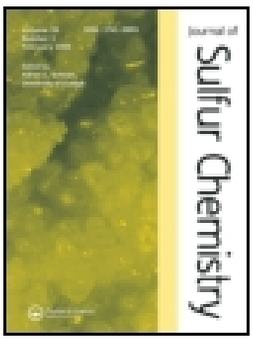

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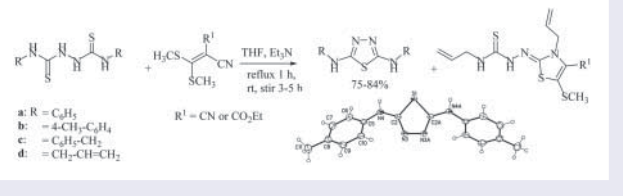
ABSTRACT

Bisthioureas reacted with either 2-(bis(methylthio)methylene)malononitrile or ethyl 2-cyano-3,3-bis(methylthio)acrylate to give 1,3,4-thiadiazoles and 1,3-thiazoles. Only, the reactive allyl derivative of bisthioureas reacted with the bis(methylthio)methylene compounds to give 1,3-thiazoles. The mechanism was discussed. The structures of products were proved by MS, IR, NMR and elemental analyses and X-ray structure analysis.



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1. Introduction

1,3,4-Thiadiazole derivatives have demonstrated a broad spectrum of biological properties in both pharmaceutical and agrochemical fields. They are known to exhibit diverse biological activities such as *in vitro* inhibition of cyclooxygenase and 5-lipoxygenase activities [1]. Acylated substituted 5-thio-β-*D*-glucopyranosylimino-1,3,4-thiadiazoles have been tested *in vitro* for antiviral activity against HIV-1, HIV-2 and human cytomegalo virus [2]. Recently, 1,3,4-thiadiazole cores have received much attention in material science due to their interesting electronic and optical properties [3]. Various methodologies that exist in the literature [4] for their synthesis are associated

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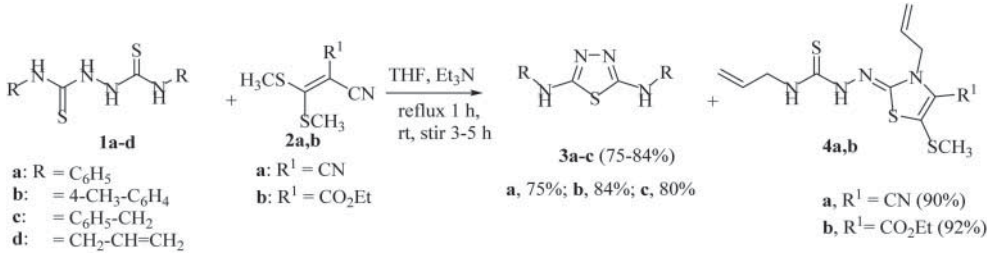
with the number of drawbacks that impedes their applicability in the long run. However, 1,3,4-thiadiazoles are commercially available antibiotic and anticancer drugs in the market, such as Acetazolamide, Methazolamide, Tebuthiuron, Megazol, Sulfamethizole, Filanesib, Cefazedone and Cefazolin [5]. On the other hand, the thiazole nucleus is found in many biologically active compounds that makes it one of the most extensively studied heterocycles [6]. Thiazoles play a pivotal role in many drug structures [7]. For example, Ritonavir (anti-HIV drug) [8], Dasatinib and Tiazofurin (antineoplastic agents) [9], Fanetizole, Fentiazac and Meloxicam (anti-inflammatory agents) [10], Nizatidine (antiulcer agent) [11], Ravuconazole (antifungal agent) [12] and Nitazoxanide (antiparasitic agent) [13]. Inspired by these interesting previous biologically active compounds, we envisioned that treatment of 2-hydrazinocarbothioyl-*N*-substituted-hydrazinecarbothioamides **1a–d** with 2-(bis(methylthio)methylene)malononitrile (**2a**) and ethyl 2-cyano-3,3-bis(methylthio)acrylate (**2b**) would form 1,3,4-thiadiazole and/or 1,3-thiazole derivatives.

