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Use of SO_3H-functionalized halogenfree ionic liquid ($[MIM(CH_2)_4SO_3H][HSO_4]$) as efficient promoter for the synthesis of structurally diverse spiroheterocycles

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ABSTRACT

Structurally diverse spiroheterocycles with fused systems incorporating medicinally privileged systems have been synthesized by an efficient and convenient synthetic method involving four component domino reaction of 2-aminobenzothiazoles with isatin and cyclic β-diketones using SO_3H-functionlized halogenfree ionic liquid ($[MIM(CH_2)_4SO_3H][HSO_4]$) in aqueous medium.

The development of synthetic methodologies, in view of sustainable chemistry,[1] giving selective access to elaborated scaffolds combined with molecular diversity[2] and eco-compatibility[3] has been a great challenge for chemical and medicinal research. Multicomponent reactions have emerged as a highly efficient and diversity oriented synthetic methodology because of their operational simplicity and ability to generate expediently only one product from three or more components in a single synthetic operation with high atomeconomy[4] and multiple bond-forming efficiency.[5] In recent years, ionic liquids (RTIL) have been successfully used not only as environmentally benign solvents, but also as catalysts due to their special features such as relatively low vapor pressure, reusability, high thermal and chemical stabilities, and their ability to dissolve a range of organic and inorganic compounds.[6] Therefore, the combination of synthetic potentialities of multicomponent reactions with ionic liquids has resulted in the development of promising eco-compatible synthetic methodologies. But, in view of biodegradability, the ionic liquids with halogen containing anions (for example, PF_6^-, BF_4^-, CF_3OO^-, $CF_3SO_3^-$, etc.) limit to some extent their greenness.[7] In continuation of our research program on the synthesis of therapeutically interesting heterocycles,[8–13] in the present work, we have combined synthetic potentialities of four component domino reactions with the dual properties of halogenfree SO_3H-functionalized ionic liquid as environmentally benign solvent and recyclable catalyst to prepare structurally diverse spiroheterocycles because of their unique structural features and highly pronounced pharmaceutical activities.[14] Moreover, the spirooxindole system spiroannulated with heterocyclic systems is present in a number of bioactive natural products.[15] Among nitrogen containing heterocyclic scaffolds, quinolines are privileged structures and are also considered important in drug development.[16] Pyranoquinolines exhibit wide range of biological activities such as psychotropic, antiallergic, anti-inflammatory, and estrogenic activities, while chromenoquinolines act as potent hPR agonists and estrogen receptor β-selective ligands.[17] Pyridopyrimidines have also been reported to exhibit wide range of pharmacological activities.[18] As a privileged structural fragment, benzothiazoles are the important key building blocks in drug discovery.[19] The hybrid pharmacophores of isatin-benzothiazoles have been reported to exhibit anti-breast cancer activity.[20]

In the present work, we have used dual-functionalized Brønsted acidic imidazolium salt (B) as a Brønsted acid-surfactant and as catalyst for the synthesis of spiroheterocycles in aqueous medium. The synthesis[22] of the Brønsted acidic imidazolium salt (B) is presented in Scheme 1.

First, the optimization of the reaction conditions was undertaken by investigating the effects of various ionic liquid/water systems on the reaction time and the product yield on a multicomponent domino reaction of 2-amino-4-methylbenzothiazole with isatin, dimedone, and 1,3-dimethylbarbituric acid as model reaction (Scheme 2).

