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Microwave-assisted one-pot synthesis of benzo[*b*][1,4]thiazin-3(4*H*)-ones via Smiles rearrangement

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ABSTRACT

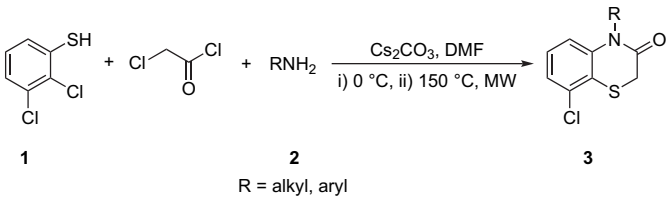
The synthesis of benzo[*b*][1,4]thiazin-3(4*H*)-one derivatives in a simple and efficient method from the one-pot reaction of substituted 2-chlorobenzenthiols, chloroacetyl chloride, and primary amines via Smiles rearrangement under microwave irradiation gave high yields (65–92%) of the products with short reaction time (15–20 min).

1. Introduction

For heterocycles containing sulfur moieties, benzo[*b*][1,4]thiazin-3(4*H*)-one derivatives' scaffold are classified as privileged structures due to the large number of biologically active molecules and natural products containing this moiety.[1–13]

To date, the benzo[*b*][1,4]thiazin-3(4*H*)-one scaffold has been generated by several methods involving: (i) direct cyclization from 2-aminobenzenethiol by reacting with halo acetyl halide;[14] (ii) starting from halonitrophenol followed by substitution of halo atom by thiol acetates and then reduction to form ring system;[10,15] (iii) treatment of 2-chloroaniline with sodium sulfide, followed by the reaction with chloroacetic acid for cyclization.[7,8] However, the limited kinds of 2-aminobenzenethiol, halonitrophenol, and 2-chloroaniline hindered the structural diversity of benzo[1,4]-thiazin-3(4*H*)-ones. Other challenges in this field are low yield because of multi-step and expensive catalysts used in the reported methods.

Recently, we reported the one-pot synthesis of benzo[*b*]-[1,4]oxazin-3(4*H*)-ones under microwave irradiation via Smiles rearrangement.[16] We have found that the good results were obtained using substituted 2-chlorophenols (1.0 equiv) and primary amines (1.2 equiv) in the presence of Cs_2CO_3 (3.6 equiv). In an ongoing studies on the development of new routes for the preparation of biologically active heterocyclic compounds,[17] we herein used substituted 2-chlorobenzenethiol **1**, chloroacetyl chloride, and primary amine **2** under microwave (MW) irradiation to synthesize benzo[*b*][1,4]thiazin-3(4*H*)-ones via Smiles rearrangement as one-pot reaction (Scheme 1). This method afforded an easy and efficient way to prepare benzo[*b*][1,4]thiazin-3(4*H*)-ones and permitted us to introduce great molecular diversity, including substitution diversity and skeleton diversity of benzo[1,4]thiazin-3(4*H*)-ones.



Scheme 1. One-pot synthesis of benzo[1,4]thiazin-3(4*H*)-ones.

2. Results and discussions

Substituted 2-chlorobenzenethiol **1**, chloroacetyl chloride, and primary amine **2** in the presence of Cs_2CO_3 in dry DMF underwent a fast 1:1:1 addition reaction at 150 °C under microwave for less than 20 min to produce corresponding benzo[*b*][1,4]-thiazin-3(4*H*)-ones. The results were excellent in terms of yields (65–92%),

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Table 1
Microwave-assisted one-pot synthesis of benzo[*b*][1,4]thiazin-3(4*H*)-ones[a]

