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ONE-POT GREEN SYNTHESIS OF 3′-(2-AMINOBENZIMIDAZOLYL)-2-PHENYL SPIRO[4H-BENZOPYRAN-4,2′-THIAZOLIDIN]-4-ONES AND ACYLATION USING TRIFLUOROACETIC ANHYDRIDE

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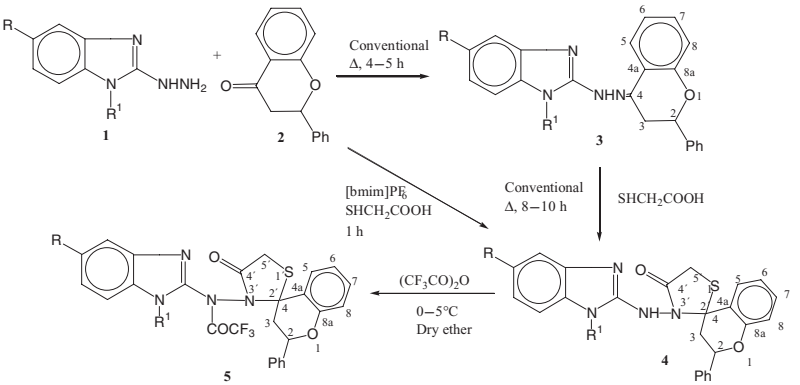
GRAPHICAL ABSTRACT



Abstract *An expeditious one-pot synthesis of a novel heterocyclic system, 3′-(2-aminobenzimidazolyl)-2-phenyl spiro[4H-benzopyran-4,2′-thiazolidin]-4-ones, has been accomplished by condensing substituted hydrazinobenzimidazole, flavanone, and mercaptoacetic acid by conventional heating in ethanol or toluene, and in an ionic liquid, viz., 1-butyl-3-methyl-imidazolium hexafluorophosphate. Excellent yields (85%–90%) and higher purity are obtained in the ionic-liquid-mediated synthesis as compared with the conventional procedure (55%–60%). Further, these compounds were acylated with trifluoroacetic anhydride. The structures of the compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass spectral data, and elemental analysis. The compounds, upon evaluation for their antibacterial, antifungal, and insecticidal activities, exhibited excellent results.*

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Keywords Ionic liquid; 3′-(2-aminobenzimidazolyl)-2-phenyl spiro[4H-benzopyran-4,2′-thiazolidin]-4-ones; trifluoroacetic anhydride; antibacterial; antifungal; insecticidal activity

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INTRODUCTION

Benzimidazoles are important in the field of biochemistry and medicine and the present era has witnessed the increasing use of these compounds in chemotherapy.[1] The benzimidazole scaffold has been reported to exhibit antimicrobial,[2,3] antifungal,[4] pesticidal,[5] antiparkinson,[6] and anticancer activities.[7] Flavanones possess strong antioxidant and antibacterial activity but only scant data on their chemical modification is available in the literature.[8] The reactions of flavanone with simple hydrazines have been reported[9–11] but no such investigation with hydrazino heterocycles has been carried out. The chemistry of 4-thiazolidinones has been reviewed[12] and found to exhibit antibacterial, herbicidal, anti-inflammatory, and analgesic activities,[13] while some derivatives are potent anti-HIV agents[14] and evaluated as selective human immunodeficiency virus type-1 reverse transcriptase (HIV-1 RT) enzyme inhibitors.[15,16] It was hypothesized that the title molecules incorporating benzimidazole, thialzolidinone, and flavanone moieties would exhibit enhanced biological properties. The investigation further appeared interesting as spiro[benzopyran-4,2′-thiazolidinone] has not been reported in literature with C-4 of flavanone ring as spiro carbon and amino benzimidazolyl group as a substituent.

