Synthesis and Anticonvulsant Activity of Some 7-Alkoxy-2*H*-1,4-benzothiazin-3(4*H*)-ones and 7-Alkoxy-4*H*-[1,2,4]triazolo[4,3-*d*]benzo[*b*][1,4]thiazines

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Received September 10, 2009; accepted October 15, 2009; published online December 4, 2009

A series of 7-alkoxy-2*H*-1,4-benzothiazin-3(4*H*)-ones and a new series of 7-alkoxy-4*H*-[1,2,4]triazolo[4,3-*d*]benzo[*b*][1,4]thiazine derivatives were synthesized using 5-methoxybenzo[*d*]thiazol-2-amine as starting material. The structures of the compounds were elucidated by IR, ^{1}H-NMR spectroscopic data and microanalyses. The anticonvulsant activity of these compounds was evaluated by maximal electroshock (MES) test and rotarod test following intraperitoneal injection in KunMing mice. Among the synthesized compounds 3a—v, 7-(hexyloxy)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (3f) could be considered potentially the most useful and safe therapeutic compound. Among the synthesized compounds 4a—u, compound 7-(2-fluorobenzyloxy)-4*H*-[1,2,4]triazolo[4,3-*d*]benzo[*b*][1,4]thiazine (4k) was the most active compound with an ED_{50} of 17.0 mg/kg, TD_{50} of 243.9 mg/kg and protective index (PI) of 14.3. Its neurotoxicity was lower than all the other synthesized compounds and also markedly lower than that of the reference drug carbamazepine.

Key words anticonvulsant; triazole; thiamine; maximal electroshock

Epilepsy, a common disease characterized by recurrent seizures, afflicts >50 million people worldwide according to epidemiological studies.[1)] For epilepsy treatment, nearly 95% of today's clinically available drugs were approved before 1985 and provide satisfactory seizure control for only 60—70% of patients. These drugs, however, also cause notable adverse side effects such as drowsiness, ataxia, gastrointestinal disturbance, hepatotoxicity and megaloblastic anemia[2—4)] and even life threatening conditions.[5)] Research to find more effective and safer antiepileptic drugs is, therefore, imperative and challenging in medicinal chemistry.

In the previous study, we reported the synthesis and anticonvulsant activities of 7-alkoxyl-3,4-dihydro-quinolin-2(1*H*)-ones (**pre. 1**),[6)] 7-alkoxyl-4,5-dihydro[1,2,4]triazolo[4,3-*a*]quinolines (**pre. 2**).[7)] In our search for new compounds with anticonvulsant activity, we changed the 4-position CH_2 of the compounds (**pre. 1**) into sulfur. 7-Alkoxyl-2*H*-benzo[*b*] [1,4]thiazin-3(4*H*)-ones (**3a**—**v**) were designed and synthesized as the bioisosterism of 7-alkoxyl-3,4-dihydro-quinolin-2(1*H*)-ones.

From compounds **pre. 1** to compounds **pre. 2**, we incorporated triazole with 7-alkoxyl-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-ones at the third and fourth position of the latter and obtained 7-alkoxyl-4*H*-[1,2,4]triazolo[4,3-*d*]benzo[*b*]-[1,4]thiazines (**4a**—**u**). Additionally, 7-alkoxyl-4*H*-[1,2,4]-triazolo[4,3-*d*]benzo[*b*][1,4]thiazines were the bioisostereomers of 7-alkoxyl-4,5-dihydro-[1,2,4]triazolo[4,3-*a*]quinolines. The structures of the compounds were elucidated by IR, ^{1}H-NMR spectroscopic data and microanalyses. The anticonvulsant activity was evaluated by maximal electroshock (MES) test; neurotoxicity was evaluated by rotarod test. Among compounds **3a**—**v** and **4a**—**u**, compound **4k** was the most active with an ED_{50} of 17.0 mg/kg, TD_{50} of 243.9 mg/kg and protective index (PI; TD_{50}/ED_{50}) of 14.3.

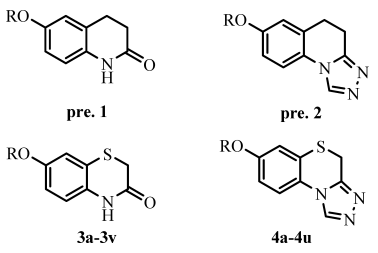

Fig. 1. Previous Work **1**, **2** and Present Work

Experimental

Chemistry Melting points were determined in open capillary tubes and were uncorrected. ^{1}H-NMR spectra were measured by AV-300 (Bruker, Switzerland); all chemical shifts are given in parts per million relative to tetramethylsilane. Mass spectra were measured by HP1100LC (Agilent Technologies, U.S.A.). Elemental analyses were performed on a 204Q CHN (PerkineElmer, U.S.A.). Microanalyses of C, N, and H were performed by Heraeus CHN Rapid Analyzer. The major chemicals were purchased from Aldrich Chemical Corp. All other chemicals were of analytical grade.

Synthesis of 2-Amino-5-methoxy-thiophenol (1) 2-Amino-6-methoxybenzothiazole (30.0 g; 172 mmol) was suspended in 50% KOH (180 g KOH dissolved in 180 ml water) and ethylene glycol (40 ml). The suspension was heated to reflux for 48 h. Upon cooling to room temperature, toluene (300 ml) was added and the reaction mixture neutralized, and the aqueous layer extracted with another 200 ml of toluene. The toluene layers were combined and washed with water and dried over $MgSO_4$. Evaporation of the solvent gave 15.3 g of 2-amino-5-methoxy-thiophenol as yellow solid.

mp 74—76 °C; yield 85%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.77 (s, 3 H), 6.43 (dd, 1H, J=2.6, 8.5 Hz), 6.57 (d, 1H, J=8.5 Hz), 6.66 (d, 1H, J=2.6 Hz).

Synthesis of 7-Methoxy-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (3a) Compound **1** (24.54 g; 158 mmol), sodium bicarbonate (53.20 g; 633 mol) and benzyltriethylammonium chloride (TEBA) (25.18 g; 110 mmol) were placed into a round-bottomed flask containing 500 ml of acetonitrile, and the mixtune was put in an ice-salt bath to keep the temperature 0—5 °C, thereafter, 2-chloroacetyl-chloride (23.26 g; 21 mmol) was added at moderate speed and reacted for 40 min. Replacing the ice-salt bath with an oil bath, the mixture was heated to reflux for 2 h, then the solvent removed under reduced pressure. The resultant product was purified by recrystallization with ethanol–water (1 : 1).

mp 169—171 °C; yield 92%; ^{1}H-NMR (DMSO, 300 MHz) δ: 3.47 (s, 2H, –S–CH_2–), 4.12 (s, 3H, –OCH_3), 6.78—6.89 (m, 3H, Ar-H), 10.38 (s, 1H, –CONH); IR (KBr) cm^{-1}: 3422 (NH), 1686 (C=O), 1490 (C–O–C), 1068

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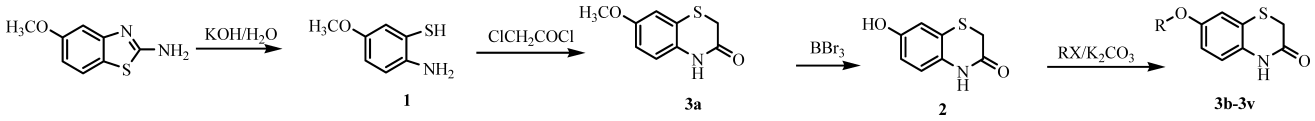


Chart 1. The Synthesis Route of Target Compounds **3a**—**v**

(C–O–C); MS *m/z*: 196 (M+1); *Anal.* Calcd for $C_9H_9NO_2S$: C, 55.37; H, 4.65; N, 7.17. Found: C, 55.18; H, 4.83; N, 7.31.

