Heteroatom Chemistry
Volume 18, Number 3, 2007

Synthesis and Anti-HIV Activity of New Chiral 1,2,4-Triazoles and 1,3,4-Thiadiazoles

Tashfeen Akhtar,[1] Shahid Hameed,[1] Najim A. Al-Masoudi,[2] and Khalid M. Khan[3]

[1]*Department of Chemistry, Quaid-I-Azam University, Islamabad 45320, Pakistan*

[2]*Formerly Fakultät für Chemie, Universität Konstanz, Potfach 5560, D-78457 Konstanz, Germany*

[3]*HEJ Research Institute of Chemistry, University of Karachi, Karachi, Pakistan*

Received 30 May 2006

ABSTRACT: *5-substituted 4-(4-chlorophenyl)-4H-1,2,4-triazol-3-thiones* **3** *and 2-substituted 5-(4-chlorophenylamino)-1,3,4-thiadiazoles* **4** *were prepared from the intermediate thiosemicarbazides* **2** *under basic and acidic conditions, respectively. The thiosemicarbazides, in turn, were prepared by the reaction of hydrazides* **1** *with 4-chlorophenylisothiocyanate in MeOH. Some of the new synthesized compounds were assayed against HIV-1 and HIV-2 in MT-4 cells. All the compounds were inactive except* **3f**, *which showed an* EC_{50} *value of 23.9 μg/mL and 9.9 μg/mL against HIV-1 and HIV-2 with a therapeutic index of 3 and 7, respectively. It means that compound* **3f** *was cytotoxic to MT-4 cells at* CC_{50} *of 72.7 μg/mL in both strains.* © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:316–322, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20282

INTRODUCTION

Several heterocyles containing 1,2,4-triazoles and 1,3,4-thiadiazoles residues have been described as potent chemotherapeutic agents. Recently, 3-amino-, 3-nitro-, and 3-mercapto-1,2,4-triazoles as well as 2,4-dihydro-3*H*-1,2,4-triazole-3-thiones and thiosemicarbazones were reported as specific antithyriod agents [1,2]; meanwhile some substituted 1,3,4-thiadiazoles exhibited anticonvulsant activity [3,4] and other pharmacological potency [5]. Other various 1,3,4-thiadiazole derivatives showed remarkable potential biological activities such as antibacterial [6], antimicrobial [7,8], and enzyme inhibition activities [9,10]. Although the synthesis of these moieties is reported [6,11,12], the synthesis of five membered chiral heterocycles is not well documented and only a few examples have been cited in the literature [13,14].

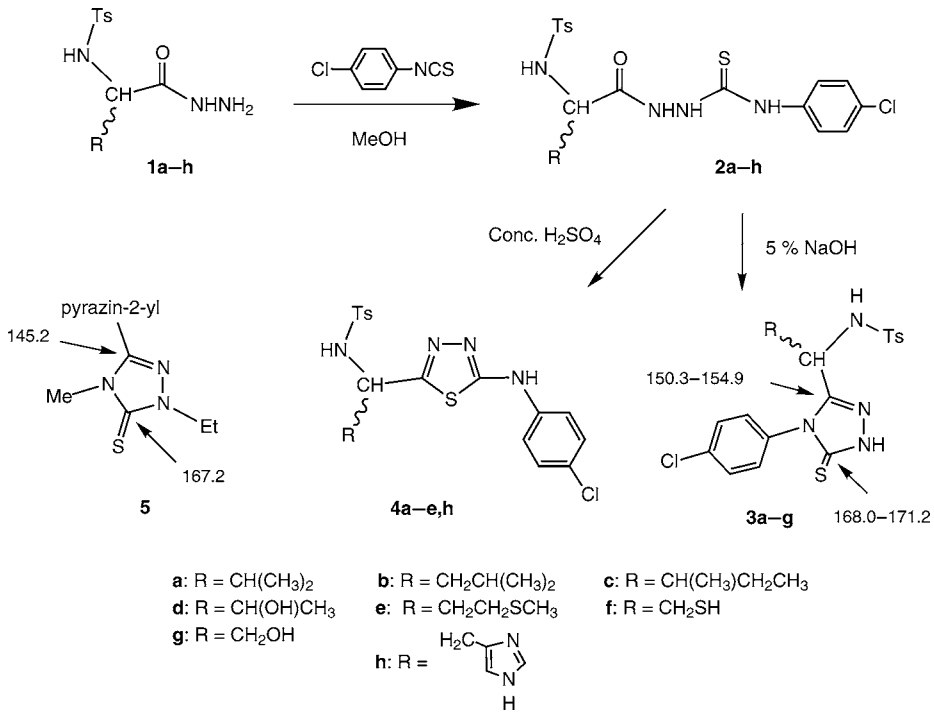
Keeping in view that chiral drugs are highly selective biological agents because of their reactivity toward the specific enzymes, we report here the synthesis of some chiral triazoles and thiadiazoles derivatives with study of their HIV inhibitory activity, because of the specificity of such derivatives from the chemical and bioactivity points of view.

RESULTS AND DISCUSSION

Chemistry

The hydrazides **1**, used in the synthesis of thiosemicarbazides, were prepared from L-amino acids, using the sequence: *N*-tosylation [15], esterification, and conversion to hydrazides on treatment with 80% hydrazine hydrate. The synthesized *N*-tosylamino acid hydrazides **1a–h** were treated with 4-chlorophenyl isothiocyanate to yield thiosemicarbazides **2a–h**,

Correspondence to: Shahid Hameed, Najim A. Al-Masoudi; e-mail: shameed@qau.edu.pk, info@al-masoudi.de.



SCHEME 1

which were used as key synthetic intermediates. IR spectra of thiosemicarbazides exhibited characteristic absorptions for C=O and C=S groups. ^{1}H NMR and mass spectral data were consistent with the structure of the synthesized compounds.

Cyclodehydration of the thiosemicarbazides **2a–h** in basic medium leads to the 1,2,4-triazoles **3a–g**, whereas acidic cyclodehydration gave 1,3,4-thiadiazoles **4a–e,h**. The synthesis of triazoles **3a–g** and thiadiazoles (**4a–e,h**) was indicated in their IR spectra by the absence of carbonyl absorption. The existence of triazoles (**3a–g**) in thione form was also indicated in the IR spectra by the absence of SH stretching in the characteristic region of 2550 cm^{-1} and presence of C=S stretching in the region of 1200 cm^{-1}. The ^{1}H NMR spectrum of each compound exhibited four doublets in the aromatic region, two for the 4-methylphenyl part and two for 4-chlorophenyl moiety in the compounds. The signal for NH of sulfonamide moiety was observed as doublet in some cases and as a broad singlet in others in the range of δ 6.74–8.34. The NH of the triazole and thiadiaozle rings appeared deshielded as expected in the range δ 12.61–13.87 and δ 8.14–10.13, respectively. The signal for NH in case of triazoles appearing downfield than δ 12.0, confirming the existence of the ring in thione form. The diastereotopic effect of chiral center was also observed in the form of complex splitting patterns for the nearby proton signals. The polarimetric studies show that racemization has not occurred during synthesis.

