Research Article

Synthesis of a New Class of Tris- and Bis(1,3,4-thiadiazol-2-amine) Methyl and Ethyl Tris- and Bis-2-(2-(2-benzoyl hydrazinyl)-4-oxothiazolidine) Acetate Derivatives

Ali Darehkordi and Somayeh Ghazi

Department of Chemistry, Faculty of Science, Vali-e-Asr University of Rafsanjan, Rafsanjan 77176, Iran

Correspondence should be addressed to Ali Darehkordi; adarehkordi@yahoo.com

Received 18 June 2012; Accepted 7 August 2012

Academic Editor: Sulekh Chandra

Copyright © 2013 A. Darehkordi and S. Ghazi. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Hydrazine, carbothioamide derivatives **2**, **3**, and **4** were synthesized by the condensation of 1, 3, 5-tri carbonyl tri chloride, Terephthaloyl dichloride, and 1, 4-dicarbonyl chloride with thiosemicarbazide in presence of pyridine as a solvent. The reaction of compounds **2**, **3**, and **4** with DMAD or DEAD led to the formation of 4-oxothiazolidine derivatives (**4b-c**), (**3a-c**), and (**2c-d**). The treatment of compounds **2**, **3**, and **4** with 1, 4'-dibromoacetophenone resulted in the formation of thiazole derivatives (**2g**, **3f**, **4f**). The treatment of compounds **2**, **3**, and **4** with sulfuric led to the formation of 4H-1,2,4-triazole-3-thiol derivatives (**2f**, **3d**, and **4d**). The cyclization of compounds **2**, **3**, and **4** in the presence of 2N NaOH resulted in the formation of compounds **2e-4e** containing two or three [1,2,4]triazole rings which are linked to the benzene ring. These compounds are important and useful monomer for synthesis of various dendrimers.

1. Introduction

Oxadiazole derivatives, an important group of heterocyclic compounds, have been the subject of extensive study in the recent years. Numerous reports have highlighted their chemistry and use [1–4]. It has also been reported in literature that certain compounds bearing 1,3,4-oxadiazole/thiadiazole and 1,2,4-triazole nucleus possess significant anti-inflammatory activity [5–7]. 4-Thiazolidinone derivatives are also known to possess antibacterial [8–11], antifungal [12–14], antiviral [15–18], and antituberculosis [19–21] properties. 4-Thiazolidinones have been reported as novel inhibitors of the bacterial enzyme [22]. The incidence of tuberculosis is increasing worldwide, partly due to poverty and inequity and partly due to the HIV/AIDS pandemic, which greatly increase the risk of infectious proceeding to overt disease. During recent years, the microorganisms have developed increasing resistance against drugs. Therefore, there is a need to develop new, potent, fast-acting antimicrobial, antiviral and antimycobacterial drugs with low toxicity. Triazoles

and in particular 1,2,4-triazole nucleus have been incorporated into a wide variety of therapeutically interesting drug candidates including anti-inflammatory, CNS stimulants, sedatives, antianxiety, and antimicrobial agents [23, 24]. Thiosemicarbazone and thiosemicarbazide derivatives are of considerable interest due to their antibacterial, antimalarial, antiviral, and antitumor activities. Heterocycles derived from thiosemicarbazide in the form of 1,2,4-triazoles and 1,2,4-triazines were also found to possess significant antifungal, antibacterial, and insecticidal properties [25]. Five-member rings are highly prevalent in the pharmacopoeia and more generally in collections of bioactive compounds.

There are a number of antimicrobial compounds containing a 1,2,4-triazole ring in their structures such as Fluconazole, Eperezolid, and Ravuconazole that are important antifungal drugs [26]. Heterocycles containing a 1,2,4-triazole or 1,3,4-thiadiazole moiety and the compounds consisting of 1,2,4-triazole and 1,3,4-thiadiazole condensed nucleus systems constitute a class of compounds possessing a wide spectrum of biological activities such as anti-inflammatory,

SCHEME 1: Synthesis of carbonyl(phenyl) hydrazinecarbothioamide derivatives.

antiviral and antimicrobial and antitumor properties [27, 28]. In view of these facts, the aim of this present study is to obtain tris- and bis[(1,3,4-thiadiazol-2-amine)], tris- and bis[2-(2-(2-benzoyl hydrazinyl) 4-oxothiazolidine)] derivatives incorporating also bis[(4-1, 2, 4-triazole-3-thiol)] structures (Schemes 2, 3, and 4) as antimicrobial agents. These derivatives can be used for synthesis of various dendrimers.

2. Results and Discussion

We started from carbonyl(phenyl) hydrazinecarbothioamide derivatives **2**, **3**, and **4**. These compounds were obtained from reaction of 1,4-dicarbonyl chloride, Terephthaloyl dichloride, 1,3,5-tricarbonyl trichloride, and thiosemicarbazide in presence of pyridine (Scheme 1). The structures of compounds **2**, **3**, and **4** were deduced from their elemental analysis, their IR, ^1H - and ^{13}C -NMR spectra. In the ^1H -NMR spectra of compounds **2**, **3**, and **4** the expected two peaks around 10 and 9 ppm corresponding to the two NH groups, two singlets at 8 ppm corresponding to the NH_2 , and aromatic-H observed. Also their ^{13}C -NMR showed signals of $\text{C}=\text{S}$, $\text{C}=\text{O}$, and aromatic carbons 182, 165, 133, 131 ppm, respectively.

