Synthesis of novel derivatives of (benz)imidazo[2,1-*b*]pyrimido[4,5-*d*][1,3] thiazine

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Several derivatives of the novel heterocyclic systems 2-substituted-imidazo- and benzimidazo-[2,1-*b*]pyrimido[4,5-*d*][1,3]thiazine have been synthesised through the one-pot cyclocondensation of 2,4-dichloro-5-(chloromethyl)-6-methylpyrimidine with imidazolidine-2-thione and 1*H*-benzimidazole-2(3*H*)-thione and subsequently substituted by various secondary amines in moderately good yields.

Keywords: pyrimidothiazine, imidazolidine, benzimidazole, one-pot cyclocondensation

The 1,3-thiazine structure plays a crucial role in pharmacological and biologically active compounds.[1–4] Among the 1,3-thiazine-containing heteroaryl-fused structures, pyrimidothiazine derivatives have attracted wide interest due to their considerable biological activities, such as anti-inflammatory, antitumour, antibacterial, antiallergic and antipyretic activity.[5–9] Examples of synthetic methods to prepare pyrimidothiazine-containing compounds include the reaction of 4-methoxy- and 4-ethoxy-5-amino-6-mercaptopyrimidines with diethyl bromomalonate in the presence of potassium hydroxide,[10] cyclisation of mercaptopyrimidine with benzylidine malononitrile in ethoxide solution,[11] the treatment of ethyl-2-cyano-3,3-bis(methylthio) acrylate and thiourea in the presence of potassium carbonate in dimethylformamide,[12] condensation reaction of thioxopyrimidine derivatives and 3-bromopropionic acid,[13] one-pot multicomponent reaction of aryl isocyanides, dialkyl acetylenedicarboxylates and thiouracils[14] and condensation of 5-amino-4-thiopyrimidines with desyl chloride in the presence of sodium acetate.[15]

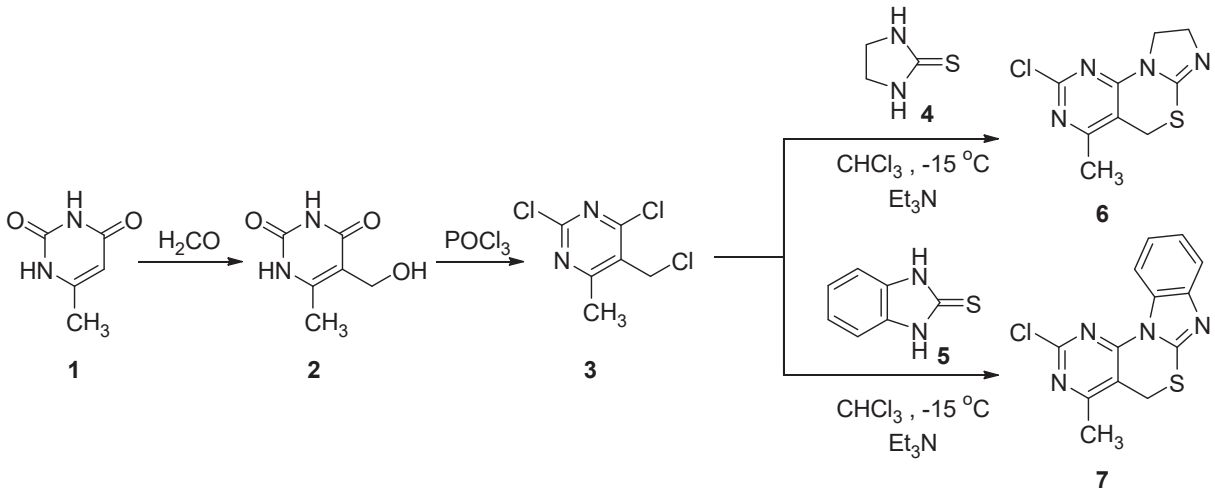
Moreover, imidazothiazines, as other thiazine-fused structures, have often been used as scaffolds in medicinal chemistry. Some medicinal properties of imidazothiazine derivatives consist of anticancer, anti-leukemia, antifungal, anti-inflammatory and antisecretory activities.[16–19] There are various methods reported for the synthesis of imidazothiazines, including the reaction of 5,5-diphenyl-2-thiohydantoin with α,β-unsaturated nitriles,[20] cyclisation of 5,5-diphenyl-2-thiohydantoins with 1,3-dibromopropane under phase-transfer catalysis conditions,[21] the reaction of 3,3-dichloro-2-phenylacryloyl chloride with mercaptoimidazoles,[22] one-step reaction of benzimidazoline-2-thione with cinnamoyl chloride[23] and cyclisation of benzimidazolethiones with ethyl 3-chloro-but-2-enoate.[24]