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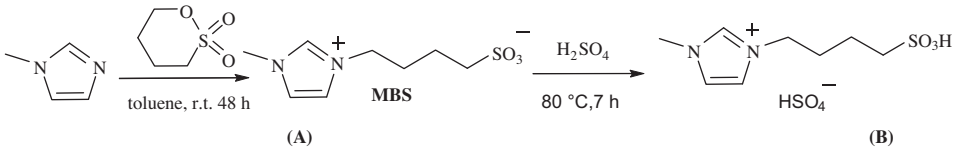
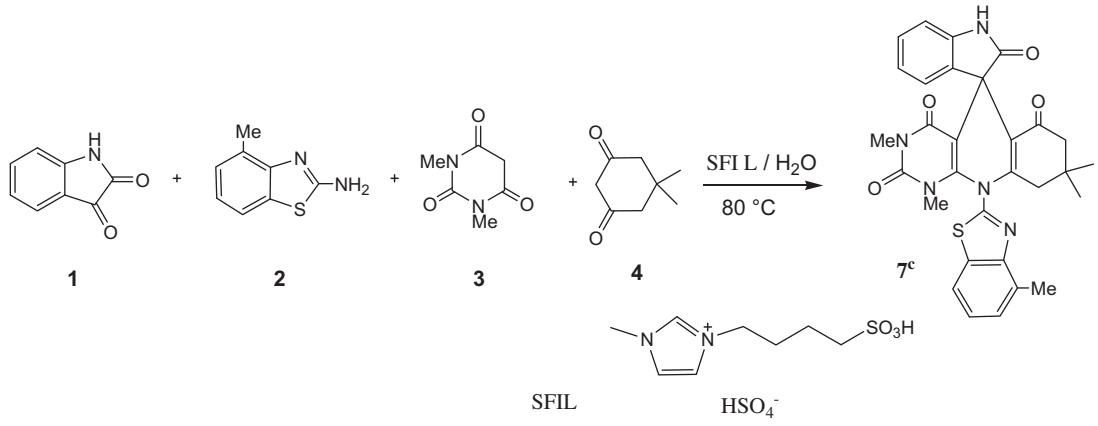


B = 3-methyl-1-(butyl-4-sulfonyl)imidazolium hydrogen sulphate
($[MIM(CH_2)_4SO_3H][HSO_4]$)

Scheme 1. Synthetic route of SO_3H-functionalized ionic liquid.



Scheme 2. Model reaction.

Table 1
Evaluation of various solvents for the reaction

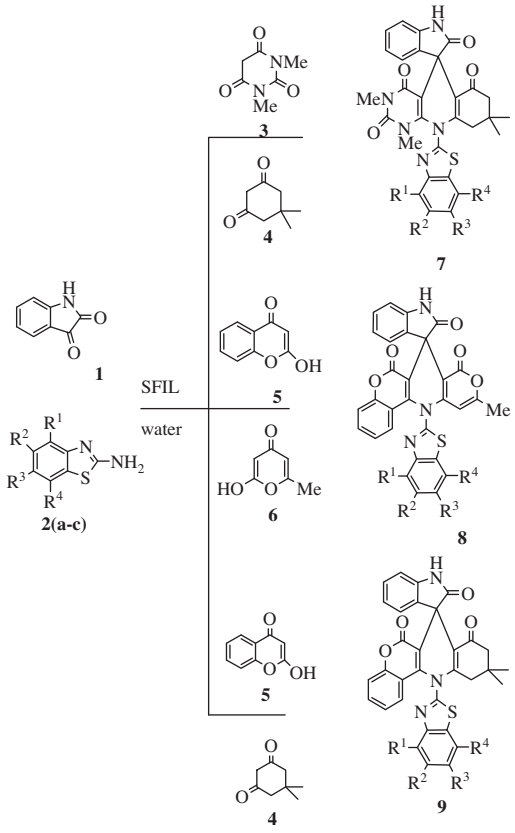
Entry	Conditions	Temperature (°C)	Time	Yield (%)
1	[SFIL]/water 1:1	80 °C	5 h	68
	[SFIL]/water 1:2	rt	5 h	0
2	[SFIL]/water 1:2	80 °C	15 min	93
3	Zwitterions (A)	80 °C	45 min	86
4	[bmim][BF_4]	rt	5 h	0
5	[bmim][BF_4]/toluene 1:1	80 °C	1 h 30 min	Isolation problem
6	Water (reflux) without IL	80 °C	2 h	0
7	[bmim][BF_4]/water 1:4	80 °C	45 min	72
8	[bmim][BF_4]/water 1:3	80 °C	25 min	80
9	[bmim][BF_4]/water 1:1	80 °C	25 min	85
10	[bmim][PF_6] /water 1:1	80 °C	35 min	70

1,3-Dimethylbarbituric acid (1 mmol), dimedone (1 mmol), isatin (1 mmol), 2-amino-4-methylbenzothiazole (1 mmol).

The results of the model reaction carried out under different reaction conditions are summarized in Table 1.