7-Hydroxy-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (2) To a stirred solution of boron tribromide (9 mmol) in anhydrous CH_2Cl_2, a CH_2Cl_2 solution of compound **3a** (0.6 g; 3 mmol) was added drop-wise and the reaction continued for 1 h at 0 °C and an additional 2 h at 20 °C. Following the addition of ice cold water, the organic layer was separated and the aqueous layer extracted with ethyl acetate. The combined organic layers were dried over with anhydrous magnesium sulfate and evaporated under reduced pressure. A brown solid was obtained.

mp 235—237 °C; yield 95%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.42 (s, 2H, –S–CH_2–), 6.69—6.97 (m, 3H, Ar-H), 7.55 (s, 1H, –OH), 7.70 (s, 1H, –CONH); IR (KBr) cm^{-1}: 3417 (NH), 1645 (C=O).

General Procedure for the Synthesis of 7-Alkoxy-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-ones (3b—v) K_2CO_3 (0.42 g; 3 mmol), absolute ethanol (40 ml) and 7-hydroxy-2*H*-benzo[*b*][1,4] thiazin-3(4*H*)-one (**2**) (0.53 g; 3 mmol) were added in a 100 ml round-bottomed flask equipped with reflux condenser. After refluxing the mixture 30 min, alkyl bromide or benzyl chloride derivative (4 mmol) was added drop-wise into the mixture. The reaction mixture was heated at reflux for 4—24 h, then poured into 100 ml of water. The aqueous layer was extracted with dichloromethane (30 ml×3). The combined layers of dichloromethane were dried by anhydrous $MgSO_4$. Evaporation of the solvents gave a crude product, which was purified by silica gel column chromatography with petroleum ether : ethyl acetate (3 : 2) to a light-yellow solid.

7-Ethoxy-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (3b) mp 154—156 °C; yield 43%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.26 (t, 3H, *J*=7.0 Hz, –CH_3), 3.43 (s, 2H, –S–CH_2–), 4.01 (q, 2H, *J*=7.0 Hz, –OCH_2–), 6.74—6.85 (m, 3H, Ar-H), 8.60 (s, 1H, –CONH); IR (KBr) cm^{-1}: 3432 (NH), 1679 (C=O), 1503 (C–O–C), 1059 (C–O–C); MS *m/z*: 210 (M+1); *Anal.* Calcd for $C_{10}H_{11}NO_2S$: C, 55.39; H, 5.30; N, 6.69. Found: C, 55.43; H, 5.45; N, 6.52.

7-Propoxy-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (3c) mp 122—124 °C; yield 40%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.01 (t, 3H, *J*=7.4 Hz, –CH_3), 1.82 (q, 2H, *J*=7.1 Hz, –CH_2–), 3.43 (s, 2H, –S–CH_2–), 3.89 (t, 2H, *J*=6.5 Hz, –OCH_2–), 6.75—6.87 (m, 3H, Ar-H), 7.94 (s, 1H, –CONH); IR (KBr) cm^{-1}: 3410 (NH), 1706 (C=O), 1520 (C–O–C), 1123 (C–O–C); MS *m/z*: 224 (M+1); *Anal.* Calcd for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.87; N, 6.27. Found: C, 59.36; H, 5.61; N, 6.44.

7-Butoxy-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (3d) mp 119—121 °C; yield 45%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.01 (t, 3H, *J*=7.5 Hz, –CH_3), 1.26—1.78 (m, 4H, –CH_2–CH_2–), 3.42 (s, 2H, –S–CH_2–), 3.93 (t, 2H, *J*=6.5 Hz, –OCH_2–), 6.74—6.87 (m, 3H, Ar-H), 7.73 (s, 1H, –CONH); IR (KBr) cm^{-1}: 3409 (NH), 1686 (C=O), 1496 (C–O–C), 1074 (C–O–C); MS *m/z*: 238 (M+1); *Anal.* Calcd for $C_{12}H_{15}NO_2S$: C, 60.73; H, 6.37; N, 5.90. Found: C, 60.82; H, 6.53; N, 6.01.

7-(Pentyloxy)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (3e) mp 118—120 °C; yield 41%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.94 (t, 3H, *J*=7.1 Hz, –CH_3), 1.27—1.60 (m, 4H, –CH_2–CH_2–), 1.76—1.80 (m, 2H, –CH_2–), 3.42 (s, 2H, –S–CH_2–), 3.92 (t, 2H, *J*=6.6 Hz, –OCH_2–), 6.74—6.86 (m, 3H, Ar-H), 8.01 (s, 1H, –CONH); IR (KBr) cm^{-1}: 3410 (NH), 1692 (C=O), 1493 (C–O–C), 1069 (C–O–C); MS *m/z*: 252 (M+1); *Anal.* Calcd for $C_{13}H_{17}NO_2S$: C, 63.21; H, 6.82; N, 5.57. Found: C, 63.36; H, 6.65; N, 5.47.

7-(Hexyloxy)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (3f) mp 112—114 °C; yield 45%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.92 (t, 3H, *J*=6.4 Hz, –CH_3), 1.34—1.58 (m, 4H, (–CH_2)$_2$), 1.72—1.74 (m, 2H, –CH_2–), 1.77—1.79 (m, 2H, –CH_2–), 3.42 (s, 2H, –S–CH_2–), 3.92 (t, 2H, *J*=6.5 Hz, –OCH_2–), 6.71—6.86 (m, 3H, Ar-H), 8.19 (s, 1H, –CONH); IR (KBr) cm^{-1}: 3521 (NH), 1703 (C=O), 1504 (C–O–C), 1071 (C–O–C); MS *m/z*: 266 (M+1); *Anal.* Calcd for $C_{14}H_{19}NO_2S$: C, 63.36; H, 7.22; N, 5.28. Found: C, 63.65; H, 7.45; N, 5.39.

7-(Heptyloxy)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (3g) mp 110—112 °C; yield 48%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.90 (t, 3H, *J*=6.6 Hz, –CH_3), 1.26—1.38 (m, 6H, (–CH_2)$_3$), 1.45—1.62 (m, 2H, –CH_2–), 1.72 (m, 2H, –CH_2–), 3.42 (s, 2H, –S–CH_2–), 3.91 (t, 2H, *J*=6.9 Hz, –OCH_2–), 6.74—6.84 (m, 3H, Ar-H), 9.17 (s, 1H, –CONH); IR (KBr) cm^{-1}: 3492 (NH), 1709 (C=O), 1495 (C–O–C), 1108 (C–O–C); MS *m/z*: 280 (M+1); *Anal.* Calcd for $C_{15}H_{21}NO_2S$: C, 64.48; H, 7.58; N, 5.01. Found: C, 64.68; H, 7.39; N, 5.30.

7-(Octyloxy)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (3h) mp 109—111 °C; yield 46%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.90 (t, 3H, *J*=6.7 Hz, –CH_3), 1.30—1.59 (m, 8H, (–CH_2)$_4$), 1.72—1.74 (m, 2H, –CH_2–), 1.77—1.79 (m, 2H, –CH_2–), 3.42 (s, 2H, –S–CH_2–), 3.92 (t, 2H, *J*=6.7 Hz, –OCH_2–), 6.75—6.86 (m, 3H, Ar-H), 8.04 (s, 1H, –CONH); IR (KBr) cm^{-1}: 3509 (NH), 1727 (C=O), 1438 (C–O–C), 1129 (C–O–C); MS *m/z*: 294 (M+1); *Anal.* Calcd for $C_{16}H_{23}NO_2S$: C, 65.49; H, 7.90; N, 4.77. Found: C, 65.71; H, 7.76; N, 4.59.

7-(Dodecyloxy)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (3i) mp 108—110 °C; yield 43%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.89 (t, 3H, *J*=6.8 Hz, –CH_3), 1.27—1.56 (m, 8H, (–CH_2)$_4$), 1.60—1.70 (m, 8H, (–CH_2)$_4$), 1.71—1.73 (m, 2H, –CH_2–), 1.74—1.76 (m, 2H, –CH_2–), 3.42 (s, 2H, –S–CH_2–), 3.91 (t, 2H, *J*=6.3 Hz, –OCH_2–), 6.73—6.86 (m, 3H, Ar-H), 7.67 (s, 1H, –CONH); IR (KBr) cm^{-1}: 3491 (NH), 1737 (C=O), 1525 (C–O–C), 1039 (C–O–C); MS *m/z*: 350 (M+1); *Anal.* Calcd for $C_{20}H_{31}NO_2S$: C, 68.72; H, 8.94; N, 4.01. Found: C, 68.92; H, 8.76; N, 4.22.