In the ^{13}C NMR spectra of triazol-3-thiones of type **5**, the value close to δ_C 168 and δ_C 145–160 were reported for C=S (C-3) and C=N (C-5), respectively [16]. According to these data, ^{13}C NMR shifts of δ_C 168.0–171.2 and δ_C 150.3–154.9 observed for compounds **3a–g** may be assigned to (C=S) C-3 and C=N (C-5), respectively, of the thiadiazoles backbone as shown in Scheme 1.

In Vitro Anti-HIV Activity

Compounds **3a–f, 4a–e**, and **4h** were tested for their in vitro anti-HIV-1 (strain III_B) and HIV-2 (strain ROD) activity in human T-lymphocyte (MT-4) cells. The results are summarized in Table 1, in which the data for efavirenz [17] and capravirine [18] were included for comparison purposes. Compound **3f** was found to be the only compound from the series inhibiting HIV-1 replication in cell culture. Compound **3f** showed an EC_{50} of 23.9 μg/mL against HIV-1 and 9.90 μg/mL against HIV-2 of CC_{50} of 72.7 ± 1.4 μg/mL, resulting in selectivity index of 3 and 7, respectively.

Based on the chemical structure and the fact that compound **3f** inhibits HIV-2, this molecule can be proposed to act as a nonnucleoside reverse transcriptase inhibitor.

TABLE 1 In Vitro Anti-HIV-1[a] and HIV-2[b] of Some New Nitroimidazoles

	Strain Virus	(μg/mL)[c] EC_{50}	(μg/mL)[d] CC_{50}	SI[e]
3a	III_B	>50.9	58.2 ± 10.1	<1
	ROD	>48.1	58.2 ± 10.1	<1
3b	III_B	>17.5	19.2± 1.2	<1
	ROD	>19.4	19.2 ± 1.2	<1
3c	III_B	>17.2	25.0 ± 8.5	<1
	ROD	>18.1	25.0 ± 8.5	<1
3d	III_B	>105.0	≥105.0	≤ 1
	III_B	>105.0	≥105.0	<1
3e	III_B	>66.0	74.3 ± 8.6	<1
	ROD	>67.7	74.3 ± 8.6	<1
3f	III_B	23.9	72.7 ± 1.4	3
	ROD	9.9	72.7 ± 1.4	7
4a	III_B	>14.0	14.0 ± 1.2	<1
	ROD	>12.4	14.0 ± 1.2	<1
4b	III_B	>125.0	>125.0	1
	ROD	>125.0	>125.0	1
4c	III_B	>47.4	56.8 ± 13.9	<1
	ROD	>67.5	56.8 ± 13.9	<1
4d	III_B	>73.3	74.2 ± 2.8	<1
	ROD	>70.6	74.2 ± 2.8	<1
4e	III_B	>12.6	13.3 ± 0.8	<1
	ROD	>12.5	13.3 ± 0.8	<1
4h	III_B	>62.7	68.9 ± 8.2	<1
	ROD	>65.9	68.9 ± 8.2	<1
Efavirenz	III_B	0.003	40	13,333 [17]
Capravirine	III_B	0.0014	11	7,857 [18]

[a]Anti-HIV-1 activity measured with strain III_B.
[b]Anti-HIV-2 activity measured with strain ROD.
[c]Compound concentration required to achieve 50% protection of MT-4 cells from the HIV-1- and 2-induced cytopathogenic effect.
[d]Compound concentration that reduces the viability of mock-infected MT-4 cells by 50%.
[e]SI: Selectivity index (CC_{50}/EC_{50}).

EXPERIMENTAL

Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Specific rotation [α] was measured as a solution in acetone on ATAGO AP-100 automatic polarimeter. IR spectra (cm^{-1}) were recorded on FTX 3000 MX BioRad Excalibar Series IR spectrophotometer, using KBr pellets. ^{1}H NMR spectra were recorded on Bruker (300 and 500 MHz) spectrometers, using TMS as an internal standard. Mass spectra were measured on a MAT-112-S spectrometer at 70 eV. Elemental analysis was carried out on Leco CHNS-932 (USA) Leco Corporation. 4-Chlorophenyl isothiocyanate was synthesized by a reported procedure [19].

*General Procedure for the Synthesis of Thiosemicarbazides (**2a–h**) [12]*

To a solution of *N*-tosylamino acid hydrazide **1a–h** (5.90 mmol) in absolute MeOH (30 mL) was added a solution of 4-chlorophenyl isothiocyanate (5.9 mmol) in absolute MeOH (20 mL) stirring, and the mixture was heated under reflux for 2–3 h. After cooling, the resulting solid was filtered and recrystallized from EtOH/water to give pure thiosemicarbazide **2**.

*1-[3-Methyl-2-(4-methylphenylsulfonamido)butanoyl]-4-(4-chlorophenyl)thiosemicarbazide (**2a**).* From **1a** (1.59 g). Yield: 2.39 g (92%), mp 212–214°C. IR (cm^{-1}) ν_{max}: 3461, 3379, 3273, 1649, 1335, 1265, 1157. ^{1}H NMR (300 MHz, C_3D_6O, δ): 0.85 (d, 3H, $J = 6.7$ Hz), 0.86 (d, 3H, $J = 6.8$ Hz), 2.02–2.09 (m, 1H), 2.40 (s, 3H), 3.47 (dd, 1H, $J = 6.4$ Hz, 6.5 Hz), 7.00 (d, 1H, $J = 5.5$ Hz), 7.35 (d, 2H, $J = 8.8$ Hz), 7.41 (d, 2H, $J = 8.1$ Hz), 7.79 (d, 2H, $J = 8.7$ Hz), 7.81 (d, 2H, $J = 8.2$ Hz), 8.95 (br s., 1H), 9.11 (bs, 1H), 9.76 (br s., 1H). EIMS (*m/z*): 327 (2.1), 226 (26.2), 171 (10.0), 170 (2.5), 169 (28.0), 155 (39.1), 127 (13.1), 111 (18.6), 91 (100.0), 65 (17.7).