Considering the pharmacological and biological activities of pyrimidothiazines and imidazothiazines and as part of our ongoing studies dealing with the synthesis of various fused pyrimidines,[25–31] we describe here a facile synthesis and structural elucidation of 2-substituted-imidazo- and benzimidazo-[2,1-*b*]pyrimido[4,5-*d*][1,3]thiazines **8a–e** and **9a–e** as novel heterocyclic systems that may be good candidates in designing new biologically active compounds.

Results and discussion

Initially, the reaction of 6-methylpyrimidine-2,4-(1*H*,3*H*)-dione **1** with formaldehyde in aqueous NaOH solution gave 5-(hydroxymethyl)-6-methylpyrimidine-2,4-(1*H*,3*H*)-dione **2**, which was subsequently treated with $POCl_3$ to produce 2,4-dichloro-5-(chloromethyl)-6-methylpyrimidine **3**.[32] In addition, imidazolidine-2-thione **4** and 1*H*-benzimidazole-2(3*H*)-thione **5**, used as binucleophiles, were prepared in quantitative yield according to the previously published methods.[33,34] The reaction of 2,4-dichloro-5-(chloromethyl)-6-methylpyrimidine **3** with binucleophiles **4** and **5** in $CHCl_3$ at –15 °C gave 2-chloro-4-methyl-8,9-dihydro-5*H*-imidazo[2,1-*b*] pyrimido[4,5-*d*][1,3]thiazine **6** and 2-chloro-4-methyl-5*H*-benzimidazo[2,1-*b*]pyrimido[4,5-*d*][1,3]thiazine **7** as new heterocyclic systems (Scheme 1).

This reaction goes forward through combined nucleophilic substitution and an addition–elimination reaction involving the nitrogen and sulfur atoms in the binucleophiles followed by elimination of two molecules of HCl. The evidence in support of initial halide displacement from the chloromethyl group, rather than the 4-Cl substituent was obtained from the comparison of the ^{1}H chemical shifts of methylene groups bonded to sulfur in thiazine moieties with the SCH_2–Ar function reported in



Scheme 1

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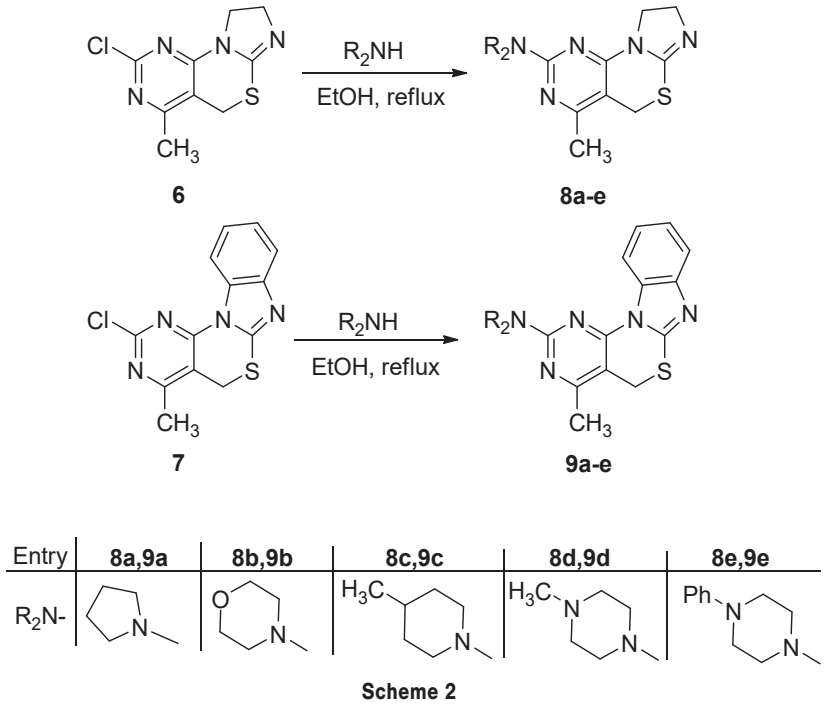

Scheme 2

the literature (δ 3.8–4.2 ppm for CH_2S).[35–37] These literature data are in accordance with the ^{1}H chemical shifts of the CH_2S moiety in the synthesised compounds **6** and **7** (δ 3.93 and 4.07 ppm, respectively).

