Synthesis of Some New Five Membered Heterocycles, A Facile Synthesis of Oxazolidinones

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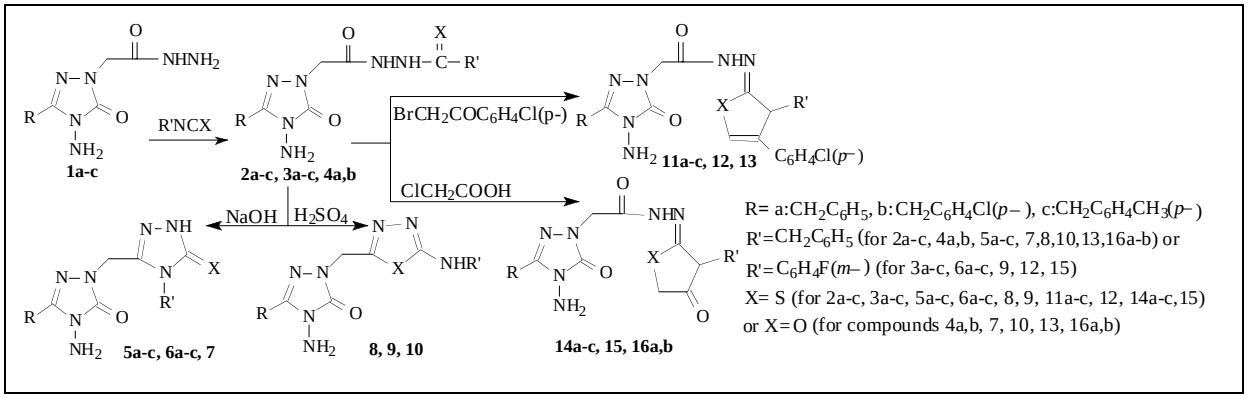

The synthesis and structural properties of two kinds of thiosemicarbazide derivatives (**2a-c** and **3a-c**) and one kind of semicarbazide derivatives (**4a, 4b**) have been described. These compounds were synthesized by treating 2-(4-amino-3-alkyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)acetohydrazides (**1a-c**) with benzyl isothiocyanate, 3-florophenyl isothiocyanate and benzylisocyanate, respectively. The synthesis of 4-amino-3-alkyl-1-[(4-alkyl-5-mercapto(or 5-oxo)-4*H*-1,2,4-triazol-3-yl)methyl]-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**5a-c, 6a-c** and **7**) have been performed from the reaction with sodium hydroxide. On the other hand, the acidic treatment of compounds **2b, 3b** and **4b** has afforded 4-amino-3-(4-chlorobenzyl)-1-[(5-alkylamino-1,3,4-thidazol(or 1,3,4-oxazol)-2-yl)methyl]-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**8, 9** and **10**). The condensation of thiosemi(or semi)carbazide derivatives (**2a-c, 3c** and **4b**) with 4-chlorophenacyl-bromide have resulted in the formation of 2-[4-amino-3-alkyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-*N*'-(3,4-dialkyl-1,3-thiazol(or oxazol)-2(3*H*)-yliden]acetohydrazides **(11a-c, 12, 13)**, while their condensation with chloroacetic acid has produced 2-[4-amino-3-alkyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-*N*'-[3-(3-alkyl)]-4-oxo-1,3-thiazolidin(or oxazolidin)-2-yliden}acetohydrazides (**14, 15** and **16**). The spectral data and elemental analyses have support the proposed structures.

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INTRODUCTION

Many compounds consisting of five member heterocyclic rings such as triazoles, oxadiazoles, thiadiazoles and imidazoles were intensively synthesized and evaluated for their diverse biological activities [1-5]. For instance, among the non-steroidal compounds used for the treatment of estrogen-dependent breast cancer, Vorozole, Letrozole and Anastrozole are very potent drugs which all have a triazole ring in their structures (Figure 1) [6]. In our previous works, we prepared some Schiff Bases of 4-amino-1,2,4-triazol-5-ones possessing antitumoral activity [7-10]. The antitumoral activities of 2-amino-1,3,4-thiadiazoles were reported about 50 years ago. However, their side effects such as hyperuricemia and painfull stomatitis limited their usefulness [11].

