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SCHIFF BASES AND TRIAZOLOTHIADIAZINES DERIVED FROM A THIOPHENE-SUBSTITUTED 4-AMINO-3-MERCAPTO-1,2,4-TRIAZOLE

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Abstract: 4-Amino-5-(thiophen-2-ylmethyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione was synthesized and converted into the corresponding Schiff bases using several aromatic aldehydes. Reaction of this aminotriazolethione with phenacyl bromides lead to triazolothiadiazines, which were subsequently reduced with $NaBH_4$ to dihydrotriazolothiadiazines. The latter type of fused heterocycle has been also obtained directly by reacting one of the previously obtained Schiff base with phenacyl bromides. NMR analysis confirmed the structures of the synthesized compounds.

***Keywords*:** Triazolethione; Imine; Ring closure; Triazolothiadiazines; Fused heterocycles

Introduction

4-Amino-1,2,4-triazole-3-thiones (**1**) (Figure 1), which could also be represented as their tautomers 4-amino-3-mercapto-1,2,4-triazoles (**2**), are a class of compounds that exhibit various biological activities (*e.g.* antimicrobial, anticancer, anticonvulsant, anti-inflammatory, antioxidant)[1] and can undergo various types of reactions.[2] These reaction could involve

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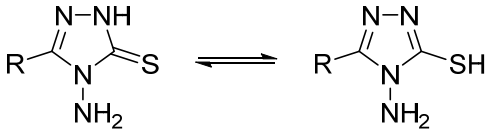
the amino group,[3] the mercapto group,[4-6] or the endocyclic *NH* in the thione tautomer.[4,7] In addition, the proximity of the aforementioned reactive sites in 4-amino-1,2,4-triazole-3-thiones is inducive of ring closure reactions in which both amino and mercapto groups are involved.[2,8,9] Formation of Schiff bases through the condensation of 4-amino-1,2,4-triazole-3-thiones with aldehydes is one of the most investigated reaction of these substrates, a process that leads to biologically active compounds[10-19] and ligands for metal complexes,[20-26] to mention only two significant applications of these derivatives of 4-amino-1,2,4-triazole-3-thiones. On the other hand, the proximity of the reactive amino and mercapto groups in these triazole derivatives could be exploited in ring closure reactions leading to fused heterocycles. For example, reaction of 4-amino-3-mercapto-1,2,4-triazoles with a variety of reagents has been extensively employed for the generation of triazolothiadiazines,[27] whose interesting biological activities have been well documented.[28]



1 **2**

Figure 1. Thione–thiol tautomerism of 4-amino-1,2,4-triazole-3-thiones.

The present contribution aims at expanding the series of previously reported derivatives of 5-(thiophen-2-ylmethyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione[29,30] by preparing several azomethines and triazolothiadiazines derived from the aforementioned scaffold featuring an amino group at position 4 of the triazole ring. Further structural modification (*e.g.* aminomethylation) of these compounds could provide access to novel chemical entities with interesting biological properties.[31]

Results and Discussion

The required starting material (**4**) was obtained through the ring closure reaction of potassium 2-(2-(thiophen-2-yl)acetyl)hydrazine-1-carbodithioate (**3**)[32] with excess hydrazine hydrate in water (Figure 2). As shown by NMR, the isolated crude material was sufficiently pure, and was used as such in the next step, although the analytical sample was purified by recrystallization prior to structural investigation.