With a view to develop an efficient and extremely fast procedure using a "green chemistry" concept, a one-pot three-component (hydrazinobenzimidazoles, flavanone, and mercaptoacetic acid) synthesis of 3′-(2-aminobenzimidazolyl)-2-phenyl spiro[4H-benzopyran-4,2′- thiazolidin]-4-ones **4** was developed for the first time by conventional method as well as using ionic liquid, viz., 1-butyl-3-methyl-imidazolium hexafluorophosphate ([bmim] PF_6) as solvent. In the conventional method, first 2-phenyl-[4-benzimidazol-2-yl]benzopyran **3** was prepared by reacting **1** and **2** in ethanol with few drops of glacial acetic acid and then reacted with mercaptoacetic acid to give **4**. The compounds **4** were further acylated with trifluoroacetic anhydride to give **5** to enhance their biological activity[17] (Scheme 1).

RESULTS AND DISCUSSION

The syntheses of **4a–d** have been performed employing two methodologies.

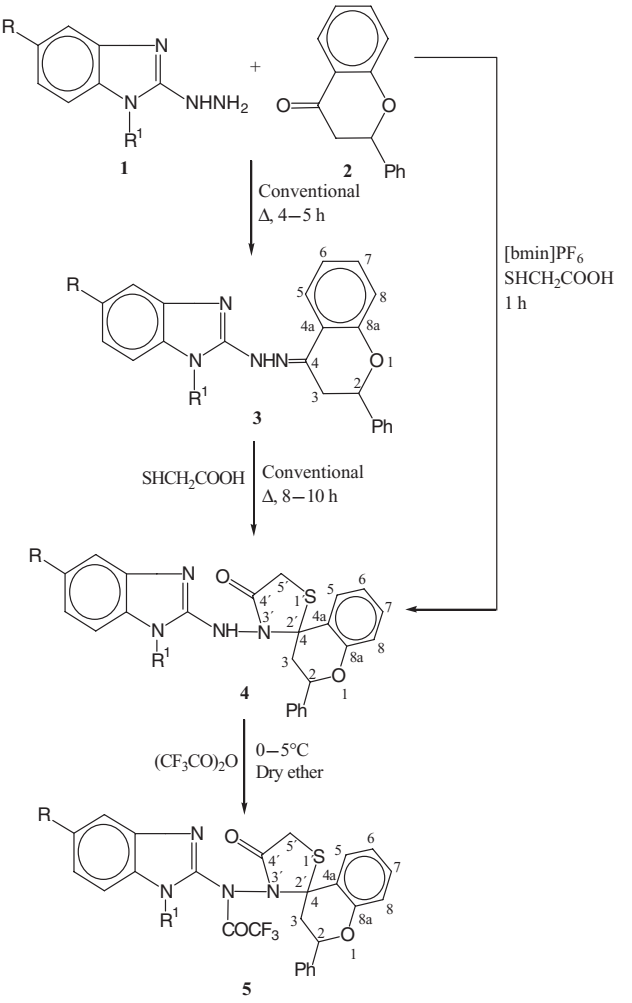
Conventional Method

Method A. In this method, 2-hydrazinobenzimidazoles, as synthesized following the method of Bednyagina et al.,[18] were first reacted with flavanone in ethanol with few drops of glacial acetic acid, for 5 h to give 2-phenyl-4-(benzimidazol-2-yl-hydrazono)benzopyran **3** in 65%–70% yield. The hydrazones **3** were refluxed with mercaptoacetic acid for 8–10 h in toluene to afford the thiazolidinone derivatives in 45%–55% yield.

Method B. Hydrazones synthesized in method A were not isolated, mercaptoacetic acid was added in situ, and heated further for 8–10 h at 70 °C–80 °C to give the thiazolidinone derivative in 55%–60% yield.

Ionic-Liquid-Mediated Synthesis

Ionic liquids are used as a green solvent because these are environmentally benign in comparison with the common solvents generally used, which can cause severe hazards such as benzene is carcinogenic and causes acute leukemia, aplastic anemia, and multiple myeloma.[19] The reactions in ionic liquid are easy to perform and need no special apparatus



Compound	R	R^1	Compound	R	R^1
3a	H	H	**4c**	H	CH_3
3b	CH_3	H	**4d**	H	CH_2Ph
3c	H	CH_3	**5a**	H	$COCF_3$
3d	H	CH_2Ph	**5b**	CH_3	$COCF_3$
4a	H	H	**5c**	H	CH_3
4b	CH_3	H	**5d**	H	CH_2Ph

or methodologies. Also, the ionic liquids can be recycled indefinitely and this leads to a reduction of the costs of the process. The ionic liquid [bmim] PF_6 is water stable and forms a triphasic mixture with water and heterocyclic compounds at the time of separation of product, which makes it useful for clean synthesis.

