Efficient One-Pot Synthesis of S-Triazolo[3,4-*b*]-[1,3,5]thiadiazines Containing a Chiral Side Chain by Double Mannich Type Reaction

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An efficient and convenience method has been developed *via* a one-pot double Mannich type reaction for the synthesis of the important chiral s-triazole derivatives: (*S*)-3-α-phenylethyl-2,4-dihydro-5-aryl-oxymethyl-1,2,4-triazolo[3,4-*b*]-1,3,5-thiadiazines.

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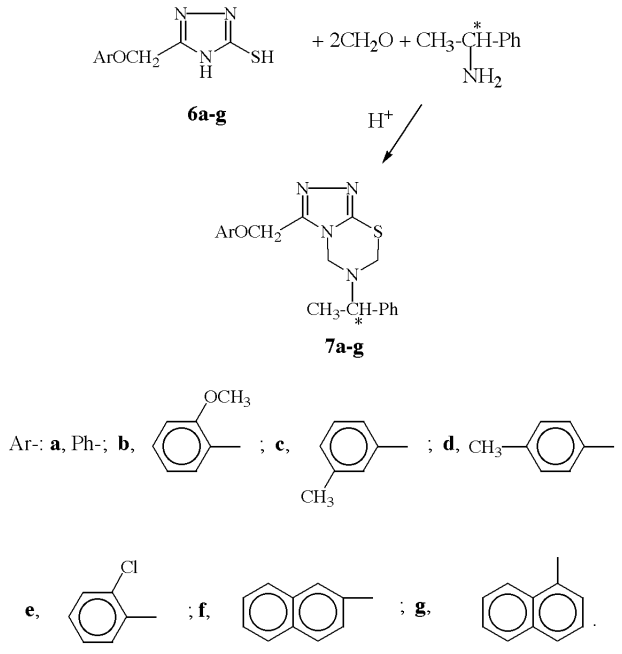
S-triazoles and their heterocyclic derivatives are very well known compounds which have been important in medicinal chemistry as potential therapeutic agent [1-2] and in agricultural chemistry *etc.* [3-6]. Derivatives of phenothiazine [7] are also a group of valuable drugs. Therefore, the apparently specific role for the triazolo-thiadiazine derivatives [8-9] in medicinal chemistry suggests they may be suitable targets for antibiotic design. We present here the first report of a new and efficient method for the synthesis of **7**. The novel chiral (*S*)-3-α-phenylethyl-2,4-dihydro-5-aryloxymethyl-1,2,4-triazolo[3,4-*b*]-1,3,5-thiadiazines (**7a-g**) have been synthesized by one-pot double Mannich type reaction of 3-mercapto-5-aryloxymethyl-1,2,4-triazoles, *S*-(-)-α-phenylethylamine and formaldehyde in the presence of acid under mild condition. All products are new and have been characterized by elemental analysis, IR, ^{1}H NMR and MS. The data confirmed the structure of the synthesized compounds as depicted in Scheme 1.

Scheme 1

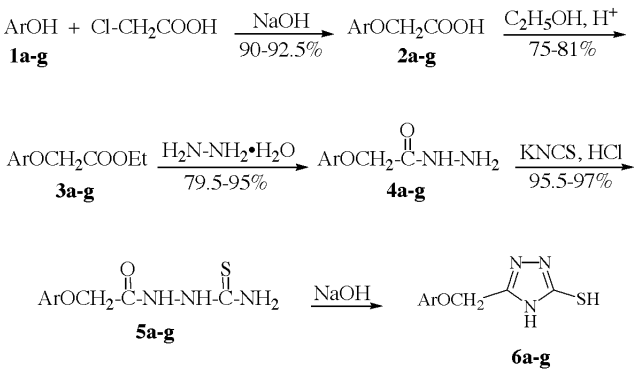


The Mannich reaction is one of the most important reactions usually available for the aminoalkylation of CH-acidic compounds. However, the hydrogen atoms of N-H and S-H groups on the ring of 3-mercapto-1,2,4-triazoles (**6a-g**) are the acidic hydrogen required for the double Mannich-type reaction. We use this type of reaction of a chiral α-phenylethylamine, formaldehyde and s-triazoles (molar ratio 1:2:1) for a one-pot procedure.

