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Synthesis and analgesic activity of some triazoles and triazolothiadiazines

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Abstract

The synthesis of some triazoles and triazolothiadiazines starting from (5,6,7,8-tetrahydronaphthalen-2-yl)oxyacetic acid is described. The chemical structure of the compounds were elucidated by analytical, IR, ^{1}H NMR and mass spectral studies. Some of the newly synthesized compounds were tested for analgesic activity and compounds **5b**, **5c**, and **5d** exhibited promising analgesic activity.

Keywords: Tetrahydronaphthalentriazoles; Triazaolothiadiazines; Analgesic activity

1. Introduction

The biological activities of various triazole derivatives [1,2] and thiadiazines [3,4] have been extensively studied. We observed from the literature that the s-triazole moiety has great versatility in fusing to various ring systems and possesses a broad spectrum of biological activities [5–11]. Among the most important effects are: anti-inflammatory [5,11], hypotensive [6], analgesic and hypnotic [7,11], and antifungal activities [2,8].

In this work, we have synthesized 3-[(5,6,7,8-tetrahydronaphthalen-2-yl)oxymethyl]-4-amino (or 4-phenyl)-5-mercapto-1,2,4-triazoles and their derivatives and 3-[(5,6,7,8-tetrahydronaphthalen-2-yl)oxymethyl]-6-aryl-7*H*-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines and tested the latter for analgesic activity.

2. Chemistry

In the present work, (5,6,7,8-tetrahydronaphthalen-2-yl)oxyacetic acid (**1**) was prepared for the first time by reacting 5,6,7,8-tetrahydro-2-naphthol with chloroacetic acid in accordance with the method described in the literature [12,13] (Scheme 1).

3-[(5,6,7,8-Tetrahydronaphthalen-2-yl)oxymethyl]-4-amino-5-mercapto-1,2,4-triazoles (**3**) were prepared according to a reported procedure [14] by heating thiocarbohydrazide **2** with **1.**

The reaction of triazole **3** with arylaldehyde in presence of concentrated sulfuric acid in dioxane gave the Schiff bases (3-[(5,6,7,8-tetrahydronaphthalen-2-yl)oxymethyl]-4-arylideneamino-5-mercapto-1,2,4-triazoles) (**4a**–**d**).

3-[(5,6,7,8-Tetrahydronaphthalen-2-yl)oxymethyl]-6-aryl-7*H*-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines (**5a**–**e**) were obtained by condensing triazole **3** with phenacyl bromides in absolute ethanol (Table 1).

3-[(5,6,7,8-Tetrahydronaphthalen-2-yl)oxymethyl]-4-phenyl-5-mercapto-1,2,4-triazole (**8**) was prepared according to a reported procedure [15] (Scheme 2).

The reaction of triazole **8** with phenacyl (or *p*-chlorophenacyl) bromide gave 3-[(5,6,7,8-tetrahydronaphthalen-2-yl)oxymethyl]-4-phenyl-5-arylacylthio-1,2,4-triazoles (**9a**–**b**).

Analytical and spectral data (IR, ^{1}H NMR, MS(FAB$^+$)) confirmed the structures of **4a**–**d**, **5a**–**e** and **6**, **7**, **8**, and **9a**–**b**.

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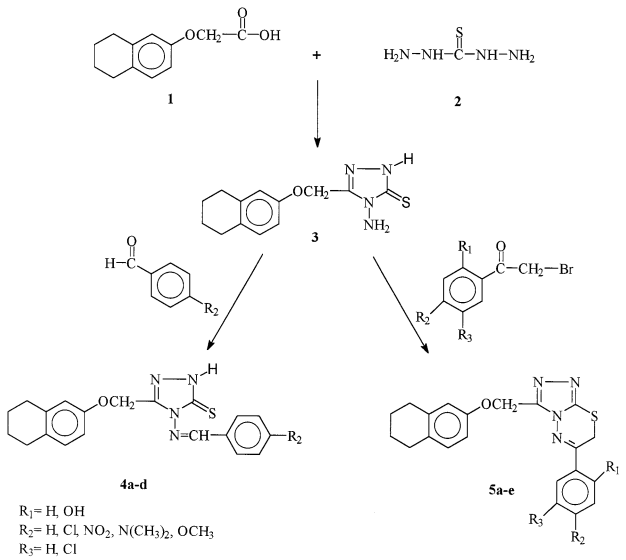


Scheme 1.