A one-pot synthesis of **4** has been accomplished by taking hydrazinobenzimidazoles, mercaptoacetic acid, and flavanone in an ionic liquid, viz., [bmim] PF_6.[20] The reaction has been carried out by heating at 60 °C–70 °C for 1 h that gives **4** in 85%–90% yield (Table 1).

Synthesis of Compounds 5a–d

Thiazolidinone derivatives **4**, prepared by either method, were reacted with trifluoroacetic anhydride taking advantage of its high reactivity where it replaced both >NH of compounds **4** to give $>NCOCF_3$ derivatives **5** in 90%–95% yield (Table 1).

Characterization

The structures of the compounds have been established from their spectral data. The IR spectrum of **3a** (where R and R^1 = H) showed characteristic bands at 3200, 3000, and 1620 cm^{-1} for >NHN=, >NH, and >C=N stretching vibrations respectively with a disappearance of the peak due to >C=O of flavanone at 1680 cm^{-1}. ^1H NMR shows peaks at δ 2.85 (dd, 1H, J = 16.8, 2.6 Hz) for H_{eq} and 3.11 (dd, 1H, J = 16.8, 12.9 Hz) for H_{axial} at C-3. Peaks at δ 5.57 (dd, 1H, J = 12.9, 2.6 Hz) appeared for the C-2 axial proton. A multiplet at δ 6.92–7.94 and singlets at δ 9.02 and 10.44 also appeared for aromatic, >NH, and >NHN=, respectively. In ^{13}C NMR, a peak appeared at δ 164.6 for >C=N while the peak due to flavanoyl >C=O at δ 180 disappeared. Further, the mass spectrum shows M^+ at *m*/*z* 354.

The formation of thiazolidinone **4** was confirmed with the appearance of peak due to >C=O at 1720 cm^{-1} in the IR spectra and a peak at δ 3.81 ppm for $–CH_2–$ of thiazolidinone ring in the ^1H NMR spectra. ^{13}C NMR spectra showed peaks at δ 46.0 and 182.6 ppm for $–\mathbf{C}H_2COS–$ and $–CH_2\mathbf{C}OS–$ respectively. Further, mass spectrum shows M^+ at *m*/*z* 428 (**4a**).

Acylation of **4** to $>NCOCF_3$ derivatives **5** was confirmed by disappearance of peak due to >NH in both IR and ^1H NMR spectra and appearance of peaks in ^{13}C NMR at δ 117.6 and 188.4 ppm due to $–\mathbf{C}F_3$ and $–\mathbf{C}OCF_3$ respectively. Further, mass spectrum shows M^+ at *m*/*z* 620 (**5a**) (Table 2).

ANTIMICROBIAL AND INSECTICIDAL ACTIVITY

Compounds **3**, **4**, and **5** have been screened for their antifungal activity against *Aspergillus niger*, *Aspgerillus flavus*, *Fusarium oxysporum*, and *Trichoderma viridae* at two different concentrations (100 and 500 ppm) and antibacterial activity against *Bacillus subtilis*, *Escherichia coli*, *Klebsiella pneumonia*, and *Staphylococcus aureus* (50 and 100 ppm) by filter paper disc diffusion plate method.[21,22] Standard antifungal drug, griseofulvin, and antibacterial drug, streptomycin, have also been screened under similar conditions for comparison (see Supplemental Materials, Tables S1–S3).