7-(Benzyloxy)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (3j) mp 172—174 °C; yield 50%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.42 (s, 2H, –S–CH_2–), 5.11 (s, 2H, –OCH_2–), 6.80—6.95 (m, 3H, Ar-H), 7.35 (d, 2H, *J*=5.8 Hz, Ar-H), 7.37 (m, 1H, Ar-H), 7.41 (d, 2H, *J*=5.2 Hz, Ar-H), 8.53 (s, 1H, –CONH); IR (KBr) cm^{-1}: 3537 (NH), 1674 (C=O), 1496 (C–O–C), 1064 (C–O–C); MS *m/z*: 272 (M+1); *Anal.* Calcd for $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; N, 5.16. Found: C, 66.50; H, 4.74; N, 5.27.

7-(2-Fluoro-benzyloxy)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (3k) mp 181—183 °C; yield 44%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.42 (s, 2H, –S–CH_2–), 5.10 (s, 2H, –OCH_2–), 6.77—6.97 (m, 3H, Ar-H), 7.07—7.51 (m, 4H, H-3, H-4, H-5, H-6), 8.21 (s, 1H, –CONH); IR (KBr) cm^{-1}: 3482 (NH), 1698 (C=O), 1654 (C–O–C), 1062 (C–O–C); MS *m/z*: 290 (M+1); *Anal.* Calcd for $C_{15}H_{12}FNO_2S$: C, 62.27; H, 4.18; N, 4.84. Found: C, 62.36; H, 4.01; N, 4.96.

7-(3-Fluoro-benzyloxy)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (3l) mp 157—159 °C; yield 43%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.42 (s, 2H, –S–CH_2–), 5.00 (s, 2H, –OCH_2–), 6.75—6.93 (m, 3H, Ar-H), 7.27—7.36 (m, 4H, H-2, H-4, H-5, H-6), 7.70 (s, 1H, –CONH); IR (KBr) cm^{-1}: 3501 (NH), 1699 (C=O), 1423 (C–O–C), 1078 (C–O–C); MS *m/z*: 290 (M+1); *Anal.* Calcd for $C_{15}H_{12}FNO_2S$: C, 62.27; H, 4.18; N, 4.84. Found: C, 62.43; H, 4.04; N, 4.79.

7-(4-Fluoro-benzyloxy)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (3m) mp 163—165 °C; yield 45%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.43 (s, 2H, –S–CH_2–), 5.04 (s, 2H, –OCH_2–), 6.75—6.94 (m, 3H, Ar-H), 7.01—7.40 (m, 4H, H-2, H-3, H-5, H-6), 7.99 (s, 1H, –CONH); IR (KBr) cm^{-1}: 3489 (NH), 1674 (C=O), 1491 (C–O–C), 1065 (C–O–C); MS *m/z*: 290 (M+1); *Anal.* Calcd for $C_{15}H_{12}FNO_2S$: C, 62.27; H, 4.18; N, 4.84. Found: C, 62.35; H, 4.00; N, 4.94.

7-(2-Chloro-benzyloxy)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (3n) mp 216—218 °C; yield 30%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.43 (s, 2H, –S–CH_2–), 5.14 (s, 2H, –OCH_2–), 6.74—6.98 (m, 3H, Ar-H), 7.30—7.60 (m, 4H, H-3, H-4, H-5, H-6), 7.70 (s, 1H, –CONH); IR (KBr) cm^{-1}: 3476 (NH), 1635 (C=O), 1428 (C–O–C), 1106 (C–O–C); MS *m/z*: 306 (M+1); *Anal.* Calcd for $C_{15}H_{12}ClNO_2S$: C, 58.92; H, 3.96; N, 4.58. Found: C, 58.76; H, 3.83; N, 4.78.

7-(3-Chloro-benzyloxy)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (3o) mp 176—178 °C; yield 32%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.43 (s, 2H, –S–CH_2–), 5.08 (s, 2H, –OCH_2–), 6.76—6.94 (m, 3H, Ar-H), 7.27—7.43 (m, 4H, H-2, H-4, H-5, H-6), 7.56 (s, 1H, –CONH); IR (KBr) cm^{-1}: 3497 (NH), 1638 (C=O), 1443 (C–O–C), 1097 (C–O–C); MS *m/z*: 306 (M+1); *Anal.* Calcd for $C_{15}H_{12}ClNO_2S$: C, 58.92; H, 3.96; N, 4.58. Found: C, 58.78; H, 3.81; N, 4.74.

7-(4-Chloro-benzyloxy)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (3p) mp 189—191 °C; yield 41%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.43 (s, 2H, –S–CH_2–), 5.02 (s, 2H, –OCH_2–), 6.76—6.94 (m, 3H, Ar-H), 7.06—7.42 (m, 4H, H-2, H-3, H-5, H-6), 8.11 (s, 1H, –CONH); IR (KBr) cm^{-1}: 3503

(NH), 1667 (C=O), 1462 (C–O–C), 1069 (C–O–C); MS *m/z*: 306 (M+1); *Anal.* Calcd for $C_{15}H_{12}ClNO_2S$: C, 58.92; H, 3.96; N, 4.58. Found: C, 58.68; H, 3.79; N, 4.76.

7-(2,6-Dichloro-benzyloxy)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (3q) mp 184—186 °C; yield 31%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.44 (s, 2H, –S–CH_2–), 5.13 (s, 2H, –OCH_2–), 6.77—6.89 (m, 3H, Ar-H), 7.02—7.40 (m, 3H, H-3, H-4, H-5), 7.83 (s, 1H, –CONH); IR (KBr) cm^{-1}: 3457 (NH), 1648 (C=O), 1430 (C–O–C), 1054 (C–O–C); MS *m/z*: 340 (M+1); *Anal.* Calcd for $C_{15}H_{11}Cl_2NO_2S$: C, 52.95; H, 3.26; N, 4.12. Found: C, 52.83; H, 3.44; N, 4.09.

7-(2-Bromo-benzyloxy)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (3r) mp 226—228 °C; yield 32%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.43 (s, 2H, –S–CH_2–), 5.11 (s, 2H, –OCH_2–), 6.74—6.83 (m, 3H, Ar-H), 7.32—7.58 (m, 4H, H-2, H-3, H-4, H-5), 8.39 (s, 1H, –CONH); IR (KBr) cm^{-1}: 3479 (NH), 1659 (C=O), 1427 (C–O–C), 1048 (C–O–C); MS *m/z*: 350 (M+1); *Anal.* Calcd for $C_{15}H_{12}BrNO_2S$: C,51.44; H, 3.45; N, 4.00. Found: C, 51.56; H, 3.26; N, 4.18.

7-(4-Bromo-benzyloxy)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (3s) mp 211—213 °C; yield 31%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.43 (s, 2H, –S–CH_2–), 4.99 (s, 2H, –OCH_2–), 6.74—6.93 (m, 3H, Ar-H), 7.30—7.54 (m, 4H, H-2, H-3, H-5, H-6), 7.94 (s, 1H, –CONH); IR (KBr) cm^{-1}: 3424 (NH), 1690 (C=O), 1458 (C–O–C), 1017 (C–O–C); MS *m/z*: 350 (M+1); *Anal.* Calcd for $C_{15}H_{12}BrNO_2S$: C,51.44; H, 3.45; N, 4.00. Found: C, 51.65; H, 3.38; N, 4.22.

7-(4-Methyl-benzyloxy)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (3t) mp 179—181 °C; yield 38%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.38 (s, 3H, –CH_3), 3.42 (s, 2H, –S–CH_2–), 5.00 (s, 2H, –OCH_2–), 6.77—6.95 (m, 3H, Ar-H), 7.21 (d, 2H, *J*=8.0 Hz, Ar-H), 7.31 (d, 2H, *J*=8.0 Hz, Ar-H), 7.88 (s, 1H, –CONH); IR (KBr) cm^{-1}: 3409 (NH), 1668 (C=O), 1430 (C–O–C), 1036 (C–O–C); MS *m/z*: 286 (M+1); *Anal.* Calcd for $C_{16}H_{15}NO_2S$: C,67.34; H, 5.30; N, 4.91. Found: C, 67.46; H, 5.21; N, 4.86.

