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An ionic liquid mediated one-pot synthesis of substituted thiazolidinones and benzimidazoles

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ABSTRACT

An expeditious one-pot synthesis of 2,3-diaryl/2-aryl-3-heteroaryl-1,3-thiazolidin-4-ones and 1-aryl-1*H*,3*H*-thiazolo[3,4-*a*]benzimidazoles have been accomplished by condensing hetero/aromatic amine, 2-mercaptoacetic acid, aromatic aldehyde and 1,2-phenylenediamine, 2-mercaptoacetic acid and aromatic aldehyde, respectively, in ionic liquids, viz, 1-butyl-3-methyl-imidazolium tetrafluoroborate and 1-methoxyethyl-3-methylimidazolium trifluoroacetate.

The molecular modelling and structural activity relationship investigations[1–4], on the development of new non-nucleoside reverse transcriptase inhibitors suggest that 2,3-diaryl-1,3-thiazolidin-4-ones, **1** and 1*H*, 3*H*-thiazolo[3,4-*a*]benzimidazoles, **2** are important class of heterocycles, as potential HIV-1RT inhibitors.

Benzimidazoles have been reported to possess important pharmacological activities such as *anti*-microbial,[5] *anti*-fungal,[6] *anti*-parkinson,[7] *anti*-cancer,[8] and *anti*-biotic,[9]. These derivatives have also been intelligently exploited as ligands for the asymmetric transformations.[10] The usual methods for their synthesis involve condensation of carboxylic acids,[11] orthoesters,[12] amides,[13] nitriles,[14] aldehydes[15] and esters with amino aromatics. The synthesis of benzoxazoles, benzthiazoles and benzimidazoles have also been carried out by condensation of substituted aromatic amines and aromatic carboxylic acid in 1-butyl-3-methylimidazolium tetrafluoroborate.[16] A microwave assisted synthesis of compounds **1** and **2** have been reported in toluene as solvent.[17] Except ionic liquid promoted synthesis described above, most of the synthetic procedures are associated with harsh reaction conditions, poor yields and environmentally black-listed solvents. In view of the diversified applications described above, we hereby report the first effective one-pot three component synthesis of thiazolidinones and benzimidazoles. The syntheses were performed in ecologically friendly conditions with the use of ionic liquids[18] and afforded the desired products in high yield.

The one-pot regioselective synthesis of compounds **1a–i** and **2a–e** have been performed by taking heteroaromatic amine/1,2-phenylenediamine with 2-mercaptoacetic acid and an aromatic aldehyde in ionic liquids, viz 1-butyl-3-methylimidazolium tetrafluroborate [BMIM]BF_4 and 1-methoxyethyl-3-methylimidazolium trifluoroacetate [MOEMIM]TFA. The reaction has been carried out by stirring the reaction mixture under nitrogen atmosphere at 80 ± 2 °C.

The formation of compounds **1a–i**[19] may be explained as follows (Scheme 1). The yield of products **1a–i** has been presented in Table 1.

The observation of these data suggests that the electron releasing group at hetero/aromatic amine and electron withdrawing group on ketone favours the reaction. All these compounds were characterized unambiguously by IR, ^{1}H NMR, ^{13}C NMR and elemental analyses.[20]

Similarly, we have carried out the synthesis of compounds **2a–e**[21] starting from 1,2-phenylenediamines as shown below (Scheme 2). The yield of the products is presented in Table 2.

These products **2a–e** were characterized by IR, ^{1}H NMR, ^{13}C NMR and elemental analyses.[22]

The data presented in Table 2 suggest that the electron releasing substituents on 1,2-phenylenediamine favours the formation of compound **2a–e**.

The observation of yields of compounds **1a–i** and **2a–e** (Table 1 and Table 2) reveal that [MOEMIM]TFA is a better reaction media in comparison to [BMIM]BF_4. This may be attributed due to the ability of [MOEMIM]TFA to hydrogen bond with aromatic/heterocyclic/1,2-phenylenediamine.