Chiral fused heterocyclic compounds are also important reagents and could have extensive application in asymmetric synthesis. The starting 5-aryloxymethyl-3-mercapto-1,2,4-triazoles (**6**) were prepared by employing our published procedures [10-11].

Aryloxyacetic acids (**2**) were prepared by Williamson reaction of phenols (**1**) and chloroacetic acid in the presence of sodium hydroxide. Compound **2** was esterified with ethanol to give ethyl aryloxy acetate (**3**). The aryloxy acetate was treated with 85% hydrazine to yield aryloxy acylhydrazine (**4**), then mixed with potassium thiocyanate and aqueous sulfuric acid and refluxed for 4 hours to give aryloxyacylamino thiourea (**5**). Compound **5** was cyclized by treated with 8% sodium hydroxide and refluxed for

Scheme 2

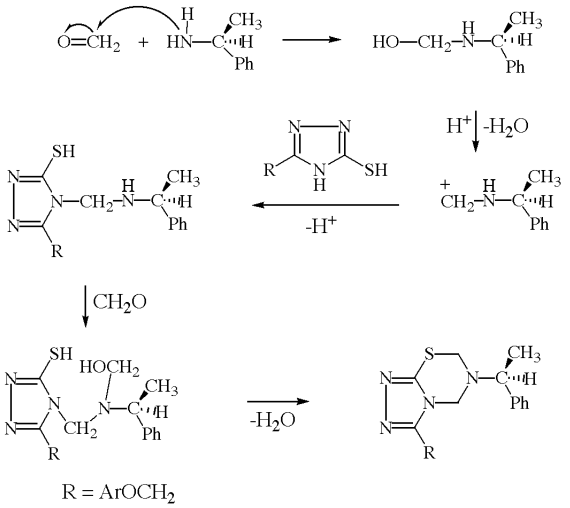


4 hours to produce the 2-aryloxymethyl-5-mercapto-1,2,4-triazoles (**6**). Compounds **6a-g** are new and have not been reported in the literature. The synthetic route to prepare **6a-g** is described in Scheme 2.

Because of the acidity of both the N-H and S-H groups, 1,2,4-s-triazoles can undergo a double Mannich reaction with *S*-(-)-α-phenylethylamine and formaldehyde under acid catalyst to give chiral condensed heterocyclic compounds, (*S*)-3-α-phenylethyl-2,4-dihydro-5-aryloxymethyl-1,2,4-triazolo[3,4-*b*]-1,3,5-thiadiazines (**7a-g**). Again these compounds have not been reported in literature.

The Mannich reaction usually occurs under acidic condition. We found that the pH of reaction system has a large effect on the reaction. The research illustrates that the reaction gives a good yield at pH 5-6, where a buffer solution is produced. By adding a catalytic amount of potassium fluoride to the reaction system and maintaining the temperature at 30 °C for 6-8 hours gives products in considerably high yields. The reaction mechanism is shown in scheme 3.