3. Experimental

3.1. Chemistry

Melting points were determined by using a Gallenkamp apparatus and are uncorrected. Spectroscopic data were recorded by the following instruments, IR: Shimadzu IR-435 spectrophotometer; ^{1}H NMR: Bruker 250 MHz, Jeol JNM-EX 90A FT 90 MHz spectrometer; MS: fast atom bombardment mass spectra (FAB-MS) were obtained by VG Quattro mass spectrometer. Microanalytical data were obtained by the Microanalytical Section of Service Center (CNRS, Ecole Normale de Chimie de Montpellier, France).

3.2. General procedure for the synthesis of the compounds

3.2.1. (5,6,7,8-Tetrahydronaphthalen-2-yl)oxyacetic acid (1)

This compound was prepared by reacting 5,6,7,8-tetrahydro-2-naphthol (0.1 mol) with chloroacetic acid (0.1 mol) in NaOH solution.

3.2.2. 3-[(5,6,7,8-Tetrahydronaphthalen-2-yl)oxymethyl]-4-amino-5-mercapto-1,2,4-triazoles (3)

A mixture of thiocarbohydrazide (**2**) (0.1 mol) and (5,6,7,8-tetrahydronaphthalen-2-yl)oxyacetic acid (**1**) was heated in an oil-bath at 160–170°C for 2 h. The fused mass thus obtained was dispersed with hot water to obtain the triazole. The product was recrystallized from methanol; m.p.: 135°C.

IR (KBr, cm^{-1}): 1600 (C=N), 1230–1100 (C–O–C), 1011 (C=S); ^{1}H NMR (250 MHz), (DMSO-d$_6$, δ (ppm)): 1.60 (4H, s, C_6 and C_7 protons of tetrahydronaphthalene), 2.6 (4H, s, C_5 and C_8 protons of tetrahydronaphthalene), 5.3 (2H, s, OCH_2), 5.61 (2H, s, $N-NH_2$), 6.6–6.9 (3H, m, aromatic protons), 13.57 (1H, s, NH).

3.2.3. 3-[(5,6,7,8-Tetrahydronaphthalen-2-yl)oxymethyl]4-arylidene-amino-5-mercapto-1,2,4-triazoles (4a–d)

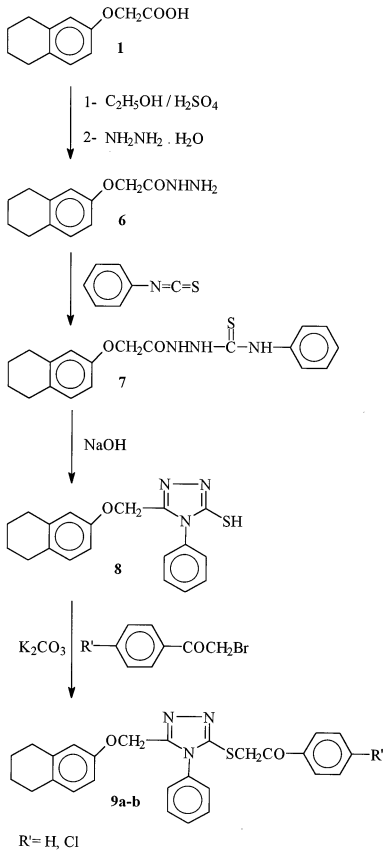
To a suspension of arylaldehyde (0.005 mol) in dioxane (10 ml), was added an equimolar amount of triazole **3**. The suspension was heated until a clear solution was obtained. A few drops of conc. sulfuric acid were added as a catalyst and the solution was refluxed for 3 h on a water bath. The precipitated solid was filtered off and recrystallized from ethanol.

4a: IR (KBr, cm^{-1}): 1600 (C=N), 1230–1100 (C–O–C),1011 (C=S); ^{1}H NMR (250 MHz), (DMSO-d$_6$, δ (ppm)): 1.65 (4H, br s, C_6 and C_7 protons of tetrahydronaphthalene), 2.6 (4H, br s, C_5 and C_8 protons of tetrahydronaphthalene), 5.2 and 5.4 (2H, two s, OCH_2), 6.6–7.9 (8H, m, aromatic protons), 9.9 and 10.0 (1H, two s, N=CH), 14.1 and 14.15 (1H, two s, NH); MS(FAB$^+$): $M+1$: m/z 365.