In order to obtain oxothiazolidine derivatives a series of 4-oxothiazolidine-5-ylidene **4b-c**, **3b-c**, and **2c-d** were synthesized (Schemes 2–4). Compounds **4b-c**, **3b-c**, and **2c-d** were obtained by coupling dialkyl acetylenedicarboxylate

with a series of hydrazinecarbothioamides in methanol as a solvent at ambient temperature. On the basis of well-established chemistry of electrophilic acetylenes, it is reasonable to assume that compounds **4b-c**, **3b-c**, and **2c-d** result from the initial conjugate addition of the sulfur atom of **3** to the acetylenic ester and then the ester group of intermediate is attacked by the amino moiety to yield **4b-c**, **3b-c**, and **2c-d** by elimination of ROH.

The H-NMR spectrum of **4c** in DMSO showed five singlet for CH_3 , $\text{H}-\text{C}=\text{C}$, aromatic protons, N-H (hydrazine), and N-H (oxothiazolidine ring) at 3.79, 6.73, 8.61, 9.48, 11.52 ppm, respectively. The ^{13}C -NMR spectrum of **4c** showed eight signals in agreement with the proposed structure. Partial assignments of these resonances are given in the experimental section. The H- and C-NMR spectra **2c-d**, **3a**, **3b-c**, and **4b** are similar to those for **4c** except for the ester moiety, which exhibit characteristic signals at appropriate chemical shifts.

The treatment of compound **4** with sulfuric acid and sodium hydroxide produced 5,5',5''-(benzene-1,3,5-triyl)-tris(1,3,4-thiadiazol-2-amine) (**4d**) and 5,5',5''-(benzene-1,3,5-triyl)tris(4H-1,2,4-triazole-3-thiol) (**4e**), respectively. These compounds displayed IR, ^1H and ^{13}C -NMR spectra and elemental analyses consistent with the assigned structures. In the ^1H -NMR spectrum of compound **4e**, additional signal due to $-\text{SH}$ group appeared at 13.89 ppm

SCHEME 2: Synthesis of **2c–2g** compounds from 1,4-dicarbonyl(phenyl)-bis(hydrazinecarbothioamide) **2**.

(controlled by changing D₂O), while the 2 –NH– and –NH₂ signals disappeared. Moreover, the IR spectrum of compound **4e** displayed and –SH stretching band at 2714 cm^{–1}. The hydrogen's of the –NH₂ group in compound **4d** resonated at 7.60 ppm in the ¹H-NMR spectrum. The –NH₂ stretching band was observed at 3187 cm^{–1} in the IR spectrum. Synthesized compounds are useful and important derivatives for synthesis of different important dendrimers.

The synthesis of compounds **2g**, **3f**, and **4f** were carried out by the reaction of 2,4'-dibromoacetophenone with compounds **2**, **3**, and **4** in DMF as a solvent and ultrasound irradiation at ambient temperature. The ¹H and ¹³C-NMR spectra of compounds **2g**, **3f**, and **4f** displayed additional signals due to the aromatic ring derived from 2, 4'-dibromoacetophenone moiety at aromatic region, while the signal belonging to the –NH₂ and –NH– groups of hydrazinecarbothioamide structure did not appear. In the ¹H-NMR spectra of compounds **2g**, **3f**, and **4f** two signals, each belonging to the two –NH– (O=C–NH–NH–) groups, observed between 11.03 and 11.15, 9.75 and 9.79 ppm, respectively. The signal belonging to thiazole ring protons (HC=C) and aromatic protons appeared between 7.30 and 7.34, 7.54, and 8.68 ppm, respectively, in the ¹H-NMR spectrum of compounds **2g**, **3f**, and **4f**. The ¹³C-NMR spectra of compounds **2g**, **3f**, and **4f** showed signals in agreement with the proposed structures. Complete assignments of these resonances are given in the experimental section.

3. Experimental

3.1. Synthesis of 1,4-Dicarbonyl(phenyl)bis(hydrazinecarbothioamide) (2). Terephthaloyl dichloride (20 mmol) in pyridine (5 mL) was stirred at room temperature for 10 min. Then

a mixture of thiosemicarbazide (40 mmol) in pyridine (5 mL) was added drop wise to these and then stirred at ambient temperature for 24 hours. The pyridine was removed under reduced pressure. To the residue, was added water, and the precipitate was filtered, washed with water and recrystallized from DMF to afford the desired product (**2**).

According to the procedure, compound **2** was obtained as white powder. Yield: 92%. Mp: 234–236°C. ¹H-NMR (DMSO-d₆, 500 MHz): δ (ppm) = 7.95 (d, J = 8.3, 2H, Ar–H), 7.95 (d, J = 8.3, 2H, Ar–H), 8.62 (s, 2H, NH₂), 9.48 (s, 1H, NH), 10.54 (s, 1H, NH). ¹³C-NMR (DMSO-d₆, 125.77 MHz): δ (ppm) = 131.27, 133.78 (4C, Arom), 165.73, 182.45 (2C, C=O, C=S). Anal. Calcd. for C₁₀H₁₂N₆O₂S₂ C, 38.45; H, 3.87; N, 26.90. Found: C, 38.12; H 3.90; N, 27.08%.

