and the process inherently more environmentally benign and atom-economic [6].

Devising such types of MCRs that achieve the formation of multiple bonds in a single operation is one of the major challenges in modern organic synthesis [7]. They provide a powerful tool toward the one-pot synthesis of diverse and complex compounds as well as small and drug-like heterocycles [8].

Thiazolidinone, an important "privileged scaffold," is a very attractive target for combinatorial library synthesis because of their structure activity relationship [9] and is an important class of N and S containing heterocycles, which are widely used as key building blocks in the field of drugs and pharmaceutical agents [10]. Further, the presence of the N–C–S linkage in the thiazolidines is also responsible for nematocidal, fungicidal, antibacterial and antiviral activities [11–13].

In addition, the spiro[indole-thiazolidine] system is a structural motif found or presented in many pharmacologically important synthetic and naturally occurring compounds e.g. spirobrassinin. The diversity of their biological functions such as anti-inflammatory, antimicrobial, antileukemic and anticonvulsant activities has stimulated efforts in the expedient development of their synthesis [14,15]. Incorporation of fluorine to different heterocycles is known to affect the course of the reaction besides influencing the biological/pharmacological activity [16]. Further, incorporation of trifluoromethyl substituents has been shown to increase the phytoxicity along with selectivity and arenes bearing trifluoromethyl substituents that comprises the largest subgroup of commercially promising pesticides and herbicides.

A literature survey shows that most of the reported methods for the synthesis of thiazolidinone involves the use of high boiling carcinogenic hydrocarbons with continuous azeotropic removal of water [17a], or requiring desiccants like anhydrous $ZnCl_2$, [17b], sodium sulphate [17c], molecular sieves [18], or use of stoichiometric amount of DCC [19a], Hünig base [19b] in solution phase

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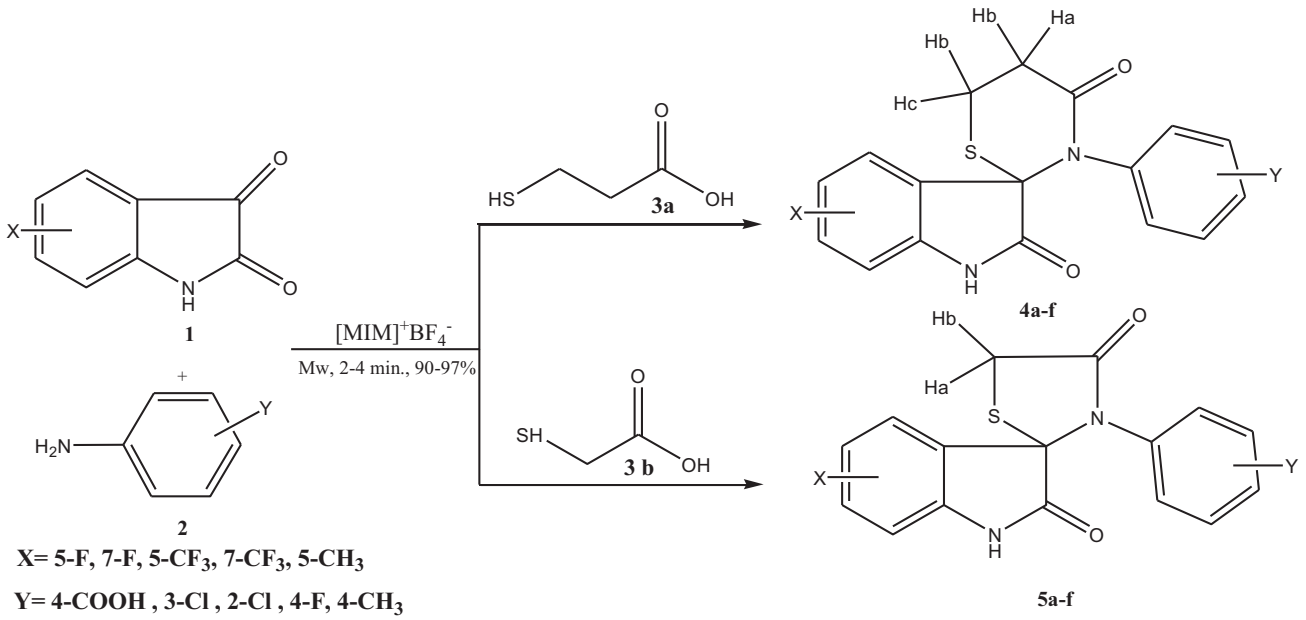

Scheme 1. Synthesis of fluorinated spiro-[indole-thiazinones] and spiro[indole-thiazolidinones].

reactions and thermally unstable ionic liquids [20]. The yield of products drastically decreased with increasing of reaction times in recycling of ionic liquids. This would make the whole procedure unsuitable for industrial applications.