4b: IR (KBr, cm^{-1}): 1603 (C=N),1235–1120 (C–O–C), 1010 (C=S); ^{1}H NMR (250 MHz), (DMSO-d$_6$, δ (ppm)): 1.6 (4H, br s, C_6 and C_7 protons of tetrahydronaphthalene), 2.6 (4H, br s, C_5 and C_8 protons of

Table 1
Physicochemical data of the compounds

No.	R_1	R_2	R_3	R′	M.p. (°C)	Yield (%)	Molecular formula	MW
4a	H	H	H	–	125	85	$C_{20}H_{20}N_4OS$	364.48
4b	H	Cl	H	–	153	78	$C_{20}H_{19}ClN_4OS$	398.92
4c	H	NO_2	H	–	172	92	$C_{20}H_{19}N_5O_3S$	409.48
4d	H	$N(CH_3)_2$	H	–	184	87	$C_{22}H_{25}N_5OS$	407.54
5a	H	H	H	–	145	67	$C_{21}H_{20}N_4OS$	376.49
5b	H	Cl	H	–	95	65	$C_{21}H_{19}ClN_4OS$	410.93
5c	H	NO_2	H	–	148	72	$C_{21}H_{19}N_5O_3S$	421.48
5d	OH	OCH_3	H	–	66	60	$C_{22}H_{21}N_4O_3S$	422.51
5e	OH	H	Cl	–	76	55	$C_{21}H_{19}ClN_4O_2S$	426.93
9a	–	–	–	H	52	47	$C_{27}H_{25}N_3O_2S$	455.59
9b	–	–	–	Cl	96	50	$C_{27}H_{24}ClN_3O_2S$	490.03



Scheme 2.

tetrahydronaphthalene), 5.15 and 5.4 (2H, two s, OCH_2), 6.6–6.75 (2H, m, C_3 and C_4 protons of tetrahydronaphthalene), 6.9 (1H, d ($J = 8.24$ Hz), C_1 proton of tetrahydronaphthalene), 7.6 (2H, d ($J = 8.50$ Hz), C_2 and C_6 aromatic protons), 7.9 (2H, d ($J = 8.53$ Hz), C_3 and C_5 aromatic protons), 9.95 and 10.1 (1H, two s, C=NH), 14.1 (1H, s, NH); MS(FAB$^+$): $M+1$: m/z 399.

4c: IR (KBr, cm^{-1}): 1597 (C=N), 1232–1120 (C–O–C), 1008 (C=S); ^{1}H NMR (90 MHz), (DMSO-d_6, δ (ppm)): 1.7 (4H, br s, C_6 and C_7 protons of tetrahydronaphthalene), 2.65 (4H, br s, C_5 and C_8 protons of tetrahydronaphthalene), 5.15 and 5.4 (2H, two s, OCH_2), 6.6–7.0 (3H, m, C_1, C_3 and C_4 protons of tetrahydronaphthalene), 7.4–7.9 (4H, m, aromatic protons), 9.9 and 10.05 (1H, two s, C=NH), 13.8 (1H, s, NH); MS(FAB$^+$): $M+1$: m/z 410.

4d: IR (KBr, cm^{-1}): 1610 (C=N), 1240–1130 (C–O–C), 1015 (C=S); ^{1}H NMR (90 MHz), (DMSO-d_6, δ (ppm)): 1.7 (4H, br s, C_6 and C_7 protons of tetrahydronaphthalene), 2.6 (4H, br s, C_5 and C_8 protons of tetrahydronaphthalene), 3.0 (6H, s, two CH_3), 5.1 (2H, s, OCH_2), 6.6–7.4 (7H, m, aromatic protons), 9.4 (1H, s, N=CH), 13.8 (1H, s, NH); MS(FAB$^+$): $M+1$: m/z 408.

*3.2.4. 3-[(5,6,7,8-Tetrahydronaphthalen-2-yl)oxymethyl]-6-aryl-7H-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazines (**5a–e**)*

A solution of triazole **3** (0.005 mol) and phenacyl bromide (0.005 mol) in absolute ethanol (30 ml) was heated under reflux for 1 h, cooled to room temperature and then neutralized with ammonium hydroxide. The product thus obtained was recrystallized from ethanol.

5a: IR (KBr, cm^{-1}): 1632 (C=N), 1239–1112 (C–O–C); ^{1}H NMR (90 MHz), (DMSO-d_6, δ (ppm)): 1.7 (4H, br s, C_6 and C_7 protons of tetrahydronaphthalene), 2.7 (4H, br s, C_5 and C_8 protons of tetrahydronaphthalene), 4.45 (2H, s, SCH_2), 5.25 (2H, s, OCH_2), 6.85–7.0 (3H, m, C_1, C_3 and C_4 protons of tetrahydronaphthalene), 7.2–8.1 (5H, m, aromatic protons); MS(FAB$^+$): $M+1$: m/z 377.