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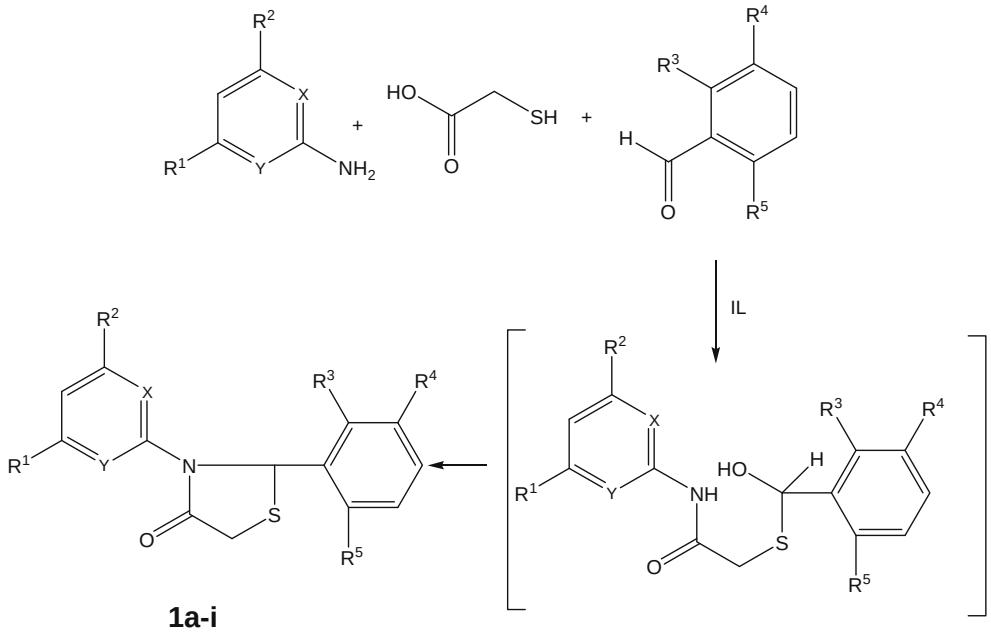


Scheme 1.

Table 1
Yield of the compounds **1a–i**

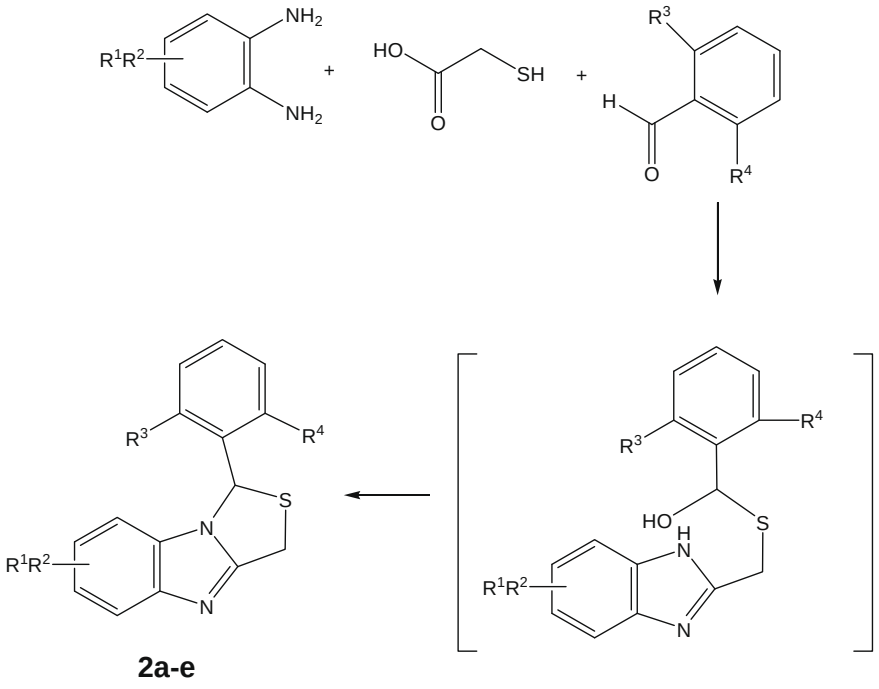
Product	X	Y	R^1	R^2	R^3	R^4	R^5	Yield[a] (%)/time (min)	
								$[BMIM]BF_4$	[MOEMIM]TFA
1a	C	C	H	H	H	H	Cl	73/100	80/90
1b	C	C	Me	H	H	H	Cl	78/100	86/90
1c	C	C	Me	H	Cl	H	Cl	82/100	90/90
1d	C	C	OMe	H	H	H	F	80/90	85/80
1e	C	C	OMe	H	F	H	F	88/90	92/80
1f	N	C	Cl	H	F	H	F	75/100	80/90
1g	N	C	Br	H	F	H	F	78/100	85/90
1h	N	N	Me	H	Cl	Me	F	81/90	86/80
1i	N	N	Me	Me	Cl	H	Cl	82/100	90/90