2. Results and discussion

Equimolar amounts of 2-(hydrazinocarbonothioyl)-*N*-substituted-hydrazinecarbothioamides **1a–d** and 2-(bis(methylthio)methylene)malononitrile (**2**) were stirred in tetrahydrofuran (THF) with catalytic amounts of trimethylamine (Et_3N) at refluxing temperature for 1 h and at room temperature for 1–3 h. Bisthioureas **1a–c** provided excellent to moderate yields of the respective diaminothiadiazoles. For the bis-arylthioureas having electron-donating substituent like **1b**, the yield of **3b** (84%) was superior to **3c** (80%, Scheme 1). In general, 1,3,4-thiazole derivatives **3a–c** were precipitated as colorless solids and as the sole products in 75–84% yields (Scheme 1). In the case of **1d** reacting with **2a** and/or **2b**, 1,3-thiazole derivatives were obtained in a different manner (Scheme 1). The mass spectrum and elemental analysis proved the molecular formula of **3a** as $C_{14}H_{12}N_4S$. The phenyl protons in the ^{1}H NMR spectrum of **3a** appeared as two triplets at $\delta_H = 6.94$ ($J = 7.6$ Hz, 2H) and 7.27 ($J = 7.6$ Hz, 4H) and a doublet at $\delta_H = 7.54$ (d, $J = 7.6$ Hz, 4H). The NH protons were absorbed as broad singlet at $\delta_H = 9.38$. The ^{13}C NMR spectrum indicated the ring of 1,3,4-thiadiazole ring structure, by revealing the C=N carbon signal at $\delta_C = 156.3$. All spectroscopic and analytical data are in a good agreement with the structure of **3a** [14]. Similarly, compound **1b** reacted with **2** to produce **3b** [15]. The structure proof of **3b** was unambiguously supported by X-ray structure analysis (Figure 1). In the same manner, 1,3,4-thiadaizole-2,5-diamine derivative **3c** [14]. was obtained in 80% yield from the



Scheme 1. Reactions of bisthioureas **1a–d** with π-deficient compounds **2a,b**.

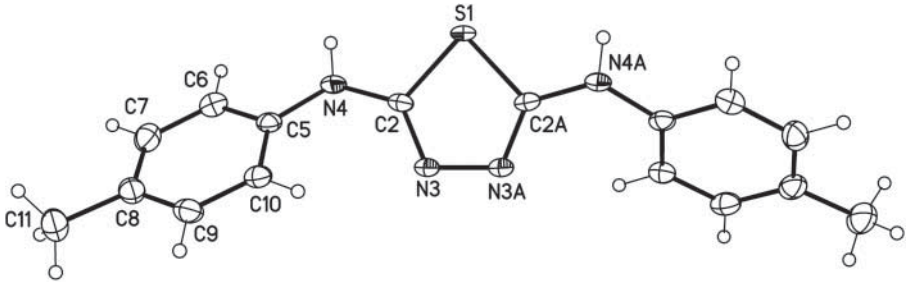
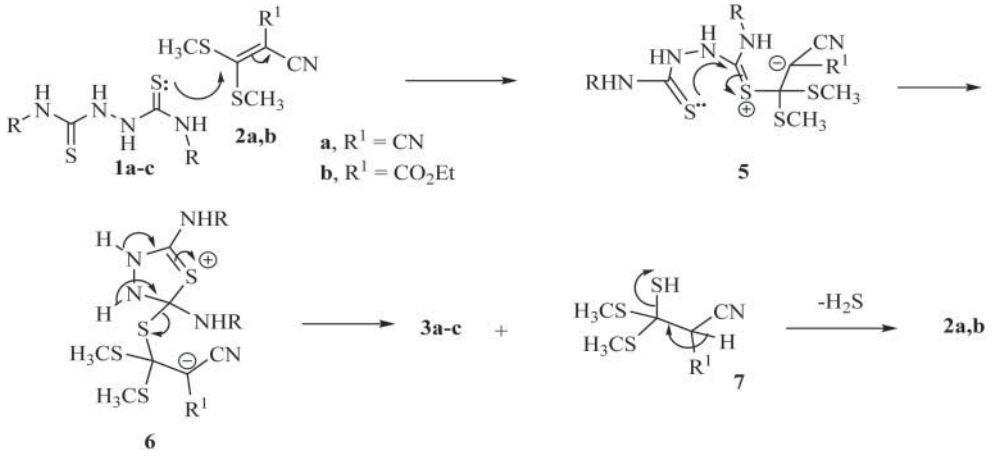