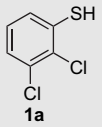
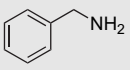
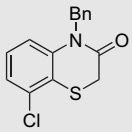
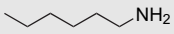
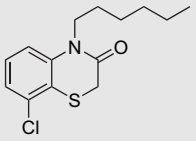
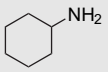
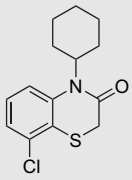
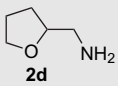
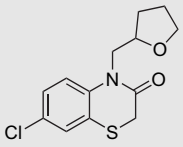
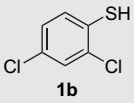
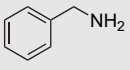
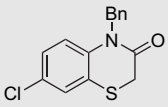
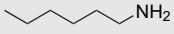
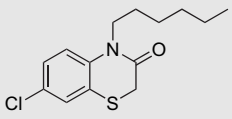
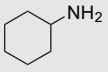
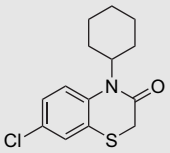
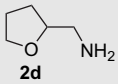
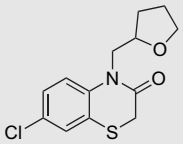
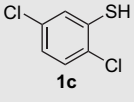
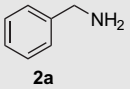
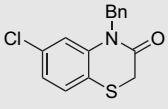
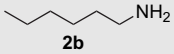
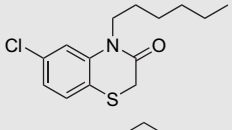
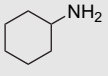
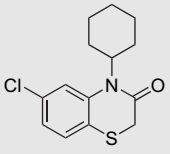
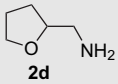
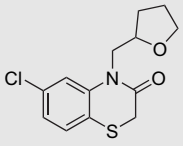
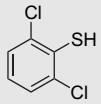
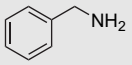
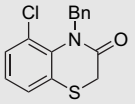
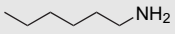
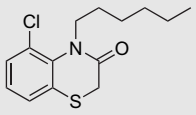
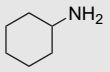
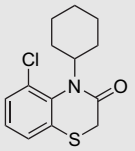
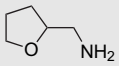
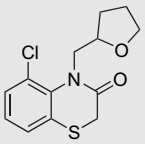
Entry	Benzenethiol	Amine	Product[b]		Time (min)	Yield[c] (%)
1	 **1a**	 **2a**		**3a**	18	85
2	**1a**	 **2b**		**3b**	15	82
3	**1a**	 **2c**		**3c**	20	65
4	**1a**	 **2d**		**3d**	20	86
5	 **1b**	 **2a**		**3e**	18	92
6	**1b**	 **2b**		**3f**	18	90
7	**1b**	 **2c**		**3g**	18	80
8	**1b**	 **2d**		**3h**	20	84
9	 **1c**	 **2a**		**3i**	18	85
10	**1c**	 **2b**		**3j**	18	72
11	**1c**	 **2c**		**3k**	20	80
12	**1c**	 **2d**		**3l**	18	75

Table 1 (*continued*)

Entry	Benzenethiol	Amine	Product[b]		Time (min)	Yield[c] (%)
13	 **1d**	 **2a**		**3m**	18	85
14	**1d**	 **2b**		**3n**	18	72
15	**1d**	 **2c**		**3o**	20	80
16	**1d**	 **2d**		**3p**	18	73

[a] Reaction conditions: $ClCH_2COCl$, Cs_2CO_3, (i) 0 °C (ii) 150 °C, MW.
[b] All the products were characterized by mp, MS, ^1H, and ^{13}C NMR spectra.
[c] Isolated yields after column purification.

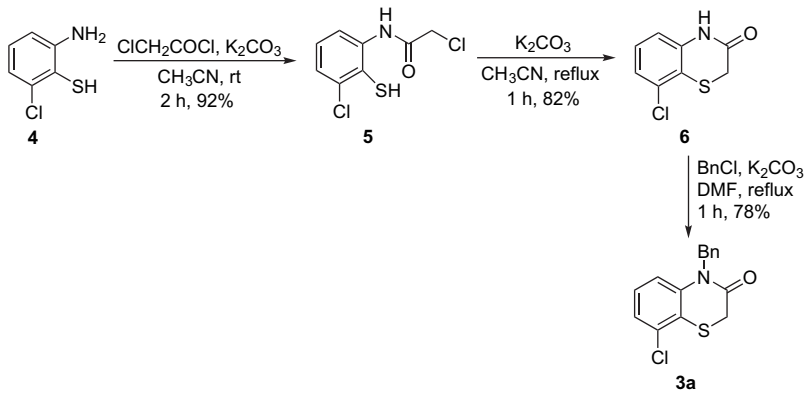
reaction time (15–20 min), and product purity. The nature of these compounds as 1:1:1 adducts was apparent from their mass spectra, which displayed, in each case, the molecular ion peak at appropriate *m*/*z* values. IR, ^1H, and ^{13}C NMR, GC–MS spectral data fully supported the predicted structures.