It was observed that when the reaction was carried out with [bmim][BF_4] (without water) at room temperature, the product was not obtained (entry 4) even after stirring for more than 5 h. But when the reaction was performed with ionic liquid [bmim][BF_4]/water system at 80 °C, the yield of the product depended on the ratio of ionic liquid and water. As indicated in Table 1, when the reaction was performed with ionic liquid/water in the ratio 1:4, 1:3 to 1:1, the yield of the product increased from 72% to 80% and 85%, respectively. Water has shown superiority over the other solvents (entry 5). The reaction was performed with [SFIL]/water 1:2 at room temperature, the product was not obtained even after the stirring for 5 h (entry 1). The reaction has also been carried out in [bmim][PF_6]/water system for comparison (entry 10). The reaction was also performed with [SFIL]/water 1:1 and [SFIL]/water 1:2, the excellent results were obtained when reaction was performed with [SFIL]/water 1:2/(80 °C) in 15 min. By considering the yields and the reaction time, the best results were obtained with [SFIL]/water 1:2 (entry 2) as the reaction was completed within 15 min with 93% yield. After optimization of the reaction conditions, to delineate this approach, particularly in regard to library construction, this methodology[23] was evaluated by using isatin, different cyclic 1,3-diketones, and 2-aminobenzothiazoles. Isatin, four commercially available cyclic 1,3-diketones, namely 1,3-dimethylbarbituric acid (**3**), dimedone (**4**), 4-hydroxycoumarin (**5**) and 4-hydroxy-6-methyl-2-pyrone (**6**), and 2-aminobenzothiazoles; 2-amino-6-bromo-4-methylbenzothiazole (**2a**), 2-amino-6-methylbenzothiazole (**2b**), 2-amino-5,7-dimethylbenzothiazole (**2c**), were selected for the library validation (Schemes 3 and 4). To our delight, under the above optimized conditions, the reactions proceeded smoothly and a variety of the desired spiroheterocycles were obtained in excellent yields. Moreover, this is perhaps the first literature regarding the comparison between task-specific ionic liquid and normal ionic liquids.

A plausible mechanism for the formation of spiroheterocycles involving SO_3H-functionalized ionic liquid catalyzed four component domino reaction is presented in Scheme 5. The reaction is



entry	R^1	R^2	R^3	R^4	time (min)	yield %
7a	CH_3	H	Br	H	25	93
7b	H	CH_3	H	CH_3	20	91
7c	H	H	CH_3	H	28	91

10-(benzothiazol-2-yl)spiropyrimido[4,5-*b*]quinoline-5,3'-indolinetetrones

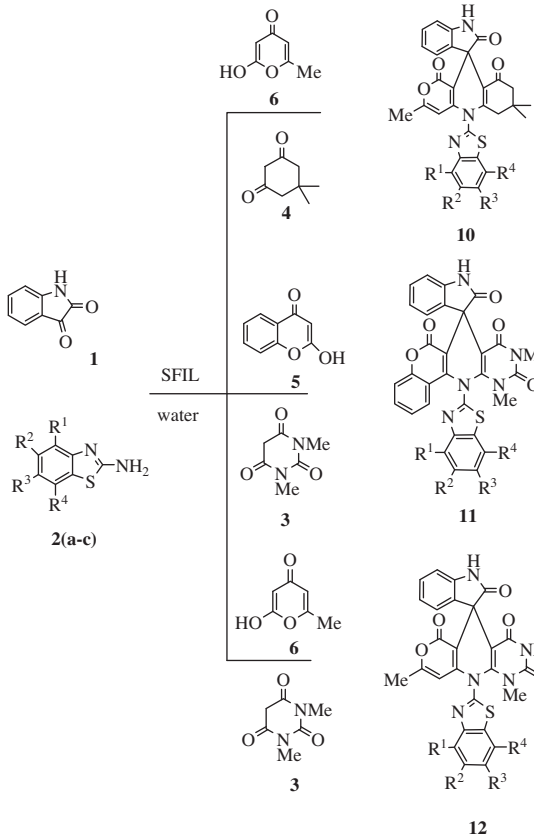
entry	R^1	R^2	R^3	R^4	time (min)	yield %
8a	CH_3	H	Br	H	19	92
8b	H	CH_3	H	CH_3	21	94
8c	H	H	CH_3	H	26	89

12-(benzothiazol-2-yl)-2-methylspiro[chromeno[3,4-*b*]pyranopyridine-5,3'-indoline]triones

entry	R^1	R^2	R^3	R^4	time (min)	yield %
9a	CH_3	H	Br	H	18	91
9b	H	CH_3	H	CH_3	27	92
9c	H	H	CH_3	H	23	91