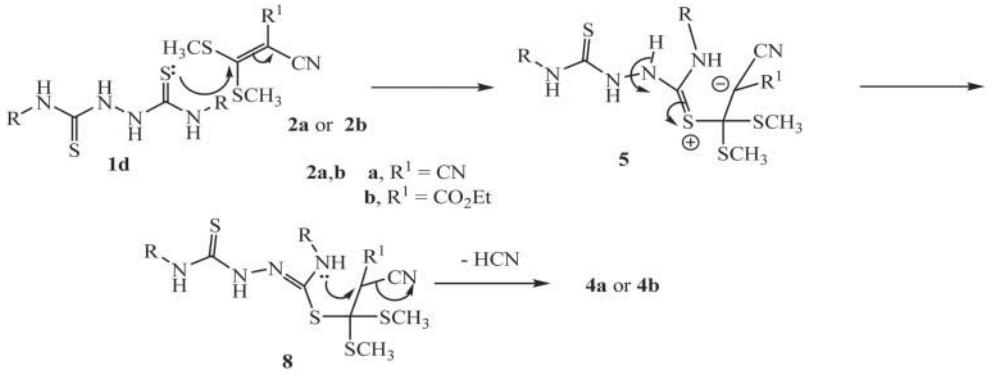
Figure 1. Molecular structure analysis of *N*,*N*′-bis(4′-methylphenyl)-1,3,4-thiadiazole-2,5-diamine (**3b**) with crystallographic C_2-symmetry (displacement parameters are drawn at 50% probability level).

reaction of **1c** with **2** (Scheme 1). The newly prepared thiazolidine-1-carbothioamide **4a** was obtained as pale red crystals in 90% yield (Scheme 1).

The results of combustion analyses and spectroscopic data suggested that the molecular weight of the products results from the sum of the two reactants **1d** with **2a** accompanied by loss of a HCN molecule (see Section 4). The IR spectrum showed the amino and nitrile groups at $\nu_{max} = 3230$ and $2210\,cm^{-1}$. The thiocarbonyl group absorbed in the IR spectra at $\nu_{max} = 1225\,cm^{-1}$. The ^1H NMR spectrum revealed the SMe protons as a singlet at $\delta_H =$ 2.60. The two allyl-CH_2N protons appeared as two broad singlets in different regions at $\delta_H =$ 4.28 and 3.90 (see Section 4). Allyl-CH= and allyl-$CH_2=$ protons resonated as two multiplets and appeared at $\delta_H =$ 5.80−5.72 (2H) and 5.20–5.14 (4H). The ^{13}C NMR spectrum of **4a** supported the allylic structure of **4a** and exhibited peaks at $\delta_C =$ 133.0, 130.8 (allyl-CH=), 118.2, 116.1 (allyl−$CH_2=$) and 44.0, 42.6 (CH_2). Moreover, the exo-azomethine carbon (thiazole C-2) appeared in the ^{13}C NMR of **4a** at $\delta_C =$ 154.0 (see Section 4). Whilst, the distinctive thioamide (C=S) and the nitrile carbons appeared at $\delta_C =$ 180.2 and 115.0, respectively. The same trend was obtained during the reaction of **1d** with ethyl 2-cyano-3,3-bis(methylthio)acrylate (**2b**). Compound **4b** was obtained during reaction of **1d** with **2b** (Scheme 1). The structure of **4b** was proved by IR, NMR and elemental analysis and was supported by mass spectroscopy and elemental analysis that gave its molecular formula as $C_{14}H_{20}N_4O_2S_3$. IR showed the NH stretching at $\nu_{max} =$ 3330–3240, whereas the aliphatic and carbonyl groups appeared at $\nu_{max} =$ 2960–2870 and $1700\,cm^{-1}$, respectively. Strong vibrational coupling was also noted due to the nitrogen containing thiocarbonyl derivative appeared at $\nu_{max} = 1390\,cm^{-1}$. ^1H NMR spectrum of **4b** revealed the ester group as a triplet at $\delta_H =$ 1.22 ($J =$ 7.2 Hz) and quartet at $\delta_H =$ 4.00. The SMe protons resonated as a singlet in the ^1H NMR spectrum centered at $\delta_H =$ 2.65, whereas the two allyl-NCH_2 protons appeared as two broad singlets in different regions at $\delta_H =$ 4.20 and 3.90 (see Section 4). Two multiplets were recognized in the ^1H NMR spectrum of **4b** indicated the allylic asymmetric structure (allyl-CH= and allyl-$CH_2=$) of **4b**, appeared at $\delta_H =$ 5.86−5.80 (2H) and 5.19–5.15 (4H). The ^{13}C NMR spectrum of **4b** indicated the allylic carbons at $\delta_C =$ 116.5, 118.0 (allyl $NCH_2=$), 133.2, 130.6 (allyl-CH=) and 44.8, 42.4 (allyl-CH_2-N). The exo-azomethine carbon of thiazole C-2 appeared at $\delta_C =$ 152.0 (see Section 4). Mechanistically, the reaction between **1a–c** and **2a** or **2b** can be described as due to nucleophilic attack of the sulfur lone pair of **1** at the C-2 carbon of **2** to form salt **5** (Scheme 2).