Scheme 3



The structures of compounds have been confirmed by elemental analysis, IR, ^{1}H NMR, and MS. The IR spectra of these compounds revealed in each case, absorption bands in the regions 3019-3029 cm^{-1}, 1610-1676 cm^{-1}, 1506-1592 cm^{-1} and 1026-1088 cm^{-1} corresponding to =C-H, C=N, N=C-S and C-O-C, respectively. The ^{1}H NMR spectra of **7d** for example, exhibited two doublets at δ 5.13-5.06 ppm (J = 13.25 Hz) and δ 4.43-4.40 ppm (J = 13.15 Hz), due to C-4 two geminal methylene protons, respectively; and the other two doublets at 4.11-4.09 ppm (J = 7.10 Hz) and 4.00-3.97 ppm (J = 7.15 Hz), due to C-2 two geminal methylene protons, respectively. The geminal coupling illustrate that the stereocenter renders the two methylene protons non-equivalent [12]. The observed chemical shift differences and hence coupling can be explained based on the similarity of the 2,4-dihydro-1,3,5-thiadiazine moiety to the chair conformation of the cyclohexane ring system, which causes the methylene protons to be spatially near the stereocenter. This leads to the observation of the coupling constant of J=12-14 Hz for H_a and H_e at C-4. Hence protons of C-2 and C-4 methylene resonate as four groups of doublet signals. The mass spectrum of **7c** exhibiteds a molecular ion peak at m/z 366. The cleavage processes of **7a-g** are similar. All of them generate fragment ions with m/z 105 and 91 due to methylcycloheptatriene positive ion and cycloheptatriene positive ion, respectively.

EXPERIMENTAL

Melting points were recorded on a micro melting point apparatus X_4 and are uncorrected. Elemental analyses were recorded on a Pekin-Elmer 2400 element analyser. IR spectra were measured as potassium bromide pellets on a BIO-RAD FTS-40 spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker AM-400 spectrometer using tetramethylsilane as an internal reference. Mass spectra were performed on HP 5989A mass spectrometer. The optical rotations were recorded on a WZZ-1 automatic polarimeter. All chemicals were analytically pure.

General Procedure for the Preparation of 2-Aryloxymethyl-5-mercapto-1,2,4-triazoles (**6a-g**).

A mixture of aryloxyacetic acids (**2**) (0.2 mol), absolute ethanol (0.4 mol) and 5 g of *p*-toluenesulfonic acid was refluxed for 5 hours and then after cooling to room temperature, was poured into water (100 ml). The organic layer was washed with 5% sodium bicarbonate solution and dried over anhydrous sodium sulfate and evaporated to give ethyl aryloxy acetate (**3**) (75-81%). To a solution of **3** (0.2 mol) in 20 ml of absolute ethanol was added 85% hydrazine (0.4 mol) and the mixture was heated under reflux for 3 hours. After cooling to room temperature, the resulting precipitates were filtered to yield aryloxy acylhydrazine (**4**) (79.5-95%). To a stirred solution of **4** (0.02 mol), 5 ml of concentrated hydrochloric acid and 20 ml of water was added potassium thiocyanate (0.071 mol). The mixture was heated under reflux for 4 hours and allowed to stand overnight at room temperature. Then the resulting precipitates were isolated by filtration and recrystallized from water to obtain aryloxyacylamino thiourea (**5**) (95.5-97%). A mixture of **5** (0.1 mol) and 8% sodium hydroxide (120 ml) was heated at 95 °C for 4 hours. Then the mixture was cooled to room temperature and acidified with dilute hydrochloric acid. The precipitate was collected by filtration and washed with water. Recrystallization from ethanol provided the 2-aryloxymethyl-5-mercapto-1, 2, 4-triazoles (**6**) (78%).

2-Phenyloxymethyl-5-mercapto-1,2,4-triazole (**6a**).

Compound **6a** was obtained as a white powder, yield (86.5%); mp 216-218 °C; ir (potassium bromide): ν 3435 (NH), 3035 (=C-H), 2985 (CH_3), 2551 (SH), 1650, 1460 (C=C, C=N), 1245, 1052 (C-O-C) cm^{-1}; ^{1}H nmr (400 MHz; DMSO-d_6): δ 8.28

(s, 1H, NH), 7.75-6.97 (m, 5H, PhH), 5.43 (s, 2H, OCH_2), 3.34 (s, 1H, SH); ms: (EI) m/z 207 (M^+, 15.82), 133 (5.28), 131 (6.67), 114 (25.36), 94 (100), 77 (38.51).