3.2. General Procedure for the Preparation of 1,4-Benzoyl-bis-alkyl 2-(2-hydrazono)-4-oxothiazolidine-5-ylidene)acetate (2c–d). A mixture of 1,4-benzoyl-bis-hydrazinecarbothioamide (1 mmol) and methanol (8 mL) was stirred at ambient temperature for 15 min. Then a solution of DMAD or DEAD (2 mmol) and methanol (2 mL) was added drop wise to it. The reaction mixture was stirred at ambient temperature for 20 hr. The produced solid was filtered off and recrystallized by DMF to give the desired compounds (**2c–d**).

3.3. 1,4-Dicarbonyl(phenyl)bis(methyl-2-((Z)-2-hydrazono-4-oxothiazolidine-5-ylidene) acetate) (2d). Yellow powder. Yield: %89, m.p 270–273°C. ¹H-NMR (DMSO-d₆, 500 MHz): δ (ppm) = 3.78 (s, 6H, 2-OCH₃), 6.88 (s, 2H, H–C=C), 8.46 (d, J = 8.1, 4H, Ar–H), 10.37 (s, 1H, NH), 11.63 (s, 1H, NH). ¹³C-NMR (DMSO-d₆, 125.77 MHz): δ (ppm) = 52.06, (2C, –OCH₃), 128.61, 132.02, 137.01, 139.58 (10C, 6Arom, 4CH=C), 146.90, 164.13, 174.08. Anal. Calcd.

SCHEME 3: Synthesis of **3a–3f** compounds from 1,3-dicarbonyl(phenyl)-bis(hydrazinecarbothioamide) **3**.

for $C_{20}H_{16}N_6O_8S_2$: C, 45.11; H, 3.03; N, 15.78. Found: C, 45.37; H, 3.12; N, 15.94%.

3.4. 1,4-Dicarbonyl(phenyl)bis(ethyl-2-((Z)-2-hydrazono-4-oxothiazolidine-5-ylidene) acetate) (2c). Yellow powder. Yield: %88, m.p 265°C . $^1\text{H-NMR}$ (DMSO- d_6 , 500 MHz): δ (ppm) = 1.24 (t, $J = 7.1$, 6H, $-\text{CH}_3$), 4.24 (q, $J = 7.1$, 4H, $-\text{CH}_2-$), 6.69 (s, 2H, $\text{H}-\text{C}=\text{C}$), 7.97 (d, $J = 8.13$, 4H, Ar-H), 10.50 (s, 1H, NH), 11.34 (s, 1H, NH). $^{13}\text{C-NMR}$ (DMSO- d_6 , 125.77 MHz): δ (ppm) = 14.24 (2C, 2- CH_3), 62.04 (2C, 2 CH_2), 128.80, 132.49, 137.66, 139.72, (8C, 6Arom, $\text{C}=\text{C}$), 146.97, 164.56, 166.30, 174.08 (8C, 6 $\text{C}=\text{O}$, 2 $\text{C}=\text{N}$). Anal. Calcd. For $C_{22}H_{20}N_6O_8S_2$: C, 47.14; H, 3.60; N, 14.99. Found: C, 47.63; H, 3.52; N, 15.06%.

3.5. Synthesis of N'_1, N'_4 -Bis(5-(4-bromophenyl) Thiazole-2(3H)-ylidene) Isophthaloyl Hydrazide (2g). A mixture of 1, 4-benzoyl-bis-hydrazinecarbothioamide (0.5 mmol) and DMF (3 mL) was prepared under ultrasonic for 15 min until fluoresced. Then a solution of 1,4'- dibromoacetophenone (1 mmol) and DMF (2 mL) drop wise was added to it. After 100 min the reaction completed (reaction accession controlled by TLC chromatography). Finally put the vessel in refrigerator for 1 hour. The precipitate was filtered and recrystallized from ethyl acetate, to give the desired compounds (**2g**).

Brown powder. Yield: %96, m.p 290°C . $^1\text{H-NMR}$ (DMSO- d_6 , 500 MHz): δ (ppm): 7.34 (s, 2H, H-thiazol ring), 7.57 (d, $J = 8.4$, 4H, Ar-H), 7.78 (d, $J = 8.4$, 4H, Ar-H), 8.04 (m, 4H, Ar-H), 9.75 (s, 2H, NH), 11.03 (s, 2H, NH). $^{13}\text{C-NMR}$ (DMSO- d_6 , 125.77 MHz): δ (ppm) = 104.48 (2C, $\text{C}=\text{thiazol rings}$), 120.48, 127.70, 131.46, 133.78, 135.37, 137.12 (18C, arom, $\text{C}=\text{C}$), 149.41, 165.76, 172.34 (6C, 2 $=\text{CH}$, 2 $\text{C}=\text{N}$,

2 $\text{C}=\text{O}$). Anal. Calcd. For $C_{26}H_{18}Br_2N_6O_2S_2$: C, 46.58; H, 2.71; N, 12.54. Found: C, 46.78; H, 2.76; N, 12.15%.