Examination of the results of the biological activity of compounds **3**, **4**, and **5** shows that compounds **3a**, **3b**, **4a**, **4b**, and **5a–d** are highly active against both selected bacteria

Table 1 The characterization data of the synthesized compounds

Compound no.	R	R^1	Reaction time (min)/yield (%)		Mp (°C) range	Molecular formula	% Carbon	% Hydrogen	% Nitrogen	% Sulfur
			IL	Δ			Calculated (found)	Calculated (found)	Calculated (found)	Calculated (found)
3a	H	H	—	300/70	192–193	$C_{22}H_{18}N_4O$	74.57 (74.51)	5.08 (5.12)	15.81 (15.90)	—
3b	CH_3	H	—	320/68	189–190	$C_{23}H_{20}N_4O$	75.00 (75.05)	5.43 (5.48)	15.21 (15.28)	—
3c	H	CH_3	—	310/66	178–180	$C_{23}H_{20}N_4O$	75.00 (75.04)	5.43 (5.40)	15.21 (15.18)	—
3d	H	CH_2Ph	—	330/65	184–185	$C_{29}H_{24}N_4O$	78.37 (78.41)	5.40 (5.46)	12.61 (12.65)	—
4a	H	H	60/90	570/60	160–162	$C_{24}H_{20}N_4O_2S$	67.28 (67.08)	4.67 (4.60)	13.08 (13.12)	7.47 (7.50)
4b	CH_3	H	60/89	540/59	140–142	$C_{25}H_{22}N_4O_2S$	67.87 (67.91)	4.97 (4.90)	12.66 (12.61)	7.23 (7.27)
4c	H	CH_3	60/85	600/58	120–121	$C_{25}H_{22}N_4O_2S$	67.87 (67.82)	4.97 (4.94)	12.66 (12.62)	7.23 (7.19)
4d	H	CH_2Ph	60/86	600/55	115–117	$C_{31}H_{26}N_4O_2S$	71.81 (71.85)	5.01 (5.05)	10.81 (10.86)	6.17 (6.21)
5a	H	H	—	15/95	196–198	$C_{28}H_{18}N_4O_4SF_6$	54.19 (54.21)	2.90 (2.94)	9.03 (9.08)	5.16 (5.20)
5b	CH_3	H	—	15/92	190–192	$C_{29}H_{20}N_4O_4SF_6$	54.88 (54.92)	3.15 (3.17)	8.83 (8.88)	5.04 (5.08)
5c	H	CH_3	—	15/91	194–195	$C_{29}H_{20}N_4O_4SF_6$	54.88 (54.93)	3.15 (3.18)	8.83 (8.87)	5.04 (5.09)
5d	H	CH_2Ph	—	15/90	200–201	$C_{35}H_{24}N_4O_4SF_6$	59.15 (59.19)	3.38 (3.41)	7.88 (7.82)	4.50 (4.55)

Note: IL, ionic liquid; Δ, conventional.