In line with our interest on spiro indoles, extensive work has been carried out in our lab on the spiro[indole-thiazolidinone] [21] system. Recently we have reported [21a] a nonconventional three-component, regioselective one-pot cyclocondensation method for the synthesis of a series of novel spiro[indole-thiazolidinones] using montmorillonite KSF as an inorganic solid support in an open vessel using a modified domestic microwave. Although this method has its own merits in comparison to a conventional two-step procedure but these microwave assisted reactions still require use of solvent for adsorption and desorption and also are not suitable for large scale preparation with reproducibility. Hence there is a scope for further development of an efficient, high yielding green protocol without the use of any solvent.

As part of our program aimed at developing new selective greener methodologies for the preparation of pharmaceutically important scaffolds [22], we undertook improvement toward an efficient and ecofriendly process for the preparation of fluorinated spiro-[indole-thiazinones] (**4a-f**) and spiro[indole-thiazolidinones] (**5a-f**) in the presence of Brønsted acidic ionic liquid as reaction medium as well as promoters without any additional catalyst at ambient temperature (Scheme 1). Synthesized compounds are screened as antihistamic and antidiabetic agents.

2. Result and discussion

The cyclocondensation of thioacids (**3a/b**) with substituted isatin (**1**) and heterocyclic amines (**2**) yielding exclusively fluorinated spiro compounds (**4, 5**) was studied using different types of Brønsted acidic ionic liquid with different inorganic anions such as BF_4^-, $PF_6^-$and $PTSA^-$. Since 1-methylimidazolium tetrafluoroborate ($[MIM]^+BF_4^-$) efficiently catalyzed the reaction, giving maximum yield (90–97%) with shortest period (2–4 min) and easier work up. All compounds listed in Table 1 have been synthesized in one pot using methylimidazolium tetrafluoroborate ($[MIM]^+BF_4^-$) as Brønsted acidic ionic liquid (Table 1).

The Lewis and Brønsted acidity of the ionic liquids has been determined using pyridine as a probe molecule by monitoring the bands in the range of 1350–1600 cm^{-1} arising from its ring vibration modes [23,24].

The FTIR spectrum of neat pyridine shows a band at 1425 cm^{-1} (Fig. 1a). On mixing pyridine with ionic liquid, the spectrum of ionic liquid shows a band near 1450 cm^{-1} indicating the

Table 1
Physical and structural characteristics of fluorinated spiro compounds.

Compounds[a]	X	Y	Time (min)	M.P. (°C)	Yield[b] (%)	Molecular formula	Found (Calcd.)		
							C	H	N
4a	5-F	4-COOH	2	215–217	93	$C_{18}H_{13}FN_2O_4S$	58.12 (58.06)	3.50 (3.52)	7.48 (7.52)
4b	7-F	3-Cl	4	199–201	96	$C_{17}H_{12}ClFN_2O_2S$	56.20 (56.28)	3.31 (3.33)	7.75 (7.72)
4c	5-CF_3	4-COOH	3	185–187	90	$C_{19}H_{13}F_3N_2O_4S$	53.94 (54.03)	3.08 (3.10)	6.67 (6.63)
4d	7-CF_3	2-Cl	3	192–194	92	$C_{18}H_{12}ClF_3N_2O_2S$	52.45 (52.37)	2.91 (2.93)	6.76 (6.79)
4e	5-CH_3	4-F	3	225–227	91	$C_{18}H_{15}FN_2O_2S$	63.05 (63.14)	4.43 (4.42)	8.15 (8.18)
4f	5-CH_3	4-CH_3	4	195–197 [16a]	95	$C_{19}H_{18}N_2O_2S$	67.32 (67.43)	5.42 (5.36)	8.35 (8.28)
5a	5-F	4-COOH	4	212–214	97	$C_{17}H_{11}FN_2O_4S$	56.89 (56.98)	3.07 (3.09)	7.85 (7.82)
5b	7-F	3-Cl	2	175–177	96	$C_{16}H_{10}ClN_2O_2S$	55.18 (55.10)	2.87 (2.89)	8.05 (8.03)
5c	5-CF_3	4-COOH	3	230–232	90	$C_{18}H_{11}F_3N_2O_4S$	52.87 (52.94)	2.74 (2.72	6.88 (6.86)
5d	7-CF_3	2-Cl	3	205–207	93	$C_{17}H_{10}ClF_3N_2O_2S$	51.14 (51.20)	2.54 (2.53)	7.04 (7.02)
5e	5-CH_3	4-F	4	278–281	95	$C_{17}H_{13}FN_2O_2S$	62.10 (62.18)	3.97 (3.99)	8.56 (8.53)
5f	5-CH_3	4-CH_3	3	>360 [21b]	96	$C_{18}H_{16}N_2O_2S$	66.50 (66.64)	4.90 (4.97)	6.61 (8.64)