5b: IR (KBr, cm^{-1}): 1624 (C=N), 1236–1122 (C–O–C); ^{1}H NMR (250 MHz), (DMSO-d_6, δ (ppm)): 1.65 (4H, br s, C_6 and C_7 protons of tetrahydronaphthalene), 2.65 (4H, br s, C_5 and C_8 protons of tetrahydronaphthalene), 4.4 (2H, s, SCH_2), 5.25 (2H, s, OCH_2), 6.7–6.8 (2H, m, C_3 and C_4 protons of tetrahydronaphthalene), 6.9 (1H, m, C_1 proton of tetrahydronaphthalene), 7.6 (2H, d ($J = 8.7$ Hz), C_2 and C_6 aromatic protons), 7.9–8.0 (2H, d ($J = 8.6$ Hz), C_3 and C_5 aromatic protons); MS(FAB$^+$): $M+1$: m/z 411.

5c: IR (KBr, cm^{-1}): 1612 (C=N), 1233–1111 (C–O–C); ^{1}H NMR (90 MHz), (DMSO-d_6, δ (ppm)): 1.7 (4H, br s, C_6 and C_7 protons of tetrahydronaphthalene), 2.65 (4H, br s, C_5 and C_8 protons of tetrahydronaphthalene), 4.5 (2H, s, SCH_2), 5.3 (2H, s, OCH_2), 6.7–7.0 (3H, m, C_1, C_3 and C_4 protons of tetrahydronaphthalene), 8.11–8.22 (2H, d ($J = 9.16$ Hz), C_2 and C_6 aromatic protons), 8.32–8.42 (2H, d ($J = 9.34$ Hz), C_3 and C_5 aromatic protons).

5d: IR (KBr, cm^{-1}): 1610 (C=N), 1225–1009 (C–O–C); ^{1}H NMR (250 MHz), (DMSO-d_6, δ (ppm)): 1.65 (4H, br s, C_6 and C_7 protons of tetrahydronaphthalene), 2.65 (4H, br s, C_5 and C_8 protons of tetrahydronaphthalene), 3.7 (3H, s, OCH_3), 4.3 (2H, s, SCH_2), 5.4 (2H, s, OCH_2), 6.4–7.0 (3H, m, C_1, C_3 and C_4 protons of tetrahydronaphthalene), 7.3–7.9 (3H, m, aromatic protons), 11.0 (1H, br, OH).

5e: IR (KBr, cm^{-1}): 1611 (C=N), 1236–1112 (C–O–C); ^{1}H NMR (250 MHz), (DMSO-d_6, δ (ppm)): 1.7 (4H, br s, C_6 and C_7 protons of tetrahydronaphthalene), 2.7 (4H, br s, C_5 and C_8 protons of tetrahydronaphthalene), 4.35 (2H, s, SCH_2), 5.3 (2H, s, OCH_2), 6.7–7.05 (3H, m, C_1, C_3 and C_4 protons of tetrahydronaphthalene), 7.4–7.9 (3H, m, aromatic protons), 11.0 (1H, br, OH); MS(FAB$^+$): $M+1$: m/z 427.

*3.2.5. (5,6,7,8-Tetrahydronaphthalen-2-yl)oxyacetic acid hydrazide (**6**)*

To prepare ethyl, (5,6,7,8-tetrahydronaphthalen-2-yl)oxyacetate, a mixture of acid **1** (0.3 mol) and 6 ml of concentrated sulfuric acid in 300 ml of anhydrous ethanol was refluxed for 6 h. The reaction mixture was concentrated under reduced pressure and upon cooling, extracted with ether. A solution of this ester (0.25 mol) and hydrazine hydrate (99%, 0.40 mol) in 100 ml of ethanol was refluxed for 2 h. The excess of ethanol was removed under reduced pressure. The concentrated solution, on cooling, gave a solid mass of **6** which was filtered, dried and recrystallized from ethanol, m.p. 132°C.