3.6. Synthesis of 5,5'-(1,4-Phenylene) Bis(4-1,2,4-triazole-3-thiol) (2f). A mixture of 1, 4-benzoyl-bis- hydrazine carbothioamide (1 mmol) and methanol (8 mL) was stirred at ambient temperature for 15 min. Then a solution of 15% sodium hydroxide (5 mL) was added and refluxed for 1 h. After the reaction completed the mixture was cooled to the room temperature and then acidified to pH 7 with acetic acid (1 N). The precipitate was filtered, washed with water, and recrystallized from DMF, to afford the desired compound (**2f**).

White powder. Yield: 95%. m.p = 320°C . $^1\text{H-NMR}$ (DMSO- d_6 , 500 MHz): δ (ppm) = 8.01 (d, $J = 8.3$, 4H, Arom), 13.74 (s, 2H, NH), 13.89 (s, 2H, SH). $^{13}\text{C-NMR}$ (DMSO- d_6 , 125.77 MHz): δ (ppm) = 128.23 (4C, Arom), 133.16 (2C, Arom), 160.43, 167.31 (4C, triazol ring). Anal. Calcd. For $C_{10}H_8N_6S_2$: C, 43.46; H, 2.92; N, 30.41. Found: C, 43.06; H, 2.80; N, 30.7%.

3.7. Synthesis of 5,5'-(1,4-Phenylene) Dithiophen-2-amine (2e). 1,4-Benzoyl-bis-hydrazinecarbothioamide (1 mmol) in 10 mL concentrated sulfuric acid (was cooled to the 0°C temperatures) was stirred for 15 min, and then left for another 10 min at room temperature. The resulting solution was poured slowly into ice-cold water, made alkaline to pH 8 with aqueous ammonia and the precipitated product was filtered, washed with water, and recrystallized from DMF.

White powder m.p = 290°C . Yield: 87%. $^1\text{H-NMR}$ (DMSO- d_6 , 500 MHz): δ (ppm) = 7.08 (s, 4H, NH_2), 7.82 (d, $J = 8.2$, 4H, Arom-H). $^{13}\text{C-NMR}$ (DMSO- d_6 , 125.77 MHz): δ (ppm) = 129.45 (4C, Arom), 135.07 (2C, Arom), 163.34,

SCHEME 4: Synthesis of **4b**–**4f** compounds from 1,3,5-tricarbonyl (phenyl) tris(hydrazine carbothioamide) **4**.

175.23 (**4c**, thiazol ring). Anal. Calcd. For C₁₀H₈N₆S₂: C, 43.46; H, 2.92; N, 30.41. Found: C, 43.01; H, 2.76; N, 30.58%.

3.8. 1,3-Dicarbonyl(phenyl)-Bis(hydrazinecarbothioamide) (3). White powder. Yield: %89, m.p 119–120°C. ¹H-NMR (DMSO-d₆, 500 MHz): δ (ppm) = 8.72 (s, 4H, NH₂), 7.69 (m, 1H, Ar-H), 8.12 (d, J = 8.0, 2H, Ar-H), 8.48 (s, 1H, Ar-H), 9.53 (s, 2H, NH), 10.58 (s, 2H, NH). ¹³C-NMR (DMSO-d₆, 125.77 MHz): δ (ppm) = 129.56, 131.00, 132.4, 134.07 (6C, Arom), 165.23, 183.11 (2C, C=O, C=S). Anal. Calcd. For C₁₀H₁₂N₆O₂S₂: C, 38.45; H, 3.87; N, 26.90. Found: C, 38.21; H, 3.67; N, 27.17%.

3.9. Ethyl 2-(2-(3-(2-carbamothioylhydrazinecarbonyl)benzoyl)hydrazono)-4-oxothiazolidine-5-ylidene)acetate (3a). Yellow powder. Yield: %69, m.p 280°C. ¹H-NMR (DMSO-d₆, 500 MHz): δ (ppm) = 1.25 (t, J = 7.1, 3H, CH₃), 6.69 (s, 1H, H-C=C), 7.90 (m, 1H, Ar-H), 7.97 (s, 1H, Ar-H), 8.01 (d, J = 8.23, 2H, Ar-H), 8.04 (s, 2H, NH₂), 9.37 (s, 1H, NH),

9.51 (s, 1H, NH), 11.28 (s, 1H, NH). ¹³C-NMR (DMSO-d₆, 125.77 MHz): δ (ppm) = 14.86 (1C, -CH₃), 62.38 (C, CH₂), 124.78, 131.09, 131.63, 132.41, 133.89, 134.57, 136.14 (8C, Arom, C=C), 147.19, 164.80, 164.96, 166.15, 175.16, 182.91 (6C, C=N, C=O, C=S). Anal. Calcd. For C₁₆H₁₆N₆O₅S₂: C, 44.03; H, 3.69; N, 19.25. Found: C, 43.71; H, 3.96; N, 19.65%.