[a] All products were characterized by ^1H NMR, mass and IR data.
[b] Isolated yields.

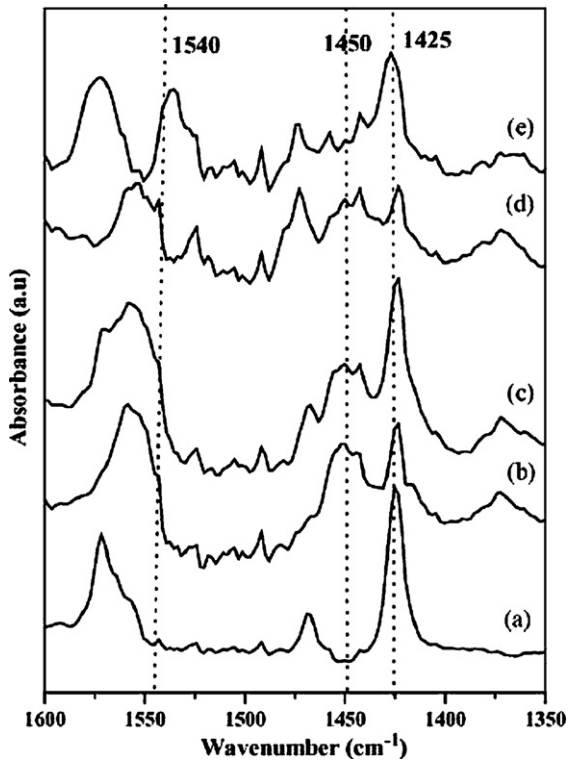

Fig. 1. FTIR spectra: (a) neat pyridine, (b) pyridine with $[BMIM]^+ PF_6^-$, (c) pyridine with$[BMIM]^+BF_4^-$, (d) pyridine with $[BMIM]^+PTSA^-$, (e) pyridine with $[MIM]^+BF_4^-$.

coordination of pyridine to the Lewis acid sites, with an additional band near 1540 cm^{-1} indicating the presence of Brønsted acid sites due to the formation of pyridinium ions (Fig. 1b–e).

The purity of $[MIM]^+BF_4^-$ ionic liquid was determined by ^1H NMR spectra using the intensity of the C-13 satellites of the imidazolium N-methyl group as internal standard. ^1H NMR spectrum shows that the protons resonate in the range δ1.18(s, 3H), 7.1(m, 2H), 9.4(s,1H). From the ^1H spectral data, it is revealed that the proton at C2 in the imidazole ring (δ9.4) might be acidic. Such a chemical shift may be due to ring-current effect of the imidazole ring. Further ionic liquids purity was also accessed by HPLC.

In order to optimize the reaction conditions, we conducted the one pot cyclocondensation of isatin, amines with thioacids (5 mmol) under microwaves with different types of Brønsted acidic ionic liquids (1 mmol or 0.05 mmol) (Table 2) or without ionic liquids.

Table 2
Optimization study of one pot cyclocondensation reaction of isatins, amines with thioacids in different ionic liquids.

