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ORIGINAL RESEARCH

Microwave-assisted synthesis of optically active *N*-substituted 2-methyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ones and -thiazin-3(4*H*)-ones via Smiles rearrangement

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Abstract: Optically active *N*-substituted-2-methyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ones and *N*-substituted-2-methyl-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-ones with potential synthetic and pharmacological interest were prepared via Smiles rearrangement using microwave irradiation in one-pot from inexpensive (*S*)-2-chloropropionic acid.

Keywords: microwave-assisted synthesis, Smiles rearrangement, optically active oxazinones, chiral thiazinones

Introduction

The 1,4-benzoxazinone and 1,4-benzoxazine systems are intriguing because they are present in clinically significant pharmaceuticals and other biologically active molecules. Benzo[1,4]oxazin-3(4*H*)-ones are also known as 5-hydroxytryptamine–receptor antagonists,[1–3] bladder-selective potassium channel openers, inhibitors of calcium channel, Na/H exchange inhibitors, antidepressants, dopamine D_2-receptor agonists, and inhibitors of phosphoinositide 3–kinase-γ.[4–6] For example, SLV314 (Figure 1) is a promising novel antipsychotic, combining strong dopamine D_2-receptor antagonism with serotonin reuptake inhibitor effects in the same dose range, and was selected for clinical development.[7–13] Some substituted [1,4]-oxazinones are also related to blocking the thromboxane A_2 receptor and activating the prostacyclin receptor.[14] Moreover, certain kinds of benzo[1,4]oxazin-3(4*H*)-ones are of interest as photochromic compounds,[15,16] and some possess herbicidal properties.[17]

Benzo[*b*][1,4]thiazin-3(4*H*)-ones exhibit different pharmacological activities: bacteriostatic,[18] antimicrobial,[19] antifungal,[20,21] Na^+/H^+ exchange–system inhibitor,[22] and calcium antagonist.[23–25] For example, levosemotiadil (Figure 1), an *S*-enantiomer of semotiadil, is an antiarrhythmic drug that blocks sodium and calcium channels. Recently, it was reported that levosemotiadil also exhibited a potassium-blocking activity. Benzo[*b*][1,4]thiazin-3(4*H*)-ones are also useful as prophylactic drugs and/or therapeutic drugs in hyperlipemia, hyperglycemia, obesity, diseases attributable to sugar-tolerance insufficiency, hypertension, osteoporosis, cachexia, and complications of diabetes such as retinopathy, nephrosis, neuropathy, cataract, coronary artery disease, and arteriosclerosis.[26] Moreover, this class of compounds is used as herbicides.[27]

[1,4]-Oxazinones and thiazinones have attracted considerable attention due to their pharmacological properties, as described above. The synthetic chiral benzo[1,4]-oxazinones and benzo[1,4]-thiazinones from substituted phenols and thio-phenols are greatly limited due to complicated methods or expensive materials. As a part of our

continuing efforts for the development of simpler and more convenient synthetic methods for interesting heterocyclic systems,[28] we herein describe a one-pot synthesis of diverse optically active *N*-substituted-2-methyl-2*H*-benzo[*b*][1,4] oxazin-3(4*H*)-ones and *N*-substituted-2-methyl-2*H*-benzo[*b*] [1,4]thiazin-3(4*H*)-ones involving Smiles rearrangement.[29–34] This work extends our previous report, in which we described the primary and optically inactive 2-chloroacetamides as starting materials.[35]

Methods and materials

Melting points were determined on a MEL-TEMP® (Burlington, NJ, USA) capillary melting-point apparatus and are uncorrected. Optical rotations were measured with a Rudolph Autopol IV digital polarimeter (Rudolph Research Analytical, Hackettstown, NJ, USA). Nuclear magnetic resonance (^{1}H and ^{13}C NMR spectra) was recorded in $CDCl_3$ (400 MHz for ^{1}H and 100 MHz for ^{13}C) with trimethylsilane (TMS) as the internal reference on an Avance 400 FT spectrometer (Bruker, Billerica, MA, USA). Chemical shifts were reported in parts per million. Mass spectrometry (MS) was measured by electron impact (EI) method. Silica gel (D-6100, 70-230 mesh, ASTM; Merck, Darmstadt, Germany) was used for flash column chromatography. All reactions were monitored by thin layer chromatography (TLC) using 0.25 mm silica gel plates (Merck 60F-254) with or without an ultraviolet indicator. *N*,*N*-dimethylformamide (DMF) was distilled over anhydrous magnesium sulfate. All other reagents were commercially available and were used without further purification. All microwave-assisted reactions were carried out on a KMIC 1.5 kW creator from Korea Microwave Instrument (Suwon, South Korea). The microwave-assisted reaction time was the hold time at the final temperature.

General procedure for synthesis of (S)-*N*-substituted-2-chloropropanamide (3a–3d)

N,*N*′-Dicyclohexylcarbodiimide (DCC) was added (2.28 g, 11.05 mmol) to a solution of (*S*)-2-chloropropanoic acid (1.0 g, 9.21 mmol) at 0°C in dichloromethane. The resulting mixture was stirred for 30 minutes at 0°C, followed by the addition of amine (9.21 mmol). The reaction mixture was stirred overnight at room temperature. The mixture was filtered, and the filtration cake was washed with dichloromethane carefully. The filtrate was concentrated to give the crude product. Pure product (yield 79%) was obtained by column chromatography using a mixture of hexane and ethyl acetate as eluent.