Table 2 Spectral data of the compounds **3a–d**, **4a–d**, and **5a–d**

Compound no.	IR (KBr) ν_{max} (cm^{-1})	^1H NMR ($CDCl_3$) δ (ppm)	^{13}C NMR ($CDCl_3$) δ (ppm)	MS *m/z* (M^+)
3a	3200 (>NHN=), 3000 (>NH), 1620 (C=N)	2.91 (dd, 1H, J = 16.8, 2.6 Hz, H_{eq}, C-3), 3.11 (dd, 1H, J = 16.8, 12.9 Hz, H_{axial}, C-3), 5.57 (dd, 1H, J = 12.9, 2.6 Hz, H_{axial}, C-2), 6.92–7.94 (m, 13H, aromatic), 9.02 (s, 1H, >NH), 10.44 (s, 1H, >NHN=)	44.6 (C-3), 79.5 (C-2), 115.4, 118.2, 120.7, 121.4, 122.8, 126.2, 127.0, 128.7, 136, 137.4, 139.6, 141.8, 161.7 (aromatic), 164.6 (C-4)	354
3b	3215 (>NHN=), 3060 (>NH), 1625 (C=N)	1.82 (s, 3H, $C\underline{H}_3$–Ph–), 2.87 (dd, 1H, J = 16.8, 2.8 Hz, H_{eq}, C-3), 3.09 (dd, 1H, J = 16.8, 12.8 Hz, H_{axial}, C-3), 5.53 (dd, 1H, J = 12.8, 2.8 Hz, H_{axial}, C-2), 6.78–7.91 (m, 12H, aromatic), 9.02 (s, 1H, >NH), 10.34 (s, 1H, >NHN=)	28 ($C\underline{H}_3$–C_6H_4–), 42.2 (C-3), 78.4 (C-2), 115.7, 118.2, 120.4, 121.6, 126.2, 126.8, 128.6, 135.8, 137.7, 138.5, 142.2, 161.2 (aromatic), 164.8 (C-4)	368
3c	3230 (>NHN=), 1620 (C=N)	2.75 (dd, 1H, J = 16.7, 2.7 Hz, H_{eq}, C-3), 3.09 (dd, 1H, J = 16.7, 12.9 Hz, H_{axial}, C-3), 3.52 (s, 3H, $>NCH_3$), 5.53 (dd, 1H, J = 12.9, 2.7 Hz, H_{axial}, C-2), 6.81–7.82 (m, 13H, aromatic), 10.26 (s, 1H, >NHN=)	33.8 ($>N–CH_3$), 44.9 (C-3), 79.8 (C-2), 115.8, 118, 120.6, 121.4, 122.8, 126.3, 126.9, 128.7, 136.1, 137.4, 138.9, 142.8, 161.4 (aromatic), 164.4 (C-4)	368
3d	3220 (>NHN=), 1630 (C=N)	2.95 (dd, 1H, J = 16.8, 3.2 Hz, H_{eq}, C-3), 3.09 (dd, 1H, J = 16.8, 12.8 Hz, H_{axial}, C-3), 3.32 (s, 3H, $–C\underline{H}_2$–Ph), 5.54 (dd, 1H, J = 12.8, 3.0 Hz, H_{axial}, C-2), 6.78–8.01 (m, 18H, aromatic), 10.24 (s, 1H, >NHN=)	43.8 ($–C\underline{H}_2$Ph), 44.9 (C-3), 78.8 (C-2), 109.4, 115.8, 118.3, 119.8, 120.6, 121.4, 122.8, 126, 126.3, 128.6, 128.9, 136.2, 137.4, 138.9, 143.02, 161, 161.8, 164.8 (C-4)	444
4a	3120 (>NH, br), 1720 ($–\underline{C}OCH_2S$–)	2.73 (dd, 1H, J = 16.7, 2.8 Hz, H_{eq}, C-3), 3.13 (dd, 1H, J = 16.7, 12.9 Hz, H_{axial}, C-3), 3.81 (s, 2H, $CO\underline{C}H_2S$), 5.57 (dd, 1H, J = 12.9, 2.8 Hz, H_{axial}, C-2), 6.82–7.89 (m, 13H, aromatic), 9.52 (s, 1H, >NH), 10.23 (s, 1H, >NHN)	44.2 (C-3), 46 (C-5′), 80.1 (C-2), 100.2, 115.6, 118, 120.8, 121.8, 123, 126, 127.1, 129, 136.2, 137.6, 138.2, 141.5, 162 (aromatic), 182.6 (C-4′)	428
4b	3100 (>NH, br), 1720 ($–\underline{C}OCH_2S$–)	1.82 (s, 3H, $–C\underline{H}_3$–Ph), 2.84 (dd, 1H, J = 16.9, 2.9 Hz, H_{eq}, C-3), 3.12 (dd, 1H, J = 16.9, 12.9 Hz, H_{axial}, C-3), 3.84 (s, 2H, $–COC\underline{H}_2S$), 5.57 (dd, 1H, J = 12.9, 2.9 Hz, H_{axial}, C-2), 6.81–7.89 (m, 13H, aromatic), 9.32 (s, 1H, >NH), 10.32 (s, 1H, >NHN)	28.4 ($C\underline{H}_3$–C_6H_4-), 44.3 (C-3), 46 (C-5′), 79.6 (C-2), 100.1, 115.8, 118.4, 120.6, 121.8, 122.7, 126, 127.2, 129.3, 136.2, 137.8, 138.2, 142.8, 162.3 (aromatic), 183.8 (C-4′)	442
4c	3240 (>NHN=), 1725 ($–\underline{C}OCH_2S$–)	2.55 (dd, 1H, J = 16.7, 2.6 Hz, H_{eq}, C-3), 2.87 (dd, 1H, J = 16.7, 12.8 Hz, H_{axial}, C-3), 3.21 (s, 3H, $>NCH_3$), 3.87 (s, 2H, $–COC\underline{H}_2S$), 5.54 (dd, 1H, J = 12.8, 2.6 Hz, H_{axial}, C-2), 6.69–8.01 (m, 13H, aromatic), 10.12 (s, 1H, >NHN)	33.6 ($>N–CH_3$), 44.6 (C-3), 46.2 (C-5′), 80.1 (C-2), 100.2, 115.6, 118.6, 120.4, 121.6, 122.8, 126, 127.5, 129.8, 136.4, 137.6, 138.6, 143.01, 162 (aromatic), 184.8 (C-4′)	442