Compounds	Ionic liquid	Ratio[a]	Time (min)	Yield (%)
4b	$[MIM]^+BF_4^-$	1:1	3	96
	$[MIM]^+BF_4^-$	1:0.5	5	93
	$[BMIM]^+BF_4^-$	1:1	5	89
	$[BMIM]^+PF_6^-$	1:1	7	91
	$[BMIM]^+PTSA^-$	1:1	6	92
	Neat	–	15	78
5a	$[MIM]^+BF_4^-$	1:1	4	97
	$[MIM]^+BF_4^-$	1:0.5	6	92
	$[BMIM]^+BF_4^-$	1:1	8	87
	$[BMIM]^+PF_6^-$	1:1	6	84
	$[BMIM]^+PTSA^-$	1:1	8	85
	Neat	–	18	69

[a] Reactant (isatins, amines and thioacids) to ionic liquids molar ratio.

Table 3
Catalyst recycling of synthesis of spiro indole [thiazine] (**4a**) using $[MIM]^+BF_4^-$.

Cycle	Time (min)	Yield (%)
Fresh	3	96
1st recycle	3	95
2nd recycle	3.5	95
3rd recycle	4	94
4th recycle	4	94

Reaction condition: ionic liquid = 1 g; temperature = 110 °C.

The results showed that the efficiency and the yield of the reaction in shorter chain length on the ionic liquid cation ($[MIM]^+BF_4^-$) were higher than those obtained in other ionic liquids and the production of side products was also lowered [25]. $[BMIM]^+ [PF_6]^-$ ionic liquid gave higher yield compared to its anion BF_4^-, $PTSA^-$, due to its hydrophobic nature. Also to illustrate the need for ionic liquids, the reaction was studied in the absence of ionic liquids. As a result, products were produced after a long time irradiation. One of the main aims of the study was to investigate the reuse and recycling of ($[MIM]^+BF_4^-$). After filtration of the cold reaction mixture to separate the product (**4a**), the filtrate was charged with the same substrates and was reused for four cycles, which gave yields similar to those obtained in the first run, although slightly increase in reaction time was observed (Table 3, Fig. 2).

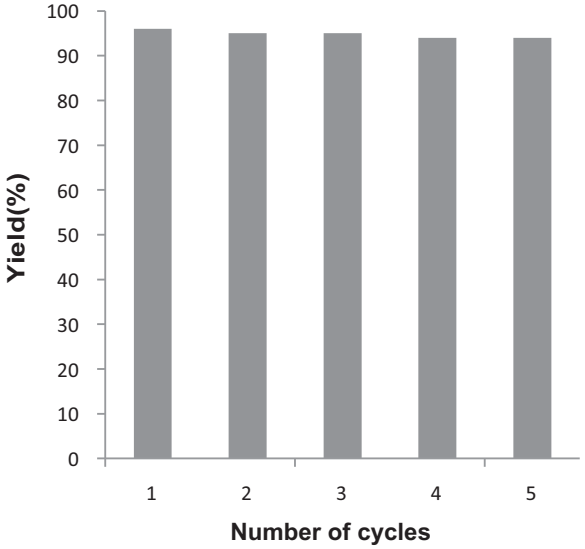

Fig. 2. Recyclability of ionic liquid $[MIM]^+BF_4^-$ (Compound **4a**, Table 1).

3. Experimental

3.1. Materials

All the anilines, thioacids and $[BMIM]^+$ ionic liquids with inorganic anions such as BF_4^-, $PF_6^-$and $PTSA^-$ were Aldrich products and were used as received. Tetrafluoroboric acid (40%) solution in water was obtained from Loba Chemie India. 1-Methylimidazole (99%) received from Lancaster (UK).

3.2. Characterization techniques

IR spectra (KBr) were recorded on a Shimadzu FT IR-8400S spectrophotometer and ^1H NMR was recorded on a Bruker DRX-300, at 300.15 MHz, using $CDCl_3$ as solvent. Direct insertion probe mass spectrum (DIPMS) values are reported in *m/z*. The microwave-assisted reactions were carried out in a monomode system,

Table 4
Spectral analysis of synthesized compounds (**4a–e** and **5a–e**).