The structural elucidation of these compounds was accomplished from their physical, chemical and spectral data. In the IR spectrum of the two synthesised compounds **6** and **7**, the NH vibration of the precursors was absent. The ^{1}H NMR spectrum of compound **6** revealed two singlet signals at δ 2.50 and 3.93 ppm due to methyl and thiomethylene groups, respectively, and a multiplet signal at δ 4.02–4.12 ppm attributed to the methylene group protons in the imidazole ring. The ^{13}C NMR spectrum plainly demonstrated nine signals for the carbons of the desired compound.

Also, in the ^{1}H NMR spectrum of compound **7**, the presence of two singlet signals at δ 2.59 and 4.07 ppm belonging to methyl and methylene group protons and the multiplet signals in the range 7.26–8.35 ppm corresponding to the aryl hydrogens confirmed the structure of the new heterocyclic system. The ^{13}C NMR spectrum showed two signals at δ 22.3 and 24.2 ppm assigned to the carbons of the methyl and methylene carbons and eleven signals at δ 111.6, 115.6, 119.1, 124.6, 125.1, 132.5, 143.6, 148.4, 155.5, 158.9 and 167.1 ppm are attributed to the unsaturated carbons. The mass spectrum also showed the molecular ion peak at *m*/*z* 288 (M^+) corresponding to the molecular formula of $C_{13}H_9ClN_4S$.

Further investigation was performed *via* nucleophilic substitution of the 2-Cl substituent with various secondary amines in boiling ethanol to synthesise substituted derivatives of the new heterocyclic rings **8a–e** and **9a–e** in good to excellent yields (Scheme 2).

The structural assignments of the synthesised compounds were confirmed by recording their elemental analyses and spectral data. The ^{1}H NMR spectrum of product **8b**, as an example, showed two singlet signals at δ 2.35 and 3.85 ppm assigned to the hydrogens of the CH_3 group of the pyrimidine and CH_2 unit of the thiazine rings and two multiple signals in the regions δ 3.74–3.79 and 3.97–4.06 ppm due to protons from the morpholine and imidazole rings, respectively. The ^{13}C NMR spectrum clearly showed seven signals at 21.9, 23.7, 44.2, 45.4, 54.0, 66.9 and 98.5 ppm for the aliphatic carbons of the desired compound **8b** and four signals for its unsaturated carbons appearing at 156.3, 159.9, 160.1 and 161.7 ppm. The mass spectrum of compound **8b** showed the molecular ion peak at *m*/*z* 291 (M+) related to the molecular formula of $C_{13}H_{17}N_5OS$.

Conclusion

We have successfully synthesised novel tri- and tetracyclic 2-substituted-imidazo- and benzimidazo-[2,1-*b*]pyrimido[4,5-*d*][1,3]thiazines **8a–e** and **9a–e** through the initial treatment of 2,4-dichloro-5-(chloromethyl)-6-methylpyrimidine **3** with imidazolidine-2-thione **4** and 1*H*-benzimidazole-2(3*H*)-thione **5** to produce 2-chloro-4-methyl-8,9-dihydro-5*H*-imidazo[2,1-*b*]pyrimido[4,5-*d*][1,3]thiazine **6** and 2-chloro-4-methyl-5*H*-benzimidazo[2,1-*b*]pyrimido[4,5-*d*][1,3]thiazine **7** as new heterocyclic systems, which were further substituted with various *sec*-amines to obtain products **8a–e** and **9a–e**.

Experimental

Melting points were recorded on an Electrothermal type 9200 melting point apparatus. The IR spectra were obtained on an Avatar 370 FTIR Thermo Nicolet spectrophotometer and only noteworthy absorptions are listed. The ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker Avance DRX-400 Fourier transform spectrometer. Chemical shifts are reported in ppm downfield from TMS as internal standard. The mass spectra were scanned on a Varian Mat CH-7 at 70 eV. Elemental analyses were performed on a Thermo Finnigan Flash EA microanalyser.