7-(4-Methoxy-benzyloxy)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (3u) mp 165—167 °C; yield 34%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.42 (s, 2H, –S–CH_2–), 4.23 (s, 3H, –OCH_3), 4.96 (s, 2H, –OCH_2–), 6.74—6.95 (m, 3H, Ar-H), 6.93 (d, 2H, *J*=8.7 Hz, Ar-H), 7.34 (d, 2H, *J*=8.7 Hz, Ar-H), 7.90 (s, 1H, –CONH); IR (KBr) cm^{-1}: 3445 (NH), 1696 (C=O), 1437 (C–O–C), 1030 (C–O–C); MS *m/z*: 302 (M+1); *Anal.* Calcd for $C_{16}H_{15}NO_3S$: C,63.77; H, 5.02; N, 4.65. Found: C, 63.57; H, 5.26; N, 4.74.

7-(3,4-Dimethoxy-benzyloxy)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (3v) mp 179—181 °C; yield 29%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.43 (s, 2H, –S–CH_2–), 3.82 (s, 3H, –OCH_3), 4.28 (s, 3H, –OCH_3), 4.96 (s, 2H, –OCH_2–), 6.66—6.79 (m, 3H, Ar-H), 6.80—6.95 (m, 3H, H-2, H-5, H-6), 7.91 (s, 1H, –CONH); IR (KBr) cm^{-1}: 3450 (NH), 1618 (C=O), 1420 (C–O–C), 1073 (C–O–C); MS *m/z*: 332 (M+1); *Anal.* Calcd for $C_{17}H_{17}NO_4S$: C,62.41; H, 5.82; N, 4.04. Found: C, 62.66; H, 5.73; N, 4.28.

Target compounds **4a**—**u** were synthesized according to Chart 2.

To a stirring mixture of acetonitrile and triethylamine in a three-necked round-bottomed flask in an ice bath, P_2S_5 (1.2 eq) was divided into multiple portions and added one portion at a time after the previous portion had completely dissolved. Then, **3a** was added, and the solution was refluxed for 3 h under nitrogen. After removing the solvent under reduced pressure, the residue was dissolved in dichloromethane (30 ml), washed with water (30 ml×3) and dried over anhydrous $MgSO_4$. Evaporation of the solvents gave a crude product, which was purified by silica gel column chromatography with dichloromethane to a light yellow solid. (compound **6**). The resulting compound **6** reacted further with formohydrazide in cyclohexanol to produce compound **4a**. 7-Hydroxy-4*H*-[1,2,4]triazolo[4,3-*d*]benzo[*b*][1,4] thiazine (**5**) was yielded by compound **4a** by demethylation. Demethylation was accomplished by treatment of the dichloromethane with boron tribromide. Then compounds **4b**—**u** were synthesized through reaction of compound **5** with halogenated hydrocarbon in ethanol with K_2CO_3.

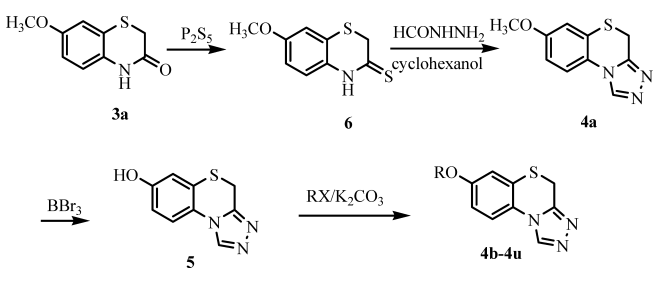


Chart 2. The Synthesis Route of Target Compounds **4a**—**u**

7-Methoxy-4*H*-[1,2,4]triazolo[4,3-*d*]benzo[*b*][1,4]thiazine (4a) mp 203—205 °C; yield 96%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.85 (s, 3H, –OCH_3), 4.19 (s, 2H, –S–CH_2–), 6.88 (dd, 1H, J_1= 2.6 Hz, J_2=6.7 Hz, Ar-H), 7.02 (d, 1H, *J*=2.6 Hz, Ar-H), 7.37 (s, 1H, Ar-H), 8.56 (s, 1H, N–CH=N–); IR (KBr) cm^{-1}: 1596 (C=N), 1301 (C–N), 1245, 1216 (C–O–C), 1032 (N–N). MS *m/z*: 220 (M+1); *Anal.* Calcd for $C_{10}H_9N_3OS$: C, 54.78; H, 4.14; N, 19.16. Found: C, 54.80; H, 4.17; N, 19.13.

7-Ethoxy-4*H*-[1,2,4]triazolo[4,3-*d*]benzo[*b*][1,4]thiazine (4b) mp 157—159 °C; yield 68%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.45 (t, 3H, *J*=7.0 Hz, –CH_3), 4.06 (t, 2H, *J*=7.1 Hz, –O–CH_2–), 4.19 (s, 2H, –S–CH_2–), 6.88 (dd, 1H, J_1=2.6 Hz, J_2=7.0 Hz, Ar-H), 7.02 (s, 1H, Ar-H), 7.37 (d, 1H, *J*=8.9 Hz, Ar-H), 8.56 (s, 1H, N–CH=N–); IR (KBr) cm^{-1}: 1595 (C=N), 1305 (C–N), 1243, 1212 (C–O–C), 1030 (N–N). MS *m/z*: 234 (M+1); *Anal.* Calcd for $C_{11}H_{11}N_3OS$: C, 56.63; H, 4.75; N, 18.01. Found: C, 56.82; H, 4.64; N, 18.23.

7-Propoxy-4*H*-[1,2,4]triazolo[4,3-*d*]benzo[*b*][1,4]thiazine (4c) mp 116—118 °C; yield 70%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.05 (t, 3H, *J*=7.4 Hz, –CH_3), 1.82 (m, 2H, –CH_2–), 3.94 (t, 2H, *J*=6.5 Hz, –OCH_2–), 4.06 (s, 2H, –S–CH_2–), 6.86 (dd, 1H, J_1= 2.7 Hz, J_2= 8.8 Hz, Ar-H), 7.01 (s, 1H, Ar-H), 7.34 (d, 1H, *J*=8.8 Hz, Ar-H), 8.54 (s, 1H, N–CH=N–); IR (KBr) cm^{-1}: 1594 (C=N), 1306 (C–N), 1241, 1209 (C–O–C), 1039 (N–N). MS *m/z*: 248 (M+1); *Anal.* Calcd for $C_{12}H_{13}N_3OS$: C, 58.28; H, 5.30; N, 16.99. Found: C, 58.48; H, 5.19; N, 16.85.

7-Butoxy-4*H*-[1,2,4]triazolo[4,3-*d*]benzo[*b*][1,4]thiazine (4d) mp 113—115 °C; yield 62%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.98 (t, 3H, *J*=7.4 Hz, –CH_3), 1.50 (m, 2H, –CH_2–), 1.78 (m, 2H, –CH_2–), 3.97 (t, 2H, *J*=6.4 Hz, –OCH_2–), 4.17 (s, 2H, –S–CH_2–), 6.86 (dd, 1H, J_1=2.6 Hz, J_2=8.8 Hz, Ar-H), 7.01 (s, 1H, Ar-H), 7.35 (d, 1H, *J*=8.9 Hz, Ar-H), 8.54 (s, 1H, N–CH=N–); IR (KBr) cm^{-1}: 1597 (C=N), 1309 (C–N), 1246, 1215 (C–O–C), 1033 (N–N). MS *m/z*: 262(M+1); *Anal.* Calcd for $C_{13}H_{15}N_3OS$: C, 59.74; H, 5.79; N, 16.08. Found: C, 59.89; H, 5.56; N, 16.19.