Compound	IR (cm^{-1})	^{1}H NMR (δ, ppm)	^{13}C NMR (δ, ppm)	^{19}F NMR (δ, ppm)	Mass $[M]^+$
4a	3480 (OH), 3290 (NH), 1725, 1705, 1690 (3 × C=O), 740 (C–F)	2.69 (dt, 1H, H_a), 3.26 (dd, 2H, 2 × H_b), 4.15 (dt, 1H, H_c), 6.75–7.38 (m, 7H, Ar H), 8.97 (br, 1H, NH^*), 10.03 (br, 1H, OH^*)	26.2 (S-$\underline{C}H_2$), 31.3 ($\underline{C}H_2$C=O), 72.04 (spiro carbon), 117.01–139.65 (aromatic carbons), 151.8 ($\underline{C}$–F), 168.93, 172.11, 174.8 (three C=O)	−118.54 (s, F)	372(M^+, 100)
4b	3270 (NH), 1715, 1695 (2 × C=O), 750 (C–F), 770 (C–Cl)	2.72 (dt, 1H, H_a), 3.20 (dd, 2H, 2 × H_b), 4.05 (dt, 1H, H_c), 6.85–7.45 (m, 7H, Ar H), 8.62 (br, 1H, NH^*)	25.4 (S-$\underline{C}H_2$), 32.4 ($\underline{C}H_2$C=O), 70.2 (spiro carbon), 115.08–142.72 (aromatic carbons), 154.2 ($\underline{C}$–F), 166.8, 171.3 (two C=O)	−119.56 (s, F)	362(M^+, 100), 364 (M^++ 2, 45)
4c	3490 (OH), 3280 (NH), 1720, 1710, 1685 (3 × C=O), 750 (C–F)	2.65(dt, 1H, H_a), 3.22 (dd, 2H, 2 × H_b), 4.13 (dt, 1H, H_c), 6.81–7.52 (m, 7H, Ar H), 8.89 (br, 1H, NH^*), 10.13 (br, 1H, OH^*)	25.8 (S-$\underline{C}H_2$), 30.9 ($\underline{C}H_2$C=O), 71.5 (spiro carbon), 119.08–138.62 (aromatic carbons), 121.8 ($\underline{C}F_3$), 135.3 ($\underline{C}$–CF_3), 169.58, 172.4, 175.2 (three C=O)	−63.47 (s, CF_3)	422(M^+, 100)
4d	3290 (NH), 1720, 1690 (2 × C=O), 745 (C–F), 765 (C–Cl)	2.70 (dt, 1H, Ha), 3.23 (dd, 2H, 2 × Hb), 4.08 (dt, 1H, Hc), 6.83–7.42 (m, 7H, Ar H), 8.73 (br, 1H, NH^*)	25.4 (S-CH_2), 32.4 (CH_2C=O), 70.2 (spiro carbon), 115.08–142.72 (aromatic carbons), 122.5 ($\underline{C}F_3$) 138.7 ($\underline{C}$–CF_3), 166.8, 171.3 (two C=O)	−63.28 (s,CF_3)	412(M^+, 100),414(M^+, 75)
4e	3260 (NH), 1715, 1680 (2 × C=O), 750 (C–F)	1.68 (s, 3H, CH_3), 2.68 (dt,1H, H_a), 3.20 (dd, 2H, 2 × H_b), 4.10 (dt, 1H, H_c), 6.71–7.28 (m, 7H, Ar H), 8.68 (br, 1H, NH^*)	20.91 (C–CH_3), 24.6 (S-$\underline{C}H_2$), 32.6 ($\underline{C}H_2$C=O), 73.1 (spiro carbon), 116.08–140.34 (aromatic carbons), 150.8 ($\underline{C}$–F), 167.2, 170.5 (two C=O)	−118.02 (s, F)	342(M^+, 100)
5a	3480 (OH), 3300 (NH), 1735, 1710, 1690 (3 × C=O), 745 (C–F)	4.05 (dd, 2H, H_a & H_b, J = 13.6 Hz), 6.73–7.45 (m, 7H, Ar H), 9.05 (br,1H, NH^*), 9.55 (br, 1H, OH^*)	33.98 (S-$\underline{C}H_2$), 74.01 (spiro carbon), 121.22–142.94 (aromatic carbons), 150.8 ($\underline{C}$–F), 172.02, 176.32, 180.21 (three C=O)	−118.48 (s, F)	358(M^+, 100)
5b	3310 (NH), 1720, 1695 (2 × C=O), 740 (C–F), 780 (C–Cl)	4.02 (dd, 2H, Ha & Hb, J = 13.5 Hz), 6.81–7.42 (m, 7H, Ar H), 9.01 (br, 1H, NH^*)	33.33 (S-$\underline{C}H_2$), 73.12 (spiro carbon), 120.08–140.86 (aromatic carbons), 154.3 ($\underline{C}$–F), 170.96, 177.12 (two C=O)	−119.42 (s, F)	348 (M^+, 100), 350 (M^++ 2, 40)
5c	3490 (OH), 3290 (NH), 1730, 1710, 1695 (3 × C=O), 750(C–F)	4.06 (dd, 2H, H_a & H_b, J = 13.7 Hz), 6.75–7.47 (m, 7H, Ar H), 9.02 (br, 1H, NH^*), 9.58 (br, 1H, OH^*)	33.98 (S-$\underline{C}H_2$), 74.01 (spiro carbon), 121.22–142.94 (aromatic carbons), 123.2 ($\underline{C}F_3$) 134.4 ($\underline{C}$–CF_3) 172.02, 176.32, 180.21 (three C=O)	−63.57 (s, CF_3)	408 (M^+, 100)
5d	3320 (NH), 1715, 1690 (2 × C = O), 745 (C–F), 770(C–Cl)	4.08 (dd, 2H, H_a & H_b, J = 13.5 Hz), 6.75–7.36 (m, 7H, Ar H), 9.15 (br, 1H, NH^*)	34.68 (S-$\underline{C}H_2$), 74.30 (spiro carbon), 120.18–140.02 (aromatic carbons), 127.3 ($\underline{C}F_3$) 133.2 ($\underline{C}$–CF_3) 171.8, 173.9, (two C=O)	−63.33(s,CF_3)	398(M^+, 100), 400 (M^+, 80)
5e	3320 (NH), 1720, 1690 (2 × C=O), 725 (C–F)	2.13 (s, 3H, CH_3), 3.99 (dd, 2H, H_a & H_b, J = 13.6 Hz), 6.70–7.51 (m, 7H, Ar H), 9.04 (br, 1H, NH^*)	13.01, (CH_3), 33.33 (S-$\underline{C}H_2$), 73.12 (spiro carbon), 120.08–140.86 (aromatic carbons), 153.2 ($\underline{C}$–F) 170.96, 177.12 (two C=O)	−117.90(s, F)	328 (M^+, 100)