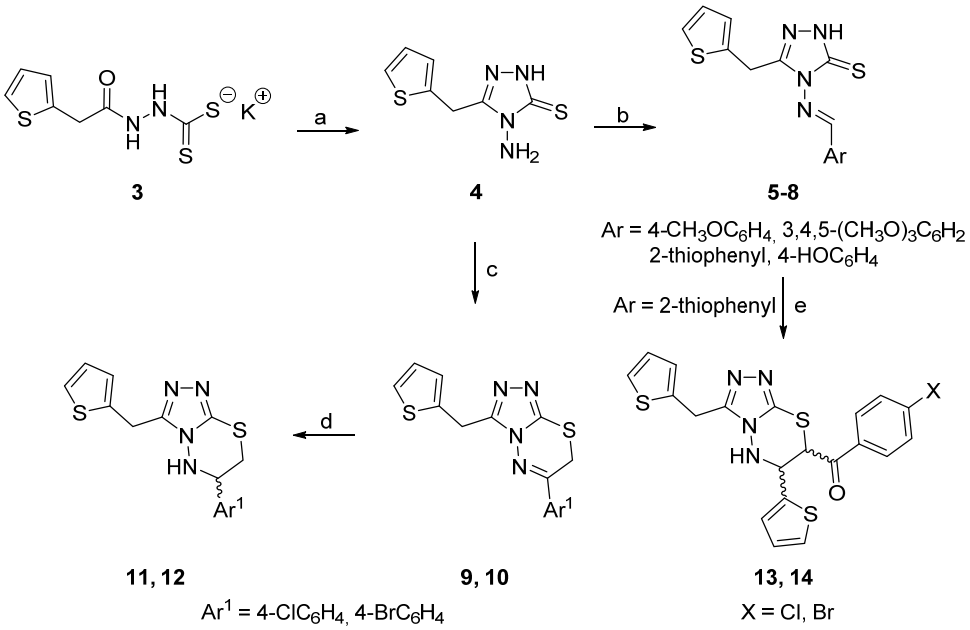


Figure 2. Synthesis and derivatization of 4-amino-5-(thiophen-2-ylmethyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (**4**). Reaction conditions : **a)** $NH_2NH_2 \cdot H_2O$, water reflux, 4 h; **b)** ArCHO, ethanol, H^+, reflux, 5 h, or ArCHO, acetic acid, reflux, 1 h; **c)** $ArCOCH_2Br$, ethanol, reflux 2 h; **d)** $NaBH_4$, methanol, rt, overnight ; **e)** $4\text{-}XC_6H_4COCH_2Br$, TEA, ethanol, reflux, 30 min.

The proton NMR spectrum of compound (**4**) showed, besides the protons in the aromatic region, three sharp singlets corresponding to the protons in the methylene group bridging the two heterocyclic ring (δ = 4.25 ppm), the protons in the amino group (δ = 5.58 ppm), and the proton at N-2

of the triazole ring (δ = 13.59 ppm). In the ^{13}C NMR spectrum, the peaks of the carbon atoms in the newly formed triazole ring can be found at 166.1 ppm (*C*-3) and 150.7 ppm (*C*-5).

Formation of imines (**5**)–(**8**) was examined under two experimental variations. Initially, these Schiff bases have been all prepared by the reaction between substrate (**4**) and the corresponding aromatic aldehydes in refluxing ethanol in the presence of conc. H_2SO_4 as catalyst. Unfortunately, under these conditions, the yields for the pure compounds (**5**)–(**7**) derived from aldehydes having electron-donating substituents were modest. NMR analysis of the crude solid that separates on cooling from the reaction mixture showed that it is a mixture of the desired azomethine and unreacted sulfate of substrate (**4**), indicating that the reaction does not reach completion under these conditions. However, under the same conditions, reaction of aminotriazolethione (**4**) with thiophene-2-carboxaldehyde went smoothly to provide Schiff base (**8**) in good yields.

The modest yields obtained for imines (**5**)–(**7**) determined us to investigate the synthesis of azomethine (**7**) under a different set of reaction conditions. Thus, substrate (**4**) was reacted with 4-hydroxybenzaldehyde in refluxing acetic acid, when a solid material separated shortly after refluxing had started. At the end of the reaction time, the isolated reaction product, which proved to be essentially the desired azomethine in pure form, was obtained in excellent yield under these conditions. Therefore, we hypothesize that the use of acetic acid both as a solvent with a higher boiling point than ethanol and also as a weaker acid catalyst compared to H_2SO_4 could be the factors that enhanced the yield observed in this synthetic variation.