(Continued on next page)

Table 2 Spectral data of the compounds **3a–d**, **4a–d**, and **5a–d** *(Continued)*

Compound no.	IR (KBr) ν_{max} (cm^{-1})	^{1}H NMR ($CDCl_3$) δ (ppm)	^{13}C NMR ($CDCl_3$) δ (ppm)	MS *m/z* (M^+)
4d	3205 (>NHN=), 1730 (–COCH$_2$S–)	2.90 (dd, 1H, J = 16.6, 2.6 Hz, H_{eq}, C-3), 3.12 (dd, 1H, J = 16.6, 12.7 Hz, H_{axial}, C-3), 3.38 (s, 2H, –CH$_2$Ph), 3.91 (s, 2H, COCH$_2$S), 5.56 (dd, 1H, J = 12.7, 2.6 Hz, H_{axial}, C-2), 6.68–8.15 (m, 18H, aromatic), 10.12 (s, 1H, >NHN)	43.8 (–CH$_2$Ph), 44.6 (C-3), 47 (C-5′), 78.5 (C-2), 100.4, 109.4, 115.6, 118.5, 119.5, 120.5, 121.6, 122.7, 126.3, 127.1, 128.2, 128.7, 136.5, 137.1, 138.7, 142.8, 161.02, 162 (aromatic), 187.2 (C-4′)	518
5a	1800 ($COCF_3$), 1720 (–COCH$_2$S–)	2.85 (dd, 1H, J = 16.9, 2.8 Hz, H_{eq}, C-3), 3.09 (dd, 1H, J = 16.9, 12.8 Hz, H_{axial}, C-3), 3.85 (s, 2H, COCH$_2$S), 5.58 (dd, 1H, J = 12.8, 2.8 Hz, H_{axial}, C-2), 6.84–7.95 (m, 13H, aromatic)	44.6 (C-3), 46.2 (C-5′), 79.8 (C-2), 100.1, 115.4, 117.6 (CF_3), 118.1, 120.5, 121.6, 123.2, 126.1, 127.3, 129.2, 136.5, 137.9, 138.3, 142.02, 161.8 (aromatic), 182.4 (C-4′), 188.4 (COCF$_3$)	620
5b	1820 ($COCF_3$), 1710 (–COCH$_2$S–)	1.89 (s, 3H, –CH$_3$–Ph), 2.70 (dd, 1H, J = 16.7, 2.9 Hz, H_{eq}, C-3), 3.06 (dd, 1H, J = 16.7, 12.9 Hz, H_{axial}, C-3), 3.86 (s, 2H, COCH$_2$S), 5.55 (dd, 1H, J = 12.9, 2.9 Hz, H_{axial}, C-2), 6.28–7.68 (m, 13H, aromatic)	28.5 (CH$_3$–C_6H_4–), 45.2 (C-3), 46.8 (C-5′), 78.5 (C-2), 100.2, 115.8, 117.5 (CF_3), 118, 120.8, 121.8, 122.9, 126.2, 127.8, 128.6, 136, 137.9, 138.6, 143.02, 162, 182.2 (C-4′), 188.4 (COCF$_3$)	634
5c	1810 ($COCF_3$), 1740 (–COCH$_2$S–)	2.86 (dd, 1H, J = 16.8, 2.6 Hz, H_{eq}, C-3), 3.13 (dd, 1H, J = 16.8, 12.9 Hz, H_{axial}, C-3), 3.28 (s, 1H, >NCH$_3$), 3.92 (s, 2H, COCH$_2$S), 5.59 (dd, 1H, J = 12.9, 2.6 Hz, H_{axial}, C-2), 6.78–7.89 (m, 13H, aromatic)	34.2 (>NCH$_3$), 44.9 (C-3), 46.3 (C-5′), 78.8 (C-2), 117.8 (CF_3), 100, 115.9, 118.2, 120.8, 121.3, 122, 126.2, 127.8, 130, 136.8, 137.9, 139, 143.5, 161.9 (aromatic), 185.1 (C-4′), 189.5 (COCF$_3$)	634
5d	1820 ($COCF_3$), 1720 (–COCH$_2$S–)	2.84 (dd, 1H, J = 16.9, 2.9 Hz, H_{eq}, C-3), 3.24 (dd, 1H, J = 16.9, 12.8 Hz, H_{axial}, C-3), 3.40 (s, 2H, –CH$_2$Ph), 4.02 (s, 2H, –COCH$_2$S), 5.55 (dd, 1H, J = 12.8, 2.9 Hz, H_{axial}, C-2), 6.68–7.99 (m, 18H, aromatic)	42.5 (–CH$_2$Ph), 44.8 (C-3), 47.2 (C-5′), 79.5 (C-2), 117.2 (CF_3), 100.1, 109.8, 115.2, 118.9, 119.6, 120.8, 121.2, 122.9, 126, 126.9, 128.0, 128.8, 136.7, 137.2, 138.8, 143.6, 161, 162.2 (aromatic), 185.5 (C-4′), 190.1 (COCF$_3$)	710