During recent years, microorganisms have increased their resistance against commonly used antibiotics. Tuberculosis (TB) is caused by one of these micro-organisms and is one of the leading causes of death due to

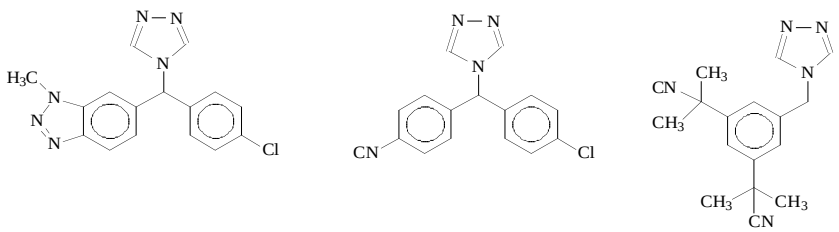


Figure 1

a single infectious organism in the world. According to the reports of Global Alliances, Geneva, there are 8-10 million new active cases of TB and approximately 3 million deaths each year. The World Health Organization (WHO) has predicted that by year 2020 there will be 1 billion new active cases if new anti-TB drugs if new treatments are not developed [12]. Therefore, it is crucial to develop new, potent, antimicrobial and antiviral compounds, which have low side effects and inhibit or kill by novel mechanisms. In the past 20 years, thiazolidinones and oxazolidinones were intensively synthesized due to their antibacterial, antifungal antiviral and antituberculosis activities, they have a novel mechanism of action that involves the inhibition of bacterial protein synthesis at a very early stage [13-19]. Linezolid, eperezolid and AZD2563, which are the members of oxazolidinone class, are efficient antimicrobial drugs used against multi-drug resistant gram positive bacteria [13,20] (Figure 2). However, they are inactive against Gram-negative bacteria and have serious side effects [21]. Beside their pharmaceutical properties, oxazolidinones are important as chiral auxiliaries and protecting groups in organic synthesis, as ligands for metal catalysts [22].

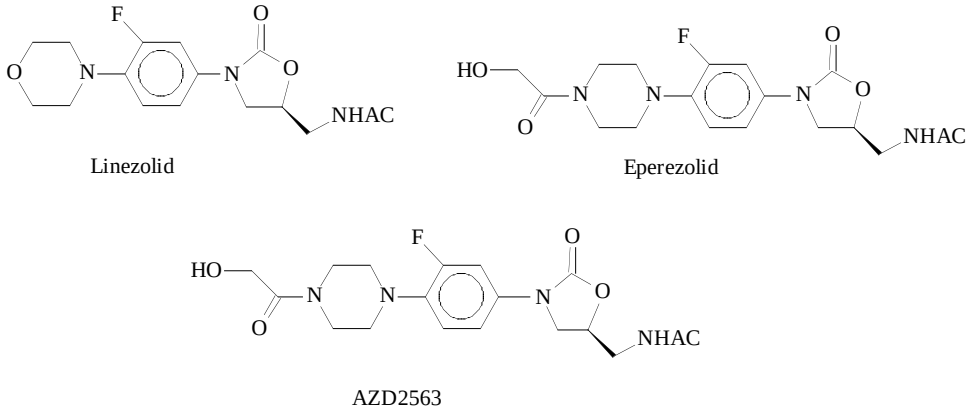


Figure 2

Ring synthesis by cyclization of relatively small and linear molecules is one of the most common methods leading to the formation of heterocyclic compounds. So, for example, the compounds containing a thiosemicarbazide structure can be considered as suitable intermediates for this purpose [8,23-25]. Recently, we reported the synthesis of some 5-mercapto-1,2,4-triazoles and 5-phenylamino-1,3,4-thiadiazoles as antimicrobial agents using thiosemicarbezide derivatives of 1*H*-1,2,4-triazol-5-ones, which were obtained from the nucleophilic addition of 1,2,4-triazol-5-one containing hydrazides to phenylisothiocyanate. In these reactions, the cyclization of *N*,*N*'-disubstituted thiosemicarbazides resulted in the formation of 1,3,4-thiadiazoles in acidic media. On the other hand, the same thiosemicarbazides underwent a cyclization to yield 1,2,4-triazole derivatives in the presence of NaOH [8]. In addition, the synthesis of 3,5-dialkyl-4-amino-4*H*-1,2,4-triazoles having antifungal activity were performed by us using ester ethoxycarbonylhydrazones, which are relatively small and acyclic molecules [26-29].