In the proton spectra of Schiff bases (**5**)–(**8**), the peak associated with the protons in the amino group in aminotriazolethione (**4**) is no longer present, whereas a singlet found at approximately 10 ppm in each spectrum of imines (**5**)–(**8**) has been attributed to proton of the carbon atom of the azomethine group. The singlet corresponding to the proton at *N*-2 of the triazole ring is still noticeable in the off-set of the proton spectra of these compounds.

The potential of 5-(thiophen-2-ylmethyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (**4**) as starting material in cyclocondensations leading to triazolothiadiazines was also briefly investigated. First, the well-documented[27,33] reaction of aminotriazolethiones with phenacyl bromides was examined. The reaction was conducted in refluxing ethanol, and the desired products (**9**) and (**10**) (Figure 2) were isolated in very good yields from their bromides by treatment with ammonia. The successful conversion of the substrate (**4**) into triazolothiadiazines (**9**) and (**10**) was confirmed by NMR analysis through the absence of the signal associated with the proton involved in the thione–thiol tautomerism (**1** ↔ **2** in Figure 1) in the off-set of the proton spectra of (**9**) and (**10**), as well as through the absence of the singlet corresponding to the protons of the amino group. Instead, a novel singlet integrating for two protons is noticeable at approximately 4.5 ppm, and this peak has been assigned to the protons in the methylene group in the newly formed thiadiazine ring.

The facile access to these triazolothiadiazines allowed a brief inspection of their reactivity. Thus, reduction of the carbon-nitrogen double bond in triazolothiadiazines could lead to dihydrotriazolothiadiazines, which could be valuable synthons as secondary cyclic amines in aminomethylations or preparations of amides, for example. Surprisingly,

hydrogenation of triazolothiadiazines has been scarcely reported in literature.[34] Reduction of triazolothiadiazines (**9**) and (**10**) with a threefold excess of $NaBH_4$ in methanol at room temperature overnight afforded smoothly the reduced derivatives (**11**) and (**12**) as a mixture of enantiomers. The ^1H NMR spectra of these dihydrotriazolothiadiazines present in the aliphatic region the signals corresponding to the two diastereotopic protons at *C*-7 of the fused ring system as a discernable pair of doublet of doublets centered at approximately 3.3 and 3.4 ppm, a multiplet corresponding to the proton at *C*-6 at approximately 4.4 ppm, and a doublet corresponding to the proton of the secondary amine above 5 ppm.

With the view to increase the structural diversity of dihydrotriazolothiadiazines based on aminotriazolethione (**4**), cyclization of a selected Schiff base (**8**) having two thiophene rings in its structure with halogen-substituted phenacyl bromides was also undertaken. This particular substrate has been selected owing to the good anticancer activity of analogous triazolothiadiazines having either a thiophene or a furan ring at position 6 of the fused ring system.[35] Similar ring closure reaction have been previously conducted using aminotriazolethiones having other substituents at position 5 of the triazole ring, such as methylthio[36] or (substituted)phenyl.[37,38] Reaction of azomethine (**8**) with phenacyl bromides in the presence of TEA led to the isolation of the desired dihydrotriazolothiadiazines (**13**) and (**14**) in excellent yields (Figure 2). Because of their limited of solubility in most organic solvents, these compounds could be recrystallized only from a DMF–ethanol mixture, albeit with considerable loss. According to literature,[38] the reaction is stereospecific and affords the *trans* diastereomer, whose stereochemistry was assigned using single crystal X ray crystallography.[38] In solution,