*Synthesis of 2-chloro-4-methyl-8,9-dihydro-5*H*-imidazo[2,1-*b*]pyrimido-[4,5-*d*][1,3]thiazine (**6**)*

Imidazolidine-2-thione **4** (1 mmol, 0.1g) in DMF (1 mL) was added dropwise to a stirred solution of 2,4-dichloro-5-(chloromethyl)-6 methylpyrimidine **3** (1 mmol, 0.211g) and triethylamine (2 mmol, 0.2 g) in $CHCl_3$ (2 mL) with vigorous stirring at −15 °C. After 4 h, distilled water (10 mL) was added and the mixture was extracted with chloroform (3 × 5 mL). The combined organic solvents were dried over anhydrous sodium sulfate and concentrated to give compound **6** as a white powder; yield 85%; m.p. 190–192 °C; IR (KBr disc) (υ_{max} cm^{-1}): 3007, 2966, 2944, 2864, 1593, 1568, 1544, 1474, 1365, 1299, 1275, 1195, 1160, 1127; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.50 (s, 3H,

CH_3–pyrimidine), 3.93 (s, 2H, CH_2–thiazine), 4.02–4.12 (m, 4H, CH_2–imidazole); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.6 ($\underline{C}H_3$), 23.4 ($\underline{C}H_2$–S), 45.7 ($\underline{C}H_2$–N), 54.4 ($\underline{C}H_2$–N), 108.0, 154.7, 157.1, 158.7, 163.4; MS (*m*/*z*): 240 (M^+). Anal. calcd for $C_9H_9ClN_4S$: C, 44.91; H, 3.77; N, 23.28; S, 13.32; found: C, 44.87; H, 3.74; N, 23.15; S, 13.30%.

*Synthesis of 2-chloro-4-methyl-5*H*-benzimidazo[2,1-*b*]pyrimido-[4,5-*d*][1,3]thiazine (***7***)*

A solution of 1*H*-benzimidazole-2(3*H*)-thione **5** (1 mmol, 0.15 g) in DMF (1 mL) was added dropwise to a cooled (–15 °C) stirred solution of 2,4-dichloro-5-(chloromethyl)-6-methylpyrimidine **3** (1 mmol, 0.21 g) and Et_3N (2 mmol, 0.2 g) in $CHCl_3$ (5 mL). The resulting mixture was allowed to warm to room temperature for 4 h, then water (10 mL) was added and the mixture was extracted with $CHCl_3$ (3 × 10 mL). The combined organic solvents were dried over anhydrous sodium sulfate and concentrated. The resulting solid was purified using silica gel column chromatography $CHCl_3$/methanol (30:1) as eluent to give compound **7** as a white powder; yield 73%; m.p. 205–207 °C; IR (KBr disc) (υ_{max} cm^{-1}): 3088, 3019, 2962, 2925, 2855, 2789, 2692, 2606, 1567, 1549, 1479, 1462, 1415, 1323, 1298, 1238, 1183, 1150; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.59 (s, 3H, CH_3–pyrimidine), 4.07 (s, 2H, CH_2–thiazine), 7.26–7.34 (m, 2H, ArH), 7.59–7.61 (m, 1H, ArH), 8.32–8.35 (m, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.3 ($\underline{C}H_3$), 24.2 ($\underline{C}H_2$–S), 111.6, 115.6, 119.1, 124.6, 125.1, 132.5, 143.6, 148.4, 155.5, 158.9, 167.1; MS (*m*/*z*): 288 (M^+). Anal. calcd for $C_{13}H_9ClN_4S$: C, 54.07; H, 3.14; N, 19.40; S, 11.10; found: C, 54.04; H, 3.10; N, 19.31; S, 11.04%.

*Synthesis of 2-substituted-4-methyl-8,9-dihydro-5*H*-imidazo[2,1-*b*]pyrimido[4,5-*d*][1,3]thiazine* (**8a–e**)*; general procedure*

A mixture of 2-chloro-4-methyl-8,9-dihydro-5*H*-imidazo[2,1-*b*]pyrimido[4,5-*d*][1,3]thiazine **6** (1 mmol, 0.24 g) and the appropriate secondary amine (3 mmol) in ethanol (5 mL) was refluxed for 4 h. After reaction completion, which was monitored by TLC using chloroform/methanol (30:1), the solvent was concentrated and the resulting white precipitate was filtered. The resulting solid was purified using silica gel column chromatography with hexane/ethyl acetate (8:1) as eluent.