*1-[4-Methyl-2-(4-methylphenylsulfonamido)pentanoyl]-4-(4-chlorophenyl)thiosemicarbazide (**2b**).* From **1b** (1.77 g). Yield: 2.46 g (89%), mp 159–161°C. IR (cm^{-1}) ν_{max}: 3469, 3358, 3267, 1657, 1333, 1248, 1161. ^{1}H NMR (500 MHz, CD_3OD, δ): 0.54 (d, 3H, $J = 5.7$ Hz), 0.81 (d, 3H, $J = 6.1$ Hz), 1.45–1.51 (m, 3H), 2.41 (s, 3H), 3.59 (br s., 1H), 7.31 (d, 2H, $J = 8.1$ Hz), 7.38 (d, 2H, $J = 8.1$ Hz), 7.65 (d, 2H, $J = 8.6$ Hz), 7.76 (d, 2H, $J = 8.2$ Hz), 8.91 (br s., 1H), 9.18 (br s., 1H), 9.87 (br s., 1H). EIMS (*m/z*): 228 (8.3), 171 (17.8), 170 (3.4), 169 (51.3), 155 (32.3), 127 (6.2), 111 (27.5), 91 (96.0), 88 (100.0), 65 (23.9).

*1-[3-Methyl-2-(4-methylphenylsulfonamido)pentanoyl]-4-(4-chlorophenyl)thiosemicarbazide (**2c**).* From **1c** (1.76 g). Yield: 2.38 g (86%); mp 84–87°C. IR (cm^{-1}) ν_{max}: 3465, 3387, 3271, 1663, 1338, 1239, 1155. ^{1}H NMR (300 MHz, C_3D_6O, δ): 0.67 (t, 3H, $J = 7.8$ Hz), 0.84 (d, 3H, $J = 6.7$ Hz), 1.02–1.25 (m, 1H), 1.41–1.55 (m, 1H), 1.68–1.85 (m, 1H), 2.40 (s, 3H), 3.72 (dd, 1H, $J = 6.6$ Hz, 9.9 Hz), 6.68 (d, 1H, $J = 9.8$ Hz), 7.34 (d, 2H, $J = 8.6$ Hz), 7.36 (d, 2H, $J = 8.7$ Hz), 7.68 (d, 2H, $J = 8.2$ Hz), 7.81 (d, 2H, $J = 8.2$ Hz), 8.96 (s, 1H), 9.14 (s, 1H), 9.78 (s, 1H). EIMS (*m/z*): 240 (100.0), 171 (3.7), 170 (6.5), 169 (12.1), 155 (85.1), 127 (6.4), 111 (15.5), 99 (18.8), 91 (73.8), 65 (15.1).

*1-[3-Hydroxy-2-(4-methylbenzenesulfonamido)butanoyl]-4-(4-chlorophenyl)thiosemicarbazide (**2d**).* From **1d** (1.69 g). Yield: 2.21 g (82%), mp 192–194°C, IR (cm^{-1}) ν_{max}: 3397–3263, 1653, 1341, 1243, 1157. ^{1}H NMR (500 MHz, CD_3OD, δ): 1.03 (d, 3H, $J = 6.3$ Hz), 2.40 (s, 3H), 3.64 (d, 1H, $J = 4.5$ Hz),

4.03–4.04 (m, 1H), 7.30 (d, 2H, $J = 8.8$ Hz), 7.36 (d, 2H, $J = 8.1$ Hz), 7.58 (d, 2H, $J = 8.7$ Hz), 7.77 (d, 2H, $J = 8.2$ Hz), 8.89 (s, 1H), 9.04 (s, 1H), 9.63 (s, 1H). EIMS (*m/z*): 228 (8.3), 171 (17.8), 170 (3.3), 169 (51.3), 155 (32.3), 127 (6.2), 111 (27.5), 91 (96.1), 88 (100.0), 65 (23.9).

*1-[4-Methylthio-2-(4-methylbenzenesulfonamido)-butanoyl]-4-(4-hlorophenyl)thiosemicarbazide (***2e***).* From **1e** (1.87 g). Yield: 2.61 g (91%), mp: 200–201°C. IR (cm^{-1}) ν_{max}: 3463, 3351, 3253, 1661, 1337, 1236, 1156. ^{1}H NMR (500 MHz, CD_3OD, δ): 1.80–1.86 (m, 1H), 1.90 (s, 3H), 1.92–1.98 (m, 1H), 2.25–2.31 (m, 1H), 2.39–2.46 (m, 4H), 3.83 (dd, 1H, $J = 5.5$ Hz, 7.4 Hz), 7.31 (d, 2H, $J = 8.7$ Hz), 7.37 (d, 2H, $J = 8.0$ Hz), 7.62 (d, 2H, $J = 8.7$ Hz), 7.72 (d, 1H, $J = 7.6$ Hz), 7.77 (d, 2H, $J = 8.2$ Hz), 8.93 (s, 1H), 9.07 (s, 1H), 9.69 (s, 1H). EIMS (*m/z*): 258 (18.8), 171 (19.3), 170 (4.1), 169 (51.9), 155 (15.4), 127 (5.8), 111 (27.3), 99 (2.8), 91 (78.1), 75 (27.0), 65 (16.2), 61 (100.0), 57 (2.4).

*1-[3-Mercapto-2-(4-methylbenzenesulfonamido)-propanoyl]-4-(4-chlorophenyl)thiosemicarbazide (***2f***).* From **1f** (1.71 g). Yield: 1.92 g (71%), mp 117–118°C. IR (cm^{-1}) ν_{max}: 3463, 3376, 3251, 2553, 1654, 1339, 1244, 1160. ^{1}H NMR (300 MHz, C_3D_6O, δ): 2.39 (s, 3H), 3.63–3.71 (m, 2H), 4.29 (d, 1H, $J = 6.4$ Hz), 4.32 (bs, 1H), 7.0 (br s., 1H), 7.31 (d, 2H, $J = 8.6$ Hz), 7.37 (d, 2H, $J = 8.2$ Hz), 7.55 (d, 2H, $J = 8.7$ Hz), 7.58 (d, 2H, $J = 8.1$ Hz). EIMS (*m/z*): 171 (19.9), 155 (19.45), 107 (14.9), 91 (100.0), 65 (33.6).