Anal. Calcd. for $C_9H_9N_3OS$: C, 52.15; H, 4.38; N, 20.28. Found: C, 52.26; H, 4.47; N, 20.11.

2-(2-Methyloxyphenyl)oxymethyl-5-mercapto-1,2,4-triazole (**6b**).

Compound **6b** was obtained as a pale yellow powder in 83.2% yield; mp 220-222 °C; ir (potassium bromide): ν 3430 (NH), 3028 (=C-H), 2920 (CH_3), 2550 (SH), 1740-1493 (C=C, C=N), 1241, 1150 (C-O-C) cm^{-1}; ^1H nmr (400 MHz; DMSO-d_6): δ 8.08 (s, 1H, NH), 7.03-6.65 (m, 4H, ArH), 5.22 (s, 2H, OCH_2), 2.68 (s, 1H, SH), 2.16 (s, 3H, CH_3); ms: (EI) m/z 221 (M^+, 21.47), 207 (1.61), 147 (5.68), 133 (3.73), 114 (100), 108 (54.28), 91 (11.88), 76 (38.75).

Anal. Calcd. for $C_{10}H_{11}N_3OS$: C, 54.28; H, 5.01; N, 18.99. Found: C, 54.36; H, 5.05; N, 18.88.

2-(3-Methylphenyl)oxymethyl-5-mercapto-1,2,4-triazole (**6c**).

Compound **6c** was obtained as a pale yellow needle crystals in 85.3% yield; mp 208-210 ºC; ir (potassium bromide): ν 3426 (NH), 3037 (=C-H), 2985 (CH_3), 2553 (SH), 1604, 1450 (C=C, C=N), 1245, 1042 (C-O-C) cm^{-1}; ^1H nmr (400 MHz; DMSO-d_6): δ 8.01 (s, 1H, NH), 7.21-6.80 (m, 4H, ArH), 5.26 (s, 2H, OCH_2), 2.69 (s, 1H, SH); 2.10 (s, 3H, CH_3); ms: (EI) m/z 221 (M^+, 26.15), 207 (3.52), 147 (6.88), 133 (5.62), 114 (100), 108 (58.38), 91 (15.23), 76 (35.21).

Anal. Calcd. for $C_{10}H_{11}N_3OS$: C, 54.28; H, 5.01; N, 18.99. Found: C, 54.22; H, 5.03; N, 18.91.

2-(4-Methylphenyl)oxymethyl-5-mercapto-1,2,4-triazole (**6d**).

Compound **6d** was obtained as a pale yellow powder in 86.5% yield; mp 205-207 °C; ir (potassium bromide): ν 3384 (NH), 3031 (=C-H), 2921 (CH_3), 2550 (SH), 1617, 1514 (C=C, C=N), 1236, 1063 (C-O-C) cm^{-1}; ^1H nmr (400 MHz; DMSO-d_6): δ 8.01 (s, 1H, NH), 7.01-6.90 (m, 4H, ArH), 5.15 (s, 2H, OCH_2), 2.59 (s, 1H, SH), 2.08 (s, 3H, CH_3); ms: (EI) m/z 221 (M^+, 41.26), 147 (4.09), 131 (5.58), 114 (19.72), 108 (100), 91 (23.66), 77 (22.40).

Anal. Calcd. for $C_{10}H_{11}N_3OS$: C, 54.28; H, 5.01; N, 18.99. Found: C, 54.23; H, 5.10; N, 18.86.

2-(2-Chlorophenyl)oxymethyl-5-mercapto-1,2,4-triazole (**6e**).