(*S*)-2-chloro-*N*-([tetrahydrofuran-2-yl]methyl) propanamide (3a)

A colorless oil; mp 73°C–74°C; $[\alpha]_D^{20}$ – 9.6 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50–1.58 (m, 1H), 1.71 (d, *J* = 7.2 Hz, 3H), 1.86–2.03 (m, 3H), 3.17–3.26 (m, 1H), 3.50–3.58 (m, 1H), 3.73–3.78 (m, 1H), 3.84–3.89 (m, 1H), 3.95–4.01 (m, 1H), 4.38 (q, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.69, 22.80, 25.93, 28.59, 43.48, 55.94, 68.28, 169.74.

(*S*)-2-chloro-*N*-cyclohexylpropanamide (3b)

A white solid; mp 99°C–100°C; $[\alpha]_D^{20}$ – 12.3 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17–1.26 (m, 3H), 1.47–1.52 (d, *J* = 6.8 Hz, 3H), 1.69–1.75 (m, 3H), 1.89–1.99 (m, 2H), 2.13–2.33 (m, 2H), 4.40–4.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.92, 25.77, 26.34, 30.72, 30.74, 37.76, 46.04, 56.30, 169.46.

(*S*)-2-chloro-*N*-hexylpropanamide (3c)

A colorless oil; $[\alpha]_D^{20}$ = –7.7 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85–0.88 (t, *J* = 5.2 Hz, 3H), 1.28 (s, 6H), 1.49 (t, *J* = 6.8 Hz, 2H), 1.69–1.71 (m, 3H), 3.22–3.27 (m, 2H), 4.36–4.41 (q, *J* = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.96, 22.50, 22.74, 26.46, 29.25, 31.40, 39.95, 55.99, 169.45.

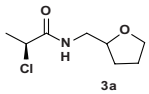
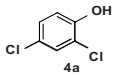
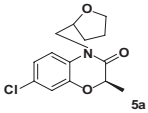
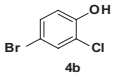
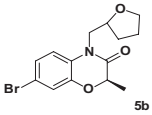
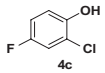
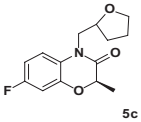
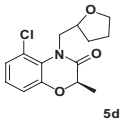
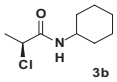
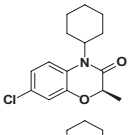
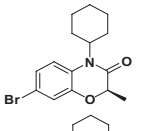
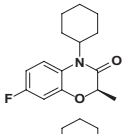
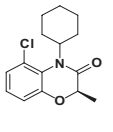
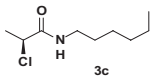
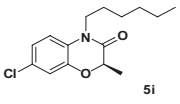
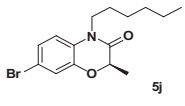
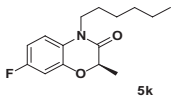
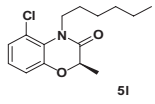
(*S*)-2-chloro-*N*-([*R*]-1-phenylethyl)propanamide (3d)

A white solid; mp 100°C–101°C; $[\alpha]_D^{20}$ +56.7 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (d, *J* = 7.2 Hz, 3H), 1.72 (d, *J* = 7.2 Hz, 3H), 4.42–4.47 (q, *J* = 7.2 Hz, 1H), 5.08–5.15 (m, 1H), 7.28–7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.80, 22.67, 49.26, 56.02, 125.97, 127.54, 128.80, 142.61, 168.56.

General procedure for synthesis of (R)-4-substituted-2-methyl-2*H*-benzo[*b*][1,4] oxazin-3(4*H*)-ones (5a–5l)

The solution of chlorophenols (2.40 mmol), chloropropanamides (2.40 mmol), Cs_2CO_3 (2.40 g, 7.36 mmol) in dry DMF was placed into a microwave oven (KMIC 1.5 kW) at 130°C and irradiated for the period listed in Table 1. The solvent was evaporated under reduced pressure. The residue was poured into water and then extracted by ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed under vacuum to obtain the crude product, which was purified by flash column chromatography on silica gel, eluting with hexane/ethyl acetate.

Table 1 Synthesis of (*R*)-*N*-substituted-2-methyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ones with microwave irradiation

Entry	Amides	Phenols	Products	Time (min)	Yield (%)[a]
1	 3a	 4a	 5a	20	80
2	3a	 4b	 5b	30	77
3	3a	 4c	 5c	20	62
4	3a	 4d	 5d	25	68
5	 3b	4a	 5e	35	77
6	3b	4b	 5f	55	82
7	3b	4c	 5g	40	74
8	3b	4d	 5h	40	80
9	 3c	4a	 5i	30	83
10	3c	4b	 5j	40	78
11	3c	4c	 5k	35	65
12	3c	4d	 5l	30	71

Note: [a]Yields refer to isolated pure compounds after column chromatography.

(2*R*)-7-chloro-2-methyl-4-([tetrahydrofuran-2-yl] methyl)-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (5a)

A colorless oil; $[\alpha]_D^{20} = -14.8$ (*c* 1.0, MeOH); infrared (KBr) ν/cm^{-1}: 3357, 3079, 2969, 2870, 1688, 1590, 1498, 1392, 1296, 1012, 863, 807, 719; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (d, J = 6.8 Hz, 3H), 1.62–1.69 (m, 1H), 1.89–1.96 (m, 3H), 3.70–3.78 (m, 3H), 4.15–4.18 (m, 2H), 4.57–4.62 (q, J = 6.8 Hz, 1H), 6.94 (t, J = 3.6, 2.0 Hz, 2H), 7.20–7.28 (dd, J = 17.2, 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.20, 25.57, 29.44, 46.74, 68.29, 73.65, 76.79, 116.70, 117.37, 122.60, 128.11,

128.62, 145.44, 166.46; MS (EI) m/z: 281 (M^+, 25%), 211 (12), 197 (62), 182 (12), 154 (61), 85 (19), 71 (100).