*1-[3-Hydroxy-2-(4-methylbenzenesulfonamido)-propanoyl]-4-(4-chlorophenyl)thiosemicarbazide (***2g***).* From **1g** (1.61 g). Yield: 1.91 g (73%), mp: 170–172°C. IR (cm^{-1}) ν_{max}: 3387–3235, 1665, 1337, 1155, 1246. ^{1}H NMR (500 MHz, CD_3OD, δ): 2.41 (s, 3H), 3.58 (dd, 1H, $J = 6.7$ Hz, 10.5 Hz), 3.70 (dd, 1H, $J = 5.5$ Hz, 10.5 Hz), 3.79 (dd, 1H, $J = 5.9$ Hz, 6.2 Hz), 5.31 (br s., 1H), 7.30 (d, 2H, $J = 8.7$ Hz), 7.37 (d, 2H, $J = 8.1$ Hz), 7.56 (d, 2H, $J = 8.7$ Hz), 7.77 (d, 2H, $J = 8.2$ Hz), 8.87 (s, 1H), 9.13 (s, 1H), 9.81 (s, 1H). EIMS (*m/z*): 240 (31.2), 171 (15.6), 170 (2.7), 169 (37.4), 155 (41.9), 127 (4.4), 111 (16.9), 99 (2.5), 91 (100.0), 75 (18.2), 65 (28.3).

*1-[3-(1H-Imidazol-5-yl)-2-(4-methylphenyl-sulfonamido)propanoyl]-4-(4-chlorophenyl)thiosemicarbazide (***2h***).* From **1h** (1.91 g). Yield: 2.47 g (85%), mp: 176–178°. IR (cm^{-1}) ν_{max}: 3421, 3361, 3297, 1658, 1336, 1244, 1156. ^{1}H NMR (500 MHz, CD_3OD, δ): 2.39 (s, 3H), 3.13–3.21 (m, 2H), 4.85 (dd, 1H, $J = 6.0$ Hz, 9.0 Hz), 7.25 (s, 1H), 7.29 (d, 2H, $J = 8.1$ Hz), 7.37 (d, 2H, $J = 6.9$ Hz), 7.43 (d, 2H, $J = 6.9$ Hz), 7.61 (d, 2H, $J = 8.2$ Hz), 8.43 (s, 1H), 8.97 (s, 1H), 9.18 (s, 1H), 9.73 (s, 1H). EIMS (*m/z*): 200 (2.0), 171 (4.7), 170 (8.3), 127 (11.6), 111 (25.6), 91 (8.3), 75 (100.0).

*General Procedure for the Synthesis of Triazoles (***3a–g***)*

Thiosemicarbazide **2** (1.10 mmol) was added portionwise to a solution of NaOH (5%, 30 mL), and the reaction mixture was heated under reflux for 4 h. After cooling, the mixture was filtered, and the filtrate was acidified with 6 N HCl to PH 2–3. The precipitated solid was filtered, washed thoroughly with water, and recrystallized from EtOH/water.

*4-(4-Chlorophenyl)-5-(2-methyl-1-(*p*-toluenesulfonylamino)propyl)-*2H*-1,2,4-triazole-3-thione (***3a***).* From **2a** (0.50 g). Yield: 0.41 g (85%), mp 100–102°C. $[\alpha]_D^{25}$ + 47° (c 1.2, acetone), IR (cm^{-1}) ν_{max}: 3476, 3277, 1335, 1235, 1156. ^{1}H NMR (500 MHz, CD_3OD, δ): 0.78 (d, 3H, $J = 6.7$ Hz), 0.81 (d, 3H, $J = 6.7$ Hz), 1.90–1.97 (m, 1H), 2.39 (s, 3H), 3.98 (dd, 1H, $J = 7.1$ Hz, 8.4 Hz), 6.99 (d, 1H, $J = 8.4$ Hz), 7.29 (d, 2H, $J = 8.7$ Hz), 7.35 (d, 2H, $J = 8.1$ Hz), 7.62 (d, 2H, $J = 8.8$ Hz), 7.63 (d, 2H, $J = 8.2$ Hz), 12.62 (br s., 1H). ^{13}C NMR (75 MHz, C_3D_6O, δ): 17.4 and 18.9 (CMe_2), 20.9 ($MeArSO_2$), 32.1 (CMe_2), 55.2 (C_5-*CHN*), 119.2 ($NHAr\text{-}C_{b,f}$), 126.7, 129.8, 130.0, 130.6 (Ar-C) , 132.5 (Ar-C-Cl), 135.2 (Ar-C-*Me*), 137.9 (Ar-*C*-SO_2), 143.0 (Ar-C-N), 151.7 (C-5), 169.5 (C=S). Anal. Calcd for $C_{19}H_{21}ClN_4O_2S_2$ (436.98): C, 52.22; H, 4.84; N, 12.82. Found: C, 52.16; H, 4.79; N, 12.61.

*4-(4-Chlorophenyl)-5-(3-methyl-1-(*p*-toluenesulfonylamino)butyl)-*2H*-1,2,4-triazole-3-thione (***3b***).* From **2b** (0.52 g). Yield: 0.41 g (83%), mp 190–192°C, $[\alpha]_D^{25}$ + 27° (c 0.66, acetone), IR (cm^{-1}) ν_{max}: 3478, 3417, 1313, 1235, 1161. ^{1}H NMR (500 MHz, CD_3OD, δ): 0.46 (d, 3H, $J = 5.9$ Hz), 0.72 (d, 3H, $J = 6.0$ Hz), 1.50–1.64 (m, 3H), 2.39 (s, 3H), 4.10 (br s., 1H), 4.12 (dd, 1H, $J = 4.3$ Hz, 8.4 Hz), 7.35 (d, 2H, $J = 8.2$ Hz), 7.36 (d, 2H, $J = 8.5$ Hz), 7.60 (d, 2H, $J = 8.2$ Hz), 7.63 (d, 2H, $J = 8.6$ Hz), 12.61 (br s., 1H). ^{13}C NMR (75 MHz, C_3D_6O, δ): 20.4 ($CHCMe_2$), 21.5 ($MeArSO_2$), 22.7 ($CHCMe_2$), 43.6 ($CHCMe_2$), 47.9 (C_5-*CHN*), 126.8, 129.7, 129.8, 130.4 (Ar-C), 130.8 (Ar-C-Cl), 136.9 (Ar-C-Me), 137.0 (Ar-*C*-SO_2), 144.2 (Ar-*C*-NH, Ar-*C*-Me), 154.9 (C-5), 168.7 (C=S). Anal. Calcd for $C_{20}H_{23}ClN_4O_2S_2$(451.01): C, 53.26; H, 5.14; N, 12.42. Found: C, 53.13; H, 5.13; N, 12.36.