12-(benzothiazol-2-yl)spirochromeno[3,4-*b*]quinoline-5,3'-indolinetriones

Scheme 3. Synthesis of spiroheterocycles in SO_3H-functionalized ionic liquid/water system.



entry	R^1	R^2	R^3	R^4	time (min)	yield %
10a	CH_3	H	Br	H	30	92
10b	H	CH_3	H	CH_3	21	94
10c	H	H	CH_3	H	28	90

10-(benzothiazol-2-yl)spiropyrano[3,4-*b*]quinoline-5,3'-indolinetriones

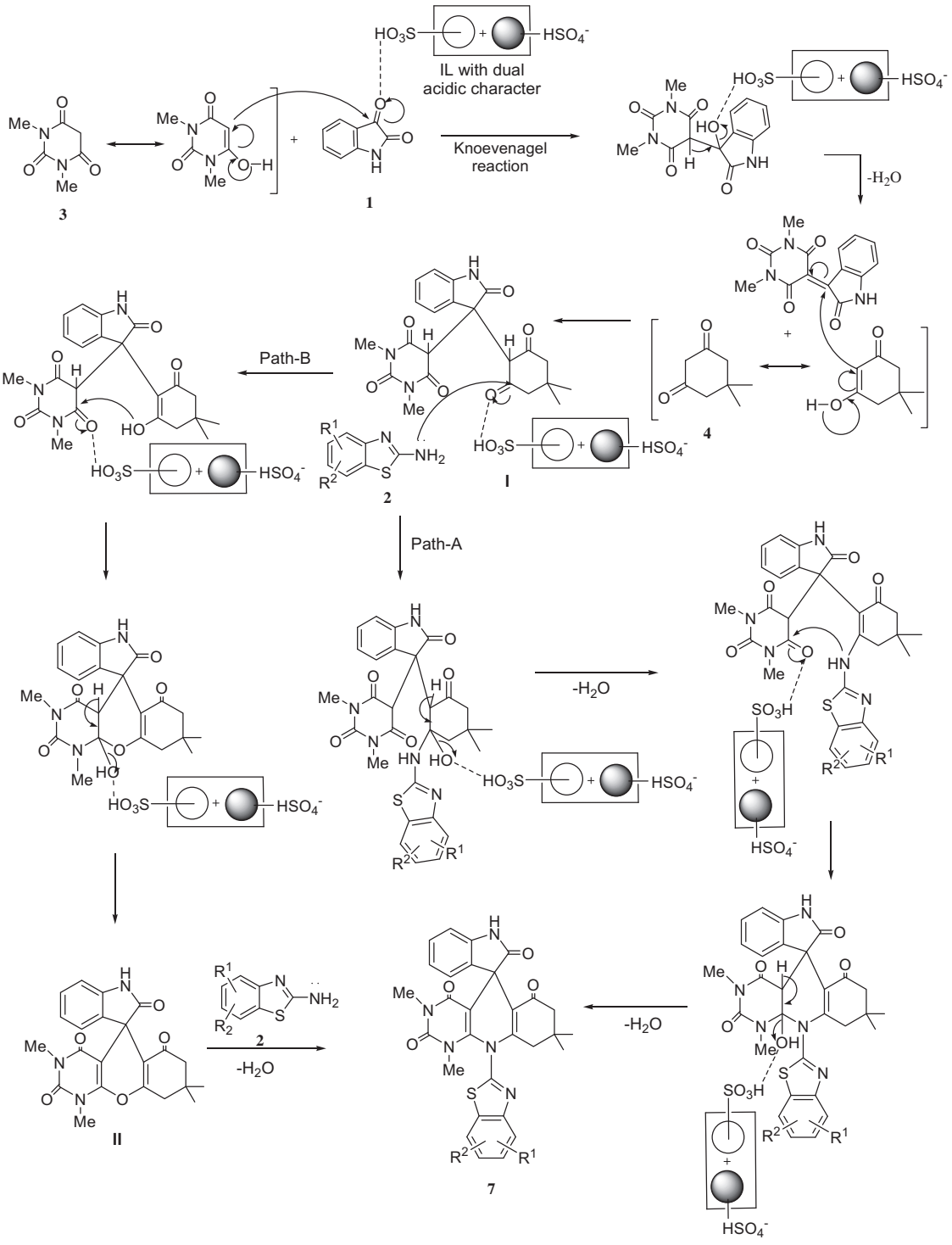
entry	R^1	R^2	R^3	R^4	time (min)	yield %
11a	CH_3	H	Br	H	25	90
11b	H	CH_3	H	CH_3	30	92
11c	H	H	CH_3	H	23	89