(2*R*)-7-bromo-2-methyl-4-([tetrahydrofuran-2-yl) methyl]-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (5b)

A colorless oil; $[\alpha]_D^{20} = -13.8$ (*c* 1.0, MeOH); IR (KBr) ν/cm^{-1}: 3357, 3083, 2969, 2870, 1684, 1586, 1494, 1388, 1296, 1073, 1012, 863, 807, 703; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (d, J = 6.8 Hz, 3H), 1.61–1.70 (m, 1H), 1.87–1.98 (m, 3H), 3.71–3.78 (m, 3H), 4.15–4.18 (m, 2H), 4.57–4.63 (q, J = 6.8 Hz, 1H), 7.13–7.19 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.21, 25.57, 29.44, 46.69, 68.29, 73.66, 76.78, 115.92, 117.40, 120.22, 125.54, 129.15, 145.58, 166.49; MS (EI) m/z: 325 (M^+, 20%), 255 (10), 241 (53), 226 (10), 200 (15), 85 (21), 71 (100).

(2*R*)-7-fluoro-2-methyl-4-([tetrahydrofuran-2-yl] methyl)-2H-benzo[*b*][1,4]oxazin-3(4*H*)-one (5c)

A colorless oil; $[\alpha]_D^{20} = -13.6$ (*c* 1.0, MeOH); IR (KBr) ν/cm^{-1}: 3353, 3075, 2962, 2874, 1684, 1609, 1509, 1445, 1403, 1296, 1145, 1069, 1012, 852, 803; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58 (d, J = 6.8 Hz, 3H), 1.63–1.71 (m, 1H), 1.89–1.97 (m, 3H), 3.69–3.75 (m, 3H), 4.16–4.20 (m, 2H), 4.66–4.71 (q, J = 6.8 Hz, 1H), 6.71–6.70 (m, 2H), 7.20–7.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.16, 25.53, 29.40, 46.97, 68.23, 73.67, 77.02, 104.72, 104.98 (d, J_{CF} = 26 Hz), 108.86, 108.96 (d, J_{CF} = 10 Hz), 116.49, 116.58 (d, J_{CF} = 9 Hz), 125.71, 125.74 (d, J_{CF} = 3 Hz), 145.02, 145.13 (d, J_{CF} = 11 Hz), 157.67, 157.72 (d, J_{CF} = 5 Hz), 116.31; MS (EI) m/z: 265 (M^+, 35%), 195 (18), 181 (78), 166 (18), 152 (7), 138 (36), 85 (20), 71 (100).

(2*R*)-5-chloro-2-methyl-4-([tetrahydrofuran-2-yl] methyl)-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (5d)

A colorless oil; $[\alpha]_D^{20} = -15.4$ (*c* 1.0, MeOH); IR (KBr) ν/cm^{-1}: 3372, 3079, 2958, 2870, 1692, 1574, 1460, 1373, 1267, 1077, 916, 783, 727; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51–1.55 (m, 4H), 1.83–1.91 (m, 3H), 3.63–3.69 (m, 2H), 3.96–4.01 (m, 1H), 4.29–4.40 (m, 1H), 4.43–4.63 (m, 2H), 6.99–7.01 (m, 2H), 7.08–7.10 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.58, 25.55, 28.81, 46.54, 67.77, 74.60, 75.46, 116.06, 123.74, 125.22, 125.53, 128.32, 150.41, 169.84; MS (EI) m/z: 281 (M^+, 6%), 211 (33), 197 (98), 182 (35), 71 (100), 168 (14), 154 (48), 85 (46).

(*R*)-7-chloro-4-cyclohexyl-2-methyl-2*H*-benzo[*b*][1,4] oxazin-3(4*H*)-one (5e)

A colorless oil; $[\alpha]_D^{20} = -17.1$ (*c* 1.0, MeOH); IR (KBr) ν/cm^{-1}: 3357, 3079, 2932, 2859, 1684, 1586, 1494, 1445, 1365, 1289, 1106, 1026, 966, 867, 803; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27–1.41 (m, 3H), 1.51 (d, J = 6.8 Hz, 3H), 1.71–1.82 (m, 3H), 1.88 (t, J = 6.4 Hz, 2H), 2.28–2.33 (m, 2H), 4.15–4.22 (m, 1H), 4.46–4.51 (q, J = 6.8 Hz, 1H), 6.98–7.02 (m, 2H), 7.08–7.10 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.01, 25.38, 26.35, 26.42, 29.22, 29.65, 56.94, 74.54, 116.92, 118.05, 122.40, 128.45, 128.64, 146.43, 167.71; MS (EI) m/z: 279 (M^+, 32%), 197 (100), 182 (10), 168 (6), 154 (43).

(*R*)-7-bromo-4-cyclohexyl-2-methyl-2*H*-benzo[*b*] [1,4]oxazin-(4*H*)-one (5f)

A colorless oil; $[\alpha]_D^{20} = -16.9$ (*c* 1.0, MeOH); IR (KBr) ν/cm^{-1}: 3353, 3075, 2932, 2859, 1684, 1590, 1494, 1369, 1289, 1110, 1069, 1026, 962, 860, 803; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23–1.40 (m, 3H), 1.51 (d, J = 6.8 Hz, 3H), 1.70–1.81 (m, 3H), 1.87 (t, J = 6.0 Hz, 2H), 2.28–2.32 (m, 2H), 4.14–4.22 (m, 1H), 4.45–4.50 (q, J = 6.8 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 7.08–7.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.02, 25.38, 26.35, 26.42, 29.20, 29.63, 58.91, 74.54, 115.64, 117.32, 120.87, 125.33, 129.14, 146.56, 167.72; MS (EI) m/z: 325 (M^+, 35%), 243 (100), 226 (10), 200 (40), 55 (10).