7-(Pentyloxy)-4*H*-[1,2,4]triazolo[4,3-*d*]benzo[*b*][1,4]thiazine (4e) mp 107—109 °C; yield 63%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.94 (t, 3H, *J*=6.9 Hz, –CH_3), 1.41 (m, 4H, –CH_2–CH_2–), 1.80 (m, 2H, –CH_2–), 3.97 (t, 2H, *J*=6.5 Hz, –OCH_2–), 4.18 (s, 2H, –S–CH_2–), 6.86 (dd, 1H, J_1=2.7 Hz, J_2=8.9 Hz, Ar-H), 7.01 (s, 1H, Ar-H), 7.35 (d, 1H, *J*=8.9 Hz, Ar-H), 8.54 (s, 1H, N–CH=N–); IR (KBr) cm^{-1}: 1596 (C=N), 1304 (C–N), 1247, 1211 (C–O–C), 1033 (N–N). MS *m/z*: 276 (M+1); *Anal.* Calcd for $C_{14}H_{17}N_3OS$: C, 61.06; H, 6.22; N, 15.26. Found: C, 61.23; H, 6.19; N, 15.33.

7-(Hexyloxy)-4*H*-[1,2,4]triazolo[4,3-*d*]benzo[*b*][1,4]thiazine (4f) mp 86—88 °C; yield 79%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.92 (t, 3H, *J*=6.6 Hz, –CH_3), 1.35 (m, 4H, –CH_2-CH_2–), 1.46—1.63 (m, 2H, –CH_2–), 1.80 (m, 2H, –CH_2–), 3.97 (t, 2H, *J*=6.5 Hz, –OCH_2–), 4.18 (s, 2H, –S–CH_2–), 6.86 (dd, 1H, J_1=2.6 Hz, J_2=8.8 Hz, Ar-H), 7.01 (s, 1H, Ar-H), 7.35 (d, 1H, *J*=8.8 Hz, Ar-H), 8.54 (s, 1H, N–CH=N–); IR (KBr) cm^{-1}: 1595 (C=N), 1306 (C–N), 1239, 1220 (C–O–C), 1039 (N–N). MS *m/z*: 290 (M+1); *Anal.* Calcd for $C_{15}H_{19}N_3OS$: C, 62.25; H, 6.62; N, 14.52. Found: C, 62.47; H, 6.54; N, 14.61.

7-(Heptyloxy)-4*H*-[1,2,4]triazolo[4,3-*d*]benzo[*b*][1,4]thiazine (4g) mp 97—99 °C; yield 77%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.89 (t, 3H, *J*=6.7 Hz, –CH_3), 1.36 (m, 6H, –CH_2–CH_2–CH_2–), 1.58—1.61 (m, 2H, –CH_2–), 1.81 (m, 2H, –CH_2–), 3.97 (t, 2H, *J*=6.5 Hz, –OCH_2–), 4.18 (s, 2H, –S–CH_2–), 6.86 (dd, 1H, J_1=2.6 Hz, J_2=8.8 Hz, Ar-H), 7.01 (s, 1H, Ar-H), 7.35 (d, 1H, *J*=8.8 Hz, Ar-H), 8.54 (s, 1H, N–CH=N–); IR (KBr) cm^{-1}: 1591 (C=N), 1308 (C–N), 1241, 1219 (C–O–C), 1035 (N–N). MS *m/z*: 304 (M+1); *Anal.* Calcd for $C_{16}H_{21}N_3OS$: C, 63.33; H, 6.98; N, 13.85. Found: C, 63.46; H, 6.82; N,13.64.

7-(Octyloxy)-4*H*-[1,2,4]triazolo[4,3-*d*]benzo[*b*][1,4]thiazine (4h) mp 96—98 °C; yield 79%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.88 (t, 3H, *J*=6.8 Hz, –CH_3), 1.30 (m, 8H, (–CH_2)$_4$), 1.46—1.67 (m, 2H, –CH_2–), 1.78 (m, 2H, –CH_2–), 3.97 (t, 2H, *J*=6.5 Hz, –OCH_2–), 4.18 (s, 2H, –S–CH_2–), 6.86 (dd, 1H, J_1=2.6 Hz, J_2=8.8 Hz, Ar-H), 7.01 (s, 1H, Ar-H), 7.35 (d, 1H, *J*=8.8 Hz, Ar-H), 8.54 (s, 1H, N–CH=N–); IR (KBr) cm^{-1}: 1599 (C=N), 1304 (C–N), 1247, 1212 (C–O–C), 1037 (N–N). MS *m/z*: 318 (M+1); *Anal.* Calcd for $C_{17}H_{23}N_3OS$: C, 64.32; H, 7.30; N, 13.24. Found: C, 64.54; H, 7.16; N,13.50.

7-(Dodecyloxy)-4*H*-[1,2,4]triazolo[4,3-*d*]benzo[*b*][1,4]thiazine (4i) mp 95—97 °C; yield 72%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.87 (t, 3H, *J*=6.8 Hz, –CH_3), 1.27—1.46 (m, 16H, (–CH_2–)$_8$), 1.57 (m, 2H, –CH_2–), 1.78 (m, 2H, –CH_2–), 3.97 (t, 2H, *J*=6.4 Hz, –OCH_2–), 4.18 (s, 2H, –S–CH_2–), 6.86 (dd, 1H, J_1=2.6 Hz, J_2=8.8 Hz, Ar-H), 7.01 (s, 1H, Ar-H), 7.35 (d, 1H, *J*=8.8 Hz, Ar-H), 8.54 (s, 1H, N–CH=N–); IR (KBr) cm^{-1}: 1600 (C=N), 1301 (C–N), 1251, 1219 (C–O–C), 1029 (N–N). MS *m/z*: 374

(M+1); *Anal.* Calcd for $C_{21}H_{31}N_3OS$: C, 67.52; H, 8.36; N, 11.25. Found: C, 67.73; H, 8.13; N, 11.40.

7-(Benzyloxy)-4*H*-[1,2,4]triazolo[4,3-*d*]benzo[*b*][1,4]thiazine (4j) mp 135—137 °C; yield 57%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 4.18 (s, 2H, –S–CH_2–), 5.09 (s, 2H, –OCH_2–), 6.94 (dd, 1H, J_1=2.6 Hz, J_2=8.8 Hz, Ar-H), 7.10 (s, 1H, Ar-H), 7.36 (d, 1H, J=8.6 Hz, Ar-H), 7.34—7.43 (m, 6H, Ar-H), 8.54 (s, 1H, N–CH=N–); IR (KBr) cm^{-1}: 1595 (C=N), 1384 (C–N), 1255, 1294 (C–O–C), 1018 (N–N). MS *m/z*: 296 (M+1); *Anal.* Calcd for $C_{16}H_{13}N_3OS$: C, 65.06; H, 4.44; N, 14.23. Found: C, 65.28; H, 4.50; N, 14.06.

7-(2-Fluorobenzyloxy)-4*H*-[1,2,4]triazolo[4,3-*d*]benzo[*b*][1,4]thiazine (4k) mp 149—151 °C; yield 62%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 4.19 (s, 2H, –S–CH_2–), 5.16 (s, 2H, –OCH_2–), 6.97 (dd, 1H, J_1=2.6 Hz, J_2=8.8 Hz, Ar-H), 7.12—7.48 (m, 6H, Ar-H), 8.54 (s, 1H, N–CH=N–); IR (KBr) cm^{-1}: 1598 (C=N), 1382 (C–N), 1255, 1296 (C–O–C), 1039 (N–N). MS *m/z*: 314 (M+1); *Anal.* Calcd for $C_{16}H_{12}FN_3OS$: C, 61.33; H, 3.86; N, 13.41. Found: C, 61.48; H, 3.66; N, 13.50.

7-(3-Fluorobenzyloxy)-4*H*-[1,2,4]triazolo[4,3-*d*]benzo[*b*][1,4]thiazine(4l) mp 121—123 °C; yield 62%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 4.19 (s, 2H, –S–CH_2–), 5.09 (s, 2H, –OCH_2–), 6.93 (dd, 1H, J_1=2.6 Hz, J_2=8.8 Hz, Ar-H), 7.05—7.38 (m, 6H, Ar-H), 8.54 (s, 1H, N–CH=N–); IR (KBr) cm^{-1}: 1598 (C=N), 1381 (C–N), 1256, 1296 (C–O–C), 1039 (N–N). MS *m/z*: 314 (M+1); *Anal.* Calcd for $C_{16}H_{12}FN_3OS$: C, 61.33; H, 3.86; N, 13.41. Found: C, 61.48; H, 3.66; N, 13.50.