[a] Isolated yield after purification.

We have studied the recyclability of the regenerated ionic liquids[19] for the products **1e** and **2e**. The yields of the product in two cycles are presented in Table 3.

From Table 3, it is clear that the yield of the products **1e** and **2e** decrease in various cycles, yet the IL can be reused with significant success. Hence, this procedure is advantageous over conventional reaction media.

In conclusion, an one-pot regioselective synthesis of compounds **1** and **2** has been developed at 80 ± 2 °C in ionic liquid, as reaction medium and promoter. The absence of catalyst and recyclability of IL, make this procedure, cleaner and promising for scale up.



Scheme 2.

Table 2
Yield of the compounds **2a–e**

Product	R^1	R^2	R^3	R^4	Yield[a] (%)/time (min)	
					[BMIM]BF_4	[MOEMIM]TFA
2a	H	H	Cl	Cl	72/90	80/80
2b	H	H	F	F	80/90	87/80
2c	5-Me	H	F	F	85/90	92/80
2d	6-Me	7-Me	F	F	90/90	94/70
2e	8-Me	H	F	F	86/90	90/80

[a] Isolated yield after purification.

Table 3
Recyclability data for product **1e** and **2e**

Product	Cycle	Yield (%)/time (min)	
		[BMIM]BF_4	[MOEMIM]TFA
1e	0	88/90	92/80
1e	1	85/90	87/80
1e	2	81/90	83/80
2e	0	90/90	94/70
2e	1	85/90	90/70
2e	2	81/90	85/70