however, the *trans* diastereomer isomerizes to the *cis* diastereomer, whose structure assignment was based on the small value of the vicinal coupling constant between the protons at *C*-6 and *C*-7 of the fused ring system.[37] The isomerization is slow in $CDCl_3$ and faster in DMSO-d_6.[38] As reaction products (**13**) and (**14**) are not soluble in $CDCl_3$, their structural investigation by NMR was conducted in DMSO-d_6. Assuming that the ring closure of Schiff base (**8**) to dihydrotriazolothiadiazines (**13**) and (**14**) also occurs stereospecifically to yield in each case the *trans* diastereomer in solid state, the NMR analysis for both compounds (**13**) and (**14**) shows that the *trans*-*cis* isomerization takes place in DMSO-d_6 to lead to a mixture of diastereomers in which *cis*-(**13**) and *cis*-(**14**), respectively, are the major component (approximately 84%). As the equilibration is a fast process, the ratio between *trans* and *cis* diastereomers of dihydrotriazolothiadiazines (**13**) and (**14**) in DMSO-d_6 does not change significantly with time. Only the NMR spectrum of the major *cis* diastereomer of these compounds has been presented in Experimental. The aliphatic region of the proton NMR spectra for the *cis* diastereomer of these dihydrotriazolothiadiazines is similar to that reported for literature analogs, and presents a triplet (a partially superimposed doublet of doublets) for the proton at *C*-6 and a doublet for the proton at *C*-7, both sets of signals having typical *cis* vicinal coupling constants (Figure 3). For the *trans* diastereomer, the proton at *C*-6 appears as a not very well resolved doublet of doublets, while the doublet at 6 ppm was assigned to the proton at *C*-7. The signal corresponding to *N*-5 proton, which has been identified through replacement with deuterium, appears as a doublet at δ values higher than 7 ppm. In addition to the proton spectra, the ^{13}C NMR spectra of products (**13**) and (**14**) also confirm the successful ring closure of Schiff base (**8**) under the experimental conditions.

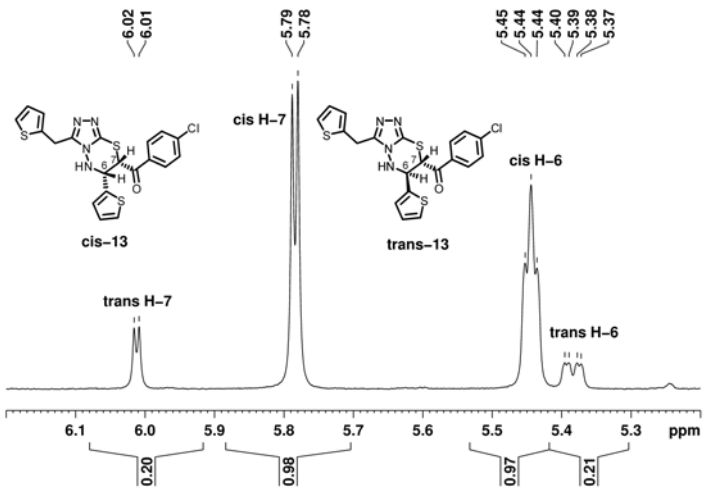


Figure 3. Excerpt of ^{1}H NMR spectrum of dihydrotriazolothiadiazine (**13**) showing the signals corresponding to protons at C-6 and C-7 in *cis* and *trans* diastereomers.

Experimental

Melting points were taken on a Mel-Temp II apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400-MHz spectrometer. The signals owing to residual protons in the deuterated solvents were used as internal standards for the ^{1}H NMR spectra. The chemical shifts for the carbon atoms are given relative to residual chloroform (δ = 77.16 ppm) or dimethyl sulfoxide (δ = 39.52 ppm) in the corresponding deuterated solvents. The chemical reagents and solvents used in this study were obtained from Sigma–Aldrich, Alfa Aesar or Merck, and were used without prior purification.

Synthesis of 4-amino-5-(thiophen-2-ylmethyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (4)

To a solution of potassium 2-(2-(thiophen-2-yl)acetyl)hydrazine-1-carbodithioate (**3**)[32] (8.1 g, 30 mmol) in water (90 mL), hydrazine hydrate (6 g, 120 mmol) was added, and then the reaction mixture was heated at

reflux temperature for 4 h. The cold reaction mixture was filtered, diluted with water (60 mL), and neutralized with 10% acetic acid under efficient stirring and external cooling (ice bath) until pH reached 5–6. The precipitate was filtered, washed thoroughly with water, and air-dried to afford colorless microcrystals (3.5 g, 55%), mp 155–156 °C (ethanol); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 4.25 (s, 2H), 5.58 (s, 2H), 6.95–7.02 (m, 2H), 7.42 (dd, J = 1.2 and 5.2 Hz, 1H), 13.59 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 24.7, 125.2, 126.6, 126.9, 136.7, 150.7, 166.1.