and fungi (having zone of inhibition 19–24 mm) and the rest of the compounds have shown good to moderate activity (having zone of inhibition 11–18 mm).

For insecticidal activity,[23,24] *Periplaneta americana* was taken and the knock down (KD) value of synthesized heterocyclic derivatives was compared with the control drug (Cypermethrin).

It was observed that compounds having $>COCF_3$ group exhibited better insecticidal activity (KD value is 3–4 min) in comparison with standard drug (KD value is 5–7 min). The rest of the compounds have significant to moderate activity (KD value is 7–10 min).

Thus, it is concluded that the synthesized compounds are capable to act as good antimicrobial agents and insecticidals. They may prove to be helpful to render the services to the humanity.

CONCLUSION

The one-pot, multicomponent condensation of 2-hydrazinobenzimidazoles **1**, carbonyl compound, i.e., flavanone **2**, and mercaptoacetic acid afforded the product, thiazolidinone **4**, which were prepared by adopting two different methodologies: (i) conventional method: yield 55%–60%, takes long time (8–10 h), and use of solvent is hazardous and (ii) using ionic liquid: yield 85%–90%, shorter reaction time (1 h), and economical as ionic liquid recycled for further use.

Therefore, the environmentally benign green synthesis, using ionic liquid, is the better way for this synthesis.

Further, trifluoroacetic anhydride is a very reactive compound and used for acylation reaction, as it replaces both the >NH of compound **4** to give **5** with enhanced antimicrobial and insecticidal activity.[1]

EXPERIMENTAL

The uncorrected melting points were taken in open glass capillaries using a Gallenkamp melting point apparatus. The IR spectra were recorded on a Nicolet Magna IR spectrometer Model 550 in KBr pellets and band positions are reported in wave numbers (cm^{-1}). ^1H NMR and ^{13}C NMR spectra were recorded on a JEOL 300 MHz using $CDCl_3$ at 300.15 and 74.46 MHz, respectively, and chemical shifts (δ) are given in ppm. TMS was used as internal reference. The mass spectra were recorded on a JEOL SX 12 (FAB). The mass spectra and elemental analyses were performed at the Central Drug Research Institute, Lucknow, India, while other spectra in the Department. Solvents were purified by standard procedures.[25,26] Commercially available (ACROS) flavanone was used for the reactions.