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19. *Typical experimental procedure for synthesis of* **1a–i:** A mixture of heteroaromatic/aromatic amine (3 mmol), aromatic aldehyde (3 mmol) and 2-mercaptoacetic acid (6 mmol) and ionic liquid (5 mL) was taken in a round bottom flask with provision to carry out the reaction under nitrogen atmosphere. The contents of the flask were stirred magnetically at 80 ± 2 °C. The progress of the reaction was monitored on TLC plate (Merck Silica gel 60 F_{254} plates) in petroleum ether-ethyl acetate (8:2) and visualization was accomplished in a iodine chamber/UV-light. After completion of the reaction, the contents were neutralized by 10% aqueous sodium bicarbonate solution and extraction was carried out with ethyl acetate (3 × 10 mL). The solvent was removed under reduced pressure (5 mm of Hg). The pasty mass, thus obtained, was extracted with diethyl ether (3 × 10 mL), dried over anhydrous sodium sulphate and ether was distilled. The product, so obtained, was purified by crystallization with ethanol/column chromatography (Merck Silica gel 60–120 mesh). The ionic liquid layer was washed with water (3 × 5 mL) and kept for 2 h at 80–85 °C under reduced pressure (5 mm of Hg). This ionic liquid was used in recycling.
20. Details of analytical data of compound **1a–i** are presented below.
Compound **1a.** 2-(2′-Chlorophenyl)-3-(phenyl)-1,3-thiazolidin-4-one: white solid, mp 117–118 °C, characteristic IR (KBr pellet, cm^{-1})1670,740. ^1H NMR (300 MHz, $CDCl_3$) δ 3.80 (d, 1H, $^2J_{HH}$ = 15 Hz, 5-H_A), 4.04 (dd, 1H, $^4J_{HH}$ = 2.0 Hz and $^2J_{HH}$ = 15.2 Hz 5-H_B), 6.90–7.31 (m, 10H, Ar–H and 2-H). ^{13}C NMR (75 MHz, $CDCl_3$) 166.10, 165.20, 140.10, 138.20, 136.10, 134.20, 130.20, 128.10, 127.40, 126.30, 121.0, 120.10, 119.50, 118.70, 48.50. Anal. Calcd for $C_{15}H_{12}ClNOS$: C, 62.14; H, 4.17, N, 4.83. Found: C, 62.26; H, 4.25; N, 4.92.
Compound **1b.** 2-(2′-Chlorophenyl)-3-(3″-methylphenyl)-1,3-thiazolidin-4-one: white solid, mp 127–128 °C, characteristic IR (KBr pellet, cm^{-1}) 1675, 745. ^1H NMR (300 MHz, $CDCl_3$) δ 2.60(s, 3H, CH_3), 3.95(d, 1H, $^2J_{HH}$ = 15 Hz, 5-H_A), 4.08 (dd, 1H, $^4J_{HH}$ = 2–1 Hz and $^2J_{HH}$ = 15.5 Hz, 5-H_B), 6.92–7.26 (m, 9H, Ar–H and 2-H). ^{13}CNMR (75 MHz, $CDCl_3$) δ 166.70, 165.20, 139.90, 137.24, 134.60, 130.10, 128.80, 128.30, 126.80, 125.10, 124.24, 122.72, 120.10, 118.10, 80.20, 49.10. Anal. Calcd for $C_{16}H_{14}Cl$ NOS: C, 63.22; H, 4.64; N, 4.61. Found: C, 63.15; H, 4.52; N, 4.51.
Compound **1c**. 2-(2′,6′-Dichlorophenyl)-3-(3″-methylphenyl)-1,3-thiazolidin-4-one: white solid, mp 132–133 °C (lit.[17], 129–132 °C), characteristic IR (KBr pellet, cm^{-1}) 1675, 750. ^1H NMR (300 MHz, $CDCl_3$) δ 2.75 (s, 3H, CH_3), 3.98 (d, 1H, $^2J_{HH}$ = 15.5 Hz, 5-H_A), 4.10 (dd, 1H, $^4J_{HH}$ = 2.1 Hz and $^2J_{HH}$ = 15.5 Hz, 5-H_B), 6.98–7.30 (m, 8H, Ar–H and 2-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.10, 168.20, 150.10, 147.20, 142.10, 140.20, 138.30, 137.20, 136.20, 130.34, 128.28, 127.20, 122.32, 120.14, 86.10, 48.90. Anal. Calcd for $C_{16}H_{13}Cl_2$ NOS: C, 56.77; H, 3.87; N, 4.14. Found: C, 56.60; H, 4.02; N, 4.25.
Compound **1d.** 2-(2′-Fluorophenyl)-3-(3″-methoxyphenyl)-1,3-thiazolidin-4-one: white solid, mp 121–122 °C, characteristic IR (KBr pellet, cm^{-1}), 1680, 750. ^1H NMR δ 3.82 (s, 3H, -OCH_3); 3.95 (d, 1H, $^2J_{HH}$ = 15.5 Hz, 5-H_A), 4.16 (dd, 1H, $^4J_{HH}$ = 2.5 Hz and $^2J_{HH}$ = 15.5 Hz, 5-H_B), 6.99–7.38 (m, 9H, Ar–H and 2-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.20, 166.20, 158.10, 154.24, 150.30, 146.10, 144.20, 139.10, 138.10, 136.10, 134.10, 128.10, 122.20, 85.20, 84.10, 82.10. Anal. Calcd for $C_{16}H_{14}FNO_2S$: C, 63.33; H, 4.65; N, 4.61. Found: C, 63.20; H, 4.55; N, 4.52.