*4-(4-Chlorophenyl)-5-(2-methyl-1-(*p*-toluenesulfonylamino)butyl)-*2H*-1,2,4-triazole-3-thione (***3c***).* From **2c** (0.52 g). Yield: 0.41 g (83%), mp 122–124°C.

$[\alpha]_D^{25}$ +42° (c 1.01, $CHCl_3$), IR (cm^{-1}) ν_{max}: 3473, 3217, 1336, 1239, 1158. ^{1}H NMR (500 MHz, CD_3OD, δ): 0.64 (t, 3H, $J = 7.4$ Hz), 0.76 (d, 3H, $J = 6.8$ Hz), 0.79–0.88 (m, 1H), 1.39–1.54 (m, 1H), 1.68–1.79 (m, 1H), 2.39 (s, 3H), 3.98 (d, 1H, $J = 6.9$ Hz), 6.99 (br s., 1H), 7.29 (d, 2H, $J = 8.6$ Hz), 7.36 (d, 2H, $J = 8.2$ Hz), 7.62 (d, 2H, $J = 8.7$ Hz), 7.64 (d, 2H, $J = 8.2$ Hz), 12.62 (br s., 1H). ^{13}C NMR (75 MHz, C_3D_6O, δ): 14.8 ($CHMeCH_2\mathit{CH}_3$), 20.5 ($CH\mathit{Me}CH_2CH_3$), 24.2 ($\mathit{Me}ArSO_2$), 37.7 ($CHMe\mathit{CH}_2CH_3$), 51.1 ($\mathit{CH}MeCH_2CH_3$), 60.5 (C_5-*CHN*), 119.0 (NHAr-$C_{b,f}$), 127.1, 128.6, 128.9, 129.2, 129.3 (Ar-C), 138.2 (Ar-*C*-SO_2), 143.1 144.2 (Ar-*C*-Me), 154.8 (C-5), 171.2 (C=S). Anal. Calcd for $C_{20}H_{23}ClN_4O_2S_2$(451.01): C, 53.26; H, 5.14; N, 12.42. Found: C, 53.31; H, 5.08; N, 12.31.

*4-(4-Chlorophenyl-5-(2-hydroxyl-1-(*p-*toluenesulfonylamino)propyl)*-2H-*1,2,4-triazole-3-thione (***3d***)*. From **2d** (0.50 g). Yield: 0.35 g (72%), mp 121–122°C, $[\alpha]_D^{25}$ + 54° (c, 1.1, $CHCl_3$), IR (cm^{-1}) ν_{max}: 3418, 3365, 3271, 1339, 1241, 1158. ^{1}H NMR (500 MHz, DMSO-d_6, δ): 0.98 (d, 3H, $J = 6.2$ Hz), 2.36 (s, 3H), 3.66 (m, 1H), 3.80 (dd, 1H, $J = 6.1$ Hz, 6.2 Hz), 4.97 (d, 1H, $J = 5.6$ Hz), 6.74 (d, 2H, $J = 8.1$ Hz), 7.17 (br s., 1H), 7.31 (d, 2H, $J = 8.0$ Hz), 7.53 (d, 2H, $J = 8.1$ Hz), 7.61 (d, 2H, $J = 8.7$ Hz), 13.8 (s, 1H). ^{13}C-NMR (75 MHz, CD_3OD, δ): 17.6 (CH*Me*OH), 20.1 ($\mathit{Me}ArSO_2$), 54.4 (C_5-*CHN*), 67.7 (*CH*MeOH), 126.9 (NHAr-$C_{b,f}$), 129.3, 129.4, 130.3, 132.0 (Ar-C), 135.6 (Ar-*C*-SO_2), 137.2 (Ar-*C*-NH), 143.8 (Ar-*C*-Me), 150.1 (C-5), 168.3 (C=S). Anal. Calcd for $C_{18}H_{19}ClN_4O_3S_2$(438.95): C, 49.25; H, 4.36; N, 12.76. Found: C, 49.19, H, 4.31; N, 12.65.

*4-(4-Chlorophenyl-5-(3-methylthio-1-(*p-*toluenesulfonylamino)propyl)*-2H-*1,2,4-triazole-3-thione (***3e***)*. From **2e** (0.54 g). Yield: 0.41 g (79%), mp 105–107°C, $[\alpha]_D^{25}$ + 38° (c 0.90, $CHCl_3$), IR (cm^{-1}) ν_{max}: 3417, 3254, 1320, 1221, 1157. ^{1}H NMR (500 MHz, C_3D_6O, δ): 1.74 (s, 3H), 1.87–1.93 (m, 2H), 2.09–2.31 (m, 2H), 2.33 (s, 3H), 4.12 (dd, 1H, $J = 7.0$ and 13.7 Hz), 7.30 (d, 2H, $J = 8.8$ Hz), 7.31 (d, 2H, $J = 8.2$ Hz), 7.47 (d, 2H, $J = 8.2$ Hz), 7.61 (d, 2H, $J = 8.8$ Hz), 8.34 (d, 1H, $J = 7.0$ Hz), 13.87 (s, 1H). ^{13}C NMR (75 MHz, C_3D_6O, δ): 15.0 (SMe), 21.6 ($\mathit{Me}ArSO_2$), 29.7 ($CH_2\mathit{CH}_2SMe$), 33.1 (CH_2CH_2SMe), 48.0 (C_5-*CHN*), 127.0, 119.2 (NHAr-$C_{b,f}$), 129.6, 129.8, 130.4, 130.9 (Ar-C), 136.8 (Ar-*C*-SO_2), 144.2 (Ar-*C*-NH, Ar-*C*-Me), 153.7 (C-5), 168.7 (C=S). Anal. Calcd for $C_{19}H_{21}ClN_4O_2S_3$ (469.04): C, 48.65; H, 4.51; N, 11.94. Found: C, 48.59; H, 4.43; N, 11.86.