*4-Methyl-2-(pyrrolidin-1-yl)-8,9-dihydro-5*H*-imidazo[2,1-*b*]pyrimido[4,5-*d*][1,3]thiazine* (**8a**): White powder; yield 75%; m.p. 158–160 °C; IR (KBr disc) (υ_{max} cm^{-1}): 2966, 2921, 2865, 1597, 1576, 1528, 1442, 1348, 1242, 1208, 1114; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.96 (t, *J* = 6.4 Hz, 4H, CH_2–pyrrolidine), 2.35 (s, 3H, CH_3–pyrimidine), 3.56 (t, *J* = 6.4 Hz, 4H, CH_2–N), 3.86 (s, 2H, CH_2–thiazine), 4.02 (br s, 4H, CH_2–imidazole); ^{13}C NMR (70 MHz, $CDCl_3$): δ 21.9 ($\underline{C}H_3$), 23.9 ($\underline{C}H_2$), 25.5 ($\underline{C}H_2$–S), 45.4 ($\underline{C}H_2$–N), 46.5 ($\underline{C}H_2$–N), 54.0 ($\underline{C}H_2$–N), 97.2, 156.2, 157.3, 159.0, 161.5; MS (*m*/*z*): 275 (M^+). Anal. calcd for $C_{13}H_{17}N_5S$: C, 56.70; H, 6.22; N, 25.43; S, 11.64; found: C, 56.65; H, 6.19; N, 25.35; S, 11.61%.

*4-(4-Methyl-8,9-dihydro-5*H*-imidazo[2,1-*b*]pyrimido[4,5-*d*][1,3]thiazin-2-yl) morpholine* (**8b**): White powder; yield 81%; m.p. 172–174 °C; IR (KBr disc) (υ_{max} cm^{-1}): 3004, 2967, 2913, 2863, 1593, 1574, 1503, 1442, 1305, 1263, 1129, 1111; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 3H, CH_3–pyrimidine), 3.74–3.79 (m, 8H, CH_2–morpholine), 3.85 (s, 2H, CH_2–thiazine), 3.97–4.06 (m, 4H, CH_2–imidazole); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.9 ($\underline{C}H_3$), 23.7 ($\underline{C}H_2$–S), 44.2 ($\underline{C}H_2$–N), 45.4 ($\underline{C}H_2$–N), 54.0 ($\underline{C}H_2$–N), 66.9 ($\underline{C}H_2$–O), 98.5, 156.3, 159.9, 160.1, 161.7; MS (*m*/*z*): 291 (M^+), 205 ($M^+ - C_9H_9N_4S$). Anal. calcd for $C_{13}H_{17}N_5OS$: C, 53.59; H, 5.88; N, 24.04; S, 11.00; found: C, 53.61; H, 5.92; N, 24.11; S, 11.03%.

*4-Methyl-2-(4-methylpiperidin-1-yl)-8,9-dihydro-5*H*-imidazo[2,1-*b*]pyrimido[4,5-*d*][1,3] thiazine* (**8c**): White powder; yield 78%; m.p. 126–128 °C; IR (KBr disc) (υ_{max} cm^{-1}): 2998, 2952, 2919, 2867, 2844, 1597, 1578, 1553, 1442, 1374, 1313, 1250, 1219, 1121, 1079, 1023; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (d, 3H, CH_3–piperidine), 1.08–1.21 (m, 3H, axial hydrogens of CH_2 and CH of piperidine), 1.60–1.72 (m, 2H, equatorial hydrogens of CH_2), 2.34 (s, 3H, CH_3–pyrimidine), 2.81 (t, *J* = 11.1 Hz, 2H, axial hydrogens of CH_2–N), 3.85 (s, 2H, CH_2–imidazole), 4.01 (br s, 4H, CH_2–imidazole and CH_2–thiazine), 4.74 (d, *J* = 13.2 Hz, 2H, equatorial hydrogens of CH_2–N); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.9 ($\underline{C}H_3$), 22.0 ($\underline{C}H_3$), 23.8 ($\underline{C}H$), 31.3 ($\underline{C}H_2$), 34.1 ($\underline{C}H_2$–S), 44.1 ($\underline{C}H_2$–N), 45.4 ($\underline{C}H_2$–N), 54 ($\underline{C}H_2$–N), 97.4, 156.3, 157.2, 160.1, 161.6; MS (*m*/*z*): 303 (M^+). Anal. calcd for $C_{15}H_{21}N_5S$: C, 59.38; H, 6.98; N, 23.08; S, 10.57; found: C, 69.41; H, 7.02; N, 23.15; S, 10.61%.