The exocyclic -NH- group of 4-amino-1*H*-1,2,4-triazole ring is nucleophilic enough for further reactions. For instance, the carbamoil- and thiocarbamoil derivatives of 4-amino-1*H*-1,2,4-triazoles were obtained by the nucleophilic addition of 4-amino-1*H*-1,2,4-triazoles to isocyanates or isothiocyanates [24]. The N-alkyl, N-phenacyl and N-ethoxycarbonyl methyl derivatives were obtained in the presence of sodium hydroxide or sodium ethoxide in our laboratories [8,30,31]. The 1,2,4-triazol-5-one compounds containing a hydrazide structure are useful intermediates for further reactions. The -NH_2 group of the hydrazide structure behaves as a good nucleophile in most reactions leading to the formation of new heterocyclic rings such as 1,3,4-oxadiazole, 1,2,4-triazole, 1,3,4-thiadiazole or 1,2,4,5-triazines [8,25,32]. In addition, we achieved the synthesis of some triazolethiadiazines and triazolothiadiazoles using the 4-amino-1*H*-1,2,4-triazol-5-one ring containing acid hydrazides *via* the formation of 4-amino-1,2,4-triazol-3-thiones. The amino and mercapto groups on 4-amino-1,2,4-triazol-3-thiones are ready-made nucleophilic centers for the synthesis of condensed heterocyclic rings [25].

The general method leading to the formation of thiazolidinones generally includes the reaction of an aromatic amine with substituted benzaldehide in the presence of mercaptoacetic acid [15-17] or the reaction of amines with isothiocyanates [18]. In addition, the method reported recently for the synthesis of thiazolidinones involves the reactions of thiosemicarbazides with

chloroacetic acid [13]. The traditional method for the preparation of oxazolidinones involves the transformation of amino alcohols to cyclic carbamates using various condensation reagents [33,34]. In the another method, the oxazolidinone ring was formed by reacting carbamic acid mono- or diesters with *n*-butyl lithium at -78°C followed by addition of glycidyl butyrate [21,35-38]. Other methods for the preparation of oxazolidinones involves the transition metal catalyzed fixation of CO_2 to propergylamine [39], Diels-Alder cycloaddition reactions of vinyl sulfonylamides as dienophiles [40,41], enzymatic desymmetrisation of diols [42] or ring expansion of aziridines to oxazolidines [21].

In view of these facts, we aimed to prepare 1,2,4-triazol-5-ones involving another heterocyclic ring such as 1,2,4-triazole, 1,3,4-thiadiazole, 1,3-thiazoline, 1,3-oxazoline, 1,3-thiazolidin-4-one and 1,3-oxazolidin-4-one rings as possible biological active compounds.