Scheme 2. Plausible mechanism of internal cyclization **1a–c** during its reaction with **2a,b**.



Scheme 3. Plausible mechanism describing reaction between **1d** and **2a,b**.

Thereafter, further nucleophilic attack of the other sulfur lone pair at the positively charged thiocarbonyl would cause cyclization to give intermediate **6**. The cyclization is followed by hydrogen transfer followed by neutralization to form **3a–c** and **7**. Ultimately, elimination of H_2S from **7** would reproduce **2** (Scheme 2). It might therefore be concluded that compound **2** initiates internal cyclization process of **1a–c**. The same trend occurs between **1d** and **2a**,**b** to form salt **5** (Scheme 3). Instead of the aforementioned second step in Scheme 2, neutralization occurred *via* proton transfer to form intermediate **8** (Scheme 3). Finally, cyclization occurs with the nitrogen lone pair accompanied by elimination of the HCN molecule to form **4a** or **4b** (Scheme 3)

3. Conclusion

Although there are many reports of the synthesis of thiadiazoles, few reports are available for the synthesis of symmetrical 2,5-disubstituted amino-1,3,4-thiadiazoles in the literature. Therefore our method is a valuable addition to the literature for the synthesis of this class of compound in good yields without requiring the aforesaid hazardous acidic conditions.

4. Experimental

Melting points are uncorrected. The IR spectra were recorded as KBr disks on a Shimadzu-408 infrared spectrophotometer, Faculty of Science, Minia University. TLC analysis was performed on analytical Merck 9385 silica aluminum sheets (Kieselgel 60) with PF_{254} indicator. The NMR spectra were measured using a Bruker AV-400 spectrometer at Institute of Organic Chemistry, Karlsruhe, Germany. Chemical shifts were expressed as δ (ppm) with tetramethylsilane as internal reference. The samples were dissolved in DMSO-d_6, s = singlet, d = doublet, dd = doublet of doublet and t = triplet. Mass spectra were recorded on a Varian MAT 312 instrument in EI mode (70 eV), Center of National Research, Dokki, Cairo, Egypt. Elemental analyses were carried out using Varian Elementary device in the National Research Center, Giza, Egypt, or by the Microanalytical Unit at Cairo University, Cairo, Egypt.

4.1. Crystal structure determination of 3b

The single-crystal X-ray diffraction study was carried out on a Bruker D8 Venture diffractometer with Photon100 detector at 123(2) K using Cu–K_α) radiation (l = 1.54178 Å. Direct Methods (SHELXS-97) [16] were used for structure solution and refinement was carried out using SHELXL-2014 (full-matrix least-squares on F^2) [17]. Hydrogen atoms were localized by difference electron density determination and refined using a riding model (H(N) free). A semi-empirical absorption corrections was applied. **3b**: colorless crystals, $C_{16}H_{16}N_4S$, M_r = 296.39, crystal size 0.36 × 0.18 × 0.09 mm, monoclinic, space group *P*bca (No. 60), a = 6.6154(3) Å, b = 8.5679(3) Å, c = 25.561(10) Å, V = 1448.80(10) Å^3, Z = 4, ρ = 1.359 Mg/m^{-3}, μ(Cu–K_α) = 1.963 mm^{-1}, $F(000)$ = 624, $2\theta_{max}$ = 144.4°, 7112 reflections, of which 1435 were independent (R_{int} = 0.026), 100 parameters, 1 restraint, R_1 = 0.031 (for 1316 $I > 2\sigma(I)$), wR_2 = 0.086 (all data), S = 1.03, largest diff. peak/hole = 0.227/−0.273 e Å^{-3}. CCDC 1494906 (**3b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

4.1.1. Starting materials

1,6-Disubstituted 2,5-dithioureas were parepared according to published procedures as were *N*,*N*′-diphenylhydrazine-1,2-dicarbothioamide (1a) and *N*,*N*′-bis(benzyl)hydrazine-1,2-dicarbothioamide (1c) [14] and *N*,*N*′-bis(4′-methylphenyl)hydrazine-1,2-dicarbothioamide (1b) [15] and *N*,*N*′-diallylhydrazine-1,2-dicarbothioamide (1d) [4,14]. 2-(bis (methylthio)-methylene)-malononitrile (2a) and ethyl 2-cyano-3,3-bis(methylthio)acrylate (2b) were bought from Fluka.