12-(benzothiazol-2-yl)spirochromeno[3,4-*b*]pyrido[2,3-*d*]pyrimidine-indolinetetrones

entry	R^1	R^2	R^3	R^4	time (min)	yield %
12a	CH_3	H	Br	H	22	93
12b	H	CH_3	H	CH_3	25	89
12c	H	H	CH_3	H	21	91

12-(benzothiazol-2-yl)spiropyrano[3,4-*b*]pyrido[2,3-*d*]pyrimidine-indolinetetrones

Scheme 4. Synthesis of spiroheterocycles in SO_3H-functionalized ionic liquid/water system.



Scheme 5. Plausible mechanism for the synthesis of spiroheterocycles in SO_3H-functionalized ionic liquid/water system.

considered to proceed with the formation of Knoevenagel condensation product between barbituric acid and isatin. In the next step the Knoevenagel product reacts with dimedone involving addition of dimedone (in its enol form) to Knoevenagel product in conjugate manner to produce the intermediate **I**. The formation of the desired product may be considered to follow two paths: In path-A, the intermediate reacts with 2-aminobenzothiazole to form the product 7, while in path-B the formation of another intermediate **II** may be considered by intramolecular dehydrative cyclization. The intermediate **II** then reacts with 2-aminobenzothiazole to produce product 7.

It was observed that the ionic liquid, [SFILs][H_2O], could be easily quantitatively recovered after completion of the reaction and readily recycled and reused for at least fives cycles without any appreciable loss of activity to provide structurally diverse spiroheterocycles in excellent yields (Fig. 1).

In conclusion, we have developed an efficient and eco-compatible synthetic methodology for the synthesis of structurally diverse

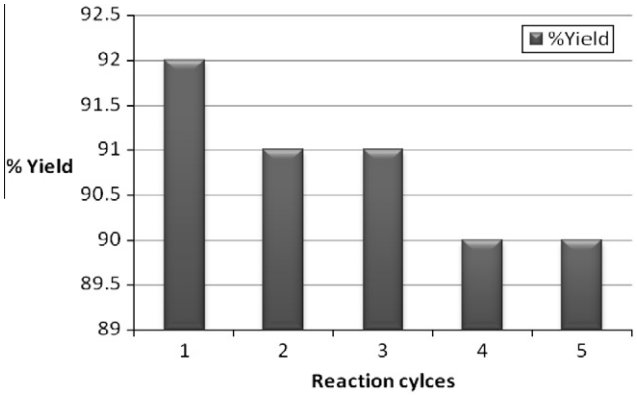


Figure 1. Reusability of ([MIM$(CH_2)_4SO_3H$][HSO_4]).

spiroheterocycles with fused heterosystems in excellent yields using a halogenfree SO_3H-functionalized ionic liquid/water as recyclable medium. To the best of our knowledge the synthesis of spiroheterocycles with such fused heterosystems in SO_3H-functionalized ionic liquid/water system has not been documented in the literature. The advantages of this synthetic protocol are mild reaction conditions, shorter reaction times, easy work-up, excellent yields, and recycled and reusable solvent/catalyst.