General procedure for the synthesis of Schiff bases of 4-amino-5-(thiophen-2-ylmethyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (4)

A mixture of aminotriazolethione (**4**) (212 mg, 1 mmol), aromatic aldehyde (1 mmol) and conc. H_2SO_4 (4–5 drops) in abs. ethanol (10 mL) was heated at reflux temperature for 5 h. The reaction mixture was allowed to reach room temperature, and then it was refrigerated overnight. The solid material was filtered and recrystallized.

(E)-4-[(4-Methoxybenzylidene)amino]-5-(thiophen-2-ylmethyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (**5**). Yield 135 mg (41%), mp 177–178 °C (ethanol); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3,87 (s, 3H), 4.36 (s, 2H), 6.95 (dd, J = 3.6 and 5.2 Hz, 1H), 7.00 (d, J = 3.8 Hz, 1H), 7.13 (d, J = 8.8 Hz, 2H), 7.40 (dd, J = 1.2 and 4.8 Hz, 1H), 7.89 (d, J = 8.8 Hz, 2H), 9.83 (s, 1H), 13.89 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 25.2, 55.5, 114.7, 124.5, 125.5, 126.9, 127.0, 130.6, 136.6, 149.6, 161.4, 162.9, 163.1.

(E)-5-(Thiophen-2-ylmethyl)-4-[(3,4,5-trimethoxybenzylidene)-amino]-2,4-dihydro-3H-1,2,4-triazole-3-thione (**6**). Yield 175 mg (45%), mp 170–171 °C (ethanol); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.75 (s, 3H), 3.86 (s, 6H), 4.38 (s, 2H), 6.95 (dd, J = 3.6 and 5.2 Hz, 1H), 7.01 (dd, J = 0.8 and 3.6 Hz, 1H), 7.23 (s, 2H), 7.40 (dd, J = 1.2 and 5.2 Hz, 1H), 9.98 (s,

1H), 13.91 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 25.3, 56.1, 60.2, 105.9, 125.5, 126.9, 127.0, 127.5, 136.7, 141.1, 149.8, 153.2, 161.4, 161.7.

(E)-4-[(4-Hydroxybenzylidene)amino]-5-(thiophen-2-ylmethyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (**7**). Yield 85 mg (27%), mp 242–244 °C (dec., dark.); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 4.34 (s, 2H), 6.90–7.12 (m, 4H), 7.40 (dd, J = 1.2 and 5.2 Hz, 1H), 7.77 (d, J = 8.4 Hz, 2H), 9.69 (s, 1H), 10.40 (br s, 1H), 13.86 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 25.2, 116.0, 123.0, 125.5, 126.9, 127.0, 130.9, 136.6, 149.5, 161.4. 161.8, 163.8.

(E)-5-(Thiophen-2-ylmethyl)-4-[(thiophen-2-ylmethylene)amino]-2,4-dihydro-3H-1,2,4-triazole-3-thione (**8**). Yield 215 mg (70%), mp 191–192 °C (ethanol); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 4.32 (s, 2H), 6.96 (dd, J = 3.2 and 5.2 Hz, 1H), 7.01 (dd, J = 0.8 and 3.6 Hz, 1H), 7.28 (dd, J = 3.6 and 4.8 Hz, 1H), 7.41 (dd, J = 1.2 and 5.2 Hz, 1H), 7.81 (dd, J = 1.2 and 3.6 Hz, 1H), 7.98 (dd, J = 0.8 and 4.8 Hz, 1H), 10.21 (s, 1H), 13.92 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 25.2, 125.6, 126.9, 127.0, 128.5, 133.0, 135.9, 136.4, 136.5, 149.5, 157.0, 161.5.