*4-(4-Chlorophenyl-5-(2-mercapto-1-(*p-*toluenesulfonylamino)propyl)*-2H-*1,2,4-triazole-3-thione (***3f***)*. From **2f** (0.50 g). Yield: 0.31 g (63%), mp 141–143°C, $[\alpha]_D^{25}$ + 22° (c 0.53, $CHCl_3$), IR (cm^{-1}) ν_{max}: 3287, 3243, 2558, 1335, 1243, 1158. ^{1}H-NMR (300 MHz, C_3D_6O, δ): 2.41 (s, 3H), 3.74–3.83 (m, 2H), 4.19 (t, 1H, $J = 6.4$ Hz), 4.38 (br s., 1H), 7.07 (br s., 1H), 7.31 (d, 2H, $J = 8.6$ Hz), 7.33 (d, 2H, $J = 7.9$ Hz), 7.56 (d, 2H, $J = 8.8$ Hz) 7.57 (d, 2H, $J = 8.0$ Hz), 12.62 (br s., 1H). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 18.9 (CH_2SH), 21.8 ($\mathit{Me}ArSO_2$), 56.5 (C_5-*CHN*), 116.5 (NHAr-$C_{b,f}$), 120.3, 125.9, 128.8, 129.4, 132.6 (Ar-C), 138.7 (Ar-*C*-SO_2), 146.7 (Ar-*C*-NH, Ar-*C*-Me), 152.3 (C-5), 170.4 (C=S). Anal. Calcd for $C_{17}H_{17}ClN_4O_2S_3$ (440.99): C, 46.30; H, 3.89; N, 12.70. Found: C, 46.25; H, 3.79; N, 12.63.

*4-(4-Chlorophenyl-5-(2-hydroxy-1-(*p-*toluenesulfonylamino)propyl)*-2H-*1,2,4-triazole-3-thione (***3g***)*. From **2g** (0.49 g). Yield: 0.32 g (69%), mp 115–118°C. $[\alpha]_D^{25}$ + 63° (c 1.51, $CHCl_3$), IR (cm^{-1}) ν_{max}: 3413, 3387, 3235, 1337, 1246, 1155. ^{1}H NMR (300 MHz, DMSO-d_6, δ): 2.36 (s, 3H), 3.46 (dd, 1H, $J = 6.5$ and 10.1 Hz), 3.57 (dd, 1H, $J = 8.7$ Hz, 10.2 Hz), 3.83 (dd, 1H, $J = 6.3$ and 8.4 Hz), 5.22 (br s., 1H), 7.22 (d, 2H, $J = 8.7$ Hz), 7.31 (d, 2H, $J = 8.1$ Hz), 7.47 (d, 2H, $J = 8.7$ Hz), 7.63 (d, 2H, $J = 8.1$ Hz), 8.32 (br s., 1H), 13.85 (br s., 1H). ^{13}CNMR (75 MHz, C_3D_6O, δ): 21.5 ($\mathit{Me}ArSO_2$), 51.1 (C_5-*CHN*), 62.9 (CH_2OH), 116.5 (NHAr-$C_{b,f}$), 127.0, 129.83, 130.0, 130.9, 132.4, 134.7 (Ar-C), 137.5 (Ar-*C*-SO_2), 143.5 (Ar-*C*-NH, Ar-*C*-Me), 151.2 (C-5), 168.0 (C=S). Anal. Calcd for $C_{17}H_{17}ClN_4O_3S_2$ (424.92): C, 48.05; H, 4.03; N, 13.19. Found: C, 47.96; H, 4.12; N, 13.09.

*General Procedure for the Synthesis of Thiadiazoles (***4a–e,h***)*

Thiosemicarbazide **2a–e,h** (1.10 mmol) was added portionwise to concentration H_2SO_4 (20 mL) at 0°C with continuous stirring. The reaction mixture was stirred for 4 h at 23°C and then allowed to stand overnight. The mixture was neutralized with dilute NaOH to give a precipitate as a crude solid, which was filtered, washed with water, and recrystallized from EtOH/water to afford the 1,3,4-thiadiazole derivatives **(4a–e,h)**.

N-*(4-Chlorophenyl-5-(2-methyl-1-(*p-*toluenesulfonylamino)propyl)-1,3,4-thiadiazol-2-amine (***4a***)*. From **2a** (0.50 g). Yield: 0.39 g (82%), mp 148–150°C, $[\alpha]_D^{25}$ + 35° (c 0.84, $CHCl_3$), IR (cm^{-1}) ν_{max}: 3276, 3223, 1328, 1155. ^{1}H NMR (500 MHz, C_3D_6O, δ): 0.83, 0.99 (2 × d, 6H, $J = 6.7$ Hz, $CH\mathit{Me}_2$), 2.04–2.11 (m, 1H, $\mathit{CH}Me_2$), 2.35 (s, 3H, $\mathit{Me}ArSO_2$), 4.44 (dd, 1H, $J = 7.8$ Hz, 8.5 Hz, N*CH*CHMe$_2$), 7.07 (d, 1H, $J =$ 8.1 Hz, Cl-Ar-H), 7.23 (d, 2H, $J = 8.1$ Hz,

Cl-*Ar*-H), 7.34 (d, 2H, $J = 8.8$ Hz, Me-*Ar*-H), 7.64 (d, 2H, $J = 8.8$ Hz, Me-*Ar*-H), 9.41 (br s., 1H, NH). ^{13}C NMR (75 MHz, C_3D_6O, δ): 19.3 (CH*Me*$_2$), 21.3 (*Me*ArSO$_2$), 33.3 (C-7), 59.9 (C-6), 119.2 (NHAr-C$_{b,f}$), 125.6, 127.2, 129.3, 129.7 (Ar-C), 140.0 (Ar-*C*-SO$_2$), 142.5 (Ar-*C*-Me), 142.8 (Ar-*C*-NH), 162.1 (C-5), 164.8 (C-2). Anal. Calcd for $C_{19}H_{21}ClN_4O_2S_2$ (436.98): C, 52.22; H, 4.84; N, 12.82. Found: C, 52.29; H, 4.82; N, 12.77.