*4-Methyl-2-(4-methylpiperazin-1-yl)-8,9-dihydro-5*H*-imidazo[2,1-*b*]pyrimido[4,5-*d*][1,3] thiazine* (**8d**): White powder; yield 72%; m.p. 146–148 °C; IR (KBr disc) (υ_{max} cm^{-1}): 3011, 2966, 2946, 2925, 2848, 2799, 2774, 1597, 1576, 1443, 1363, 1307, 1249, 1201, 1118, 1003; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.34 (br s, 6H, CH_3–pyrimidine and CH_3–piperazine), 2.45 (t, *J* = 5.1 Hz, 4H, CH_2–piperazine), 3.81–3.84 (m, 6H, CH_2–piperazine and CH_2–thiazine), 4.00 (br s, 4H, CH_2–imidazole); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.9 ($\underline{C}H_3$), 23.8 ($\underline{C}H_2$–S), 43.7 ($\underline{C}H_3$–N), 45.4 ($\underline{C}H_2$–N), 46.3 ($\underline{C}H_2$–N), 54.0 ($\underline{C}H_2$–N), 55.0 ($\underline{C}H_2$–N), 98.1, 156.3, 157.0, 160.1, 161.7; MS (*m*/*z*): 304 (M^+), 276 ($M^+ - C_2H_6$). Anal. calcd for $C_{14}H_{20}N_6S$: C, 55.24; H, 6.62; N, 27.61; S, 10.53; found: C, 55.21; H, 6.58; N, 27.54; S, 10.49%.

*4-Methyl-2-(4-phenylpiperazin-1-yl)-8,9-dihydro-5*H*-imidazo[2,1-*b*]pyrimido[4,5-*d*][1,3] thiazine* (**8e**): White powder; yield 84%; m.p. 242–246 °C; IR (KBr disc) (υ_{max} cm^{-1}): 3060, 2962, 2861, 2799, 2745, 1601, 1573, 1509, 1443, 1372, 1322, 1269, 1227, 1151, 1116; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.38 (s, 3H, CH_3–pyrimidine), 3.25 (t, *J* = 5.1 Hz, 4H, CH_2–piperazine), 3.88 (s, 2H, CH_2 of thiazine), 3.99 (t, *J* = 5.1 Hz, 4H, CH_2 of piperazine), 4.05 (br s, 4H, CH_2 of imidazole), 6.92 (t, *J* = 7.2 Hz, 1H, phenyl), 7.01 (d, *J* = 8.1 Hz, 1H, phenyl), 7.32 (t, *J* = 8.4 Hz, 2H, phenyl); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.9 ($\underline{C}H_3$), 23.8 ($\underline{C}H_2$–S), 43.8 ($\underline{C}H_2$–N), 45.4 ($\underline{C}H_2$–N), 49.5 ($\underline{C}H_2$–N), 54.3 ($\underline{C}H_2$–N), 98.4, 116.6, 120.2, 129.2, 151.5, 156.4, 157.0, 160.1, 161.8; MS (*m*/*z*): 366 (M^+). Anal. calcd for $C_{19}H_{22}N_6S$: C, 62.27; H, 6.05; N, 22.93; S, 8.75; found: C, 62.24; H, 6.03; N, 23.82; S, 8.71%.

*Synthesis of 2-substituted-4-methyl-5*H*-benzimidazo[2,1-*b*]pyrimido-[4,5-*d*][1,3]thiazines (***9a–e***); general procedure*

The appropriate secondary amine (3 mmol) was added to a stirred solution of 2-chloro-4-methyl-5*H*-benzimidazo[2,1-*b*]pyrimido[4,5-*d*][1,3]thiazine (**7**) (1 mmol, 0.29 g) in EtOH (5 mL) and the solution was refluxed for 4 h. After being cooled to room temperature, the resulting precipitate was filtered off and washed with ethanol (3 mL).