3.10. 1,3-Dicarbonyl(phenyl)bis(methyl-2-((Z)-2-hydrazono-4-oxothiazolidine-5-ylidene) acetate (3b). Yellow powder. Yield: %92, m.p 223–226°C. ¹H-NMR (DMSO-d₆, 500 MHz): δ (ppm) = 3.80 (s, 6H, 2-OCH₃), 6.72 (s, 2H, H-C=C), 7.69 (m, 1H, Ar-H), 8.10 (d, 2H, J = 7.8, 2H, Ar-H), 8.39 (s, 1H, Ar-H), 10.90 (s, 2H, NH), 11.41 (s, 2H, NH). ¹³C-NMR (DMSO-d₆, 125.77 MHz): δ (ppm) = 52.12, (2C, -OCH₃), 129.43, 132.27, 135.12, 140.04 (8C, Arom, CH=C), 147.02, 164.50, 166.58, 174.83 (8C, C=N, C=O). Anal. Calcd. For C₂₀H₁₆N₆O₈S₂: C, 45.11; H, 3.03; N, 15.78. Found: C, 45.66; H, 3.19; N, 15.42%.

3.11. N'_1, N'_4 -Bis(5-(4-bromophenyl)thiazol-2-yl)isophthalohydrazide (**3f**). Yield: %96, m.p 290. $^1\text{H-NMR}$ (DMSO- d_6 , 500 MHz): δ (ppm): 7.32 (s, 2H, thiazol rings), 7.59 (d, J = 8.4 Hz, 4H, Ar-H), 7.80 (d, J = 8.4, 4H, Ar-H), 7.87 (m, 1H, Ar-H), 8.14 (m, 2H, Ar-H), 8.30 (s, 1H, Ar-H). $^{13}\text{C-NMR}$ (DMSO- d_6 , 125.77 MHz): δ (ppm) = 105.03 (2C, C= thiazol rings), 120.35, 130.36, 131.78, 133.46, 133.65, 135.42, 134.60, 137.52 (18C, arom, C=C), 149.48, 165.80, 173.08 (6C, 2 =CH, 2C=N, 2C=O). Anal. Calcd. For $\text{C}_{26}\text{H}_{18}\text{Br}_2\text{N}_6\text{O}_2\text{S}_2$: C, 46.58; H, 2.71; N, 12.54. Found: C, 46.27; H, 2.9; N, 15.42%.

3.12. 5,5'-(1,3-Phenylene)bis(4H-1,2,4-triazole-3-thiol) (**3d**). White powder m.p = 315°C. Yield: 62%. $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ (ppm) = 7.56 (d, 2H J = 6.4, Arom-H), 7.94 (m, 1H, Arom-H), 8.46 (s, 1H, Arom-H), 13.47 (s, 2H, SH). $^{13}\text{C-NMR}$ (DMSO- d_6 , 100 MHz): δ (ppm) = 124.32, 132.18, 128.52, 130.64 (6C, Arom), 158.55, 160.13 (4C, 4C=N). Anal. Calcd. For $\text{C}_{10}\text{H}_8\text{N}_6\text{O}_3\text{S}_3$: C, 43.46; H, 2.92; N, 30.41. Found: C, 43.17; H, 3.06; N, 30.82%.

3.13. Synthesis of 1,3,5-Tricarbonyl(phenyl) tris(hydrazinecarbothioamide) (**4**). A mixture of 1,3,5-tri carbonyl trichloride (20 mmol) in pyridine (5 mL) was stirred at room temperature for 10 min. Then a mixture of thiosemicarbazide (60 mmol) in pyridine (10 mL) was added drop wise to it, and then stirred for 24 hours. The pyridine was removed under reduced pressure. To the residue, was added water and the precipitate was filtered, washed with water, and recrystallized from DMF to afford the desired product (**4**).

Cream powder. Yield: %90. m.p 168–170. $^1\text{H-NMR}$ (DMSO- d_6 , 500 MHz): δ (ppm) = 8.63 (s, 6H, NH₂), 8.79 (s, 3H, Ar-H), 9.48 (s, 3H, NH), 10.48 (s, 3H, NH). $^{13}\text{C-NMR}$ (DMSO- d_6 , 125.77 MHz): δ (ppm) = 131.21, 133.73 (6C, Arom), 165.79, 182.87 (6C, 3C=O, 3C=S). Anal. Calcd. For $\text{C}_{12}\text{H}_{15}\text{N}_9\text{O}_3\text{S}_3$: C, 33.56; H, 3.52; N, 29.35. Found: C, 33.07; H, 3.65; N, 29.77%.

3.14. General Procedure for the Synthesis of 1,3,5-Benzoyl-tris-alkyl 2-(hydrazono)-4-oxothiazolidine-5-ylidene) Acetate (**4c**, **4d**). A mixture of 1,3,5-benzoyl tris(hydrazine carbothioamide) (0.5 mmol) and methanol (8 mL) was stirred at room temperature for 15 min. Then a solution of DMAD or DEAD (1.5 mmol) and methanol (2 mL) was added drop wise to it. The reaction mixture was then stirred at ambient temperature for 22 hr. The separated solid was filtered off and recrystallized by DMF to give the desired compounds.