7-(4-Fluorobenzyloxy)-4*H*-[1,2,4]triazolo[4,3-*d*]benzo[*b*][1,4]thiazine (4m) mp 151—153 °C; yield 63%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 4.23 (s, 2H, –S–CH_2–), 5.05 (s, 2H, –OCH_2–), 6.93 (dd, 1H, J_1=2.7 Hz, J_2=7.5 Hz, Ar-H), 7.07—7.13 (m, 3H, Ar-H), 7.35—7.43 (m, 3H, Ar-H), 8.54 (s, 1H, N–CH=N–); IR (KBr) cm^{-1}: 1599 (C=N), 1384 (C–N), 1254, 1296 (C–O–C), 1039 (N–N). MS *m/z*: 314 (M+1); *Anal.* Calcd for $C_{16}H_{12}FN_3OS$: C, 61.33; H, 3.86; N, 13.41. Found: C, 61.48; H, 3.66; N, 13.50.

7-(2-Chlorobenzyloxy)-4*H*-[1,2,4]triazolo[4,3-*d*]benzo[*b*][1,4]thiazine (4n) mp 148—150 °C; yield 52%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 4.23 (s, 2H, –S–CH_2–), 5.19 (s, 2H, –OCH_2–), 6.96 (dd, 1H, J_1=2.6 Hz, J_2=7.5 Hz, Ar-H), 7.13 (d, 1H, J=2.6 Hz, Ar-H), 7.30—7.51 (m, 5H, Ar-H), 8.54 (s, 1H, N–CH=N–); IR (KBr) cm^{-1}: 1597 (C=N), 1385 (C–N), 1255, 1297 (C–O–C), 1034 (N–N). MS *m/z*: 330 (M+1); *Anal.* Calcd for $C_{16}H_{12}ClN_3OS$: C, 58.27; H, 3.67; N, 12.74. Found: C, 58.51; H, 3.59; N, 12.60.

7-(3-Chlorobenzyloxy)-4*H*-[1,2,4]triazolo[4,3-*d*]benzo[*b*][1,4]thiazine (4o) mp 123—125 °C; yield 51%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 4.23 (s, 2H, –S–CH_2–), 5.10 (s, 2H, –OCH_2–), 6.93 (dd, 1H, J_1=2.6 Hz, J_2=6.2 Hz, Ar-H), 7.10 (d, 1H, J=2.6 Hz, Ar-H), 7.31—7.43 (m, 5H, Ar-H), 8.54 (s, 1H, N–CH=N–); IR (KBr) cm^{-1}: 1598 (C=N), 1379 (C–N), 1255, 1296 (C–O–C), 1036 (N–N). MS *m/z*: 330 (M+1); *Anal.* Calcd for $C_{16}H_{12}ClN_3OS$: C, 58.27; H, 3.67; N, 12.74. Found: C, 58.51; H, 3.59; N, 12.60.

7-(4-Chlorobenzyloxy)-4*H*-[1,2,4]triazolo[4,3-*d*]benzo[*b*][1,4]thiazine (4p) mp 142—144 °C; yield 50%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 4.18 (s, 2H, –S–CH_2–), 5.06 (s, 2H, –OCH_2–), 6.92 (dd, 1H, J_1=2.6 Hz, J_2=8.8 Hz, Ar-H), 7.09 (d, 1H, J=2.6 Hz, Ar-H), 7.35—7.40 (m, 5H, Ar-H), 8.54 (s, 1H, N–CH=N–); IR (KBr) cm^{-1}: 1596 (C=N), 1378 (C–N), 1254, 1294 (C–O–C), 1033 (N–N). MS *m/z*: 330 (M+1); *Anal.* Calcd for $C_{16}H_{12}ClN_3OS$: C, 58.27; H, 3.67; N, 12.74. Found: C, 58.51; H, 3.59; N, 12.60.

7-(2,4-Dichlorobenzyloxy)-4*H*-[1,2,4]triazolo[4,3-*d*]benzo[*b*][1,4]thiazine (4q) mp 172—174 °C; yield 54%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 4.24 (s, 2H, –S–CH_2–), 5.14 (s, 2H, –OCH_2–), 6.94 (dd, 1H, J_1=2.7 Hz, J_2=8.8 Hz, Ar-H), 7.11 (d, 1H, J=2.7 Hz, Ar-H), 7.29—7.48 (m, 4H, Ar-H), 8.54 (s, 1H, N–CH=N–); IR (KBr) cm^{-1}: 1595 (C=N), 1380 (C–N), 1255, 1286 (C–O–C), 1029 (N–N). MS *m/z*: 364 (M+1); *Anal.* Calcd for $C_{16}H_{11}Cl_2N_3OS$: C, 52.76; H, 3.04; N, 11.54. Found: C, 52.88; H, 3.13; N, 11.27.

7-(2-Bromobenzyloxy)-4*H*-[1,2,4]triazolo[4,3-*d*]benzo[*b*][1,4]thiazine (4r) mp 186—188 °C; yield 55%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.84 (s, 2H, –S–CH_2–), 5.15 (s, 2H, –OCH_2–), 6.95 (dd, 1H, J_1=2.6 Hz, J_2=8.7 Hz, Ar-H), 7.12 (d, 1H, J=2.5 Hz, Ar-H), 7.21—7.70 (m, 5H, Ar-H), 8.54 (s, 1H, N–CH=N–); IR (KBr) cm^{-1}: 1591 (C=N), 1380 (C–N), 1249, 1296 (C–O–C), 1040 (N–N). MS *m/z*: 374 (M+1); *Anal.* Calcd for $C_{16}H_{12}BrN_3OS$: C, 51.35; H, 3.23; N, 11.23. Found: C, 51.54; H, 3.06; N, 11.43.

7-(4-Bromobenzyloxy)-4*H*-[1,2,4]triazolo[4,3-*d*]benzo[*b*][1,4]thiazine (4s) mp 151—153 °C; yield 58%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 4.18 (s, 2H, –S–CH_2–), 5.05 (s, 2H, –OCH_2–), 6.93 (dd, 1H, J_1=2.8 Hz, J_2=7.5 Hz, Ar-H), 7.09 (d, 1H, J=2.6 Hz, Ar-H), 7.29—7.55 (m, 5H, Ar-H), 8.54 (s, 1H, N–CH=N–); IR (KBr) cm^{-1}: 1590 (C=N), 1368 (C–N), 1255, 1284 (C–O–C), 1035 (N–N). MS *m/z*: 374 (M+1); *Anal.* Calcd for $C_{16}H_{12}BrN_3OS$: C, 51.35; H, 3.23; N, 11.23. Found: C, 51.54; H, 3.06; N, 11.43.

7-(4-Methylbenzyloxy)-4*H*-[1,2,4]triazolo[4,3-*d*]benzo[*b*][1,4]thiazine (4t) mp 126—128 °C; yield 49%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.38 (s, 3H, Ar-CH_3), 4.18 (s, 2H, –S–CH_2–), 5.05 (s, 2H, –OCH_2–), 6.93 (dd, 1H, J_1=2.6 Hz, J_2=8.8 Hz, Ar-H), 7.10 (d, 1H, J=2.9 Hz, Ar-H), 7.20—7.36 (m, 5H, Ar-H), 8.54 (s, 1H, N–CH=N–); IR (KBr) cm^{-1}: 1597 (C=N), 1381 (C–N), 1255, 1286 (C–O–C), 1035 (N–N). MS *m/z*: 310 (M+1); *Anal.* Calcd for $C_{17}H_{15}N_3OS$: C, 66.00; H, 4.89; N, 13.58. Found: C, 66.18; H, 4.67; N, 13.42.