Compound **6e** was obtained as pale yellow prism crystals in 87.1% yield; mp 153-154 °C; ir (potassium bromide): ν 3383 (NH), 3187 (=C-H), 2980 (CH_2), 2553 (SH), 1628, 1488 (C=C, C=N), 1239, 1015 (C-O-C), 648 (C-Cl); ^1H nmr (400 MHz; DMSO-d_6): δ 7.41-6.88 (m, 4H, ArH), 5.43 (s, 1H, NH), 5.14 (s, 2H, OCH_2), 4.20 (s, 1H, SH); ms: (EI) m/z 243 (M+2, 15.47), 241 (M^+, 38.93), 206 (0.77), 182 (0.72), 169 (0.87), 167 (1.98), 131 (2.91), 130 (32.54), 128 (95.13), 114 (100), 59 (15.54).

Anal. Calcd. for $C_9H_8N_3OClS$: C, 44.72; H, 3.34; N, 17.39. Found: C, 44.63; H, 3.31; N, 17.32.

2-β–Naphthyloxymethyl-5-mercapto-1,2,4-triazole (**6f**).

Compound **6f** was obtained as a pale yellow powder in 81.2% yield; mp 216-218 °C; ir (potassium bromide): ν 3428 (NH), 3055 (=C-H), 2980 (CH_2), 2553 (SH), 1628, 1513 (C=C, C=N), 1212, 1006 (C-O-C); ^1H nmr (400 MHz; DMSO-d_6): δ 8.13 (s, 1H, NH), 8.05-6.90 (m, 7H, β–$C_{10}H_7$-), 5.58 (s, 2H, OCH_2), 4.25 (s, 1H, SH); ms: (EI) m/z 257 (M^+, 8.37), 144 (100), 130 (1.60), 127 (14.07), 115 (62.87), 114 (17.67).

Anal. Calcd. for $C_{13}H_{11}N_3OS$: C, 60.68; H, 4.31; N, 16.33. Found: C, 60.59; H, 4.28; N, 16.26.

2-α–Naphthyloxymethyl-5-mercapto-1,2,4-triazole (**6g**).

Compound **6g** was obtained as a cream-colored powder in 80.8% yield; mp >220 °C; ir (potassium bromide): ν 3432 (NH), 3055 (=C-H), 2912 (CH_2), 2550 (SH), 1744, 1587 (C=C, C=N), 1212, 1080 (C-O-C); ^1H nmr (400 MHz; DMSO-d_6): δ 8.15 (s, 1H, NH), 7.70-6.73 (m, 7H, α–$C_{10}H_7$-), 5.47 (s, 2H, OCH_2), 4.14 (s, 1H, SH); ms: (EI) m/z 257 (M^+, 9.25), 144 (100), 127 (18.52), 115 (58.13), 114 (20.38).

Anal. Calcd. for $C_{13}H_{11}N_3OS$: C, 60.68; H, 4.31; N, 16.33. Found: C, 60.61; H, 4.29; N, 16.27.

General procedure for Preparing (*S*)-3-α-phenylethyl-2,4-dihydro-5-aryloxymethyl-1,2,4-triazolo[3,4-*b*]-1,3,5-thiadiazines (**7a-g)**.

To a solution of absolute ethanol (5 mL), polyformaldehyde (6 mmol) and *S*-(-)-α-phenylethylamine (3 mmol), was added (**6**) (3 mmol). The mixture was acidified with hydrochloric acid to pH 4-5, followed by addition of potassium fluoride (0.1 g). After the mixture was stirred at 30 °C for 30 minutes, the solution was heated up to 55 °C for 6-8 hours, and then left to stand overnight. The solvent was then removed by distillation to leave a solid that was washed with water and 8% sodium hydroxide, then washed again with water to neutrality. The solid was recrystallized from absolute ethanol and purified by column chromatography to obtain the products **7**.

(*S*)-3-α-Phenylethyl-2,4-dihydro-5-phenyloxymethyl-1,2,4-triazolo[3,4-*b*]-1,3,5-thiadiazine (**7a**).