Modified synthesis of Schiff base (**7**)

A mixture of aminotriazolethione (**4**) (212 mg, 1 mmol), 4-hydroxybenzaldehyde (122 mg, 1 mmol) in glacial acetic acid (5 mL) was heated at reflux temperature for 1 h. The reaction mixture was cooled to room temperature, gradually diluted with water (45 mL), and stirred at room temperature for 1 h. The solid was filtered, washed thoroughly with water, and air-dried to give azomethine (**7**) (285 mg, 90%).

General procedure for the synthesis of triazolothiadiazines (9) and (10)

4-Amino-5-(thiophen-2-ylmethyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione **(4)** (318 mg, 1.5 mmol) and the corresponding phenacyl bromide (1.5 mmol) were heated at reflux temperature in abs. ethanol (10 mL) for 2 h. The mixture was allowed to reach room temperature, and then it was treated dropwise with excess aq. 25% NH_3 (0.5 mL). The mixture was then gradually diluted with water (20 mL), the solid was filtered, washed thoroughly with water, and air-dried.

6-(4-Chlorophenyl)-3-(thiophen-2-ylmethyl)-7H-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine (**9**). Recrystallization from 96% ethanol afforded colorless crystals (340 mg, 65%), mp 175–176 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.92 (s, 2H), 4.52 (s, 2H), 6.88–6.95 (m, 1H), 6.91 (dd, *J* = 3.8 and 4.8 Hz, 1H)), 6.99 (d, *J* = 3.6 Hz, 1H), 7.15 (d, *J* = 4.8 Hz, 1H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.84 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.5, 25.5, 125.0, 126.8, 127.2, 128.7, 129.6, 132.0, 137.3, 138.6, 140.5, 152.2, 152.7.

6-(4-Bromophenyl)-3-(thiophen-2-ylmethyl)-7H-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine **(10)**. Recrystallization from 96% ethanol afforded colorless crystals (370 mg, 63%), mp 185–186 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.92 (s, 2H), 4.53 (s, 2H), 6.92 (dd, *J* = 3.6 and 5.2 Hz, 1H). 6.99 (dd, *J* = 0.8 and 3.6 Hz, 1H), 7.15 (dd, *J* = 0.8 and 5.2 Hz, 1H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.77 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.4, 25.5, 125.0, 126.8, 127.1, 127.2, 128.7, 132.5, 132.6, 137.2, 140.4, 152.2, 152.7.

General procedure for the reduction of triazolothiadiazines (9) and (10) to dihydrotriazolothiadiazines (11) and (12)

A suspension of triazolothiadiazine (0.8 mmol) in methanol (10 mL) was gradually treated with $NaBH_4$ (92 mg, 2.4 mmol). The resulting solution was stirred in a stoppered flask at room temperature overnight, and then it was gradually diluted with water (40 mL) under efficient stirring. The solid was filtered, washed with water, and air-dried.

6-(4-Chlorophenyl)-3-(thiophen-2-ylmethyl)-6,7-dihydro-5H-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine (**11**). Recrystallization from 96% ethanol–water (3:1, *v*/*v*) gave colorless crystals (175 mg, 63%), mp 101–102 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.29 (dd, *J* = 2.8 and 12.8 Hz, 1H), 3.44 (dd, *J* = 9.2 and 12.8 Hz, 1H), 4.31 (d, *J* = 4.4 Hz, 2H), 4.37–4.46 (m, 1H), 5.27 (d, *J* = 10.0 Hz, 1H), 6.88–6.95 (m, 2H), 7.16 (dd, *J* = 2.4 and 4.4 Hz, 1H), 7.28 (d, *J* = 8.8 Hz, 2H), 7.36 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.1, 29.0, 57.6, 125.0, 126.7, 127.2, 128.2, 129.5, 135.0, 135.2, 137.7, 141.7, 152.3.