5. General procedure

5.1. Reaction of bisthioureas 1a-d with compounds 2a or 2b

A mixture of a dithiouears (**1a–c**, 1 mmol), an activated nitrile **2a** or **2b** (1 mmol) and a few drops of triethylamine in THF (30 mL) was gently refluxed for 1 h; the reaction was followed by TLC analysis. After cooling at room temperature, the preceiptates of **3a–c**

were collected by suction filtration, washed with THF and dried at room temperature. Compounds **3a–c** were identified by comparing their mp,s, IR and NMR spectra and their analytical data.

N,N'-Diphenyl-1,3,4-thiadiazole-2,5-diamine (**3a**), colorless crystals (DMF), 0.20 g, (75%), m.p. 239–240°C (lit. [14] 239–240°C).

N,N'-Bis(4′-methylphenyl)-1,3,4-thiadiazole-2,5-diamine (**3b**), colorless crystals (DMF), 0.25 g (85%), m.p. 137–138°C (lit. [15] 240–243°C).

N,N'-Bis(benzyl)-1,3,4-thiadiazole-2,5-diamine (**3c**). colorless crystals (MeOH), 0.24 (80%), m. p. 138–140°C (lit. [14] 137–139°C).

Z-N-Allyl-2-(3-allyl-4-cyano-5-(methylthio)thiazol-2(3*H*)ylidene)hydrazine-1-carbothioamide (**4a**). Pale yellow crystals ($CHCl_3$/MeOH), 0.28 g (90%), m.p. 166–168°C. IR (ν_{max}): = 2980–2860 (Aliph-CH), 3230 (NH), 2210 (CN), 1225 (C = S) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ_H = 10.20 (s, 1H, NH), 9.40 (s,1H, NH), 5.80−5.72 (m, 2H, allyl = CH), 5.20–5.14 (m, 4H, allyl-CH_2 =), 4.28 (bs, 2H, allyl-NCH_2), 3.90 (bs, 2H, allyl-NCH_2), 2.60 (s, 3H, SCH_3). ^{13}C NMR (DMSO-d_6): δ_C = 180.2 (C = S), 154.0 (C = N), 133.0, (allyl-CH =), 131.6 (C-4), 130.8 (allyl-CH =), 129.2 (C-5), 118.2, 116.1 (allyl-NCH_2), 115.0 (CN), 44.0, 42.6 (CH_2), 15.4 (SCH_3). MS (70 eV, %): *m/z* = 325 (M^+, 100), 310 (22), 278 (18), 252 (24), 137 (24). Calcd for $C_{12}H_{15}N_5S_3$ (325.47): C, 44.28; H, 4.65; N, 21.52. Found: C, 44.10; H, 4.55; N, 21.65.

Ethyl (*Z*)-3-allyl-2-(3-allylcarbamothioyl)hydrazono-5-(methylthio)-2,3-dihydrothiazole-4-carboxylate (**4b**). Pale yellow crystals (MeOH), 0.34 g (92%), m.p. 198–200°C. IR (ν_{max}): = 2960–2870 (Aliph-CH), 3240 (NH), 1700 (CO-ester), 1390 (C = S) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ_H = 10.20 (s, 1H, NH), 9.40 (s,1H, NH), 5.86−5.80 (m, 2H, allyl = CH), 5.19–5.15 (m, 4H, allyl-CH_2 =), 4.20 (bs, 2H, allyl-NCH_2), 4.00 (q, 2H, CH_2-ester), 3.90 (bs, 2H, allyl-NCH_2), 2.65 (s, 3H, SCH_3), 1.22 (t, J = 7.2 Hz). ^{13}C NMR (DMSO-d_6): δ_C = 180.4 (C = S), 165.4 (CO-ester), 152.0 (C = N), 133.2, 130.6 (NCH =), 130.2 (C-4), 129.2 (C-5), 118.0, 116.5 (allyl = CH_2), 50.0 (CH_2-ester), 44.8, 42.4 (allyl-NCH_2), 15.4 (SCH_3), 12.4 (CH_3-ester). MS (70 eV, %): *m/z* = 325 (M^+, 100), 310 (22), 278 (18), 252 (24), 137 (24). Calcd for $C_{14}H_{20}N_4O_2S_3$ (372.52): C, 45.14; H, 5.41; N, 15.04. Found: C, 45.30; H, 5.55; N, 15.20.