This compound was prepared as a pale yellow powder in 75.6% yield, mp 80-82 °C; $[\alpha]^{20}_D$ -166.6° (c = 1.2 x 10^{-4}, DMSO); ir (potassium bromide): ν 3029 (=C-H), 2980 (CH_2-H), 1676 (C=N), 1591 (N=C-S), 1275, 1029 (C-O-C) and 688 (C-S-C) cm^{-1}; ^1H nmr (400 MHz; DMSO-d_6): δ 7.39-7.28 (m, 10H, Ph-H), 7.11-7.09 (q, 1H, CH, *J* = 6.73 Hz), 5.45 (s, 1H, N-CH_2-N), 5.08 (s, 1H, N-CH_2-N), 4.68 (s, 1H, N-CH_2-S), 4.40 (s, 1H, N-CH_2-S), 1.46-1.44 (d, 3H, CH_3, *J* = 6.48 Hz); ms: (EI) m/z 352 (M^+, 1.13), 260 (0.51), 259 (2.00), 156 (1.65), 147 (1.67), 128 (1.41), 115 (4.03), 107 (2.75), 105 (100), 91 (13.29), 90 (2.20).

Anal. Calcd. for $C_{19}H_{20}N_4OS$: C, 64.75; H, 5.72; N, 15.90. Found: C, 64.39; H, 5.58; N, 15.61.

(*S*)-3-α-Phenylethyl-2,4-dihydro-5-(2-methyloxyphenyl)-oxymethyl-1,2,4-triazolo[3,4-*b*]-1,3,5-thiadiazine (**7b**).

This compound was prepared as a yellow powder in 55.5% yield, mp 174-176 °C; $[\alpha]^{20}_D$ –50° (c = 2 x 10^{-4}, DMSO); IR (potassium bromide) ν 3019 (=C-H), 2931 (CH_2-H), 1670 (C=N), 1585 (N=C-S), 1234, 1042 (C-O-C) and 696 (C-S-C) cm^{-1}; ^1H NMR (400 MHz; DMSO-d_6): δ 7.97-7.27 (m, 9H, Ar-H), 7.15-7.09 (q, 1H, CH, *J* = 6.62 Hz), 5.59 (s, 2H, CH_2-O), 5.36 (s, 1H, N-CH_2-N), 4.81 (s, 1H, N-CH_2-N), 4.69 (s, 1H, N-CH_2-S), 4.59 (s, 1H, N-CH_2-S), 2.18 (s, 3H, CH_3-Ph), 1.56-1.54 (d, 3H, CH_3, *J* = 6.72 Hz); MS (EI) m/z 259 (7.36), 156 (21.83), 147 (10.68), 128 (8.36), 115 (17.46), 114 (100), 108 (67.85), 105 (36.61), 91 (33.92), 90 (11.20).

Anal. Calcd. for $C_{20}H_{22}N_4OS$, C, 65.54; H, 6.05; N, 15.29. Found: C, 65.36; H, 6.17; N, 15.01.

(*S*)-3-α-Phenylethyl-2,4-dihydro-5-(3-methylphenyl)oxymethyl-1,2,4-triazolo[3,4-*b*]-1,3,5-thiadiazine (**7c**).

This compound was prepared as a pale yellow powder in 95.6% yield, mp 75-77 °C; $[\alpha]^{20}_D$ + 46.6º (c = 2 x 10^{-4}, DMSO); ir (potassium bromide) ν 3028 (=C-H), 2975 (CH_2-H), 1620 (C=N), 1592 (N=C-S), 1261, 1057 (C-O-C) and 698 (C-S-C) cm^{-1}; ^{1}H nmr (400 MHz; DMSO-d_6): δ 7.38-7.13 (m, 9H, Ar-H), 6.92-6.84 (q, 1H, CH, *J* = 8.90 Hz), 6.79 (s, 2H, CH_2-O), 5.52 (s, 1H, N-CH_2-N), 5.33 (s, 1H, N-CH_2-N), 4.79 (s, 1H, N-CH_2-S), 4.67 (s, 1H, N-CH_2-S), 2.27 (s, 3H, CH_3-Ph), 1.45-1.43 (d, 3H, CH_3, *J* = 6.27 Hz); ms (EI) m/z 366 (M^+, 3.39), 260 (2.62), 259 (10.01), 156 (4.38), 147 (6.79), 128 (3.97), 115 (10.14), 114 (34.88), 105 (100), 91 (17.31), 90 (4.27);