purchased from CEM DISCOVER (m = 2450 MHz, 300 W) and coupled with a microcomputer. C and N analyses were carried out on a Perkin–Elmer model 240 analyzers.

3.3. Catalyst preparation and its applications

Preparation of 1-methylimidazolium tetrafluoroborate ([MIM]$^+BF_4^-$)

Tetrafluoroboric acid (8.06 g, 0.03 mol, 40% solution in water) was slowly added to a precooled solution (0 °C) of 1-methylimidazole (3 g, 0.03 mol) placed in a two-necked flask with a magnetic stirrer. The mixture was maintained at that temperature and stirred for 2 h. The resulting colorless ionic liquid was dried in a rotavapor for 2 h at 60 °C to remove water and used for synthesis of spiro compounds.

*Fluorinated spiro[3H-indole-3,2′-tetrahydro-1,3-thiazine]-2,4′ (1H)-diones (**4a-f**) and Spiro[indole-3,2′-thiazolidine]-2,4′ (1H)-diones (**5a-f**)*

Fluorinated spiro compounds **4/5** have been synthesized in one-step without isolating the intermediate using 1-methylimidazolium tetrafluoroborate ([MIM]$^+BF_4^-$) under microwave irradiation.

Pyrex glass vial containing an equimolar mixture (5 mmol) of appropriate indole-2,3-dione (**1**) and substituted aniline (**2**) and thioacids (**3a/b**) adsorbed on 1-methylimidazolium tetrafluoroborate ([MIM]$^+BF_4^-$) (1 gm) was placed in a screw capped Teflon vessel. Microwave was applied for 5 min at 140 °C. After the completion of reaction (TLC analysis), recyclable ionic liquid was separated by filtration after eluting the product with ethanol under reduced pressure and the residue washed with methanol gave a pure product in high yield (Table 1). All synthesized compounds were characterized by spectral analysis and data summarized in Table 4.

4. Pharmacological evaluation

Synthesized fluorinated spiro compounds (**4a–f, 5a–f**) were tested for new antidiabetic agents and in vitro for histamine HI-antagonist activity of the inhibition of the histamine-induced contractions on the isolated guinea pig ileum [26]. The activities have been reported in Tables 5–7.