(*R*)-7-fluoro-4-cyclohexyl-2-methyl-2*H*-benzo[*b*][1,4] oxazin-(4*H*)-one (5g)

A colorless oil; $[\alpha]_D^{20} = -17.2$ (*c* 1.0, MeOH); IR (KBr) ν/cm^{-1}: 3433, 3075, 2932, 2863, 1680, 1498, 1369, 1289, 1216, 1149, 1110, 1026, 981, 867, 799; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27–1.41 (m, 3H), 1.51 (d, J = 6.8 Hz, 3H), 1.71–1.82 (m, 3H), 1.88 (t, J = 6.4 Hz, 2H), 2.28–2.33 (m, 2H), 4.15–4.22 (m, 1H), 4.46–4.51 (q, J = 6.8 Hz, 1H), 6.98–7.02 (m, 2H), 7.08–7.10 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.96, 25.38, 26.34, 26.41, 29.24, 29.70, 56.98, 74.61, 105.36, 105.61 (d, J_{CF} = 25 Hz), 108.75, 108.97 (d, J_{CF} = 22 Hz), 116.68, 116.77 (d, J_{CF} = 9 Hz), 126.24, 126.27 (d, J_{CF} = 3 Hz), 146.73, 146.84 (d, J_{CF} = 11 Hz), 157.42, 159.85 (d, J_{CF} = 43 Hz), 167.58; MS (EI) m/z: 263 (M^+, 40%), 181 (100), 166 (14), 152 (8), 138 (57).

(*R*)-5-chloro-4-cyclohexyl-2-methyl-2*H*-benzo[*b*][1,4] oxazin-(4*H*)-one (5h)

A colorless oil; $[\alpha]_D^{20} = -21.6$ (*c* 1.0, MeOH); IR (KBr) ν/cm^{-1}: 3353, 3083, 2969, 2928, 2859, 1684, 1464, 1570, 1407, 1365, 1224, 1087, 1023, 932, 886, 734; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20–1.30 (m, 3H), 1.51 (d, J = 6.8 Hz, 3H), 1.65 (d, J = 11.6 Hz, 1H), 1.80–1.88 (m, 3H), 2.16 (d, J = 12.4 Hz, 1H), 2.38–2.63 (m, 2H), 3.71–3.78 (m, 1H),

4.23–4.28 (q, J = 6.8 Hz, 1H), 6.95–7.01 (m, 2H), 7.09–7.13 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.14, 25.34, 26.59, 26.76, 29.26, 30.34, 63.22, 75.83, 115.60, 124.14, 124.88, 125.66, 130.61, 150.68, 169.91; MS (EI) m/z: 279 (M^+, 19%), 197 (100), 182 (11), 168 (6), 154 (63).

(*R*)-7-chloro-4-hexyl-2-methyl-2*H*-benzo[*b*][1,4] oxazin-3(4*H*)-one (5i)

A colorless oil; $[\alpha]_D^{20}$ = –9.7 (*c* 1.0, MeOH); IR (KBr) ν/cm^{-1}: 3353, 3075, 2932, 2863, 1688, 1590, 1498, 1400, 1293, 1149, 1110, 1012, 954, 867, 807, 723; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 7.2 Hz, 3H), 1.31–1.39 (m, 6H), 1.54 (d, J = 6.8 Hz, 3H), 1.60–1.65 (m, 2H), 3.87 (t, J = 8.0 Hz, 2H), 4.60–4.65 (q, J = 6.8 Hz, 1H), 6.87–6.90 (m, 1H), 6.99–7.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.97, 16.39, 22.53, 26.45, 27.01, 31.44, 41.63, 73.63, 115.39, 117.84, 122.50, 127.61, 128.46, 145.19, 166.02; MS (EI) m/z: 281 (M^+, 85%), 211 (10), 197 (100), 182 (61), 168 (12), 154 (68).

(*R*)-7-bromo-4-hexyl-2-methyl-2*H*-benzo[*b*][1,4] oxazin-3(4*H*)-one (5j)

A colorless oil; $[\alpha]_D^{20}$ = –9.3 (*c* 1.0, MeOH); IR (KBr) ν/cm^{-1}: 3345, 3072, 2932, 2859, 1684, 1593, 1494, 1369, 1293, 1149, 1106, 1069, 1016, 951, 863, 803, 719; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, J = 6.8 Hz, 3H), 1.31–1.38 (m, 6H), 1.54 (d, J = 6.8 Hz, 3H), 1.60–1.66 (m, 2H), 3.87 (t, J = 7.6 Hz, 2H), 4.61–4.66 (q, J = 6.8 Hz, 1H), 6.83 (t, J = 4.8 Hz, 1H), 7.14–7.17 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.99, 16.41, 22.54, 26.46, 27.01, 31.45, 41.61, 73.65, 115.81, 120.69, 125.46, 128.11, 131.25, 145.34, 166.06; MS (EI) m/z: 325 (M^+, 94%), 282 (14), 200 (64), 241 (100), 226 (62), 212 (11).