Anal. Calcd. for $C_{20}H_{22}N_4OS$, C, 65.54; H, 6.05; N, 15.29. Found: C, 65.31; H, 6.18; N, 15.66.

(*S*)-3-α-Phenylethyl-2,4-dihydro-5-(4-methylphenyl)oxymethyl-1,2,4-triazolo[3,4-*b*]-1,3,5-thiadiazine (**7d**).

This compound was prepared as a yellow powder in 79.2% yield, mp 77-79 °C; $[\alpha]^{20}_D$ +75º (c = 2 x 10^{-4}, DMSO); ir (potassium bromide) ν 3028 (=C-H), 2950 (CH_2-H), 1610 (C=N), 1506 (N=C-S), 1222, 1026 (C-O-C) and 699 (C-S-C) cm^{-1}; ^{1}H nmr (400 MHz; DMSO-d_6): δ 7.28-7.00 (m, 9H, Ar-H), 6.90-6.85 (q, 1H, CH, *J* = 8.5Hz), 5.33 (s, 2H, CH_2-O), 5.13-5.06 (d, 1H, N-CH_2-N, J = 13.25 Hz), 4.43-4.40 (d, 1H, N-CH_2-N, *J* = 13.15 Hz), 4.11-4.09 (d, 1H, N-CH_2-S, *J* = 7.10Hz), 4.00-3.97 (d, 1H, N-CH_2-S, *J* = 7.15 Hz), 2.27 (s, 3H, CH_3-Ph), 1.43-1.42 (d, 3H, CH_3, *J* = 6.39 Hz); ms (EI) m/z 366 (M^+, 7.01), 260 (11.92), 156 (9.16), 147 (9.36), 128 (4.16), 115 (10.43), 108 (76.79), 105 (100), 91 (19.98), 90 (6.36).

Anal. Calcd. for $C_{20}H_{22}N_4OS$, C, 65.54; H, 6.05; N, 15.29. Found: C, 65.19; H, 6.30; N, 15.68.

(*S*)-3-α-Phenylethyl-2,4-dihydro-5-(2-chlorophenyl)oxymethyl-1,2,4-triazolo[3,4-*b*]-1,3,5-thiadiazine (**7e**).

This compound was prepared as a dark yellow powder in 56.1% yield, mp 127-129 °C; $[\alpha]^{20}_D$ -54° (c = 3.24 x 10^{-4}, DMSO); ir (potassium bromide) ν 3029 (=C-H), 2970 (CH_2-H), 1626 (C=N), 1586 (N=C-S), 1229, 1088 (C-O-C) and 629 (C-S-C) cm^{-1}; ^{1}H nmr (400 MHz; DMSO-d_6): δ 7.39-7.28 (m, 9H, Ar-H), 7.14-7.12 (q, 1H, CH, *J* = 8.97 Hz), 5.67-5.63 (d, 1H, N-CH_2-N, *J* = 12.93 Hz), 5.46 (s, 2H, -CH_2-O), 5.25-5.22 (d, 1H, N-CH_2-N, *J* = 13.25 Hz), 4.63-4.60 (d, 1H, N-CH_2-S, *J* = 12.91 Hz), 4.33-4.30 (d, 1H, N-CH_2-S, *J* = 13.12 Hz), 1.47-1.46 (d, 3H, CH_3, *J* = 6.80 Hz); ms (EI) m/z 260 (2.17), 156 (7.44), 148 (4.54), 128 (44.56), 115 (20.76), 114 (100), 105 (75.10), 91 (7.05), 90 (2.24).