RESULTS AND DISCUSSION

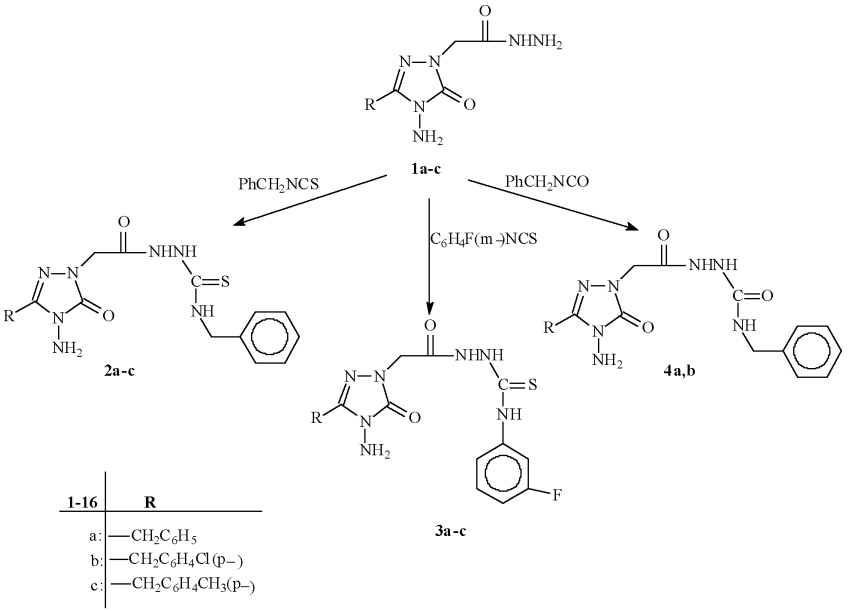
1-(4-Amino-3-alkyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)acetyl-4-alkyl thiosemi-carbazides (**2a-c** and **3a-c**) and 1-(4-amino-3-alkyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-acetyl-4-benzyl semicarbazides (**4a,b**) were obtained from the reaction of 2-(4-amino-3-alkyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)acetohyrazides (**1a-c**) with benzylisothiocyanate,3-florophenylisothiocyanate or benzylisocyanate, respectively (Scheme 1). In the ^1H and ^{13}C NMR spectra of compounds **2a-c**, **3a-c** and **4a,b**, new signals due to the 4-alkyl thiosemicarbazide (or semicarbazide) group are observed.

The synthesis of 4-amino-3-alkyl-2-[(5-mercapto-4-benzyl(or 3-florophenyl)-4*H*-1,2,4-triazol-3-yl)methyl]-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**5a-c** and **6a-c**) was performed by the reaction of compounds **2a-c** (or **3a-c**) with NaOH, while the NaOH treatment of compound **4a** afforded compounds (**7**) having two 5-oxo-1,2,4-triazole rings.

In addition, the mass spectra and elemental analysis of compounds **2**, **3** and **4** were consistent with their structures.

These reactions began with the nucleophilic attack of thiosemicarbazide (or semicarbazide)-N-4 to carbonyl group in side change of compounds **2a-c**, **3a-c** and **4a**. The structures of compounds **5a-c, 6a-c** and **7** were confirmed on the basis of elemental analysis, IR, ^1H NMR, ^{13}C NMR and mass spectroscopic methods. In the ^1H NMR spectra of compounds **5** and **6** the signal belonging to –SH group appeared at 13.86-13.98 ppm resonated for one proton (changeable with D_2O), while the signals derived from three –NH- groups of compounds **2, 3** and **4** were not observed. The signal belonging to the –NH_2 group on 1,2,4-triazole ring was recorded at about 5-20-5.30 ppm as consistent with the values reported in literature (Scheme 1) [6-9].

The synthesis of 4-amino-3-alkyl-2-[(5-mercapto-4-benzyl(or 3-florophenyl)-4*H*-1,2,4-triazol-3-yl)methyl]-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**5a-c** and **6a-c**) was performed by the reaction of compounds **2a-c** (or **3a-c**) with NaOH, while the NaOH treatment of compound **4a** afforded the compounds (**7**) having two 5-oxo-1,2,4-triazole rings. These reactions began with the nucleophilic attack of thiosemicarbazide (or semicarbazide)-N-4 to carbonyl group in the side chains of compounds **2a-c**, **3a-c** and **4a**. The structures of compounds **5a-c, 6a-c** and **7** were confirmed on the basis of elemental analysis, IR, ^1H