5. Antihistamic activity

The competitive HI-receptor antagonism was evaluated by pA_2 data summarized in Table 5 and the potency of antagonistic effect of the tested compounds was compared to the activity of mepyramine. According to current research on antihistamine drugs, four elements are required for the histamine HI-receptor pharmacophore: two π sites, basic nitrogen, and a site for a heteroatom [27].

On the basis of the reported results, it seems that the pharmacophore proposed by Naruto [27b] are present in spiro indole [thiazine/thiazolidinone] moieties. The carbonyl and the N(2)-phenyl group could mimic the two π sites, and the nitrogen atom of thiazolidine ring could correspond to the heteroatom capable of hydrogen bonding. In regard to the substituent effect on the N(2)-phenyl group, it is noteworthy that the activity seems to be affected by the nature (electron-donating or electron-withdrawing) of the substituents in the phenyl group position. Apart from this, presence of electron-withdrawing or donating group on indole moieties in spiro [indole-thiazolidinone] system also affected the biological activities [28]. In Table 5, compounds **4a**, **4c–d**, **4e** and **5a**, **5c–d**, **5e**, all carry electron-withdrawing groups on ortho and para position of phenyl ring, but in compounds **4a**, **4e** and **5a**, **5e** fluorine atom on indole moiety would show weak electron-withdrawing power compared to CF_3 group on indole moiety in compounds **4c, d** and **5c, d**. Therefore compounds **4a**, **4c–d**, **4e** and **5a**, **5c–d**, **5e** were less active towards histaminic activities. However, electron-withdrawing groups achieved best results on both, either phenyl ring or indole moieties, compared to electron donating group (compounds **4f** and **5f**, Table 5).

Guinea pig ileum in vitro assay for H_1-receptor histamine antagonism

The assay was performed on ileum of either sex (weighing −250 g) percentage inhibition for guinea pig [26] was calculated on the response caused by 0.5 μM histamine in the absence of drugs. Six observations were carried out for each drug concentration. The results, IC_{50}, listed in Table 5, are reported as concentration of drug causing 50% inhibition of the submaximal contractions induced by histamine.

The dissociation constant (K_B), for pA_2 value calculations (pA_2 = −log K_B), was evaluated according to the method of Schild [29], from the equation $K_B = B/(x-1)$, where x is the respective ratio

Table 5
Histamine antagonist activity in vitro on guinea pig ileum.

Compounds	IC_{50} μM	pA_2 ± 0.2	Compounds	IC_{50} μM	pA_2 ± 0.2
4a	60	5.8	5b	24	7.1
4b	60	6.4	5c	20	8.7
4c	10	8.6	5d	21	8.2
4d	20	7.9	5e	>100	4.3
4e	60	5.6	5f	>100	1.9
4f	>100	2.7	**Mepyramin**	1.0	9.0
5a	>100	5.3			

Table 6
Intraday effect of different aryl substituted thiazolidinone derivatives on serum glucose at 1st day.

Compounds	Average serum glucose level (mg/dL) at (1st day)			
	0 h	1 h	4 h	7 h
Control	277.30 ± 1.46	278.24 ± 1.45	268.02 ± 2.13	265.12 ± 3.09
Alloxan	272.41 ± 2.56	277.35 ± 3.02	298.12 ± 1.78	306.66 ± 1.78
Standard	282.29 ± 2.75	238.36 ± 2.42	155.23 ± 1.89	118.24 ± 3.98
4a	270.13 ± 3.89	239.56 ± 1.25	165.78 ± 2.89	122.45 ± 4.49
4b	289.46 ± 4.79	269.35 ± 3.98	187.79 ± 1.53	132.33 ± 2.05
4c	292.14 ± 5.78	283.25 ± 1.02	214.27 ± 4.76	178.67 ± 1.39
4d	288.27 ± 2.46	285.49 ± 1.75	242.36 ± 4.56	241.44 ± 0.79
4e	278.19 ± 2.34	265.89 ± 4.02	172.65 ± 0.58	135.24 ± 1.22
5a	249.75 ± 2.88	233.34 ± 2.76	134.37 ± 1.78	119.22 ± 0.77
5b	283.27 ± 5.07	272.21 ± 2.98	179.67 ± 2.98	131.95 ± 1.09
5c	289.22 ± 2.90	275.43 ± 2.05	222.65 ± 5.09	170.55 ± 3.87
5d	294.74 ± 3.70	273.22 ± 2.90	234.98 ± 4.07	232.67 ± 2.30
5e	284.55 ± 1.78	268.46 ± 3.08	165.43 ± 3.09	127.11 ± 0.87

The values are presented as mean ± S.E.M. of six determinations $p < 0.01$.