(*R*)-7-fluoro-4-hexyl-2-methyl-2*H*-benzo[*b*][1,4] oxazin-3(4*H*)-one (5k)

A colorless oil; $[\alpha]_D^{20}$ = –9.9 (*c* 1.0, MeOH); IR (KBr) ν/cm^{-1}: 3353, 3079, 2932, 2863, 1684, 1609, 1509, 1453, 1407, 1296, 1194, 1141, 1012, 852, 799, 727; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J = 6.8 Hz, 3H), 1.29–139 (m, 6H), 1.54 (d, J = 6.8 Hz, 3H), 1.60–1.66 (m, 2H), 3.87 (t, J = 7.6 Hz, 2H), 4.60–4.65 (q, J = 6.8 Hz, 1H), 6.73–6.77 (m, 2H), 6.88–6.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.02, 16.38, 22.57, 26.48, 27.04, 31.47, 41.71, 73.67, 105.25, 105.50 (d, J_{CF} = 25 Hz), 108.84, 109.07(d, J_{CF} = 23 Hz), 115.12, 115.21 (d, J_{CF} = 9 Hz), 125.21, 125.24 (d, J_{CF} = 3 Hz), 145.45, 145.56 (d, J_{CF} = 11 Hz), 157.52, 159.45 (d, J_{CF} = 193 Hz), 165.84; MS (EI) m/z: 265 (M^+, 92%), 194 (13), 181 (100), 166 (81), 152 (17), 138 (83).

(*R*)-5-chloro-4-hexyl-2-methyl-2*H*-benzo[*b*][1,4] oxazin-3(4*H*)-one (5l)

A colorless oil; $[\alpha]_D^{20}$ = –10.4 (*c* 1.0, MeOH); IR (KBr) ν/cm^{-1}: 3376, 3075, 2928, 2863, 1692, 1574, 1464, 1376, 1270, 1194, 1114, 1069, 940, 879, 776, 727; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (t, J = 6.8 Hz, 3H), 1.23–138 (m, 6H), 1.51–1.59 (m, 5H), 4.10–4.17 (m, 1H), 4.23–4.30 (m, 1H), 4.35–4.40 (q, J = 6.8 Hz, 1H), 6.95–7.00 (m, 2H), 6.91–7.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.95, 15.38, 22.48, 26.06, 27.61, 31.27, 44.43, 74.56, 115.90, 123.46, 125.00, 125.64, 127.85, 150.00, 168.90; MS (EI) m/z: 281 (M^+, 42%), 246 (20), 197 (100), 182 (44), 168 (8), 154 (70).

General procedure for synthesis of (R)-4-substituted-2-methyl-2*H*-benzo[*b*][1,4] thiazin-3(4*H*)-ones (7a–7j)

A solution of chlorobenzenethiol (2.23 mmol), (*S*)-*N*-furfuryl-2-chloropropanamide (0.427 g, 2.23 mmol), Cs_2CO_3 (2.18 g, 6.69 mmol) in dry DMF was placed into a microwave oven (KMIC 1.5 kW) at 130°C and irradiated for the period listed in Table 2. The solvent was evaporated under reduced pressure. The residue was poured into water and was then extracted by ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed under vacuum to obtain the crude product, which was purified by flash column chromatography on silica gel, eluting with hexane/ethyl acetate.

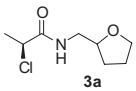
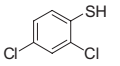
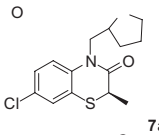
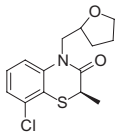
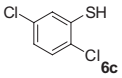
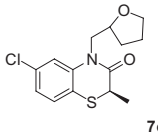
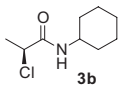
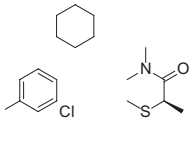
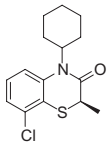
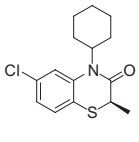
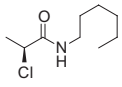
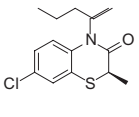
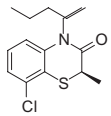
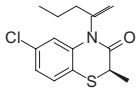
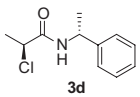
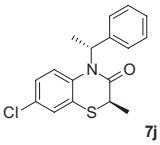
(2*R*)-7-chloro-2-methyl-4-((tetrahydrofuran-2-yl) methyl)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (7a)

A colorless oil; $[\alpha]_D^{20}$ = –11.3 (*c* 1.0, MeOH); IR (KBr) ν/cm^{-1}: 3323, 3087, 2973, 2870, 1670, 1582, 1472, 1400, 1361, 1255, 1016, 867, 814, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (d, J = 6.8 Hz, 3H), 1.57–1.60 (m, 1H), 1.86–1.96 (m, 3H), 3.45–3.55 (m, 1H), 3.65–3.70 (q, J = 6.8 Hz, 1H), 3.86–3.95 (m, 2H), 4.30–4.37 (m, 2H), 7.20–7.22 (m, 1H), 7.32–7.34 (m, 1H), 7.50 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.28, 29.46, 37.79, 51.07, 68.23, 77.30, 120.39, 125.50, 127.23, 127.56, 128.59, 138.89, 167.56; MS (EI) m/z: 297 (M^+, 17%), 227 (13), 213 (100), 198 (20), 170 (23), 85 (24), 71 (86).

(2*R*)-8-chloro-2-methyl-4-([tetrahydrofuran-2-yl] methyl)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (7b)

A colorless oil; $[\alpha]_D^{20}$ = –10.6 (*c* 1.0, MeOH); IR (KBr) ν/cm^{-1}: 3327, 3079, 2962, 2870, 1673, 1570, 1445, 1373, 1247, 1069, 973, 776, 711; ^{1}H NMR (400 MHz, $CDCl_3$)

Table 2 Synthesis of (*R*)-*N*-substituted-2-methyl-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-ones with microwave irradiation

Entry	Amide	Benzenethiol	Products	Time (h)	Yield (%)[a]
1	 3a	 6a	 7a	18	92
2	3a	 6b	 7b	18	90
3	3a	 6c	 7c	25	82
4	 3b	6a	 7d	30	85
5	3b	6b	 7e	25	72
6	3b	6c	 7f	30	80
7	 3c	6a	 7g	18	85
8	3c	6b	 7h	18	72
9	3c	6c	 7i	20	80
10	 3d	6d	 7j	18	72

Note: [a]Yields refer to isolated pure compounds after column chromatography.