Compound **1e**. 2-(2′,6′-Difluorophenyl)-3-(3″-methoxyphenyl)-1,3-thiazolidin-4-one: White solid, mp 100–101 °C, (lit.[17], 100–102 °C), Characteristic IR (KBr pellet, cm^{-1}), 1690, 1010. ^1H NMR (300 MHz, $CDCl_3$) δ 3.75 (s, 3H, -OCH_3), 3.89 (d, 1H, $^2J_{HH}$ = 15.5 Hz, 5-H_A), 4.15 (dd, 1H, $^4J_{HH}$ = 2.1 Hz and $^2J_{HH}$ = 15.5 Hz, 5-H_B), 6.58 (d, 1H, $^4J_{HH}$ = 2.0 Hz,2-H), 6.75–7.25 (m, 7H, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.40, 169.30, 162.40, 158.10, 156.20, 153.10, 148.40, 138.30, 135.40, 128.10, 127.10, 126.10, 120.30, 82.48, 79.10, 74.50, Anal. Calcd for $C_{16}H_{13}F_2NO_2S$: C, 59.78; H, 4.07; N, 4.36. Found: C, 59.87; H, 3.93; N, 4.27.
Compound **1f**. 3-(4′-Chloropyridin-2′-yl)-2-(2″,6″-difluorophenyl)-1,3-thiazolidin-4-one: white solid, mp 128–129 °C, characteristic IR (KBr pellet, cm^{-1}), 1700, 1020. ^1H NMR (300 MHz, $CDCl_3$) δ 3.80 (d, 1H, $^2J_{HH}$ = 15.5 Hz, 5-H_A), 4.26 (dd, 1H, $^4J_{HH}$ = 1.4 Hz and $^2J_{HH}$ = 16.0 Hz, 5-H_B), 6.86 (dd, 1H, $^3J_{HH}$ = 7.9 Hz and $^3J_{HH}$ = 8.20 Hz 4″-H), 7.06 (d, 1H, $^4J_{HH}$ = 1.4 Hz, 2-H), 7.18–7.28 (m, 2H, 3″-H and 5′-H), 7.50 (m, 2H, 3′-H and 5′-H), 8.30 (d,1H, $^3J_{HH}$ = 8.1 Hz, 6′-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.18, 170.60, 168.20, 165.25, 160.15, 150.10, 146.20, 141.20, 140.10, 138.10, 136.10, 128.10, 78.10, 87.10. Anal. Calcd for $C_{14}H_9ClF_2N_2OS$: C, 51.43; H, 2.77; N, 8.57. Found: C, 51.34; H, 2.66; N, 8.43.
Compound **1g.** 3-(4′-Bromopyridin-2′-yl)-2-(2″,6″-difluorophenyl)-1,3-thiazolidin-4-one: pale yellow solid, mp 130–131 °C, (lit.[1] 126–130 °C), characteristic IR (KBr pellet, cm^{-1}) 1710, 1570, 1010. ^1H NMR (300 MHz, $CDCl_3$) δ 3.86 (d, 1H, $^2J_{HH}$ = 16.0 Hz, 5-H_A), 4.25 (dd, 1H, $^4J_{HH}$ = 1.5 Hz and $^2J_{HH}$ = 16.0 Hz, 5-H_B), 6.86 (dd, 1H, $^3J_{HH}$ = 8.0 Hz and $^3J_{HH}$ = 8.2 Hz, 4″-H), 7.10 (d, 1H, $^4J_{HH}$ = 1.4 Hz, 2-H), 7.18–7.28 (m, 2H, 3″-H and 5″-H), 7.55 (m, 2H, 3′-H and 5′-H), 8.30 (d,1H, $^3J_{HH}$ = 8.1 Hz, 6′-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.10, 166.10, 160.18, 158.18, 151.15, 146.18, 142.35, 139.20, 136.10, 133.15, 132.15, 128.25, 86.10, 78.10. Anal. Calcd for $C_{14}H_9BrF_2N_2OS$: C, 45.27; H, 2.44; N, 7.54. Found: C, 45.21, H, 2.34; N, 7.43.
Compound **1h.** 2-(2′-Chloro-6′-fluoro-3′-methylphenyl)-3-(4″-methylpyrimidin-2″-yl)-1,3-thiazolidin-4-one: White solid, mp 125–126 °C, (lit.[17] 126 °C); Characteristic IR (KBr pellet, cm^{-1}) 1690, 1565,1030. ^1H NMR (300 MHz, $CDCl_3$) δ 2.18 (s, 3H, CH_3) and 2.40 (s, 3H, CH_3), 3.90 (d, 1H, $^2J_{HH}$ = 15.8 Hz, 5-H_A), 4.25 (dd, 1H, $^4J_{HH}$ = 2.0 Hz and $^2J_{HH}$ = 15.7 Hz, 5-H_B), 6.88–8.54 (m, 5H, Ar–H, 4′,5′, 5″,6″). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.10, 172.20, 166.30, 162.10, 157.15, 152.20, 148.15, 142.10, 136.15, 132.15, 128.25, 86.10, 76.10, 49.10, 48.20. Anal. Calcd for $C_{15}H_{13}ClFN_3OS$: C,53.30; H, 3.88; N, 12.44. Found: C, 53.26; H, 3.72; N, 12.37.
Compound **1i**. 2-(2′,6′-Dichlorophenyl)-3-(4″,6″-dimethylpyrimidin-2″-yl)-1,3-thiazolidin-4-one: white solid, mp 201–202 °C, (lit.[17] 200–202 °C), characteristic IR (KBr pellet, cm^{-1}) 1710, 810,720. ^1H NMR (300 MHz, $CDCl_3$) δ 2.39 (s, 6H, -CH_3), 3.92 (d, 1H, $^2J_{HH}$ = 15.8 Hz, 5-H_A), 4.20 (dd, 1H, $^4J_{HH}$ = 1.9 Hz and $^2J_{HH}$ = 15.8 Hz, 5-H_B), 6.70–7.30 (m, 4H, 3′,4′, 5′ and 5″), 7.50 (d, 1H, $^4J_{HH}$ = 1.9 Hz, 2-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.10, 152.10, 146.10, 143.20, 142.10, 138.10, 137.20, 136.10, 132.10, 86.10, 78.20, 66.20, 65.10, 62.10, 60.17. Anal. Calcd for $C_{15}H_{13}Cl_2N_3OS$: C, 50.82; H, 3.69; N, 11.86. Found: C, 50.72; H, 3.60; N, 11.77.