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22. Preparation of ionic liquids: The method involves the reaction of 1-methylimidazole with 1,4-butane sultone in equimolar ratio to afford the zwitterions (A) that is further converted into SO_3H-functionalised ionic liquid (B) by acidification with sulfuric acid (Scheme 1). The ionic liquid was obtained in quantitative yield with high purity.
(a) Preparation of 1-alkyl-3-(butyl-4-sulfonate) imidazolium salt (A): 1-Methylimidazole (10.0 g, 1.2 mol) and 1,4-butane sultone (16.6 g, 1.2 mol) were vigorously stirred overnight at 70 °C in dry toluene (80 mL). The white precipitate was filtered off, thoroughly washed with diethyl ether and finally dried in vacuum. Spectroscopic data for (A): Mp 233–235 °C. ^{1}H NMR (300 MHz, DMSO-d_6, TMS); 1.54 (m, 2H), 1.87 (m, 2H), 2.6 (t, 2H,), 3.79 (s, 3H), 4.20 (t, 2H), 7.32 (s, 1H), 7.4 (s, 1H), 9.27 (s, 1H), 11.60 (bs, 2H). ^{13}C NMR (75 MHz, DMSO-d_6, TMS); 22.09, 28.17, 36.34, 48.96, 51.88, 123.06, 124.28, 138.03.
(b) Preparation of SO_3H-functionalized ionic liquid ([MIM$(CH_2)_4SO_3H$][HSO_4]) (B): Stoichiometric amount of sulfuric acid was added to the zwitterions **A** and the mixture was stirred at 80 °C for 7 h to obtain the ionic liquid. The ionic liquids $BmimPF_6$ and $BmimBF_4$ have also been prepared according to the method reported in literature.[21]
23. Representative procedure: A dry 25 ml round bottomed flask was charged with substituted 2-aminobenzothiazole (1 mmol), isatin (1 mmol), two different 1,3-dicarbonyl compounds (1 mmol each) and [SFIL] (1.0 ml)/H_2O (1.0 ml). The mixture solution was heated at 80 °C, under magnetic stirring, for 15 min. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and filtered to afford the crude product, which was washed and purified by recrystallization from ethanol. The ionic liquid was recovered from the aqueous solution by evaporating under reduced pressure and reused in the next cycle.
10-(6-Methylbenzothiazol-2-yl)-1,3,8,8-tetramethyl-1*H*,3*H*-8,9-dihydro-7*H*-spiro[pyrimido[4,5-*b*]quinoline-5,3′-indoline]-2,2′,4,6-tetrone (**7c**) Mp 221–223 °C, IR (KBr): 3210, 1740, 1700 and 620 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ (ppm): 0.99 (3H, s, CH_3), 1.08 (3H, s, CH_3), 2.07–2.15 (2H, m, CH_2), 2.41 (3H, s, CH_3), 2.45–2.60 (2H, m, CH_2), 3.01 (3H, s, CH_3), 3.45 (3H, s, CH_3), 6.86–7.43 (7H, m, H-Ar), 10.95 (1H, s, NH). ^{13}C NMR (DMSO-d_6) δ (ppm) : 19.3, 20.9, 25.7, 26.6, 28.3, 30.2, 45.8, 47.3, 53.1, 79.9, 108.5, 120.8, 122.0, 122.9, 123.6, 124.3, 125.1, 127.1, 130.5, 135.5, 142.4, 144.6, 145.1, 153.5, 167.9, 170.0, 174.1, 197.2. HRMS-FAB: *m*/*z* Calcd for [M+H]$^+$ 553.1784. Found: 553.1779. Anal. Calcd (%) for $C_{30}H_{27}N_5O_4S$: C 65.08, H 4.92, N 12.65. Found: C 65.01, H 5.01, N 12.59.
12-(6-Bromo-4-methylbenzothiazol-2-yl)-2-methylspiro[chromeno[3,4-*b*]pyrano-pyridine-5,3′-indoline]-2′,4,6-trione (**8a**) Mp 218–221 °C, IR (KBr): 3285, 3210, 3190, 1700, 1650 and 1610 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ (ppm): 2.22 (3H, s, CH_3), 2.49 (3H, s, CH_3), 6.75–7.92 (11H, m, HAr), 10.43 (1H, s, NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 15.3, 18.5, 38.6, 38.9, 39.2, 39.7, 40.0, 40.3, 50.7, 53.4, 56.0, 109.4, 119.0, 120.9, 121.4, 124.7, 128.0, 128.7, 128.9, 130.2, 143.1, 150.1, 151.6, 153.0, 167.2, 167.6, 175.6. Anal. Calcd (%) for $C_{31}H_{18}BrN_3O_5S$: C 59.62, H 2.91, N 6.73. Found: C 59.61, H 2.89, N 6.77.