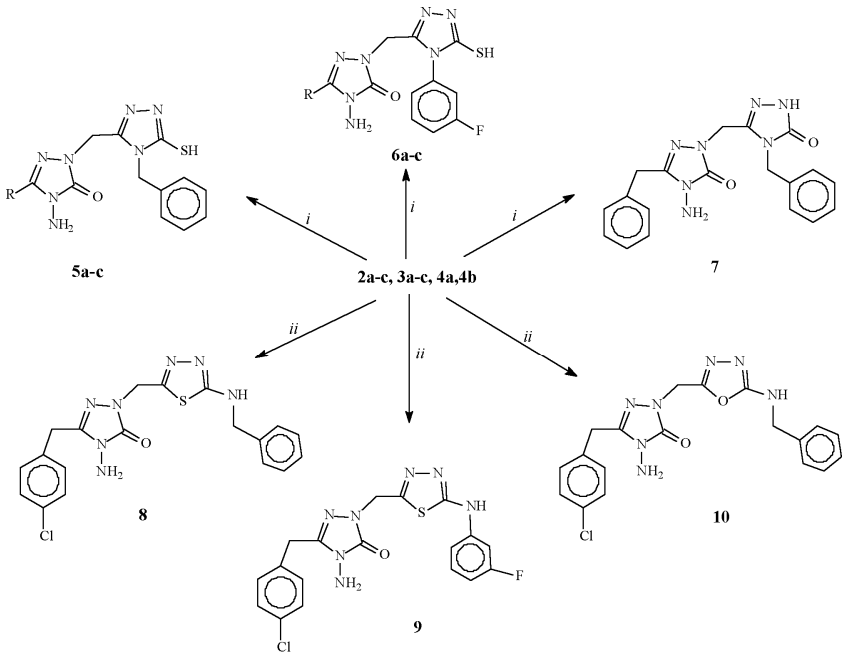
Scheme 1: Synthetic rout for the preparation of compounds **2-4**.

NMR, ^{13}C NMR and mass spectroscopic methods. In the ^{1}H NMR spectra of compounds **5** and **6** the signal belonging to –SH group appeared at 13.86-13.98 ppm resonated for one proton (changeable with D_2O), while the signals derived from three –NH- groups of compounds **2**, **3** and **4** were not observed. The signal belonging to $-NH_2$ group on 1,2,4-triazole ring was recorded about 5-20-5.30 ppm as consistent with the values reported in literature (Scheme 2) [6-9].

The treatment of compounds **2b, 3b** and **4b** with concentrated H_2SO_4 resulted in an intramolecular cyclization leading to the formation the of 1,3,4-thiadiazole ring, thus, compounds **8**, **9** and **10** were obtained. The reactions involved the nucleophilic attack of sulfur atom on C=S group to carbonyl group in side change of compounds **2b**, **3b** and **4b**. The –NH- signals of compounds **8**, **9** and **10** appeared at the higher field, about 10.40-10.42 ppm, than the –SH signals of isomer compounds **5c, 6c** and **7**. These signals were verified by exchanging with D_2O.

Compounds **11a-c, 12** and **13** were synthesized by the reactions of compounds **2a-c, 3c** or **4b** with 4-chlorophenacyl bromide in the presence of dried sodium acetate. On the other hand, the chloroacetic acid treatment of compounds **2a-c, 3b** or **4a,b** produced 2-(4-amino-3-alkyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-*N*'-[3-alkyl-4-oxo-1,3-thiazolylidin(or oxazolidin)-2-yliden]acetohydrazides (**14a-c, 15** and **16a,b**). The reactions leading to the formation of compounds **11-16** began with nucleophilic attach of N-4 of thiosemicarbazide (**2a-c** or **3a-c**) or semicarbazide (**4a,b**) derivatives at the carbonyl group of 4-chlorophenacyl bromide (for compounds **11a-c, 12** and **13**) or chloroacetic acid (for compounds **14a-c, 15** and **16a,b**) following the elimination of H_2O and HX. A halogen atom and carbonyl structure on adjacent positions is essential for H_2O and HX eliminations (Scheme 3).