7-(4-Methoxybenzyloxy)-4*H*-[1,2,4]triazolo[4,3-*d*]benzo[*b*][1,4]thiazine (4u) mp 137—139 °C; yield 52%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.92 (s, 3H, Ar-O–CH_3), 4.13 (s, 2H, –S–CH_2–), 5.05 (s, 2H, –OCH_2–), 6.93 (d, 3H, J=8.4 Hz, Ar-H), 7.08 (d, 1H, J=2.9 Hz, Ar-H), 7.33—7.36 (m, 3H, Ar-H), 8.54 (s, 1H, N–CH=N–); IR (KBr) cm^{-1}: 1590 (C=N), 1377 (C–N), 1260, 1276 (C–O–C), 1036 (N–N). MS *m/z*: 326 (M+1); *Anal.* Calcd for $C_{17}H_{15}N_3O_2S$: C, 62.75; H, 4.65; N, 12.91. Found: C, 62.94; H, 4.53; N, 12.88.

Pharmacology The MES test and rotarod test were carried out according to procedures described in the Antiepileptic Drug Development Program (ADD) of the National Institutes of Health (U.S.A.).[11,12] All compounds, which were dissolved in polyethyleneglycol-400, were evaluated for anticonvulsant activities in KunMing mice in the 18—25 g weight range. Groups of 10 mice were given a range of intraperitoneal doses of the test drug until at least three points were established in the range of 10—90% seizure protection or minimal observed neurotoxicity. From the plots of these data, the respective ED_{50} and TD_{50} values, 95% confidence intervals, slopes of the regression line and the standard error of the slopes were calculated by computer program written by the National Institute of Neurological Disorders and Stroke.

MES Test Seizures were elicited with a 60 Hz alternating current of 50 mA intensity in mice. The current was applied *via* corneal electrodes for 0.2 s. Protection against the spread of MES-induced seizures was defined as the abolition of the hind leg and tonic maximal extension component of the seizure. The derivatives in MES test were evaluated 15 min after administration of the compounds.

Rotarod Test[10] Fifteen minutes after administration of the compounds (with different doses), the animals were tested on a 2.5-cm diameter knurled plastic rod rotating at 6 rpm for 1 min. Neurotoxicity was indicated by the inability of an animal to maintain equilibrium in each of three trials.

Results and Discussion

Chemistry Target compounds **3a**—**v** were synthesized according to Chart 1. Compound **1** was prepared by 2-amino-6-methoxy-benzothiazole reacting with KOH solution for 48 h according to the reference method,[11] compound **3a** was prepared according to the reference method,[12] 7-hydroxy-2*H*-benzo[*b*][1,4] thiazin-3(4*H*)-one (**2**) was achieved by compound **3a** by demethylation. Demethylation was accomplished by treatment of the dichloromethane with boron tribromide as described by Bauer *et al.*[13] Then compounds **3b**—**v** were synthesized through the reaction of compound **2** with halogenated hydrocarbon in ethanol with K_2CO_3.

Target compounds **4a**—**u** were synthesized according to Chart 2. Compound **6** was achieved by compound **3a** reacted further with P_2S_5 according to the reference method,[10] and compound **6** reacted further with formohydrazide in cyclohexanol to produce compound **4a** according to a previously reported method.[7] 7-Hydroxy-4*H*-[1,2,4]triazolo[4,3-*d*]-benzo[*b*] [1,4]thiazine (**5**) was achieved by compound **4a** by demethylation. Demethylation was accomplished by treatment of the dichloromethane with boron tribromide as described by Bauer *et al.*[13] Then compounds **4b**—**u** were synthesized through the reaction of compound **5** with halogenated hydrocarbon in ethanol with K_2CO_3.

Pharmacology All compounds, which were dissolved in polyethylene glycol-400, were evaluated for anticonvulsant activities with KunMing mice in the 18—22 g weight range. In the MES test, seizures were elicited with a 60-Hz alternating current of 50 mA intensity in mice. The current was applied *via* corneal electrodes for 0.2 s. Protection against the spread of MES-induced seizures was defined as the abolition of the hind leg and tonic maximal extension component of the seizure.

The activity profile for the tested compounds is summarized in Table 1 and Table 2 along with the literature data for a standard drug. All the compounds were active in the MES test, indicative of their ability to prevent seizure spread. All synthesized compounds **3a**—**v** exhibited weak anticonvulsant activity; among the 22 compounds **3a**—**v**: **3n**, **3q**, **3t** and **3v** hardly exhibited anticonvulsant activity at the dose of 200 mg/kg; **3a**, **3i**, **3o**, **3p**, **3r**, **3s** and **3u** exhibited weak anticonvulsant activity at the dose of 200 mg/kg; **3h**, **3j**, **3l** and **3m** exhibited median anticonvulsant activity; other compounds exhibited stronger anticonvulsant activity at a dose of 100 mg/kg.

Compared with compounds **3a**—**v**, compounds **4a**—**u** were more active. The results suggest that the incorporated triazole with 7-alkoxyl-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-ones at the third and fourth position could improve the anticonvulsant activity of the derivatives.

All synthesized compounds **4a**—**u** exhibited stronger anticonvulsant activity, among the 21 compounds. **4a**, **4b**, **4i** and **4n** exhibited lower anticonvulsant activity; **4d**, **4e**, **4f**, **4k**, **4l** and **4o** exhibited stronger anticonvulsant activity.

As a result of preliminary screening, compounds **3b**—**g** and **3k** among **3a**—**v** and compounds **4d**, **4e**, **4f**, **4k**, **4l** and **4o** among **4a**—**u** were considered for the phase II trials. This provides an evaluation of the median effective dose and median neuotoxic dose. The slope of the regression line and SE of the alope were then calculated. These data are shown in Table 3. Compound **3e** was the most active compound with an ED_{50} of 34.1 mg/kg, TD_{50} of 305.5 mg/kg and PI of 8.9. So, among the seven compounds, **3f** could be considered potentially the most useful and safe therapeutic compound with $ED_{50}=52.8$ mg/kg, $TD_{50}>600$ mg/kg and PI>11.4. Compound **4k** was the most active compound with an ED_{50} of 17.0 mg/kg, TD_{50} of 243.9 mg/kg and PI of 14.3. The neurotoxicity of both **3f** and **4k** was markedly lower than that of the reference drug carbamazepine.

Analyzing the activities of the synthesized compounds **3a**—**v** and **4a**—**u**, the following structure–activity relationship (SAR) was gained. Among **3a**—**v**, the three F-substituted phenyl derivatives, the potency order was *o*-F>*p*-F>*m*-F. Among the four Cl-substituted phenyl derivatives, the potency order was *m*-Cl=*p*-Cl>*o*-Cl_2>2,6-Cl_2. Between the two Br-substituted phenyl derivatives, the potency order was *p*-Br>*o*-Br. Among the three electron-donor phenyl derivatives, the potency order was *p*-OCH_3>*p*-CH_3=3,4-$(OCH_3)_2$. Among the six *p*-substituted phenyl derivatives, the potency order was H=F>Br=CH_3O>Cl>CH_3. Compound **3e** was the most active compound with an ED_{50} of 34.1 mg/kg, TD_{50} of 305.5 mg/kg and PI of 8.9. So, among the 22 compounds, **3f** could be considered potentially the most useful and safe therapeutic compound with an $ED_{50}=52.79$ mg/kg, $TD_{50}>600$ mg/kg and PI>11.4. Its neurotoxicity was the lowest among all the synthesized compounds. The SAR of compounds **4a**—**u** was similar to that of **3a**—**v**. Among **4a**—**u**, the length of the alkoxyl chain appeared to have an impact on anticonvulsant activity of the derivatives. From **4a** to **4e**, as the alkoxyl chain length increased, anticonvulsant activity

Table 1. Anticonvulsant Data in Mice (Test Drug Administered i.p.)[a] (Phase I)