12-(6-Bromo-4-methylbenzothiazol-2-yl)-2,2-dimethyl-2,3-dihydro-1*H*-spiro[chromeno [3,4-*b*]quinoline-5,3′-indoline]-2′,4,6-trione (**9a**) Mp 212–217 °C, IR (KBr): 3285, 3210, 3190, 1700, 1650 and 1610 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ (ppm): 0.99 (3H, s, CH_3), 1.07 (3H, s, CH_3), 2.09–2.32 (4H, m, CH_2), 3.02 (3H, s, CH_3), 6.69–7.59 (10H, m, H-Ar), 11.16 (1H, s, NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 18.3, 28.2, 28.3, 38.6, 38.9, 39.2, 39.7, 40.0, 40.3, 51.7, 54.2, 109.2, 120.6, 120.9, 124.9, 129.0, 137.7, 138.9, 139.6, 143.0, 148.7, 151.1, 165.7, 168.0, 175.7, 196.1. Anal. Calcd (%) for $C_{33}H_{24}BrN_3O_4S$: C 62.07, H 3.79, N 6.58. Found: C 62.10, H 3.81, N 6.57.
10-(6-Bromo-4-methylbenzothiazol-2-yl)-2,8,8-trimethyl-8,9-dihydro-7*H*-spiro[pyrano [3,4-*b*]quinoline-5,3′-indoline]-2′,4,6-trione (**10a**) Mp 223–226 °C, IR (KBr): 3285, 3210, 3190, 1700, 1650 and 1610 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ (ppm) : 1.06 (3H, s, CH_3), 1.24 (3H, s, CH_3), 3.08–3.12 (4H, m, CH_2), 3.37 (3H, s, CH_3), 3.71 (3H, s, CH_3), 6.74–7.62 (7H, m, H-Ar), 10.6 (1H, s, NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 20.9, 27.7, 28.2, 38.7, 38.9, 39.2, 39.8, 40.0, 40.3, 51.8, 101.1, 102.3, 109.3, 120.8, 121.5, 125.0, 126.0, 133.7, 137.8, 138.6, 161.1, 165.8, 180.7, 196.7. Anal. Calcd (%) for $C_{30}H_{24}BrN_3O_4S$: C 59.80, H 4.02, N 6.97. Found: C 59.25, H 4.12, N 6.90.
12-(6-Bromo-4-methylbenzothiazol-2-yl)-1,3-dimethyl-1*H*,3*H*-spiro[chromeno[3,4-*b*]pyrido[2,3-*d*]pyrimidine-indoline]-2,2′,4,6-tetrone (**11a**) Mp 220–224 °C, IR (KBr): 3285, 1732, 1710, 1670 and 1630 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ (ppm): 2.48 (3H, s, CH_3), 3.08 (3H, s, CH_3), 3.50 (3H, s, CH_3), 6.68–8.07 (10H, m, H-Ar), 10.6 (1H, s, NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 20.9, 38.6, 38.9, 39.2, 39.7, 40.0, 40.3, 78.2, 100.8, 109.7, 115.6, 116.1, 120.8, 121.6, 123.1, 123.8, 124.3, 126.8, 129.8, 130.7, 132.8, 137.8, 138.6, 142.9, 152.1, 159.4, 164.8, 175.4, 180.7. Anal. Calcd (%) for $C_{31}H_{20}BrN_5O_5S$: C 56.89, H 3.08, N 10.70. Found: C 56.91, H 3.11, N 10.68.
10-(6-Bromo-4-methylbenzothiazol-2-yl)-1,3,8-trimethyl-1*H*,3*H*-spiro[pyrano[3,4-*b*]pyrido[2,3-*d*]pyrimidine-indoline]-2,2′,4,6-tetrone (**12a**) Mp 218–221 °C, IR (KBr): 3285, 3210, 3190, 1700, 1650 and 1610 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ (ppm): 3.01 (3H, s, CH_3), 3.06 (3H, s, CH_3), 3.12 (3H, s, CH_3), 3.36 (3H, s, CH_3), 6.81–7.79 (7H, m, H-Ar), 10.55 (1H, s, NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 19.0, 20.9, 38.6, 38.9, 39.2, 39.7, 40.0, 40.3, 77.4, 98.3, 100.9, 109.5, 120.8, 121.5, 123.5, 126.0, 129.5, 131.0, 137.8, 138.6, 142.7, 161.6, 162.0, 169.0, 175.6, 180.7. Anal. Calcd (%) for $C_{28}H_{20}BrN_5O_5S$: C 54.38, H 3.26, N 11.32. Found: C 54.41, H 3.25, N 11.35.