*4-Methyl-2-(pyrrolidin-1-yl)-5*H*-benzimidazo[2,1-*b*]pyrimido[4,5-*d*][1,3]thiazine* (**9a**): White powder; yield 91%; m.p. 155–157 °C; IR (KBr disc) (υ_{max} cm^{-1}): 3052, 2962, 2861, 1614, 1583, 1540, 1447, 1341, 1272, 1220, 1169, 1112; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.07 (t, *J* = 6.3 Hz, 4H, CH_2–pyrrolidine), 2.50 (s, 3H, CH_3–pyrimidine), 3.70 (br s, 4H, CH_2–N), 4.07 (s, 2H, CH_2–thiazine), 7.31–7.36 (m, 2H, ArH), 7.68–7.72 (m, 1H, ArH), 8.47–8.53 (m, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.4 ($\underline{C}H_3$), 24.4 ($\underline{C}H_2$), 25.3 ($\underline{C}H_2$–S), 46.9 ($\underline{C}H_2$–N), 99.9, 115.3, 118.8, 123.5, 123.9, 133.1, 143.6, 149.8, 154.6, 158.5, 164.6; MS (*m*/*z*) 323 (M^+). Anal. calcd for $C_{17}H_{17}N_5S$: C, 63.13; H, 5.30; N, 21.65; S, 9.91; found: C, 63.16; H, 5.32; N, 21.73; S, 9.95%.

*4-(4-Methyl-5*H*-benzimidazo[2,1-*b*]pyrimido[4,5-*d*][1,3]thiazin-2-yl)morpholine* (**9b**): White powder; yield 85%; m.p. 142–144 °C; IR (KBr disc) (υ_{max} cm^{-1}): 2982, 2962, 2856, 1638, 1613, 1583, 1545, 1473, 1445, 1362, 1298, 1260, 1171, 1114, 1070, 1008; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.51 (s, 3H, CH_3–pyrimidine), 3.84 (t, *J* = 3.9 Hz, 4H, CH_2–morpholine), 3.92 (t, *J* = 3.9 Hz, 4H, CH_2–morpholine), 4.06 (s, 2H, CH_2–thiazine), 7.31–7.37 (m, 2H, ArH), 7.68–7.72 (m, 1H, ArH), 8.29–8.33 (m, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.5 ($\underline{C}H_3$), 24.4 ($\underline{C}H_2$–S), 44.5 ($\underline{C}H_2$–N), 66.8 ($\underline{C}H_2$–O), 101.7, 114.8, 118.9, 123.6, 124.1, 132.8, 143.6, 149.9, 154.8, 160.0, 165.0; MS (*m*/*z*): 339 (M^+), 280 ($M^+ - Cl$), 239 ($M^+ - C_6H_4$). Anal. calcd for $C_{17}H_{17}N_5OS$: C, 60.16; H, 5.05; N, 20.63; S, 9.45; found: C, 60.13; H, 5.02; N, 20.52; S, 9.41%.

*4-Methyl-2-(4-methylpiperidin-1-yl)-5*H*-benzimidazo[2,1-*b*]pyrimido[4,5-*d*][1,3]thiazine* (**9c**): White powder; yield 87%; m.p. 110–112 °C; IR (KBr disc) (υ_{max} cm^{-1}): 2999, 2985, 2933, 2856, 2790, 2680, 1614, 1598, 1581, 1539, 1446, 1409, 1361, 1296, 1263, 1213,