In view of the high efficiency of Cs_2CO_3/DMF system in our earlier work on the synthesis of the benzo[*b*][1,4]oxazin-3(4*H*)-ones,[16] we chose it as a base to perform this one-pot reaction of benzo[1,4]thiazin-3(4*H*)-ones, and the results were given in Table 1. The desired benzo[1,4]thiazin-3(4*H*)-one **3a** was obtained by the reaction of 2,3-dichlorobenzenethiol **1a** and benzyl amine **2a** in the presence of Cs_2CO_3 at 150 °C for 18 min in 85% yield (entry 1). Accordingly, the other benzo[1,4]thiazin-3(4*H*)-ones were also performed in the same approach yielding from 65% to 92% (entries 2–16). It is interesting to note that the position of chloro at aromatic ring did not interfere with the outcome of the reaction. The presence of an alkyl or aryl substituent of amine also did not show any significant influence on the reaction. In all cases studied, Cs_2CO_3/DMF exhibited a good system, while either decreasing the ratio of Cs_2CO_3 or using K_2CO_3 instead of Cs_2CO_3 only caused the incompletion of the reaction. This method provided a convenient and efficient route for preparing a variety of benzo[1,4]thiazin-3(4*H*)-ones. Representative primary amines possessing a straight-chain alkyl group, branched-chain alkyl group, aryl group, and tetrahydrofuran group reacting with substituted chlorobenzenethiols afforded **3** in high yields (entries 1–16).

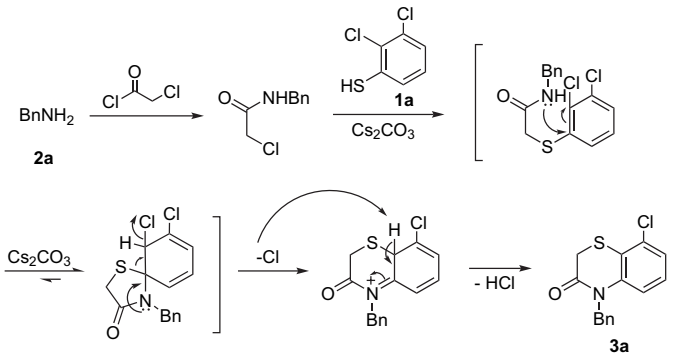
The formation of **3a** was confirmed by the reaction of 2-amino-6-benzenethiol **4** with chloroacetyl chloride using known method (Scheme 2). Chloroacetyl chloride was reacted with **4** to afford the intermediate **5**, which was cyclized to afford **6**. Compound **6** was then treated with benzyl chloride to furnish compound **3a**. Product **3a** obtained by two different synthetic routes, that is, from **1a** (Scheme 1) and from **4** (Scheme 2) was compared using physical and spectral data. R_f value of TLC, melting point, GC–MS, and NMR spectral data of the two compounds were found to be the same.

The formation of benzo[*b*][1,4]thiazin-3(4*H*)-ones is explained by a mechanism in Scheme 3 (exemplified by **3a**). As the reaction is conducted in the presence of Cs_2CO_3 as base, it facilitates the formation of *S*-alkylated product.

It is then possible for the cyclization by Smiles rearrangement via two steps: the spiro-type intermediate was formed in the first



Scheme 2. Alternative route for the synthesis of **3a**.



Scheme 3. Proposed mechanism.

step, and was rearranged in the second step with the loss of HCl yielding compound **3a**.

3. Conclusions

A new and one-pot route to benzo[*b*][1,4]thiazin-3(4*H*)-ones by microwave irradiation via Smiles rearrangement was developed. The use of simple starting materials, moderate to excellent yields, short reaction time, and easy purification procedure present the notable advantages of this method. The chemistry developed herein together with our previous work should be thus particularly useful in the diversity-oriented synthesis of oxazin-3(4*H*)-ones and thiazin-3(4*H*)-ones. To the best of our knowledge, this new procedure provides the first example of the efficient synthetic method for benzo[*b*][1,4]thiazin-3(4*H*)-ones by a one-pot reaction via Smiles rearrangement. Studies on the biological activities of these products are currently undergoing.

4. Experimental section

4.1. General

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ (400 MHz for ^{1}H and 100 MHz for ^{13}C, respectively) with TMS as the internal reference on Bruker Advance 400 FT spectrometer. Chemicals shifts were reported in parts per million. Mass spectra (MS) were measured by the EI method. Melting points are uncorrected. Silica gel (70–230 mesh) was used for flash column chromatography. All the reactions were monitored by TLC using 0.25 mm silica gel plates (Merck $60F_{254}$) with UV indicator. All microwave-assisted reactions were carried out on KMIC-1.5 kW creator from Korea Microwave Instrument Company. The microwave-assisted reaction time is the hold time at the final temperature. All chemicals were used as delivered from Sigma–Aldrich or Acros. *N*,*N*-Dimethyl-formamide was distilled from anhydrous magnesium sulfate prior to use. Acetonitrile was distilled over phosphorus oxide before use.