N-*(4-Chlorophenyl-5-(3-methyl-1-(*p-*toluenesulfonylamino)butyl)-1,3,4-thiadiazol-2-amine (***4b***)*. From **2b** (0.52 g). Yield: 0.39 g (79%), mp 208–210°C, $[\alpha]_D^{25} + 37°$ (c 0.88, $CHCl_3$), IR (cm^{-1}) ν_{max}: 3315, 3227, 1325, 1159. ^{1}H-NMR (500 MHz, CD_3OD, δ): 0.78 (d, 3H, $J = 6.46$ Hz), 0.85 (d, 3H, $J = 6.5$ Hz), 1.59–1.63 (m, 1H), 1.69 (dd, 2H, $J = 7.0$ Hz, 7.5 Hz), 2.28 (s, 3H), 4.71 (dd, 1H, $J = 4.5$ Hz, 7.8 Hz), 7.17 (br s., 1H), 7.27 (d, 2H, $J = 8.1$ Hz), 7.35 (d, 2H, $J = 8.9$ Hz), 7.64 (d, 2H, $J = 8.3$ Hz), 7.65 (d, 2H, $J = 8.9$ Hz), 9.51 (br s., 1H). ^{13}C NMR (75 MHz, C_3D_6O, δ): 19.3 (CH*C*Me$_2$), 21.3 (CHC*Me*$_2$, *Me*ArSO$_2$), 33.3 (*CH*CMe$_2$), 59.9 (C$_5$-*CHN*), 119.2 (NHAr-C$_{b,f}$), 125.6, 127.1, 129.3, 129.7 (Ar-C), 140.0 (Ar-*C*-SO$_2$), 142.4 (Ar-*C*-NH), 142.8 (Ar-*C*-Me), 162.1 (C-5), 164.8 (C-2). Anal. Calcd for $C_{20}H_{23}ClN_4O_2S_2$ (451.01): C, 53.26; H, 5.14; N, 12.42. Found: C, 53.37; H, 5.06; N, 12.37.

N-*(4-Chlorophenyl-5-(2-methyl-1-(*p-*toluenesulfonylamino)butyl)-1,3,4-thiadiazol-2-amine (***4c***)*. From **2c** (0.52 g). Yield: 0.38 g (76%), mp 74–76°C, $[\alpha]_D^{25} + 72°$ (c 1.7, $CHCl_3$), IR (cm^{-1}) ν_{max}: 3287, 3197, 1332, 1156. ^{1}H NMR (500 MHz, CD_3OD, δ): 0.80–0.86 (m, 6H), 1.15–1.20 (m, 1H), 1.45–1.50 (m, 1H), 1.71–1.74 (m, 1H), 3.72 (dd, 1H, $J = 6.70$ Hz, 9.80 Hz), 6.74 (d, 1H, $J = 9.80$ Hz), 7.36 (d, 2H, $J = 8.50$ Hz), 7.59 (d, 2H, $J = 8.13$ Hz), 7.64 (d, 2H, $J = 8.80$ Hz), 7.68 (d, 2H, $J = 8.17$ Hz), 10.13 (br s., 1H). ^{13}C NMR (75 MHz, C_3D_6O, δ): 14.8 (CHMeCH$_2$*CH*$_3$), 20.5 (CH*Me*CH$_2$CH$_3$), 24.7 (*Me*ArSO$_2$), 37.7 (CHMe*CH*$_2$CH$_3$), 51.1 (*CH*MeCH$_2$CH$_3$), 60.4 (C$_5$-*CHN*), 119.0 (NHAr-C$_{b,f}$), 127.1, 128.6, 128.9, 129.3, 129.4 (Ar-C), 138.2 (Ar-*C*-SO$_2$), 143.1 (Ar-*C*-NH, Ar-*C*-Me), 162.9 (C-5), 164.9 (C-2). Anal. Calcd for $C_{20}H_{23}ClN_4O_2S_2$ (451.01): C, 53.26; H, 5.14; N, 12.42. Found: C, 53.33; H, 5.18; N, 12.33.

*1-(5-(4-Chlorophenylamino)-1,3,4-thiadiazol-2-yl)-1-(*p-*toluenesulfonylamino)propan-2-ol (***4d***)*. From **2d** (0.50 g). Yield: 0.32 g (67%), mp 180–182°C, $[\alpha]_D^{25}$ + 28° (c 0.66, $CHCl_3$). IR (cm^{-1}) ν_{max}: 3487, 3361, 3279, 1341, 1157. ^{1}H NMR (500 MHz, C_3D_3O, δ): 1.10 (d, 3H, $J = 6.3$ Hz), 2.33 (s, 3H), 3.65 (br s., 1H), 4.13–4.15 (m, 1H), 4.61 (dd, 1H, $J = 3.6$ Hz, 7.9 Hz), 6.93 (d, 1H, $J = 8.0$ Hz), 7.32 (d, 2H, $J = 8.0$), 7.37 (d, 2H, $J = 8.6$ Hz), 7.53 (d, 2H, $J = 8.9$ Hz), 7.74 (d, 2H, $J = 8.2$ Hz), 9.87 (br s., 1H). ^{13}C NMR (75 MHz, C_3D_6O, δ): 16.8 (CH*Me*OH), 21.0 (*Me*ArSO$_2$), 58.2 (C$_5$-*CHN*), 75.0 (*CH*MeOH), 120.2 (NHAr-C$_{b,f}$), 125.6, 127.4, 129.2, 129.5 (Ar-C), 137.4 (Ar-*C*-SO$_2$), 138.3 (Ar-*C*-NH), 143.0 (Ar-*C*-Me), 160.1 (C-5), 166.4 (C-2). Anal. Calcd for $C_{18}H_{19}ClN_4O_3S_2$ (438.95): C, 49.25; H, 4.36; N, 12.76. Found: C, 49.33; H, 4.30; N, 12.81.

N-*(4-Chlorophenyl-5-(3-methylthio)-1-(*p-*toluenesulfonylamino)propyl)-1,3,4-thiadiazol-2-amine (***4e***)*. From **2e** (0.54 g). Yield: 0.38 g (73%), mp 174–176°C, $[\alpha]_D^{25}$ + 74° (c 1.78, $CHCl_3$), IR (cm^{-1}) ν_{max}: 3324, 3221, 1335, 1154. ^{1}H NMR (500 MHz, C_3D_6O, δ): 1.95 (s, 3H), 2.18 (m, 2H), 2.39–2.48 (m, 2H), 2.33 (s, 3H), 4.87 (dd, 1H, $J = 7.9$ Hz, 14.5 Hz), 7.20 (br s., 1H), 7.32 (d, 2H, $J = 8.1$ Hz), 7.35 (d, 2H, $J = 8.8$ Hz), 7.65 (d, 2H, $J = 8.8$ Hz), 7.69 (d, 2H, $J = 8.2$ Hz), 8.14 (br s., 1H), 9.37 (bs, 1H). ^{13}C NMR (75 MHz, C_3D_6O, δ): 14.8 (SMe), 21.4 (*Me*ArSO$_2$), 29.6 (CH$_2$*CH*$_2$SMe), 34.5 (*CH*$_2$CH$_2$SMe), 52.5 (C$_5$-*CHN*), 119.2 (NHAr-C$_{b,f}$), 125.7, 127.1, 129.4, 129.9 (Ar-C), 138.4 (Ar-*C*-SO$_2$), 139.9 (Ar-*C*-NH), 143.2 (Ar-*C*-Me), 162.7 (C-5), 165.0 (C-2). Anal. Calcd for $C_{19}H_{21}ClN_4O_2S_3$(469.04): C, 48.65; H, 4.51; N, 11.94. Found: C, 48.57; H, 4.57; N, 11.87.