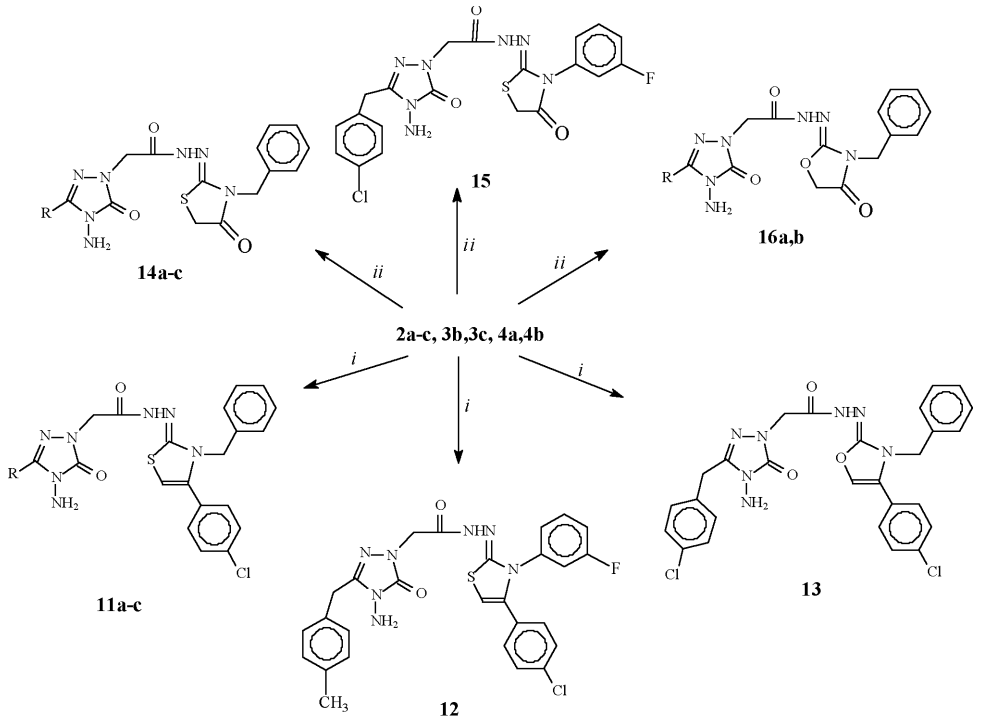
The IR spectra of compounds **14a-c, 15** and **16a,b** displayed additional C=O absorption different from those



Scheme 2: Reagents for the preparation of compounds **5-10**: *i*: NaOH, *ii*: H_2SO_4.

The treatment of compounds **2b, 3b** and **4b** with concentrated H_2SO_4 resulted in an intramolecular cyclization leading to the formation of the 1,3,4-thiadiazole ring, thus, compounds **8**, **9** and **10** were obtained. The reactions involved the nucleophilic attack of sulfur atom on C=S group to carbonyl group in side change of compounds **2b**, **3b** and **4b**. The –NH- signals of compounds **8**, **9** and **10** appeared at the higher field, about 10.40-10.42 ppm, than the –SH signals of isomer compounds **5c, 6c** and **7**. Again, these signals were verified by exchanging with D_2O.

of compounds **11a-c, 12** and **13**. The proton signals belonging to C-5-H of 1,3-thiazole (or 1,3-oxazole) ring on compounds **11a-c, 12** and **13** were observed in the ethylenic region, between 4.62-5.03 ppm, while the signals derived from C-5-H of thiazolidin (or oxazolidin) ring of compounds **14a-c**, **15** and **16a,b** were observed between 3.38-3.87 ppm. Moreover, ^{13}C NMR signals due to C-5 carbon of compounds **11a-c, 12** and **13** resonated at 125.96-134.64 ppm, while the corresponding carbon signals of compounds **14a-c**, **15** and **16a,b** were observed



Scheme 3: Synthetic pathway for the preparation of compounds **11-16**. *i*: $BrCH_2COC_6H_4Cl(p-)$, *ii*: $ClCH_2COOH$

within DMSO-d_6 signals at about 38.50-40.10 ppm, in the ^{13}C NMR spectra. In addition, Compounds **8-13** displayed molecular ion peaks consisting of their structures.

The triazole-C-3 and triazole C-5 carbons of all newly synthesized compounds resonated about 140-150 ppm and 152-154 ppm, respectively, in the ^{13}C NMR spectra. These chemical shifts are consistent with the values reported in literature [6-9,18,19,33]. Moreover, all elemental analyses of new compounds are consistent with their assigned structures.