4.2. General procedure for the synthesis of benzo[*b*][1,4]thiazin-3(4*H*)-ones (3)

To a magnetically stirred solution of the appropriate primary amine **2** (1.0 mmol) and Cs_2CO_3 (3.6 mmol) in dry DMF cooled by ice bath were added chloroacetyl chloride (1.1 mmol) and **1** (0.8 mmol). The reaction mixture was then placed into microwave oven (KMIC-1.5 kW) at 150 °C and irradiated for the period listed in Table 1. The solvent was removed under vacuum and the residue was poured into water. It was then extracted by ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$ and evaporated under vacuum to obtain the crude product. Pure product was obtained by column chromatography on silica gel.

4.2.1. 4-Benzyl-8-chloro-2H-benzo[b][1,4]thiazin-3(4H)-one (**3a**)

A light-yellow powder; mp 96–97 °C; IR (KBr) ν/cm^{-1}: 3070, 3026, 3001, 2955, 2916, 1662, 1575, 1562, 1494, 1450, 1375, 1312, 1275, 1148, 883, 776, 733, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.53 (s, 2H), 5.20 (s, 2H), 6.92 (dd, *J*=8.0, 1.2 Hz, 1H), 7.00–7.09 (m, 2H), 7.17–7.33 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 31.1, 48.8, 116.6, 124.6, 126.3, 127.1, 127.4, 128.9, 129.1, 132.6, 136.3, 140.8, 164.9; MS (EI) *m*/*z*: 289 (M^+, 69%), 246 (7), 170 (28), 134 (7), 108 (7), 91 (100), 65 (12).

4.2.2. 8-Chloro-4-hexyl-2H-benzo[b][1,4]thiazin-3(4H)-one (**3b**)

A light-yellow oil; IR (KBr) ν/cm^{-1}: 3068, 2955, 2929, 2858, 1675, 1578, 1564, 1452, 1377, 1306, 1269, 1144, 1056, 772, 740, 708; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 (t, *J*=6.4 Hz, 3H), 1.30–1.36 (m, 6H), 1.56–1.65 (m, 2H), 3.38 (s, 2H), 3.97 (t, *J*=7.6 Hz, 2H), 7.04 (d, *J*=8.0 Hz, 1H), 7.12 (d, *J*=8.0 Hz, 1H), 7.18 (t, *J*=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 22.6, 26.4, 27.4, 31.2, 31.4, 45.2, 116.1, 124.3, 124.8, 127.0, 132.8, 140.5, 164.5; MS (EI) *m*/*z*: 283 (M^+, 55%), 236 (69), 212 (23), 199 (100), 184 (55), 170 (48), 154 (11), 134 (12), 108 (10).

4.2.3. 8-Chloro-4-cyclohexyl-2H-benzo[b][1,4]thiazin-3(4H)-one (**3c**)

An off-white solid; mp 110–112 °C; IR (KBr) ν/cm^{-1}: 3008, 2955, 2925, 2853, 1670, 1575, 1561, 1448, 1342, 1313, 1131, 1078, 773, 740, 712, 687; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.21–1.41 (m, 3H), 1.78–1.87 (m, 4H), 2.23–2.33 (m, 2H), 3.29 (s, 2H), 4.05–4.13 (m, 1H), 7.11–7.18 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.4, 26.5, 30.2, 33.5, 61.4, 117.9, 124.7, 126.6, 127.3, 132.9, 141.7, 166.6; MS (EI) *m*/*z*: 281 (M^+, 33%), 199 (100), 170 (42), 154 (15), 55 (8).

4.2.4. 8-Chloro-4-((tetrahydrofuran-2-yl)methyl)-2H-benzo[b][1,4]thiazin-3(4H)-one (**3d**)

A light-yellow oil; IR (KBr) ν/cm^{-1}: 3081, 2973, 2952, 2871, 1674, 1578, 1563, 1454, 1433, 1376, 1305, 1271, 1149, 1075, 1053, 942, 774, 741, 709; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.48–1.56 (m, 1H), 1.77–1.91 (m, 2H), 1.93–2.02 (m, 1H), 3.32 (dd, *J*=20.8, 14.4 Hz, 2H), 3.63–3.70 (m, 2H), 3.82 (dd, *J*=15.2, 7.2 Hz, 1H), 4.08–4.14 (m, 1H), 4.24 (dd, *J*=14.4, 3.6 Hz, 1H), 7.03 (dd, *J*=8.0, 1.2 Hz, 1H), 7.09 (t, *J*=8.0 Hz, 1H), 7.39 (dd, *J*=8.0, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.6, 29.5, 31.3, 50.4, 68.2, 77.0, 117.7, 124.5, 124.8, 127.1, 132.3, 141.4, 164.8; MS (EI) *m*/*z*: 283 (M^+, 10%), 213 (18), 199 (75), 184 (19), 170 (19), 108 (11), 85 (35), 71 (100), 43 (26).