21. Typical experimental procedure for synthesis of 1-aryl-1*H*,3*H*-thiazolo[3,4-*a*]benzimidazoles **(2a–e)**: A mixture of 1,2-phenylenediamine (3 mmol), aromatic aldehyde (3 mmol), 2-mercaptoacetic acid (6 mmol) was taken in round bottom flask. The reaction was performed in the same way as described above.
22. Details of analytical data of compound **2a–e** are given below.

Compound **2a.** 1-(2′,6′-Dichlorophenyl)-1*H*,3*H*-thiazolo[3,4-*a*]benzimidazole: pale yellow, mp 132–134 °C, characteristic IR (KBr pellet, cm^{-1}) 1610, 780, 710. ^1H NMR (300 MHz, $CDCl_3$) δ 4.26 (d, 1H, $^2J_{HH}$ = 14.3 Hz, 3-H_A), 4.52 (dd, 1H, $^4J_{HH}$ = 1.8 Hz and $^2J_{HH}$ = 14.4 Hz, 3-H_B), 6.70–7.72 (m, 8H, Ar–H and 1-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.10, 162.10, 160.10, 158.20, 156.10, 152.30, 149.40, 138.10, 136.10, 135.20, 126.30, 125.80, 123.30, 76.10, 72.20. Anal. Calcd for $C_{15}H_{10}Cl_2N_2S$: C, 56.05; H, 3.13; N, 8.72. Found: C, 55.92; H, 3.08; N, 8.61.