EXPERIMENTAL

Instrumentation. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. ^1H NMR and ^{13}C NMR (as APT and Dept) spectra were recorded on a Varian-Mercury 200 MHz spectrometer. The IR spectra were measured as potassium bromide pellets using a Perkin-Elmer 1600 series FTIR spectrometer. Mass spectra were obtained using a Quattro LC-MS (70 eV) Instrument (except compounds **3a-c, 5a, 5b, 6a, 6c, 7, 8, 10, 15**). Combustion analysis was performed on a Carlo Erba 1106 elemental analyzer. All the chemicals were obtained from Fluka Chemie AG Buchs (Switzerland). Compounds **1a-c** were synthesized by published methods [7].

General method for the synthesis of compounds 2a-c, 3a-c and 4a,b. A mixture of corresponding compound **1** (10 mmol) and benzyl isothiocyanate (1.49 g, 10 mmol) (for compounds **2**), 3-florophenylisothiocyanate (1.53 g, 10 mmol) (for compounds **3**) or benzylisocyanate (1.33 g, 10 mmol) (for compounds **4**) was refluxed in ethanol for 3 h. Then, the solution was cooled to room temperature and a white solid appeared, which was collected by filtration and recrystallized from ethanol (**2a, 2b, 3a, 3b, 4a, 4b**) or dimethyl sulfoxide-water (1:1) (**2c** and **3c**) to afford the desired compound.

1-(4-Amino-3-benzyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)acetyl-4-benzyl thiosemicarbazide (2a). This compound was obtained as colorless needles (yield: 3.52 g, 85.64 %); m.p. 186°C; ir (KBr) (ν, cm^{-1}): 3327-3214 (NH_2), 3167 (3NH), 1720 and 1680 (2C=O), 1576 (C=N), 1196 (C=S); ^1H nmr (DMSO-d6, δ ppm): 3.82 (s, benzylic CH_2), 4.43 (s, NCH_2), 4.72 (s, $NHCH_2$), 5.33 (s, NH_2), 7.28 (bs, 10H, arom-H), 8.59 (bs, NH), 9.49 (bs, NH), 10.37 (s, NH); ^{13}C NMR (DMSO-d_6, δ ppm): 30.21 (CH_2), 38.10-40.59 ($NHCH_2$+DMSO-d_6), 46.46 (NCH_2), arom-C: [126.52 (2CH), 126.80 (2CH), 127.96 (2CH), 128.29 (2CH), 128.71 (2CH), 135.65 (C), 139.04 (C)], 146.90 (triazole-C-3), 153.33 (triazole-C-5), 166.46 (C=O), 181.62 (C=S); ms: m/z (%) 412 (M^+, 100), 264 (12), 263 (12), 154 (19), 126 (11), 119 (12). *Anal.* Calcd. (%) for $C_{19}H_{21}N_7O_2S$: C, 55.46; H, 5.14, N, 23.83. Found; C, 55.59; H, 5.19; N, 24.02.

1-[4-Amino-3-(4-chlorobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetyl-4-benzyl thiosemicarbazide (2b). This compound was obtained as colorless powder (yield: 3.88 g, 87.01 %); m.p. 155°C; ir (KBr) (ν, cm^{-1}): 3324-3230 (NH_2), 3169 (3NH), 1718 and 1686 (2C=O), 1546 (C=N), 1197 (C=S); ^1H nmr (DMSO-d_6, δ ppm): 3.87 (s, benzylic CH_2), 4.42 (s, NCH_2), 4.74 (s, $NHCH_2$), 5.33 (s, NH_2), 7.27-7.38 (m, 9H, arom-H), 8.59 (bs, NH), 9.49 (bs, NH), 10.37 (s, NH); ^{13}C nmr (DMSO-d_6, δ ppm): 30.20 (CH_2), 38.12-40.59 ($NHCH_2$+DMSO-d_6), 46.45 (NCH_2), arom-C: [126.51

(2CH), 126.88 (2CH), 127.92 (2CH), 128.36 (2CH), 128.71 (CH), 135.65 (C), 139.04 (C), 143.17 (C)], 146.90 (triazole-C-3), 153.37 (triazole-C-5), 166.48 (C=O), 181.62 (C=S); ms: *m/z* (%) 446 (M^+, 38), 361 (28), 359 (53), 337 (19), 305 (22), 304 (100), 282 (34), 101 (25). *Anal*. Calcd. (%) for $C_{19}H_{20}ClN_7O_2S$: C, 51.18; H, 4.52; N, 21.72. Found: C, 51.19; H, 4.57; N, 21.99.