4.2.5. 4-Benzyl-7-chloro-2H-benzo[b][1,4]thiazin-3(4H)-one (**3e**)

A colorless oil; IR (KBr) ν/cm^{-1}: 3063, 3027, 2928, 1665, 1584, 1477, 1405, 1360, 1317, 1266, 1234, 1141, 1106, 875, 812, 723, 693; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.50 (s, 2H), 5.20 (s, 2H), 6.90 (d, *J*=8.8 Hz, 1H), 7.03 (dd, *J*=8.8, 2.4 Hz, 1H), 7.16–7.33 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 31.4, 48.4, 119.3, 125.6, 126.3, 127.6, 127.4, 128.0, 128.8, 128.9, 136.2, 138.2, 165.0; MS (EI) *m*/*z*: 289 (M^+, 55%), 170 (15), 91 (100), 65 (10).

4.2.6. 7-Chloro-4-hexyl-2H-benzo[b][1,4]thiazin-3(4H)-one (**3f**)

A colorless oil; IR (KBr) ν/cm^{-1}: 3065, 2955, 2929, 2858, 1674, 1583, 1563, 1476, 1403, 1362, 1311, 1266, 1138, 1112, 869, 810, 782; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 (t, *J*=6.4 Hz, 3H), 1.24–1.34 (m, 6H), 1.61 (t, *J*=6.4 Hz, 2H), 3.37 (s, 2H), 3.96 (t, *J*=7.6 Hz, 2H), 7.03 (d, *J*=8.8 Hz, 1H), 7.19 (dd, *J*=8.8, 2.0 Hz, 1H), 7.34 (d, *J*=2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 22.6, 26.3, 27.3, 31.4, 31.5, 44.8, 118.8, 125.9, 127.1, 128.1, 128.4, 138.0, 164.6; MS (EI) *m*/*z*: 283 (M^+, 55%), 236 (45), 212 (21), 199 (100), 184 (49), 170 (42), 154 (10), 134 (9), 108 (9).

4.2.7. 7-Chloro-4-cyclohexyl-2H-benzo[b][1,4]thiazin-3(4H)-one (**3g**)

A colorless oil; IR (KBr) ν/cm^{-1}: 3065, 2931, 2854, 1671, 1581, 1560, 1474, 1453, 1416, 1382, 1347, 1315, 1289, 1261, 1237, 1142, 1109,

895, 868, 819, 788; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.21–1.41 (m, 3H), 1.68 (d, J=12.4 Hz, 1H), 1.77–1.87 (m, 4H), 2.20–2.29 (m, 2H), 3.28 (s, 2H), 4.07–4.15 (m, 1H), 7.17–7.18 (m, 2H), 7.36 (t, J=1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.4, 26.5, 30.2, 33.7, 60.1, 120.7, 126.8, 128.3, 128.4, 128.7, 139.0, 166.7; MS (EI) m/z: 281 (M^+, 27%), 199 (100), 170 (33), 154 (11), 55 (8).

4.2.8. 7-Chloro-4-((tetrahydrofuran-2-yl)methyl)-2H-benzo[b][1,4]thiazin-3(4H)-one (**3h**)

A light-yellow oil; IR (KBr) ν/cm^{-1}: 3093, 2973, 2872, 1674, 1584, 1563, 1477, 1402, 1357, 1308, 1267, 1237, 1109, 1084, 868, 810, 782; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.55–1.64 (m, 1H), 1.86–1.99 (m, 2H), 2.02–2.10 (m, 1H), 3.39 (dd, J=31.6, 14.4 Hz, 2H), 3.68–3.78 (m, 2H), 3.46 (J=15.2, 7.2 Hz, 1H), 4.16–4.23 (m, 1H), 4.33 (dd, J=14.4, 4.0 Hz, 1H), 7.19 (dd, J=8.8, 2.4 Hz, 1H), 7.33 (d, J=2.4 Hz, 1H), 7.48 (d, J=8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.6, 29.5, 31.6, 50.1, 68.2, 77.1, 120.5, 125.8, 127.2, 127.7, 128.7, 139.0, 164.9; MS (EI) m/z: 283 (M^+, 14%), 213 (15), 199 (68), 184 (17), 170 (16), 151 (6), 108 (10), 85 (29), 71 (100), 43 (20).