Anal. Calcd. for $C_{19}H_{19}N_4OS$, C, 58.98; H, 4.95; N, 14.48. Found: C, 58.65; H, 4.77; N, 14.09.

(*S*)-3-α-Phenylethyl-2,4-dihydro-5-β–naphthyloxymethyl-1,2,4-triazolo[3,4-*b*]-1,3,5-thiadiazine (**7f**).

This compound was prepared as a dark yellow powder in 50% yield, mp 87-89 °C; $[\alpha]^{20}_D$ -50° (c = 2.0 x 10^{-4}, DMSO); ir (potassium bromide): ν 3085, 3035 (naphthyl =C-H), 2982 (CH_2-H), 1625 (C=N), 1515 (N=C-S), 1213, 1011 (C-O-C), 844, 816, 735 (β-substituted naphthyl =C-H) and 692 (C-S-C) cm^{-1}; ^{1}H nmr (400 MHz; DMSO-d_6): δ 7.86-7.27 (m, 12H, Ar-H), 7.09-7.03 (q, 1H, CH, *J* = 9.09 Hz), 5.97 (s, 2H, CH_2-O), 5.20-5.18 (d, 1H, N-CH_2-N, *J* = 10.20 Hz), 4.96-4.93 (d, 1H, N-CH_2-N, *J* = 10.11 Hz), 4.46-4.42 (d, 1H, N-CH_2-S, *J* = 16.91 Hz), 4.18-4.13 (d, 1H, N-CH_2-S, *J* = 16.99 Hz), 1.50-1.48 (d, 3H, CH_3, *J* = 6.35 Hz); ms (EI) m/z 275 (2.69), 170 (4.42), 156 (49.95), 144 (15.73), 142 (0.81), 128 (100), 115 (15.12), 105 (98.38), 91 (12.20), 90 (2.34).

Anal. Calcd. for $C_{23}H_{22}N_4OS$, C, 68.63; H, 5.51; N, 13.92. Found: C, 68.31; H, 5.70; N, 13.65.

(*S*)-3-α-Phenylethyl-2,4-dihydro-5-α-naphthyloxymethyl-1,2,4-triazolo[3,4-*b*]-1,3,5-thiadiazine (**7g**).

This compound was prepared as a pale yellow powder in 90.4% yield, mp 122-124 °C; $[\alpha]^{20}_D$ -53° (c = 2.0 x 10^{-4}, DMSO); ir (potassium bromide): ν 3065, 3038 (naphthyl =C-H), 2985 (CH_2-H), 1615 (C=N), 1514 (N=C-S), 1213, 1010 (C-O-C), 815, 782 (α-substituted naphthyl =C-H), and 695 (C-S-C) cm^{-1}; ^{1}H nmr (400 MHz; DMSO-d_6): δ 8.16-7.29 (m, 12H, Ar-H), 7.09-7.07 (q, 1H, CH, *J* = 9.20 Hz), 5.66 (s, 2H, CH_2-O), 5.27-5.25 (d, 1H, N-CH_2-N, *J* = 10.07 Hz), 5.04-5.02 (d, 1H, N-CH_2-N, *J* = 10.20 Hz), 4.24-4.21 (d, 1H, N-CH_2-S, *J* = 10.28 Hz), 4.06-4.03 (d, 1H, N-CH_2-S, *J* = 10.25 Hz), 1.51-1.49 (d, 3H, CH_3, *J* = 6.50 Hz); ms (EI) m/z 260 (3.44), 156 (5.31), 147 (12.32), 144 (100), 128 (14.87), 115 (71.89), 105 (83.65), 91 (5.91), 89 (8.65).

Anal. Calcd. for $C_{23}H_{22}N_4OS$, C, 68.63; H, 5.51; N, 13.92. Found: C, 68.35; H, 5.71; N, 13.61.

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