IR (KBr, cm^{-1}): 3340 (NH_2), 3200 (NH), 1660 (C=O), 1225–1000 (C–O–C); ^1H NMR (250 MHz), (DMSO-d_6, δ (ppm)): 1.6 (4H, br s, C_6 and C_7 protons of tetrahydronaphthalene), 2.6 (4H, br s, C_5 and C_8 protons of tetrahydronaphthalene), 5.1 (2H, s, OCH_2), 6.3 (1H, br, NH), 6.45–6.60 (2H, m, C_1, C_3 protons of tetrahydronaphthalene), 6.85 (1H, d (J = 8.28 Hz) C_4 proton of tetrahydronaphthalene) 7.4–8.0 (5H, m, aromatic protons).

*3.2.6. 1-[(5,6,7,8-Tetrahydronaphthalen-2-yl)oxyacetyl]-4-phenyl-3-thiosemicarbazide (**7**)*

To a solution of the acid hydrazide **6** (0.01 mol) in hot ethanol (40 ml) was added an equivalent amount of the phenylisothiocyanate in ethanol (10 ml) and the mixture was refluxed for 1 h. The solid separated upon cooling was filtered, washed with ethanol, dried and recrystallized from ethanol, m.p. 148°C.

IR (KBr, cm^{-1}): 3330, 3180 (NH), 1640 (C=O), 1225–1000 (C–O–C); ^1H NMR (250 MHz), (DMSO-d_6, δ (ppm)): 1.55 (4H, br s, C_6 and C_7 protons of tetrahydronaphthalene), 2.5 (4H, br s, C_5 and C_8 protons of tetrahydronaphthalene), 5.2 (2H, s, OCH_2), 6.45–6.65 (2H, m, C_1, C_3 protons of tetrahydronaphthalene), 6.85 (1H, d (J = 8.18 Hz) C_4 proton of tetrahydronaphthalene) 7.2–7.6 (5H, m, aromatic protons), 7.9 (1H, br, CSNH), 9.40 and 10.65 (1H and 1H, br, NHCS and CONH, respectively).

*3.2.7. 3-[(5,6,7,8-Tetrahydronaphthalen-2-yl)oxymethyl]-4-phenyl-5-mercapto-1,2,4-triazole (**8**)*

Substituted thiosemicarbazide **7** (0.0175 mol) was dissolved in 2 N NaOH (50 ml) and the resulting solution was refluxed for 2–3 h. After cooling, the reaction mixture was filtered and the filtrate was acidified with dilute hydrochloric acid until complete precipitation occurred. The solid mass which precipitated out was filtered, washed with water, dried and recrystallized from ethanol, m.p. 173°C.

IR (KBr, cm^{-1}): 1620 (C=N), 1225–1000 (C–O–C); ^1H NMR (250 MHz), (DMSO-d_6, δ (ppm)): 1.60 (4H, br s, C_6 and C_7 protons of tetrahydronaphthalene), 2.6 (4H, br s, C_5 and C_8 protons of tetrahydronaphthalene), 4.85 (2H, s, OCH_2), 6.45 (1H, d (J = 2.38 Hz), C_1 proton of tetrahydronaphthalene), 6.5 (1H, dd (J = 8.29 and 2.58 Hz) C_3 proton of tetrahydronaphthalene) 6.85 (1H, d (J = 8.30) C_4 proton of tetrahydronaphthalene) 7.3–7.6 (5H, m, aromatic protons), 14 (1H, br, NH); MS(FAB$^+$): $M+1$: m/z 338.

*3.2.8. 3-[(5,6,7,8-Tetrahydronaphthalen-2-yl)oxymethyl]-4-phenyl-5-phenacyl (or p-chlorophenacyl) thio-1,2,4-triazole (**9a–b**)*

A mixture of phenacyl chloride (0.015 mol), triazole **8** (0.015 mol) and anhydrous potassium carbonate (0.018 mol) in acetone (60 ml) was refluxed for 4–5 h. The reaction mixture was filtered and an excess of acetone was removed under reduced pressure to give **9a–b**. Finally the crude products were recrystallized from ethanol.

9a: IR (KBr, cm^{-1}): 1620 (C=N), 1225–1000 (C–O–C); ^1H NMR (250 MHz), (DMSO-d_6, δ (ppm)): 1.60 (4H, br s, C_6 and C_7 protons of tetrahydronaphthalene), 2.6 (4H, br s, C_5 and C_8 protons of tetrahydronaphthalene), 4.93 (2H, s, SCH_2), 4.98 (2H, s, OCH_2), 6.45–6.60 (2H, m, C_1, C_3 protons of tetrahydronaphthalene), 6.85 (1H, d (J = 8.18 Hz) C_4 proton of tetrahydronaphthalene), 7.40–8.05 (10H, m, aromatic protons); MS(FAB$^+$): $M+1$: m/z 456.