δ 1.46 (d, J = 7.2 Hz, 3H), 1.68–1.75 (m, 1H), 1.84–1.86 (m, 3H), 3.24–3.35 (m, 2H), 3.84–3.95 (m, 2H), 4.08–4.16 (m, 2H), 7.14–7.17 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.30, 25.46, 26.49, 26.58, 29.89, 30.56, 39.71, 61.67, 117.76, 124.60, 126.56, 126.74, 132.95, 141.06, 168.89; MS (EI) m/z: 297 (M^+, 19%), 227 (15), 213 (100), 198 (18), 170 (23), 85 (22), 71 (87).

(2*R*)-6-chloro-2-methyl-4-([tetrahydrofuran-2-yl] methyl)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (7c)

A colorless oil; $[\alpha]_D^{20}$ = −11.8 (c 1.0, MeOH); IR (KBr) ν/cm^{-1}: 3083, 2973, 2870, 1670, 1574, 1468, 1411, 1347, 1247, 1103, 1073, 1019, 973, 871, 810, 723; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (d, J = 6.8 Hz, 3H), 1.57–1.65 (m, 1H), 1.87–2.00 (m, 3H), 3.41–3.47 (q, J = 6.8 Hz, 1H),

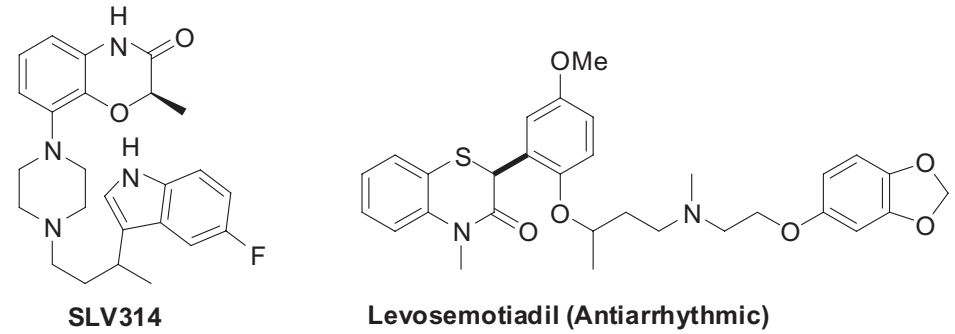


Figure 1 Compounds containing 2*H*-benzo[*b*][1,4]-oxazin-3(4*H*)-one and 2*H*-benzo[*b*][1,4]-thazine-3(4H)-one moieties.

3.61–3.67 (m, 1H), 3.88–3.97 (m, 2H), 4.18–4.35 (m, 2H), 6.97–7.01 (m, 1H), 7.23–7.26 (m, 1H), 7.60 (dd, $J = 1.2$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.22, 25.62, 29.45, 37.72, 51.18, 68.16, 77.14, 119.52, 122.12, 123.45, 128.80, 132.74, 141.2, 167.62; MS (EI) m/z: 297 (M^+, 16%), 227 (12), 213 (100), 198 (20), 170 (21), 85 (24), 71 (84).

(*R*)-7-chloro-4-cyclohexyl-2-methyl-2*H*-benzo[*b*][1,4] thiazin-3(4*H*)-one (7d)

A colorless oil; $[\alpha]_D^{20} = -15.8$ (*c* 1.0, MeOH); IR (KBr) ν/cm^{-1}: 3323, 3068, 2932, 2859, 2251, 1875, 1670, 1574, 1464, 1331, 1263, 1106, 1042, 901, 814, 734; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22–1.39 (m, 3H), 1.42 (d, $J = 7.2$ Hz, 3H), 1.68–1.88 (m, 5H), 2.22–2.29 (m, 2H), 3.14–3.36 (q, $J = 7.2$ Hz, 1H), 4.10–4.18 (m, 1H), 7.16–7.21 (m, 2H), 7.37 (d, $J = 2.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.50, 25.47, 26.48, 26.54, 29.99, 30.52, 39.94, 61.07, 120.44, 126.79, 127.64, 128.44, 128.71, 138.42, 168.96; MS (EI) m/z: 295 (M^+, 28%), 213 (100), 198 (20), 184 (7), 170 (28), 154 (22).

(*R*)-8-chloro-4-cyclohexyl-2-methyl-2*H*-benzo[*b*][1,4] thiazin-3(4*H*)-one (7e)

A colorless oil; $[\alpha]_D^{20} = -13.5$ (*c* 1.0, MeOH); IR (KBr) ν/cm^{-1}: 3331, 3072, 2932, 2859, 2662, 2251, 1673, 1570, 1449, 1347, 1247, 1190, 1050, 997, 901, 780, 727; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21–1.42 (m, 3H), 1.46 (d, $J = 7.2$ Hz, 3H), 1.68–1.75 (m, 2H), 1.84–1.86 (m, 3H), 2.24–2.33 (m, 2H), 3.29–3.35 (q, $J = 7.2$ Hz, 1H), 4.08–4.16 (m, 1H), 7.14–7.17 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.30, 25.46, 26.49, 26.58, 29.89, 30.56, 39.71, 61.67, 117.76, 124.60, 126.56, 126.74, 132.95, 141.06, 168.89; MS (EI) m/z: 295 (M^+, 40%), 213 (100), 198 (36), 184 (8), 170 (33), 154 (20).