3.15. 1,3,5-Benzoyl-tris-ethyl 2-(2-Hydrazono)-4-oxothiazolidine-5-ylidene)acetate (**4d**). Yellow powder. Yield: %72, m.p 245°C (decom.). $^1\text{H-NMR}$ (DMSO- d_6 , 500 MHz): δ (ppm) = 3.79 (s, 9H, -OCH₃), 6.73 (s, 3H, H-C=C), 8.61 (s, 3H, Ar-H), 9.48 (s, 3H, NH), 11.52 (s, 3H, NH). $^{13}\text{C-NMR}$ (DMSO- d_6 , 125.77 MHz): δ (ppm) = 52.43 (3C, -OCH₃), 129.61, 132.61, 134.57, 139.66 (8C, Arom, CH=C), 147.15 (3C, C=N thiazole), 164.07, 166.62, 175.23 (9C, C=O). Anal. Calcd. For: $\text{C}_{30}\text{H}_{27}\text{N}_9\text{O}_{12}\text{S}_3$: C, 44.94; H, 3.39; N, 15.72. Found: C, 45.07; H, 3.75; N, 16.11%.

3.16. 1,3,5-Tricarbonyl(phenyl)tris(methyl-2-((E)-2-hydrazono-4-oxothiazolidine-5-ylidene)acetate) (**4c**). Yellow powder. Yield: %72, m.p 245°C (decom.). $^1\text{H-NMR}$ (DMSO- d_6 , 500 MHz): δ (ppm) = 3.79 (s, 9H, -OCH₃), 6.73 (s, 3H, H-C=C), 8.61 (s, 3H, Ar-H), 9.48 (s, 3H, NH), 11.52 (s, 3H, NH). $^{13}\text{C-NMR}$ (DMSO- d_6 , 125.77 MHz): δ (ppm) = 52.43 (3C, -OCH₃), 129.61, 132.61, 134.57, 139.66 (8C, Arom, CH=C), 147.15 (3C, C=N thiazole), 164.07, 166.62, 175.23 (9C, C=O). Anal. Calcd. For $\text{C}_{27}\text{H}_{19}\text{N}_9\text{O}_{12}\text{S}_3$: C, 42.69; H, 2.79; N, 16.59. Found: C, 43.01; H, 3.11; N, 16.35%.

3.17. Synthesis of 5,5',5''-(Benzene-1,3,5-tril) Tris(1,3,4-thiadiazole-2-amine) (**4e**). A mixture of 1,3,5-benzoyl-tris-hydrazinecarbothioamide (0.5 mmol) and methanol (8 mL) was stirred at room temperature for 15 min. Then a solution of 15% sodium hydroxide (5 mL) was added and refluxed for 1 h. The reaction mixture was cooled and then acidified to pH 7 with acetic acid (1 N). The precipitate was filtered, washed with water, and recrystallized from DMF, to give the desired compound (**4e**).

White powder. Yield: %61, m.p 310°C (decom.). $^1\text{H-NMR}$ (DMSO- d_6 , 500 MHz): δ (ppm) = 7.60 (s, 6H, NH₂), 8.06 (s, 3H, Ar-H). $^{13}\text{C-NMR}$ (DMSO- d_6 , 125.77 MHz): δ (ppm) = 124.82, 133.44 (6C, Arom), 155.66, 170.06 (6C, 6C=N). Anal. Calcd. For $\text{C}_{12}\text{H}_9\text{N}_9\text{S}_3$: C, 38.39; H, 2.42; N, 33.58. Found: C, 38.14; H, 2.32; N, 33.67%.

3.18. Synthesis of 5,5',5''-(Benzene-1,3,5-tril) Tris (4-1,2,4-thiazole-3-thiol) (**4d**). A mixture of 1, 3, 5-benzoyl-tris-hydrazine carbothioamide (1 mmol) and concentrated sulfuric acid (10 mL) in ice-cold water was stirred for 15 min, and then was refluxed for 2 hours. The resulting solution was poured slowly into ice-cold water, made alkaline to pH 8 with aqueous ammonia and the precipitated product was filtered, washed with water, and recrystallized from DMF.

Brown powder. Yield: %58, m.p 320°C. $^1\text{H-NMR}$ (DMSO- d_6 , 500 MHz): δ (ppm) = 8.37 (3H, Ar-H), 13.05 (s, 3H, SH). $^{13}\text{C-NMR}$ (DMSO- d_6 , 125.77 MHz): δ (ppm) = 124.87, 133.70 (6C, Arom), 158.96, 160.32 (6C, 6C=N). Anal. Calcd. For $\text{C}_{12}\text{H}_9\text{N}_9\text{S}_3$: C, 38.39; H, 2.42; N, 33.58. Found: C, 38.18; H, 2.33; N, 33.77%.

3.19. Synthesis of N'_1, N'_3, N'_5 -Tris(4-bromophenyl)thiazole-2(3H)-ylidene)benzene-1,3,5-thricarbonyl Hydrazide (**4f**). A mixture of 1, 3, 5-tricarbonyl (phenyl)tris(hydrazine carbothioamide) (0.5 mmol) and DMF (3 mL) was prepared under ultrasonic for 15 min until fluoresced. Then a solution of 1,4'-dibromoacetophenone (1.5 mmol) and DMF (2 mL) was added to it drop wise. After 100 min the reaction completed (reaction accession controlled by TLC chromatography). Finally put the vessel in refrigerator for 1 hour. The precipitate was filtered and recrystallized from ethyl acetate, to give the desired compound (**4f**).