4.2.9. 4-Benzyl-6-chloro-2H-benzo[b][1,4]thiazin-3(4H)-one (**3i**)

A white solid; mp 105–106 °C; IR (KBr) ν/cm^{-1}: 3080, 3054, 3032, 3000, 2974, 2923, 1658, 1576, 1559, 1494, 1474, 1456, 1416, 1368, 1349, 1313, 1253, 1229, 1139, 1103, 1081, 1030, 927, 893, 870, 818, 779, 745, 717, 702, 674, 642; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.51 (s, 2H), 5.20 (s, 2H), 6.95 (dd, J=8.4, 2.0 Hz, 1H), 7.00 (d, J=2.0 Hz, 1H), 7.20 (d, J=8.4 Hz, 2H), 7.25–7.34 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 31.4, 48.5, 118.4, 122.2, 123.6, 126.3, 127.5, 129.0, 129.1, 132.9, 136.1, 140.6, 165.1; MS (EI) m/z: 289 (M^+, 75%), 246 (7), 170 (25), 91 (100), 65 (12).

4.2.10. 6-Chloro-4-hexyl-2H-benzo[b][1,4]thiazin-3(4H)-one (**3j**)

A light-yellow oil; IR (KBr) ν/cm^{-1}: 3051, 2955, 2929, 2857, 1678, 1581, 1560, 1475, 1416, 1378, 1349, 1312, 1252, 1136, 1104, 964, 900, 857, 806, 726, 674; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, J=7.6 Hz, 3H), 1.25–1.38 (m, 6H), 1.59–1.66 (m, 2H), 3.36 (s, 2H), 3.95 (t, J=7.6 Hz, 2H), 6.99 (dd, J=8.4, 2.0 Hz, 1H), 7.09 (d, J=2.0 Hz, 1H), 7.28 (d, J=8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 22.6, 26.3, 27.3, 31.4, 31.5, 44.8, 118.0, 122.4, 123.2, 129.3, 132.8, 140.4, 164.7; MS (EI) m/z: 283 (M^+, 66%), 236 (63), 212 (22), 199 (100), 184 (44), 170 (41), 154 (17), 134 (11), 108 (11).

4.2.11. 6-Chloro-4-cyclohexyl-2H-benzo[b][1,4]thiazin-3(4H)-one (**3k**)

A colorless oil; IR (KBr) ν/cm^{-1}: 3067, 2931, 2854, 1675, 1580, 1558, 1472, 1453, 1422, 1384, 1343, 1312, 1247, 1236, 1135, 1101, 997, 977, 896, 862, 806, 791, 767, 740, 710, 674; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.23–1.43 (m, 3H), 1.69 (d, J=12.4 Hz, 1H), 1.78–1.89 (m, 4H), 2.24–2.35 (m, 2H), 3.27 (s, 2H), 4.03–4.15 (m, 1H), 7.00 (dd, J=8.0, 2.0 Hz, 1H), 7.21 (d, J=2.0 Hz, 1H), 7.30 (d, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.4, 26.5, 30.1, 33.8, 61.2, 119.8, 123.6, 124.9, 129.5, 132.4, 141.5, 166.8; MS (EI) m/z: 281 (M^+, 27%), 199 (100), 170 (27), 154 (18), 55 (7).

4.2.12. 6-Chloro-4-((tetrahydrofuran-2-yl)methyl)-2H-benzo[b][1,4]thiazin-3(4H)-one (**3l**)

A light-yellow oil; IR (KBr) ν/cm^{-1}: 3091, 3070, 2973, 2920, 2872, 1675, 1581, 1560, 1475, 1415, 1347, 1308, 1255, 1137, 1105, 1081,1014, 942, 807, 780, 730, 676; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.57–1.66 (m, 1H), 1.87–2.02 (m, 2H), 2.06–2.12 (m, 1H), 3.39 (dd, J=31.2, 18.4 Hz, 2H), 3.69 (dd, J=14.4, 7.6 Hz, 1H), 3.76–3.81 (m, 1H), 3.91–3.96 (m, 1H), 4.19–4.26 (m, 1H), 4.32 (dd, J=14.4, 3.6 Hz, 1H), 6.99 (dd, J=8.4, 2.4 Hz, 1H), 7.26 (d, J=8.4 Hz, 1H), 7.58 (d, J=2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.6, 29.5, 31.6, 50.3, 68.3, 77.0, 119.7, 122.3, 123.6, 128.9, 132.8, 141.4, 165.0; MS (EI) m/z: 283 (M^+, 20%), 213 (19), 199 (100), 184 (18), 170 (17), 134 (9), 108 (12), 85 (19), 71 (100), 43 (23).