Compound	R	MES[c] 0.5 h	MES[c] 4 h
3a	$-CH_3$	200 (3/5)[b]	—[d]
3b	$-C_2H_5$	100 (5/5)	—
3c	*n*-C_3H_7	100 (5/5)	—
3d	*n*-C_4H_9	100 (5/5)	—
3e	*n*-C_5H_{11}	100 (4/5)	—
3f	*n*-C_6H_{13}	100 (4/5)	—
3g	*n*-C_7H_{15}	100 (3/5)	—
3h	*n*-C_8H_{17}	200 (5/5)	—
3i	*n*-$C_{12}H_{25}$	200 (3/5)	—
3j	$-CH_2C_6H_5$	200 (5/5)	—
3k	$-CH_2C_6H_4$ (*o*-F)	100 (3/5)	—
3l	$-CH_2C_6H_4$ (*m*-F)	200 (4/5)	—
3m	$-CH_2C_6H_4$ (*p*-F)	200 (5/5)	—
3n	$-CH_2C_6H_4$ (*o*-Cl)	200 (1/5)	—
3o	$-CH_2C_6H_4$ (*m*-Cl)	200 (2/5)	—
3p	$-CH_2C_6H_4$ (*p*-Cl)	200 (2/5)	—
3q	$-CH_2C_6H_3$ (2,6-Cl_2)	200 (0/5)	—
3r	$-CH_2C_6H_4$ (*o*-Br)	200 (2/5)	—
3s	$-CH_2C_6H_4$ (*p*-Br)	200 (3/5)	—
3t	$-CH_2C_6H_4$ (*p*-CH_3)	200 (1/5)	—
3u	$-CH_2C_6H_4$ (*p*-OCH_3)	200 (3/5)	—
3v	$-CH_2C_6H_3$ (3,4-$(OCH_3)_2$)	200 (1/5)	—

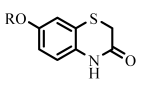
a) All of the tested compounds were dissolved in polyethylene glycol-400; *b*) the maximal electroshock test was conducted 30 min after administration of the test compounds; *c*) doses are in mg/kg; *d*) —=no activity at 300 mg/kg.

Table 2. Anticonvulsant Data in Mice (Test Drug Administered i.p.)[a] (Phase I)

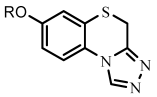
Compound	R	MES[c] 0.5 h	MES[c] 4 h
4a	$-CH_3$	200 (5/5)[b]	—[d]
4b	$-C_2H_5$	200 (5/5)	—
4c	*n*-C_3H_7	100 (4/5)	—
4d	*n*-C_4H_9	100 (5/5)	—
4e	*n*-C_5H_{11}	100 (5/5)	—
4f	*n*-C_6H_{13}	100 (5/5)	—
4g	*n*-C_7H_{15}	100 (4/5)	—
4h	*n*-C_8H_{17}	100 (3/5)	—
4i	*n*-$C_{12}H_{25}$	200 (5/5)	—
4j	$-CH_2C_6H_5$	100 (5/5)[e]	—
4k	$-CH_2C_6H_4$ (*o*-F)	100 (5/5)	—
4l	$-CH_2C_6H_4$ (*m*-F)	100 (5/5)	—
4m	$-CH_2C_6H_4$ (*p*-F)	100 (4/5)	—
4n	$-CH_2C_6H_4$ (*o*-Cl)	200 (5/5)	—
4o	$-CH_2C_6H_4$ (*m*-Cl)	100 (5/5)	—
4p	$-CH_2C_6H_4$ (*p*-Cl)	200 (4/5)	—
4q	$-CH_2C_6H_3$ (2,4-Cl_2)	200 (2/5)	—
4r	$-CH_2C_6H_4$ (*o*-Br)	200 (4/5)	—
4s	$-CH_2C_6H_4$ (*p*-Br)	200 (2/5)	—
4t	$-CH_2C_6H_4$ (*p*-CH_3)	100 (5/5)[e]	—
4u	$-CH_2C_6H_4$ (*p*-OCH_3)	100 (1/5)	—

a) All of the tested compounds were dissolved in polyethylene glycol-400; *b*) the maximal electroshock test was conducted 30 min after administration of the test compounds; *c*) doses are in mg/kg; *d*) —=no activity at 300 mg/kg; *e*) too much neurotoxicity.

Table 3. Quantitative Anticonvulsant Data in Mice (Test Drug Administered i.p.) (Phase II)



3a-3v



4a-4u

Compound	R	MES; ED_{50} [a]	Rotarod toxicity TD_{50} [c]	MES; PI [b]
3b	$-C_2H_5$	76.18 (53.4—108.7) [d]	353.5 (249.1—501.7)	4.6
3c	*n*-C_3H_7	68.14 (47.7—97.4)	254.6 (181.1—358.0)	3.7
3d	*n*-C_4H_9	52.79 (37.2—74.9)	366.6 (260.7—515.5)	7.0
3e	*n*-C_5H_{11}	34.08 (23.9—48.6)	305.5 (217.3—429.6)	8.9
3f	*n*-C_6H_{13}	52.79 (37.2—74.9)	>600	>11.4
3g	*n*-C_7H_{15}	91.23 (64.9—128.3)	>600	>6.5
3k	$-CH_2C_6H_4$ (*o*-F)	81.77 (57.2—116.9)	>600	>7.3
4d	*n*-C_4H_9	20.45 (12.19—34.28)	65.40 (41.49—103.06)	3.2
4e	*n*-C_5H_{11}	18.34 (11.34—29.65)	72.98 (49.42—107.77)	3.9
4f	*n*-C_6H_{13}	24.54 (16.23—37.11)	110.0 (71.53—169.15)	4.5
4k	$-CH_2C_6H_4$ (*o*-F)	17.04 (10.98—26.43)	243.9 (148.32—401.36)	14.3
4l	$-CH_2C_6H_4$ (*m*-F)	18.33 (12.41—27.07)	227.2 (147.76—349.40)	12.4
4o	$-CH_2C_6H_4$ (*m*-Cl)	20.45 (13.29—31.45)	253.5 (177.33—362.38)	12.4
CPZ	—	11.80 (8.5—16.4)	76.1 (55.8—103.7)	6.4

a) Doses are in mg/kg; *b*) PI=TD_{50}/ED_{50}; *c*) minimal neurotoxicity was determined by therotarod test 30 min after administration of the test compounds; *d*) the 95% confidence limits.

gradually increased with compound **4e** (with the 7-pentyloxy group) being the most active compound. From **4e** to **4i**, as the alkoxyl chain length increased, anticonvulsant activity gradually decreased. Among the substituted benzyloxyl, the three F-substituted phenyl derivatives, the potency order was *o*-F=*m*-F>*p*-F. Among the four Cl-substituted phenyl derivatives, the potency order was *m*-Cl>*o*-Cl>*p*-Cl>2,4-Cl_2. Between the two Br-substituted phenyl derivatives, the potency order was *o*-Br>*p*-Br. Among the three electron-donor phenyl derivatives, the potency order was *p*-CH_3>*p*-OCH_3. Among the six *p*-substituted phenyl derivatives, the potency order was H=CH_3>F>CH_3O>Cl>Br. Compound **4k** was the most active compound with an ED_{50} of 17.0 mg/kg, TD_{50} value of 243.9 mg/kg and PI value of 14.3. Its neurotoxicity was lower than all the other synthesized compounds and also markedly lower than that of the reference drug carbamazepine.

Conclusion

A series of 7-alkoxy-2*H*-1,4-benzothiazin-3(4*H*)-ones and a new series of 7-alkoxy-4*H*-[1,2,4]triazolo[4,3-*d*]benzo[*b*]-[1,4]thiazine derivatives were synthesized. The anticonvulsant activity of these compounds was evaluated with MES test and rotarod test with intraperitoneal injection in Kun-Ming mice. Among the synthesized compounds **3a**—**v**, 7-(hexyloxy)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (**3f**) could be considered potentially the most useful and safe therapeutic compound. Among the synthesized compounds **4a**—**u**, compound 7-(2-fluorobenzyloxy)-4*H*-[1,2,4]triazolo[4,3-*d*]-benzo[*b*][1,4]thiazine **4k** was the most active compound with ED_{50} of 17.0 mg/kg, TD_{50} of 243.9 mg/kg and PI of 14.3. Its neurotoxicity was lower than all other synthesized compounds and also markedly lower than that of the reference drug carbamazepine.

Acknowledgment This work was supported by the National Natural Science Foundation of China (No. 30760290 and No. 30860340) and Important Item Foundation of Ministry of Education P. R. China (No. 20070422029).

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