Disclosure statement

No potential conflict of interest was reported by the authors.

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References

[1] Boschelli DH, Connor DT, Bornemeier DA, et al. 1,3,4-oxadiazole, 1,3,4-thiadiazole, and 1,2,4-triazole analogs of the fenamates: in-vitro inhibition of cyclooxygenase and 5-lipoxygenase activities. J Med Chem. 1993;36:1802–1810. doi:10.1021/jm00065a002

[2] Al-Masoudi NA, Al-Soud YA, Al-Masoudi WA. Thiosugar nucleosides. Synthesis and biological activity of 1,3,4-thiadiazole, thiazoline and thiourea derivatives of 5-thio-*D*-glucose. Nucleos Nucleot Nucl. 2004;23(11):1739–1749. doi:10.1081/NCN-200034040

[3] Zhu Y, Champion RD, Jenekhe SA. Conjugated donor-acceptor copolymer semiconductors with large intramolecular charge transfer: synthesis, optical properties, electrochemistry, and field effect carrier mobility of thienopyrazine-based copolymers. Macromolecules. 2006;39:8712–8719. doi:10.1021/ma061861g
[4] Hassan AA, Mourad AE, El-Shaieb KN, et al. Synthesis of 1,3,4-thiadiazole, 1,3,4-thiadiazine, 1,3,6-thiadiazepane and quinoxaline derivatives from symmetrical dithiobiureas and thioureidoethylthiourea derivatives. Molecules. 2005;10:822–832. doi:10.3390/10070822
[5] Bräse S, editor. Privileged scaffolds in medicinal chemistry: design, synthesis and evaluation. Cambridge, UK: RSC publisher; 2015.
[6] Siddiqui N, Arshad MF, Ahsan W, et al. Thiazoles: a valuable insight into the recent advances and biological activities. Int J Pharm Sci Drug Res. 2009;1:136–143.
[7] De Souza MVN, AlMeida VD. Drugs anti-HIV: past, present and future perspectives. Nova. 2003;26:366–372.
[8] Das GWAJ, Chen P, Norris D, et al. 2-Aminothiazole as a novel kinase inhibitor template. Structure-activity relationship studies toward the discovery of *N*-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl)]-2-methyl-4-pyrimidinyl]-amino)]-1,3-thiazole-5-carboxamide (Dasatinib, BMS-354825) as a potent *pan*-Src kinase inhibitor. J Med Chem. 2006;49:6819–6832. doi:10.1021/jm060727j
[9] Rehman MZ, Anwar CJ, Ahmad S. An efficient synthesis of 2-alkyl-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxides. Bull Korean Chem Soc. 2005;26:1771–1775. doi:10.5012/bkcs.2005.26.11.1771
[10] Bharti SK, Singh SK. Design, synthesis and biological evaluation of some novel benzylidene-2-(4-phenylthiazol-2-yl) hydrazines as potential anti-inflammatory agents. Med Chem Res. 2014;23:1004–1015. doi:10.1007/s00044-013-0708-z
[11] Knadler MP, Bergstrom RF, Callaghan JT, et al. Nizatidine, an H_2-blocker. Its metabolism and disposition in man. Drug Metab Dispos. 1986;14:175–182.
[12] Pasqualotto AC, Thiele KO, Goldani LZ. Novel triazole antifungal drugs: focus on isavuconazole, ravuconazole and albaconazole. Curr Opin Invest Drugs. 2010;11:165–174. 179.
[13] Fox LM, Saravolatz LD. Nitazoxanide: a new thiazolide antiparasitic agent. Clin Infect Dis. 2005;40:1173–1180. doi:10.1086/428839
[14] Guin S, Rout SK, Gogoi A, et al. Desulfurization strategy in the construction of azoles possessing additional nitrogen, oxygen or sulfur using a copper(I) catalyst. Adv Synth Catal. 2012;354:2757–2770. doi:10.1002/adsc.201200408
[15] Heinz E, Berscheid R. Preparation and application of thiosemicarbazide and thiocarbazide derivatives as antimicrobial agent. SOFW. 1994;120:286–290. [C. A. 1996,124: 55859 w].
[16] Sheldrick GM. A short history of SHELX. Acta crystallogr. 2008;A64:112–122.
[17] Sheldrick GM. Crystal structure refinement with SHELXL. Acta crystallogr. 2015;C71:3–8.