Synthesis of Compounds 4a–d by Conventional Method

Method A. *2-Phenyl-4-[Benzimidazol-2-Yl-Hydrazono]Benzopyran **3a***. A mixture of 2-hydrazinobenzimidazole **1** (10 mmol) and flavanone **2** (10 mmol) in equimolar amount was dissolved in ethanol (50 mL), and then a few drops of acetic acid were added and refluxed for 5 h. On cooling, crystals appeared that were filtered and washed with water. It was further recrystallized from ethanol to give **3a** in 70% yield; mp 192 °C–193 °C.

Compounds **3b–d** have been prepared similarly and their characterization and spectral data are recorded in Tables 1 and 2, respectively.

3′-(2-Aminobenzimidazolyl)-2-Phenyl Spiro[4H-Benzopyran-4-2′-Thiazolidin]-4-One ***4a***. Hydrazone **3a** (5 mmol) in dry toluene (10 mL) was taken in a round bottom flask and mercaptoacetic acid (10 mmol) was added and refluxed for 8–10 h using a Dean-Stark apparatus to remove the water formed azeotropically. The solvent was then evaporated in vacuum and the residual solid mass was treated with water and neutralized with 10% sodium bicarbonate solution. The solid thus obtained was filtered. It was further purified by recrystallization from ethanol to give **4a** in 55% yield; mp 160 °C–162 °C.

Compounds **4b–d** have been prepared similarly and their characterization and spectral data are recorded in Tables 1 and 2, respectively.

Method B. To the hydrazone synthesized by method A, mercaptoacetic acid (10 mmol) was added in situ, refluxed further for 8–10 h [as checked by thin layer chromatography (TLC)], and worked up as earlier in method A to give **4a** in 55%–60% yield.

Compounds **4b–d** have been prepared similarly and their characterization and spectral data are the same as in method A.

Ionic-Liquid-Mediated One-Pot Synthesis of 4a–d

A mixture of 2-hydrazinobenzimidazole (3 mmol), flavanone (3 mmol), mercaptoacetic acid (6 mmol), and ionic liquid [bmim] PF_6 (5 mL) was taken in a round bottom flask. It was heated at 60 °C–70 °C for 1 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the contents were neutralized by 10% aqueous sodium bicarbonate solution and extraction was carried out with ethyl acetate (three times, 10 mL). The solvent was removed under reduced pressure. The pasty mass thus obtained was extracted with diethyl ether (three times, 10 mL), dried over anhydrous sodium sulfate, and ether distilled off. The product so obtained was purified by crystallization with ethanol/column chromatography to give **4a–d** in 85%–90% yield. The ionic liquid layer was washed with water (three times, 5 mL) and kept for 2 h at 80 °C–85 °C under reduced pressure. It was recycled for use in further synthesis.

The characterization and analytical data are identical to those prepared by the conventional methodology.

3′-(1-Trifluoroacetyl-2-Trifluoroacetylamino Benzimidazolyl)-2-Phenyl Spiro[4H-Benzopyran-4,2′-Thiazolidin]-4-One 5a

3′-2(aminobenzimidazolyl)-2-phenyl spiro[4H-benzopyran-4,2′-thiazolidin]-4-one **4a** (2 mmol) was dissolved in dry ether (10 mL) and trifluoroacetic anhydride (4 mmol) in dry ether (5 mL) was added with stirring at 0 °C–5 °C. It was further stirred for 15 min. The ether was distilled under reduced pressure and water (10 mL) was added to it. The solid obtained was filtered after some time and recrystallized from ethanol to give **5a**, yield 95%; mp 196 °C–198 °C.

Compounds **5b–d** have been prepared similarly and their characterization and spectral data are recorded in Tables 1 and 2 respectively.

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