4.2.13. 4-Benzyl-5-chloro-2H-benzo[b][1,4]thiazin-3(4H)-one (**3m**)

A light-yellow oil; IR (KBr) ν/cm^{-1}: 3064, 3030, 2961, 2927, 1682, 1573, 1557, 1496, 1443, 1355, 1303, 1261, 1226, 1206, 1134, 1110, 1081, 1028, 903, 800, 774, 732, 722, 698, 675; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.27 (s, 2H), 5.31 (s, 2H), 6.82 (t, J=7.6 Hz, 1H), 7.03–7.10 (m, 6H), 7.16 (dd, J=7.6, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 34.2, 48.8, 125.4, 127.0, 127.2, 127.3, 127.7, 128.2, 129.6, 133.1, 136.5, 136.9, 167.5; MS (EI) m/z: 289 (M^+, 40%), 246 (8), 183 (10), 170 (40), 134 (8), 91 (100), 65 (11).

4.2.14. 5-Chloro-4-hexyl-2H-benzo[b][1,4]thiazin-3(4H)-one (**3n**)

A light-yellow oil; IR (KBr) ν/cm^{-1}: 3064, 2956, 2928, 2857, 1682, 1573, 1557, 1444, 1358, 1303, 1261, 1219, 1207, 1133, 1102, 1083, 902, 800, 773, 724, 674; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.81 (t, J=6.8 Hz, 3H), 1.17–1.25 (m, 6H), 1.42 (m, 2H), 3.32 (s, 2H), 4.12 (s, 2H), 7.02 (d, J=8.0 Hz, 1H), 7.28 (dd, J=8.0, 0.8 Hz, 1H), 7.36 (dd, J=8.0, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 22.5, 26.2, 27.4, 31.3, 34.4, 46.4, 125.1, 127.1, 127.3, 130.0, 133.0, 137.3, 167.8; MS (EI) m/z: 283 (M^+, 31%), 248 (20), 236 (27), 212 (15), 199 (100), 184 (44), 170 (53), 154 (13), 134 (15), 108 (7).

4.2.15. 5-Chloro-4-cyclohexyl-2H-benzo[b][1,4]thiazin-3(4H)-one (**3o**)

A colorless oil; IR (KBr) ν/cm^{-1}: 3063, 2927, 2852, 1681, 1571, 1557, 1468, 1440, 1430, 1345, 1306, 1298, 1274, 1259, 1237, 1206, 1131, 1106, 1081, 1056, 895, 815, 792, 772, 725, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.25–1.32 (m, 3H), 1.49 (d, J=12.4 Hz, 1H), 1.48–1.50 (m, 1H), 1.78–1.89 (m, 2H), 2.26–2.38 (m, 2H), 2.68–2.72 (m, 1H), 3.22 (s, 2H), 3.34–3.42 (m, 1H), 6.99 (t, J=8.0 Hz, 1H), 7.29 (dd, J=8.0, 1.2 Hz, 1H), 7.34 (dd, J=8.0, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.5, 26.7, 30.8, 36.2, 66.4, 124.8, 126.9, 128.0, 129.6, 133.6, 140.1, 167.8; MS (EI) m/z: 281 (M^+, 17%), 199 (100), 170 (57), 154 (20), 134 (12), 55 (13), 41 (10).

4.2.16. 5-Chloro-4-((tetrahydrofuran-2-yl)methyl)-2H-benzo[b][1,4]thiazin-3(4H)-one (**3p**)

A white solid; mp 124–125 °C; IR (KBr) ν/cm^{-1}: 3070, 3063, 2967, 2950, 2874, 1681, 1562, 1551, 1458, 1426, 1406, 1321, 1205, 1108, 1149, 1079, 1016, 919, 824, 775, 682; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.48–1.55 (m, 1H), 1.84–1.98 (m, 3H), 3.14–3.21 (m, 1H), 3.47–3.53 (m, 1H), 3.68 (s, 2H), 3.68–3.77 (m, 1H), 3.84–3.89 (m, 1H), 3.92–3.98 (m, 1H), 7.20–7.28 (m, 2H), 7.39 (d, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.8, 28.7, 38.7, 43.6, 68.1, 77.4, 129.0, 129.1, 130.4, 130.6, 131.6, 140.8, 167.8; MS (EI) m/z: 284 ($[M+1]^+$, 44%), 236 (10), 236 (27), 214 (13), 191 (16), 155 (6), 142 (27), 84 (59), 71 (100), 43 (29).