(*R*)-6-chloro-4-cyclohexyl-2-methyl-2*H*-benzo[*b*][1,4] thiazin-3(4*H*)-one (7f)

A colorless oil; $[\alpha]_D^{20} = -16.0$ (*c* 1.0, MeOH); IR (KBr) ν/cm^{-1}: 3334, 3072, 2932, 2859, 2662, 1666, 1574, 1456, 1331, 1232, 1099, 1046, 993, 867, 807, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27–1.42 (m, 6H), 1.68–1.76 (m, 2H), 1.81–1.89 (m, 3H), 2.27–2.33 (m, 2H), 3.27–3.33 (q, $J = 6.8$ Hz, 1H), 4.05–4.14 (m, 1H), 6.99–7.01 (dd, $J = 8.0$, 2.0 Hz, 1H), 7.20 (d, $J = 2.0$ Hz, 1 H), 7.28 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.46, 25.43, 26.47, 26.53, 29.83, 30.37, 39.87, 61.43, 119.46, 123.56, 124.12, 129.65, 132.29, 140.88, 169.00; MS (EI) m/z: 295 (M^+, 38%), 213 (100), 198 (21), 184 (9), 170 (30), 154 (22).

(*R*)-7-chloro-4-hexyl-2-methyl-2*H*-benzo[*b*][1,4] thiazin-3(4*H*)-one (7g)

A colorless oil; $[\alpha]_D^{20} = -7.7$ (*c* 1.0, MeOH); IR (KBr) ν/cm^{-1}: 3334, 3068, 2932, 2863, 1673, 1578, 1472, 1403, 1365, 1312, 1255, 871, 810, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ 87 (t, $J = 6.8$ Hz, 3H), 1.28–1.38 (m, 6H), 1.45 (d, $J = 7.2$ Hz, 3H), 1.58–1.66 (m, 2H), 3.45–3.50 (q, $J = 7.2$ Hz, 1H), 3.92–4.01 (m, 2H), 7.02 (d, $J = 8.8$ Hz, 1H), 7.20–7.23 (dd, $J = 8.8$, 2.4 Hz, 1H), 7.35 (d, $J = 2.4$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.00, 15.04, 22.55, 26.35, 27.41, 31.44, 27.84, 45.23, 118.45, 124.83, 127.16, 128.35, 128.67, 137.58, 167.17; MS (EI) m/z: 297 (M^+, 61%), 236 (25), 226 (25), 213 (100), 198 (45), 170 (40), 154 (12).

(*R*)-8-chloro-4-hexyl-2-methyl-2*H*-benzo[*b*][1,4] thiazin-3(4*H*)-one (7h)

A colorless oil; $[\alpha]_D^{20} = -6.8$ (*c* 1.0, MeOH); IR (KBr) ν/cm^{-1}: 3331, 3072, 2928, 2859, 1916, 1677, 1570, 1453, 1373, 1304, 1251, 1190, 1099, 1038, 985, 772, 730; ^{1}H NMR (400 MHz,

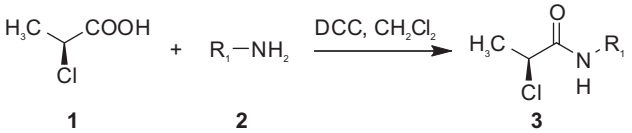
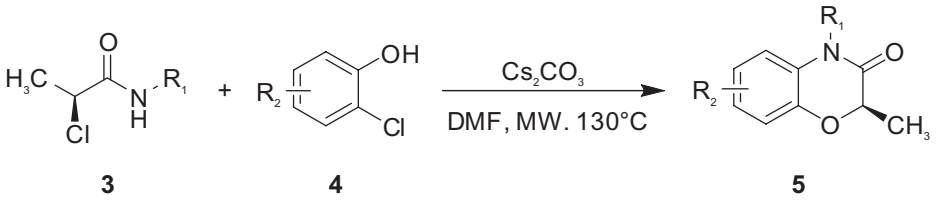


Figure 2 Synthesis of *N*-substituted-(*S*)-2-chloropropanamide (3) from (*S*)-2-chloropropionic acid (1) and alkyl amines (2).
Abbreviation: DCC, N,N'-Dicyclohexylcarbodiimide.



3 4 5

Figure 3 Synthesis of *N*-substituted-(*R*)-2-methyl -2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ones (5).
Note: 3 = *N*-substituted-(*S*)-chloro propanamides; 4 = 2-chlorophenols.
Abbreviations: DMF, Dimethylformamide; MW, Microwave.

$CDCl_3$) δ0.87 (t, J = 6.8 Hz, 3H), 1.27–1.36 (m, 6H), 1.48 (d, J = 7.2 Hz, 3H), 1.50–1.64 (m, 2H), 3.43–3.49 (q, J = 7.2 Hz, 1H), 3.95–4.00 (m, 2H), 7.03–7.05 (dd, J = 8.8, 1.2 Hz, 1H), 7.12–7.19 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.99, 14.85, 22.54, 26.38, 27.49, 31.43, 37.56, 45.74, 115.81, 123.98, 124.20, 126.95, 132.91, 140.15, 167.06; MS (EI) m/z: 297 (M^+, 58%), 236 (40), 213 (100), 198 (56), 170 (46), 154 (18).