Brown powder. Yield: %86, m.p 330°C. $^1\text{H-NMR}$ (DMSO- d_6 , 500 MHz): δ (ppm) = 7.30 (s, 3H, thiazol rings), 7.64 (d, J = 8.3 Hz, 6H, Ar-H), 7.83 (d, J = 8.3 Hz, 6H, Ar-H), 8.68 (s, 3H, Ar-H), 9.79 (s, 3H, NH), 11.15 (s, 3H, NH). $^{13}\text{C-NMR}$ (DMSO- d_6 , 125.77 MHz): δ (ppm) = 106.22

(3C, C= thiazol rings), 121.02, 132.83, 133.44, 134.21, 136.98, 139.03 (24C, arom), 150.74, 166.59, 174.39 (12C, CH= thiazol rings, C=N, C=O). Anal. Calcd. For $C_{36}H_{24}Br_3N_9O_3S_3$: C, 44.74; H, 2.50; N, 13.04. Found: C, 45.07; H, 2.64; N, 12.79%.

Acknowledgment

The authors gratefully acknowledge the financial support for this paper, of Vali-e-Asr University of Rafsanjan, Faculty Research Grant.

References

- [1] Y. D. Kulkarni and A. Rowhani, "Synthesis of 5-(3,5-dinitrophenyl)-3-[(substituted-amino)methyl]-1,3,4-oxadiazole-2 (3H)-thione as potential biological active agents," *Journal of the Indian Chemical Society*, vol. 66, no. 7, pp. 492–493, 1989.
- [2] K. Obi, A. Kojima, H. Fukuda, and K. Hirai, "Synthesis and biological activity of a novel class of cephalosporins with a oxadiazolyl hydroxypyridone moiety at C-7," *Bioorganic & Medicinal Chemistry Letters*, vol. 5, no. 23, pp. 2777–2782, 1995.
- [3] M. D. Mullican, M. W. Wilson, D. T. Connor, C. R. Kostlan, D. J. Schrier, and R. D. Dyer, "Design of 5-(3,5-Di-tert-butyl-4-hydroxyphenyl)-1,3,4-thiadiazoles, -1,3,4-oxadiazoles, and -1,2,4-triazoles as orally-active, nonulcerogenic antiinflammatory agents," *Journal of Medicinal Chemistry*, vol. 36, no. 8, pp. 1090–1099, 1993.
- [4] B. Tozcoparan, B. N. Gokhan, G. Aktay, E. Yesilada, and M. Ertan, "6-Benzylidenethiazolo[3,2-b]-1,2,4-triazole-5(6H)-ones substituted with ibuprofen: synthesis, characterization and evaluation of anti-inflammatory activity," *European Journal of Medicinal Chemistry*, vol. 35, no. 7-8, pp. 743–750, 2000.
- [5] B. Tozcoparan, E. Kupeli, G. Aktay, E. Yesilada, and M. Ertan, "Preparation of 5-aryl-3-alkylthio-1,2,4-triazoles and corresponding sulfones with antiinflammatory-analgesic activity," *Bioorganic & Medicinal Chemistry*, vol. 15, no. 4, pp. 1808–1814, 2007.
- [6] O. Ates, A. Kocabalkanl, G. Sanis-Otuk, A. C. Ekinci, and A. Vidin, *Arzneimittel Forschung*, vol. 47, p. 1134, 1997.
- [7] O. Ates, H. Altintas, and G. Otuk, "Synthesis and antimicrobial activity of 4-carbethoxymethyl-2-[(alpha-haloacyl)-amino] thiazoles and 5-nonsubstituted/substituted 2-[(4-carbethoxymethylthiazol-2-yl)imino]-4-thiazolidinones," *Arzneimittel Forschung*, vol. 50, no. 6, pp. 569–575, 2000.
- [8] S. G. Kucukguzel, E. E. Oruc, S. Rollas, F. Sahin, and A. Ozbek, "Synthesis, characterisation and biological activity of novel 4-thiazolidinones, 1,3,4-oxadiazoles and some related compounds," *European Journal of Medicinal Chemistry*, vol. 37, no. 3, pp. 197–206, 2002.
- [9] C. G. Bonde and N. J. Gaikwad, "Synthesis and preliminary evaluation of some pyrazine containing thiazolines and thiazolidinones as antimicrobial agents," *Bioorganic & Medicinal Chemistry*, vol. 12, no. 9, pp. 2151–2161, 2004.
- [10] N. Cesur, Z. Cesur, N. Ergenc et al., "Synthesis and antifungal activity of some 2-aryl-3-substituted 4-thiazolidinones," *Archiv der Pharmazie*, vol. 327, no. 4, pp. 271–272, 1994.
- [11] N. Karali, E. Ilhan, A. Gürsoy, and M. Kiraz, "New cyclohexylidenehydrazide and 4-aza-1-thiaspiro[4.5] decan-3-one derivatives of 3-phenyl-4 (3H)-quinazolinones," *Farmaco*, vol. 53, no. 5, pp. 346–349, 1998.
- [12] H. T. Y. Fahmy, "Synthesis of some new triazoles as potential antifungal agents," *Bollettino Chimico Farmaceutico*, vol. 140, no. 6, pp. 422–427, 2001.
- [13] M. L. Barreca, A. Chimirri, L. D. Luca et al., "Discovery of 2,3-diaryl-1,3-thiazolidin-4-ones as potent anti-HIV-1 agents," *Bioorganic and Medicinal Chemistry Letters*, vol. 11, no. 13, pp. 1793–1796, 2001.