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References and notes

1. Ulrich, L.; Rainer, H. E.P. Patent 0303180, 1989.
2. Kajino, M.; Mizuno, K.; Tawada, H.; Shibouta, Y.; Nishikawa, K.; Meguro, K. *Chem. Pharm. Bull.* **1991**, *39*, 2888–2895.
3. Matsui, T.; Nakamura, Y.; Ishikawa, H.; Matsuura, A.; Kobayashi, F. *Jpn. J. Pharmacol.* **1994**, *64*, 115–124.
4. Kawashima, Y.; Ota, A.; Mibu, H. W.O. Patent 9405647, 1994.
5. Fujita, M.; Ito, S.; Ota, A.; Kato, N.; Yamamoto, K.; Kawashima, Y.; Yamauchi, H.; Iwao, J. *J. Med. Chem.* **1990**, *33*, 1898–1905.
6. Qar, J.; Barhanin, J.; Romey, G.; Henning, R.; Lerch, U.; Oekonomopulos, R.; Urbach, H.; Lazdunski, M. *Mol. Pharmacol.* **1988**, *33*, 363–369.

7. Guarda, V. L. M.; Perrissin, M.; Thomasson, F.; Ximenes, E. A.; Galdino, S. L.; Pitta, I. R.; Luu-Duc, C.; Barbe, J. *Eur. J. Med. Chem.* **2003**, *38*, 769–773.
8. Guarda, V. L. M.; Perrissin, M.; Thomasson, F.; Ximenes, E. A.; Galdino, S. L.; Pitta, I. R.; Luu-Duc, C. *Il Farmaco* **2001**, *56*, 689–693.
9. (a) Pitzurra, L.; Fringuelli, R.; Perito, S.; Schiaffella, F.; Barluzzi, R.; Bistoni, F.; Vecchiarelli, A. *Antimicrob. Agents Chemother.* **1999**, *43*, 2170–2175; (b) Fringuelli, R.; Schiaffella, F.; Bistoni, F.; Pitzurra, L.; Vecchiarelli, A. *Bioorg. Med. Chem.* **1998**, *6*, 103–108.
10. Yamamoto, T.; Watanabe, I. W.O. Patent 9813357, 1998.
11. (a) Iwao, J.; Iso, T.; Oya, M. U.S. Patent 4,584,300, 1986; (b) Rainer, H.; Ulrich, L. U.S. 4,595,685, 1986; (c) Ulrich, L.; Rainer, H. U.S. Patent 4,831,028, 1989.
12. Okami, Y.; Kawashima, Y. J.P. Patent 9012576, 1997.
13. Wuemachu, T.; Oshio, H. K.R. Patent 8200849, 1982.
14. (a) Chhikara, B. S.; Mishra, A. K.; Tandon, V. *Heterocycles* **2004**, *63*, 1057–1065; (b) Jacques, B. G.B. Patent 1115888, 1968; (c) Heravi, M. M.; Nami, N.; Oskooie, H. A.; Hekmatshoar, R. *Phosphorus, Sulfur Silicon Relat. Elem.* **2005**, *180*, 1873–1878.
15. (a) Wang, Z.; Yuan, Y.; Chen, Y.; Sun, G.; Wu, X.; Zhang, S.; Han, C.; Wang, G.; Li, L.; Liu, G. *J. Comb. Chem.* **2007**, *9*, 652–660; (b) Dartois, C. G. Y.; Markwell, R. E.; Madler, G. M. M. G.; Pearson, N. D.W.O. Patent 096907, 2002; (c) Miller, W. H.; Pearson, N. D.; Pendrak, I.; Seefeld, M. A. W.O. Patent 064421, 2003.
16. Zuo, H.; Meng, L.; Ghate, M.; Hwang, K.-H.; Cho, Y.-K.; Chandrasekhar, S.; Reddy, C. R.; Shin, D.-S. *Tetrahedron Lett.* **2008**, *49*, 3827–3830.
17. (a) Cho, S.-D.; Song, S.-Y.; Park, Y.-D.; Kim, J.-J.; Joo, W.-H.; Shiro, M.; Falck, J. R.; Shin, D.-S.; Yoon, Y.-J. *Tetrahedron Lett.* **2003**, *44*, 8995–8998; (b) Cho, S.-D.; Park, Y.-D.; Kim, J.-J.; Joo, W.-H.; Shiro, M.; Esser, L.; Falck, J. R.; Ahn, C.; Shin, D.-S.; Yoon, Y.-J. *Tetrahedron* **2004**, *60*, 3763–3773; (c) Cho, S.-D.; Park, Y.-D.; Kim, J.-J.; Lee, S.-G.; Ma, C.; Song, S.-Y.; Joo, W.-H.; Falck, J. R.; Shiro, M.; Shin, D.-S.; Yoon, Y.-J. *J. Org. Chem.* **2003**, *68*, 7918–7920; (d) Shin, D.-S.; Park, J. K. *Bull. Korean Chem. Soc.* **2007**, *28*, 2219–2225.