Table 7
Effect of different aryl substituted thiazolidinone derivatives on serum glucose at 1st, 3rd, 7th day.

Compounds	Average serum glucose level (mg/dL)		
	1st day	3rd day	7th day
Control	245.74 ± 2.88	222.67 ± 2.83	183.79 ± 5.90
Alloxan	272.41 ± 2.56	324.67 ± 0.63	298.75 ± 1.78
Standard	122.24 ± 2.03	115.67 ± 1.37	108.98 ± 4.88
4a	167.89 ± 0.97	137.54 ± 4.09	116.76 ± 2.33
4b	188.34 ± 2.09	160.25 ± 1.56	122.78 ± 0.33
4c	245.89 ± 2.36	234.72 ± 2.88	218.90 ± 1.97
4d	222.37 ± 1.62	204.73 ± 1.55	178.30 ± 3.99
4e	205.86 ± 2.74	180.22 ± 3.22	127.57 ± 0.46
5a	145.73 ± 1.57	127.89 ± 2.90	110.99 ± 3.89
5b	198.22 ± 3.09	172.86 ± 2.49	127.39 ± 1.99
5c	225.75 ± 4.55	199.67 ± 1.23	167.57 ± 2.02
5d	209.56 ± 3.76	181.32 ± 2.22	145.32 ± 1.57
5e	199.87 ± 1.11	178.90 ± 4.37	119.90 ± 2.17

The values are presented as mean ± S.E.M. of six determinations $p < 0.01$.

of concentrations of histamine needed to produce half-maximal responses in the presence and absence of different concentrations (B) of antagonists. pA_2 values, reported in Table 5, are the average of five observations.

6. Antidiabetic activity

6.1. Cut-off lethal dose (LD_{50})

All the compounds synthesized were tested for acute toxicity test. Toxicity was observed at the doses of 300, 1000, 2000 mg/kg of body weight. More than 50% of animals died at the dose of 2000 mg/kg of body weight. Thus for the screening of antidiabetic activity, the dose selected was 200 mg/kg of body weight (i.e., 1\10 of the 2000 mg/kg of body weight) as per the OECD guidelines [30]. Metformin drug was used as standard and given to rats at dose of 5 mg/kg body weight. A single dose (150 mg/kg, body weight) of Alloxan monohydrate (5%, w/v in sterile water) was dissolved in normal saline used for the induction of diabetes and injected intraperitoneally to Wistar albino rats weighing 150–200 g. The induction of diabetes was confirmed by estimation of elevated fasting blood glucose level. The rats having blood glucose level above 200 mg/dl of blood were selected for the study. Blood was collected from retro orbital plexus of the eye under light ether anesthesia using capillary tube. Sodium fluoride and sodium oxalate were used as anti coagulant. All the compounds synthesized were tested for antidiabetic activity, the fasting serum glucose levels were determined according to GOD-POD method [31].

Antidiabetic activity of test compounds given in Table 6, Table 7 shows that compounds **4a**, **4b**, **4e**, **5a**, **5b** and **5e** were found to be most efficient for reduction of serum glucose level at 200 mg/kg dose and antidiabetic data of these compounds was comparable with standard drugs (Metformin) at 7th day of the study.

7. Conclusion

Improved synthesis of biologically active scaffold fluorinated spiro indole [thiazine/thiazolidinone] using catalytic amount of ionic liquids gave high substrate conversion and product selectivity. Synthesis of spiro compounds with ionic liquid as reaction medium proceeded smoothly towards completion and products were conveniently decanted out from the ionic liquid. Use of such a reaction medium should be appreciated for its easy preparation, convenient separation, and recycle of the catalyst, low cost and eco-friendly nature. The titled compounds also inhibit the contractions induced by histamine on guinea pig ileum. The measurement of pA_2 values suggested that the reported compounds showed H1-antagonism.

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