6-(4-Bromophenyl)-3-(thiophen-2-ylmethyl)-6,7-dihydro-5H-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine (**12**). Recrystallization from 96% ethanol gave colorless crystals (175 mg, 64%), mp 105–106 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.30 (dd, *J* = 3.2 and 12.8 Hz, 1H), 3.41 (dd, *J* = 9.2 and 12.8 Hz, 1H), 4.31 (d, *J* = 4.4 Hz, 2H), 4.35–4.46 (m, 1H), 5.06 (d, *J* = 10.0 Hz, 1H), 6.88–6.95 (m, 2H), 7.17 (dd, *J* = 1.6 and 4.8 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.2, 29.1, 57.8, 123.2, 125.0, 126.6, 127.3, 128.5, 132.5, 135.6, 137.7, 141.7, 152.2.

General procedure for the synthesis of dihydrotriazolothiadiazines (13) and (14)

To a suspension of Schiff base (**8**) (153 mg, 0.5 mmol) and the appropriate phenacyl bromide (0.5 mmol) in 96% ethanol (15 mL), TEA (75 mg, 0.75 mmol, 1.5 equiv.) was added, and the mixture was heated at reflux temperature for 30 min. The reaction mixture was allowed to cool to room temperature, and then the solid that separated was filtered, washed with 96% ethanol (2 × 10 mL), and air-dried. Recrystallization from DMF–ethanol (2:1, *v/v*) afforded the desired dihydrotriazolothiadiazines.

(4-Chlorophenyl)[6-(thiophen-2-yl)-3-(thiophen-2-ylmethyl)-6,7-dihydro-5H-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazin-7-yl]methanone (**13**). Colorless crystals (129 mg, 56%), mp 211–215 °C; *cis* diastereomer: ^{1}H NMR (DMSO-d_6, 400 MHz): δ 4.36 (d, J = 4.0 Hz, 2H), 5.44 (t, J = 3.0 Hz, 1H), 5.78 (d, J = 3.2 Hz, 1H), 6.96–7.03 (m, 3H), 7.19 (d, J = 4.4 Hz, 1H, exchangeable with D), 7.35 (dd, J = 1.2 and 2.4 Hz, 1H), 7.38–7.46 (m, 2H), 7.71 (d, J = 8.8 Hz, 2H), 8.16 (d, J = 8.8 Hz, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 24.3, 40.6, 52.9, 125.1, 125.9, 126.1, 126.6, 126.8, 127.0, 129.2, 130.9, 133.1, 137.7, 138.9, 139.2, 140.4, 152.1, 194.5.

(4-Bromophenyl)[6-(thiophen-2-yl)-3-(thiophen-2-ylmethyl)-6,7-dihydro-5H-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazin-7-yl]methanone (**14**). Colorless crystals (136 mg, 55%), mp 214–217 °C; *cis* diastereomer: ^{1}H NMR (DMSO-d_6, 400 MHz): δ 4.36 (d, J = 3.6 Hz, 2H), 5.44 (t, J = 3.0 Hz, 1H), 5.78 (d, J = 3.2 Hz, 1H), 6.96–7.03 (m, 3H), 7.18 (d, J = 4.4 Hz, 1H, exchangeable with D), 7.35 (dd, J = 1.2 and 2.0 Hz, 1H), 7.38–7.46 (m, 2H), 7.85 (d, J = 8.8 Hz, 2H), 8.08 (d, J = 8.8 Hz, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 24.3, 40.7, 52.9, 125.1, 125.9, 126.1, 126.5, 126.8, 127.0, 128.5, 130.9, 132.1, 133.4, 137.7, 138.9, 140.4, 152.1, 194.7.

Conclusions

The synthesis and structural characterization of a small number of Schiff bases based on of 5-(thiophen-2-ylmethyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione, which could prove to be biologically active compounds, useful synthons in the development of fused heterocycles, or interesting ligands for the generation of metal complexes with various topologies, is presented. Several triazolothiadiazines derived from the same substrate were also prepared, and their reduction to dihydrotriazolothiadiazines was successfully investigated. A different approach to dihydrotriazolothiadiazines was also pursued through ring closure relying on an intramolecular base catalyzed *C–C* bond formation and starting from one of the previously synthesized Schiff bases. The study advances the current state of knowledge in the chemistry of aminotriazolethiones and triazolothiadiazines.

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