- [14] A. Rao, A. Carbone, A. Chimirri et al., "Synthesis and anti-HIV activity of 2,3-diaryl-1,3-thiazolidin-4-(thi)one derivatives," *Farmaco*, vol. 57, no. 9, pp. 747–751, 2002.
- [15] A. Rao, A. Carbone, A. Chimirri et al., "Synthesis and anti-HIV activity of 2,3-diaryl-1,3-thiazolidin-4-ones," *Farmaco*, vol. 58, no. 2, pp. 115–120, 2003.
- [16] A. Rao, J. Balzarini, A. Carbone et al., "Synthesis of new 2,3-diaryl-1,3-thiazolidin-4-ones as anti-HIV agents," *Farmaco*, vol. 59, no. 1, pp. 33–39, 2004.
- [17] L. Bukowski, M. Janowiec, Z. Zwolska-Kwiek, and Z. Andrzejczyk, "Some reactions of 2-cyanomethylimidazo[4,5-b]pyridine with isothiocyanates. Antituberculous activity of the obtained compounds," *Pharmazie*, vol. 53, no. 6, pp. 373–376, 1998.
- [18] N. Ulusoy, "Synthesis and antituberculosis activity of cycloalkylidenehydrazide and 4-aza-1-thiaspiro[4.5]decan-3-one derivatives of imidazo[2,1-b]thiazole," *Arzneimittel Forschung*, vol. 52, no. 7, pp. 565–571, 2002.
- [19] K. Babaoglu, M. A. Page, V. C. Jones et al., "Novel inhibitors of an emerging target in mycobacterium tuberculosis; substituted thiazolidinones as inhibitors of dTDP-rhamnose synthesis," *Bioorganic and Medicinal Chemistry Letters*, vol. 13, no. 19, pp. 3227–3230, 2003.
- [20] C. J. Andres, J. J. Bronson, S. V. D'Andrea et al., "4-Thiazolidinones: novel inhibitors of the bacterial enzyme MurB," *Bioorganic and Medicinal Chemistry Letters*, vol. 10, no. 8, pp. 715–717, 2000.
- [21] N. D. Heindel and J. R. Reid, "4-amino-3-mercapto-4H-1,2,4-triazoles and propargyl aldehydes: a new route to 3-R-8-aryl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazepines," *Journal of Heterocyclic Chemistry*, vol. 17, no. 5, pp. 1087–1088, 1980.
- [22] B. S. Holla, B. Kalluraya, K. R. Sridhar et al., "Synthesis, structural characterization, crystallographic analysis and antibacterial properties of some nitrofuryl triazolo[3,4-b]-1,3,4-thiadiazines," *European Journal of Medicinal Chemistry*, vol. 29, no. 4, pp. 301–308, 1994.
- [23] H. Beraldo and D. Gambino, "The wide pharmacological versatility of semicarbazones, thiosemicarbazones and their metal complexes," *Mini Reviews In Medicinal Chemistry*, vol. 4, no. 1, pp. 31–39, 2004.
- [24] I. Kucukguzel, S. G. Kucukguzel, S. Rollas, and M. Kiraz, "Some 3-thioxo/alkylthio-1,2,4-triazoles with a substituted thiourea moiety as possible antimycobacterials," *Bioorganic and Medicinal Chemistry Letters*, vol. 11, no. 13, pp. 1703–1707, 2001.
- [25] R. F. Poulain, A. L. Tartar, and B. P. Déprez, "Parallel synthesis of 1,2,4-oxadiazoles from carboxylic acids using an improved, uronium-based, activation," *Tetrahedron Letters*, vol. 42, pp. 1495–1498, 2001.

- [26] S. Castellano, G. Stefancich, A. Chillotti, and G. Poni, "Synthesis and antimicrobial properties of 3-aryl-1-(1,1'-biphenyl-4-yl)-2-(1H-imidazol-1-yl)propanes as "carba-analogues" of the N-arylmethyl-N-[(1,1'-biphenyl)-4-ylmethyl]-1H-imidazol-1-amines, a new class of antifungal agents," *Il Farmaco*, vol. 58, no. 8, pp. 563–568, 2003.
- [27] M. Amir, H. Kumar, and S. A. Javed, "Condensed bridgehead nitrogen heterocyclic system: synthesis and pharmacological activities of 1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazole derivatives of ibuprofen and biphenyl-4-yloxy acetic acid," *European Journal of Medicinal Chemistry*, vol. 43, no. 10, pp. 2056–2066, 2008.
- [28] L. Navidpour, H. Shafaroodi, K. Abdi et al., "Design, synthesis, and biological evaluation of substituted 3-alkylthio-4,5-diaryl-4H-1,2,4-triazoles as selective COX-2 inhibitors," *Bioorganic and Medicinal Chemistry*, vol. 14, no. 8, pp. 2507–2517, 2006.