9b: IR (KBr, cm^{-1}): 1610 (C=N), 1225–1009 (C–O–C); ^1H NMR (250 MHz), (DMSO-d_6, δ (ppm)): 1.65 (4H, br s, C_6 and C_7 protons of tetrahydronaphthalene), 2.6–2.7 (4H, br s, C_5 and C_8 protons of tetrahydronaphthalene), 4.85 (2H, s, SCH_2), 5.00 (2H, s, OCH_2), 6.4–6.6 (2H, m, C_1 and C_3 protons of tetrahydronaphthalene), 6.80 (1H, d (J = 8.19 Hz) C_4 proton of tetrahydronaphthalene) 7.35–7.50 (5H, m, aromatic protons), 7.55 (2H, d (J = 8.62 Hz), C_3 and C_5 phenacyl protons), 8.00 (2H, d (J = 9.02 Hz) C_2 and C_6 phenacyl protons); MS(FAB$^+$): $M+1$: m/z 491.

3.3. Biological activity

Compounds **5a–e** were screened for analgesic activity. To test for analgesic activity, the acetic acid test (Modified Koster Test) [16] was performed in male albino mice (25–30 g). Aspirin was used as the reference analgesic agent. The substances were dissolved in DMSO and water (1:1) (dose: 50 mg/kg) and were given orally at a 0.3 ml volume to the animals using a stomach tube. Each group (control, aspirin and substances (**5a–e**)) included five mice. Some 60 min after drug administration, 0.6% acetic acid solution was injected i.p. (60 mg/kg). Then, each control group of mice was given the same amount of DMSO/water orally. Mean stretching numbers were recorded 5 min after the injection of acetic acid solution. Per-

Table 2
Analgesic activity

Substances	Mean stretching number	% Analgesic activity
Control	39.0 ± 3.39	–
Aspirin	17.6 ± 2.83	55
5a	13.6 ± 2.70	65
5b	23.6 ± 2.30	39.5
5c	17.0 ± 1.40	56
5d	13.0 ± 2.83	67
5e	31.8 ± 3.80	18

centage analgesic activity was calculated according to the following equation:

$$\text{Percentage analgesic activity} = N - N'/N \times 100$$

where N is the mean stretching number of the control group, and N' is the mean stretching of the experimental group. A student's t-test was used for statistical analysis (Table 2).

4. Results and discussion

In the present work, nine new compounds including triazoles and triazolothiadiazines were synthesized.

IR spectra of triazole (**3**) showed the characteristic N–H absorption at 3300 cm^{-1}. The absence of bands in the region of 3500–3200 cm^{-1} in the IR spectrum of Schiff bases (**4a**–**d**) and of triazolothiadiazines (**5a**–**e**) indicates the involvement of an amino group in the condensation reaction. Moderately strong bands observed in these spectra at 1600, 1200 and 1010 cm^{-1} are characteristic of C=N, C–O–C, and C=S groups, respectively.

In the NMR spectra of Schiff bases (**4a**–**d**), we observed paired peaks for OCH_2 protons, N=CH proton and NH proton, corresponding to *trans*(*E*) and *cis*(*Z*) forms, at 5.2, 10.0 and 14.0 ppm, respectively.

In the NMR spectra of thiazolothiadiazine (**5a**–**e**), the protons of OCH_2 group resonated as a singlet at 5.2 ppm, while the SCH_2 protons' signal appeared as a singlet at 4.3 ppm.

The protons of C_6, C_7 and C_5, C_8 of tetrahydronaphthalene were observed as a broad singlet at 1.6–1.7 and 2.6–2.65 ppm, respectively.

The chemical structure of 3-substituted-6-aryl-7*H*-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines showed analgesic activity [11]. Thus, only compounds **5a**–**e** were investigated for analgesic activity.

From the results summarized in Table 2, it is apparent that compounds **5a**–**e** exhibited an interesting profile of analgesic activity. Values obtained with aspirin and test compounds **5a**–**d** are significantly different from the control values ($P < 0.01$) and **5e** also showed analgesic activity ($P < 0.05$).

Compounds **5a**,**c**,**d** exhibited promising analgesic activity (65, 56 and 67%, respectively) in comparison to aspirin (55%).

Introduction of a chloride atom into the phenyl ring at the 6-position of the fused heterocycle led to reduction of the analgesic activity (39.5% for **5b** and 18% for **5e**).

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