*5-(2-(*1H-*Imidazol-4-yl)-1-(*p-*toluenesulfonylamino)ethyl)-*N-*(4-chlorophenyl)-1,3,4-thiadiazol-2-amine (***4h***)*. From **2h** (0.54 g). Yield: 0.40 g (77%), mp 247–248°C (dec.), $[\alpha]_D^{25} + 68°$ (c 1.62, $CHCl_3$), IR (cm^{-1}) ν_{max}: 3406, 3368, 3297, 1336, 1156. ^{1}H NMR (500 MHz, CD_3OD, δ): 2.31 (s, 3H), 3.30–3.33 (m, 2H), 4.97 (dd, 1H, $J = 6.0$ Hz, 9.0 Hz), 7.15 (s, 1H), 7.23 (d, 2H, $J = 8.10$ Hz), 7.29 (d, 2H, $J = 6.90$ Hz), 7.48 (d, 2H, $J = 6.9$ Hz), 7.56 (d, 2H, $J = 8.2$ Hz), 8.40 (s, 1H), 9.47 (br s., 1H). ^{13}C NMR (75 MHz, CD_3OD, δ): 21.4 (*Me*ArSO$_2$), 31.8 (*CH*$_2$-imidazole), 53.4 (C$_5$-*CHN*), 117.7 (imidazole-C), 119.2 (NHAr-C$_{b,f}$), 125.7, 126.8, 129.4 (Ar-C), 130.9 (imidazole-C), 134.9 (imidazole-C), 138.1 (Ar-*C*-SO$_2$), 139.9 (Ar-*C*-NH), 143.1 (Ar-*C*-Me), 161.9 (C-5), 165.1 (C-2). Anal. Calcd for $C_{20}H_{19}ClN_6O_2S_2$(474.99): C, 50.57; H, 4.03; N, 17.69. Found: C, 50.53; H, 4.06; N, 17.55.

REFERENCES

[1] Takaoka, M.; Manabe, S.; Yamoto, T.; Teranishi, M., Matsunuma, N.; Masuda, H.; Goto, N. J Vet Med Sci 1994, 56, 341–346.

[2] Kumamoto, T.; Toyooka, K.; Nishida, M.; Kuwahara, H.; Yoshimura, Y.; Kawada, J.; Kubota, S. Chem Pharm Bull 1990, 38, 2595–2596.
[3] Malawska, B. Curr Top Med Chem 2005, 5, 69–85, and references therein.
[4] (a) Chapleo, C. B.; Myers, P. L.; Smith, A. C. B.; Tulloch, I. F.; Turner, T.; Walter, D. S. J Med Chem 1987, 30, 951–954. (b) Chapleo, C. B.; Myers, P. L.; Smith, A. C. B.; Tulloch, I. F.; Turner, T.; Walter, D. S. J Med Chem 1988, 31, 7–11.
[5] Modzelewska-Banachiewicz, B.; Jagiello-Wojtowicz, E.; Tokarzewska-Wielosz, E. Acta Pol Pharm 2000, 57, 199–204.
[6] Goswami, B. N.; Kataky, J. C. S.; Baruah, J. N. J Heterocycl Chem 1984, 21, 1225–1229.
[7] Ulusoy, N.; Ates, O.; Kucukbasmac, O.; Kiraz, M.; Yegenoglu, Y. Monatsh Chem 2003, 134, 465–474.
[8] Turan-Zitouni, G.; Kaplancikli, Z. A.; Yildiz, M. T.; Chevallet, P.; Kaya, D. Eur J Med Chem 2005, 40, 607–613.
[9] Almajan, G. L.; Innocenti, A.; Puccetti, L.; Manole, G.; Barbuceanu, S.; Saramet, I.; Scozzafava, A., Supuran, C. T. Bioorg Med Chem Lett 2005, 15, 2347–2352.
[10] Messina, F., Botta, M.; Corelli, F.; Paladino, A. Tetrahedron: Asymmetry 2000, 11, 4895–4901.
[11] Molina, P.; Tarraga, A.; Espinosa, A. Synthesis 1989, 923–929.
[12] Zamani, K.; Faghihi, K.; Sangi, M. R.; Zolgharnein, J. Turk J Chem 2003, 27, 119–125.
[13] Wang, Z.; Shi, H. J Heterocycl Chem 2001, 38, 355–357.
[14] Elsharief, A. M. Sh.; Ghorab, M. M.; Al-Gaby, M. S. A.; Mohamed, Sh. I.; Ammar, Y. A. Heteroatom Chem 2002, 13, 316–323.
[15] McChesney, E. W.; Kirkswamm, W. M. J A Chem Soc 1937, 59, 1116–1118.
[16] A-Masoudi, N. A.; Hassan, N. A.; Al-Soud, Y. A.; Schmidt, P.; Gaafer, A. E.-D. M.; Weng, M.; Marino, S.; Schoch, A.; Amer, A.; Jochims, J. C. J Chem Soc Perkin Trans 1 1998, 947–953, and references therein.
[17] Young, S. D.; Britcher, S. F.; Tran, L. O.; Payne, L. S.; Lumma, W. C.; Lyle, T. A.; Huff, J. R.; Anderson, P. S.; Olsen, D. B.; Carroll, S. S.; Pettibone, D. J:, Obrien, J. A.; Ball, R. G.; Balani, S. K.; Lin, J. H.; Chen, I. W.; Schleif, W. A.; Sardana, V. V.; Long, W. J.; Byrnes, V. W.; Emini, E. A. Antimicrob Agents Chemother 1995, 39, 2602–2605.
[18] Fujiwara, T.; Sato, A.; El-Farrash, M.; Miki, S.; Kabe, K.; Isaka, Y.; Kodama, M.; Wu, Y. M.; Chen, L. B.; Harada, H.; Sugimoto, H.; Hatanaka, M.; Hinuma, Y. Antimicrob Agents Chemother 1998, 42, 1340–1345.
[19] van der Kerk, G. J. M; Pluygers, C. W.; de Vries, G. Org Synth, Coll 1973, 5, 273.