1169, 1141, 1003; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.9 (d, *J* = 6.3 Hz, 3H, CH_3–piperidine), 1.05–1.17 (m, 2H, axial hydrogens of CH_2), 1.57–1.70 (m, 3H, equatorial hydrogens of CH_2 and CH–piperidine), 2.36 (s, 3H, CH_3–pyrimidine), 2.86 (t, *J* = 12 Hz, 2H, axial hydrogens of CH_2–N), 3.92 (s, 2H, CH_2–thiazine), 4.71 (d, *J* = 13 Hz, 2H, equatorial hydrogens of CH_2–N), 7.18–7.23 (m, 2H, ArH), 7.57–7.60 (m, 1H, ArH), 8.23–8.26 (m, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.9 ($\underline{C}H_3$), 22.6 ($\underline{C}H_3$), 24.5 ($\underline{C}H$), 31.3 ($\underline{C}H_2$), 34.0 ($\underline{C}H_2$–S), 44.5 ($\underline{C}H_2$–N), 100.4, 114.9, 118.8, 123.5, 123.9, 132.9, 143.7, 150.0, 154.7, 159.9, 164.8. Anal. calcd for $C_{19}H_{21}N_5S$: C, 64.93; H, 6.02; N, 19.93; S, 9.12; found: C, 64.96; H, 5.98; N, 20.02; S, 9.15%.

*4-Methyl-2-(4-methylpiperazin-1-yl)-5*H*-benzimidazo[2,1-*b*]pyrimido[4,5-*d*][1,3]thiazine* (**9d**): White powder; yield 85%; m.p. 140–142 °C; IR (KBr disc) (υ_{max} cm^{-1}): 2999, 2958, 2933, 2856, 2790, 2680, 1614, 1598, 1581, 1539, 1446, 1361, 1296, 1274, 1213, 1169, 1142; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.38 (s, 3H, CH_3–pyrimidine), 2.46 (s, 3H, CH_3–piperazine), 2.53 (t, *J* = 4.8 Hz, 4H, CH_2–piperazine), 3.94 (t, *J* = 4.8 Hz, 4H, CH_2–piperazine), 4.00 (s, 2H, CH_2–thiazine), 7.29–7.32 (m, 2H, ArH), 7.65–7.68 (m, 1H, ArH), 8.28–8.31 (m, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.5 ($\underline{C}H_3$), 24.4 ($\underline{C}H_2$–S), 43.9 ($\underline{C}H_3$–N), 46.2 ($\underline{C}H_2$–N), 54.9 ($\underline{C}H_2$–N), 101.2, 114.8, 118.9, 123.5, 123.9, 132.8, 143.7, 149.9, 154.7, 159.9, 164.9; MS (*m*/*z*): 352 (M^+), 276 ($M^+ - C_6H_4$). Anal. calcd for $C_{18}H_{20}N_6S$: C, 61.34; H, 5.72; N, 23.84; S, 9.10; found: C, 61.36; H, 5.75; N, 23.90; S, 9.14%.

*4-Methyl-2-(4-phenylpiperazin-1-yl)-5*H*-benzimidazo[2,1-*b*]pyrimido[4,5-*d*][1,3]thiazine* (**9e**): White powder; yield 82%; m.p. 242–243 °C; IR (KBr disc) (υ_{max} cm^{-1}): 3052, 2974, 2896, 2853, 2827, 1617, 1597, 1544, 1490, 1445; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.53 (s, 3H, CH_3–pyrimidine), 3.34 (t, *J* = 5.1 Hz, 4H, CH_2–piperazine), 4.07 (s, 2H, CH_2–thiazine), 4.11 (t, *J* = 5.1 Hz, 4H, CH_2–piperazine), 6.94 (t, *J* = 7.2 Hz, 1H, ArH), 7.04 (d, *J* = 8.1 Hz, 2H, ArH), 7.32–7.40 (m, 4H, ArH), 7.69–7.74 (m, 1H, ArH), 8.35–8.41 (m, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.6 ($\underline{C}H_3$), 24.4 ($\underline{C}H_2$–S), 44.0 ($\underline{C}H_2$–N), 49.4 ($\underline{C}H_2$–N), 101.5, 114.9, 116.6, 118.9, 120.3, 123.6, 124.1, 129.3, 132.8, 143.8, 149.9, 151.3, 154.8, 159.9, 165.0; MS (*m*/*z*): 414 (M^+). Anal. calcd for $C_{23}H_{22}N_6S$: C, 66.64; H, 5.35; N, 20.27; S, 7.74; found: C, 66.61; H, 5.32; N, 20.19; S, 7.71%.

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Electronic Supplementary Information

The ^{1}H and ^{13}C NMR spectra for all new compounds are available in the ESI through http://ingentaconnect.com/content/stl/jcr/2017/00000041/00000012/art00014

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