(*R*)-6-chloro-4-hexyl-2-methyl-2*H*-benzo[*b*][1,4] thiazin-3(4*H*)-one (7i)

A colorless oil; $[\alpha]_D^{20}$ = −7.9 (*c* 1.0, MeOH); IR (KBr) ν/cm^{-1}: 3338, 3072, 2928, 2863, 1677, 1578, 1468, 1414, 1263, 1106, 981, 860, 814, 756, 727; ^{1}H NMR (400 MHz, $CDCl_3$) δ0.87 (t, J = 7.2 Hz, 3H), 1.32–1.37 (m, 6H), 1.43 (d, J = 7.2 Hz, 3H), 1.61–1.65 (m, 2H), 3.42–3.47 (q, J = 7.2 Hz, 1H), 3.89–4.02 (m, 2H), 6.99–7.01 (dd, J = 8.4, 2.0 Hz, 1H), 7.09 (d, J = 2.0 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ13.99, 14.97, 22.54, 26.33, 27.39, 31.40, 37.75, 45.27, 117.59, 121.38, 123.21, 129.58, 132.75, 139.97, 167.26; MS (EI) m/z: 297 (M^+, 67%), 236 (25), 226 (21), 213 (100), 198 (44), 170 (40), 154 (12).

(*R*)-7-chloro-2-methyl-4-([*R*]-1-phenylethyl)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (7j)

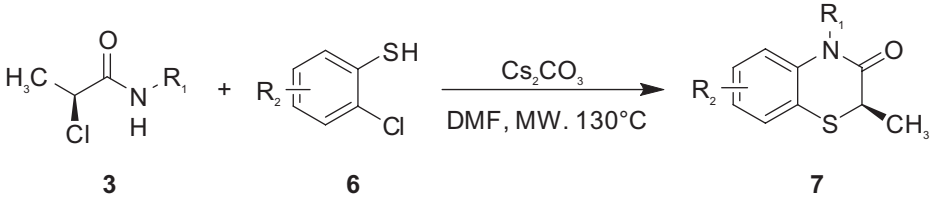
A colorless oil; $[\alpha]_D^{20}$ = −104.0 (*c* 1.0, MeOH); IR (KBr) ν/cm^{-1}: 3323, 3065, 3034, 2985, 2938, 2247, 1673, 1582, 1472, 1403, 1376, 1335, 1243, 1099, 913, 871, 814, 746, 703; ^{1}H NMR (400 MHz, $CDCl_3$) δ1.57 (d, J = 6.8 Hz, 3H), 1.66 (d, J = 6.8 Hz, 3H), 3.49–3.54 (q, J = 6.8 Hz, 1H), 6.37–6.42 (q, J = 6.8 Hz, 1H), 6.74 (d, J = 8.8 Hz, 1H), 6.96–6.99 (dd, J = 8.8, 2.4 Hz, 1H), 7.29–7.32 (m, 3H), 7.36–7.40 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.44, 16.61, 38.95, 52.76, 120.84, 125.93, 126.55, 127.08, 127.70, 128.24, 128.80, 128.89, 136.38, 141.16, 168.84; MS (EI) m/z: 317 (M^+, 22%), 246 (5), 213 (100), 198 (10), 170 (17), 154 (12), 105 (84), 77 (15).

Results and discussion

Our synthesis started with preparation of optically active *N*-substituted-(*S*)-2-chloropropanamides (3). The optically active (*S*)-2-chloropropionic acid (1)[36] was successfully coupled with various amines (2), with DCC affording the corresponding amides (3) (Figure 2).

The reaction of *N*-substituted-(*S*)-2-chloropropanamide (3) with 2-chlorophenols (4) gave the corresponding (*R*)-*N*-substituted-2-methyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ones (**5a-5l**) via Smiles rearrangement in one pot. The reaction proceeded smoothly at 130°C under microwave irradiation in DMF solvent (Figure 3).

The results and reaction conditions for the synthesis of various novel (*R*)-2-methyl-benzo[*b*][1,4]oxazin-3(4*H*)-ones are given in Table 1. The successful one-pot synthesis of (*R*)-*N*-substituted-2-methyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ones encouraged us to explore the same approach to prepare (*R*)-*N*-substituted-2-methyl-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-ones. Similarly, this one-pot reaction was carried out by mixing



3 6 7

Figure 4 Synthesis of *N*-substituted-(*R*)-2-methyl -2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-ones (7).
Note: 3 = *N*-substituted-(*S*)-chloro propanamides; 6 = 2-chlorothiophenols.
Abbreviations: DMF, Dimethylformamide; MW, Microwave.

1 equiv of amide (3), 1 equiv of 2-chlorobenzenethiols (6) and 2.5 equiv of Cs_2CO_3 in dry DMF and then heating under microwave irradiation. The reaction temperature was maintained at 130°C for 30 minutes to obtain the corresponding (*R*)-*N*-substituted-2-methyl-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-ones (**7a-7j**) in 65%–90% yield (Table 2 and Figure 4).

The optical activities of final products indicate that *O*- or *S*-alkylation takes place via S_N2 process.[37] The gas chromatography–MS spectra of all the corresponding products clearly indicated the formation of the corresponding product, and IR, ^{1}H NMR and ^{13}C NMR spectra further confirmed the structures of various *N*-substituted-2-methyl-2*H*-benzo[*b*](1,4)-oxazin-3(4*H*)ones and *N*-substituted-2-methyl-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-ones.

Conclusion

Novel optically active *N*-substituted-2-methyl-2*H*-benzo[*b*][1,4] oxazin-3(4*H*)-ones and *N*-substituted-2 methyl-2*H*-benzo[*b*] [1,4]thiazin-3(4*H*)-ones with potential synthetic and pharmacological interest were synthesized via Smiles rearrangement by microwave irradiation in one pot. Further studies including biological activity testing and expansion of more derivatives are currently in progress in our laboratory.

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Disclosure

The authors report no conflicts of interest in this work.

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