Compound **2b.** 1-(2′,6′-Difluorophenyl)-1*H*,3*H*-thiazolo[3,4-*a*]benzimidazole: pale yellow, mp 141–142 °C, characteristic IR (KBr pellet, cm^{-1}) 1615, 1030. ^1H NMR (300 MHz, $CDCl_3$) δ 4.30 (d, 1H, $^2J_{HH}$ = 14.5 Hz, 3-H_A), 4.58 (dd, 1H, $^4J_{HH}$ = 1.8 Hz and $^2J_{HH}$ = 14.5 Hz, 3-H_B), 6.75–7.76 (m, 8H, Ar–H and 1-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.10, 166.30, 161.25, 160.11, 158.11, 140.12, 137.10, 136.50, 128.50, 122.10, 120.30, 116.10, 90.15, 82.10, 72.15. Anal. Calcd for $C_{15}H_{10}F_2N_2S$: C, 62.46; H, 3.49; N, 9.71. Found: C, 62.38; H, 3.39; N, 9.69.

Compound **2c**. 1-(2′,6′-Difulorophenyl)-5-methyl-1*H*,3*H*-thiazolo[3,4-*a*]benzimidazole: White solid, mp 159–161 °C, (lit.[17] 159–161 °C), Characteristic IR (KBr pellet, cm^{-1}) 1630, 1030, 805. ^1H NMR (300 MHz, $CDCl_3$) δ 2.68 (s, 3H, CH_3-5), 4.35 (d, 1H, $^2J_{HH}$ = 14.2 Hz, 3-H_A), 4.69 (dd, 1H, $^4J_{HH}$ = 1.9 Hz and $^2J_{HH}$ = 14.2 Hz, 3-H_B), 6.78–7.36 (m, 7H, Ar–H and 1-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.10, 160.15, 157.15, 155.21, 151.15, 149.10, 146.20, 145.10, 143.20, 139.15, 128.15, 122.85, 111.15, 95.10, 86.15, 66.10. Anal. Calcd for $C_{16}H_{12}F_2N_2S$: C, 63.57; H, 4.00; N, 9.26. Found: C, 63.46; H, 3.89; N, 9.15.

Compound **2d.** 1-(2′,6′-Difluorophenyl)-6,7-dimethyl-1*H*,3*H*-thiazolo[3,4-*a*]-benzimidazole: light yellow solid, mp 177–179 °C, (lit.[17] 178–179 °C), characteristic IR (KBr pellet, cm^{-1}) 1630, 1025, 810. ^1H NMR (300 MHz, $CDCl_3$) δ 2.26 (s, 3H, 7-CH_3), 2.34 (s, 3H, 6-CH_3), 4.42 (d, 1H, $^2J_{HH}$ = 14.5 Hz, 3-H_A), 4.69 (dd, 1H, $^4J_{HH}$ = 2.1 Hz and $^2J_{HH}$ = 14.5 Hz, 3-H_B), 6.76–7.73(m, 6H, Ar–H and 1-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.15, 166.10, 162.15, 155.15, 147.15, 145.50, 140.10, 138.11, 133.25, 130.55, 128.55, 122.15, 124.15, 94.15, 88.20, 56.15, 49.55. Anal. Calcd for $C_{17}H_{14}F_2N_2S$: C, 64.52; H, 4.46; N, 8.85. Found: C, 64.45; H, 4.38; N, 8.78.

Compound **2e.** 1-(2′,6′-difluorophenyl)-8-methyl-1*H*,3*H*-thiazolo[3,4-*a*]benz-imidazole: white solid, mp 149–150 °C, (lit[17] 149–150 °C), characteristic IR (KBr pellet, cm^{-1}) 1625, 1040, 815. ^1H NMR (300 MHz, $CDCl_3$) δ 2.32 (s, 3H, 8-CH_3), 4.30 (d, 1H, $^2J_{HH}$ = 14.2 Hz, 3-H_A), 4.61(dd, 1H, $^4J_{HH}$ = 1.7 Hz and $^2J_{HH}$ = 14.2 Hz, 3-H_B), 6.90–7.59 (m, 7H, Ar–H and 1-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.10, 160.11, 157.15, 155.28, 150.12, 149.11, 147.25, 143.10, 140.10, 136.10, 133.28, 127.10, 110.25, 93.15, 78.10, 49.10. Anal. Calcd for $C_{16}H_{12}N_2F_2S$: C, 63.5; H, 4.00; N, 9.26. Found: C, 63.40; H, 3.91; N, 9.18.