1-[4-Amino-3-(4-tolyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetyl-4-benzyl thiosemicarbazide (2c). This compound was obtained as colorless needles (yield: 3.54 g, 83.09 %); m.p. < 300 °C; ir (KBr) (ν, cm^{-1}): 3324-3214 (NH_2), 3189 (3NH), 1720 and 1686 (2C=O), 1543 (C=N), 1196 (C=S); ^{1}H nmr (DMSO-d_6, δ ppm): 2.11 (s, CH_3), 3.81 (s, benzylic CH_2), 4.43 (s, NCH_2), 4.70 (s, $NHCH_2$), 5.30 (s, NH_2), 7.32 (bs, 9H, arom-H), 8.58 (bs, NH), 9.49 (bs, NH), 10.35 (s, NH); ^{13}C nmr (DMSO-d_6, δ ppm): 21.65 (CH_3), 30.21 (CH_2), 38.10-40.60 ($NHCH_2$+DMSO-d_6), 46.46 (NCH_2), arom-C: [125.31 (2CH), 126.58 (2CH), 127.96 (2CH), 128.33 (2CH), 128.72 (CH), 135.65 (C), 139.04 (C), 139.79 (C)], 146.84 (triazole-C-3), 153.34 (triazole-C-5), 166.46 (C=O), 181.68 (C=S); ms: *m/z* (%) 426 (M^+, 28), 396 (12), 318 (12), 317 (66), 296 (19), 277 (28), 249 (34), 232 (39), 217 (100), 205 (53), 159 (53), 105 (36). *Anal*. Calcd. (%) for $C_{20}H_{23}N_7O_2S$: C, 56.45; H, 5.45; N, 23.04. Found: C, 56.39; H, 5.36; N, 22.82.

1-(4-Amino-3-benzyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)acetyl-4-(3-florophenyl)thiosemicarbazide (3a). This compound was obtained as colorless needles (yield: 3.59 g, 86.41 %); m.p. 155°C; ir (KBr) (ν, cm^{-1}): 3325-3217 (NH_2), 3169 (3NH), 1721 and 1688 (2C=O), 1579 (C=N), 1196 (C=S); ^{1}H nmr (DMSO-d_6, δ ppm): 3.80 (s, benzylic CH_2), 4.41 (s, NCH_2), 5.38 (s, NH_2), 7.20-7.38 (m, 9H, arom-H), 8.61 (bs, NH), 9.50 (bs, NH), 10.59 (s, NH); ^{13}C nmr (DMSO-d_6, δ ppm): 30.22 (CH_2), 46.49 (NCH_2), arom-C: [126.71 (2CH), 126.80 (2CH), 127.84 (CH), 128.33 (2CH), 128.70 (2CH), 136.69 (C), 138.14 (C), 140.07 (C)], 145.68 (triazole-C-3), 154.38 (triazole-C-5), 166.35 (C=O), 181.60 (C=S). *Anal*. Calcd. (%) for $C_{18}H_{18}FN_7O_2S$: C, 52.04; H, 4.37; N, 23.60. Found: C, 52.26; H, 4.38; N, 23.52.

1-[4-Amino-3-(4-chlorobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-acetyl-4-(3-florophenyl)thiosemicarbazide (3b). This compound was obtained as colorless needles (yield: 3.91 g, 86.88 %); m.p. 168°C; ir (KBr) (ν, cm^{-1}): 3325-3219 (NH_2), 3157 (3NH), 1720 and 1684 (2C=O), 1609 (C=N), 1195 (C=S); ^{1}H nmr (DMSO-d_6, δ ppm): 3.80 (s, benzylic CH_2), 4.45 (s, NCH_2), 5.27 (s, NH_2), 7.21-7.32 (m, 8H, arom-H), 8.61 (bs, NH), 9.59 (bs, NH), 10.03 (s, NH); ^{13}C nmr (DMSO-d_6, δ ppm): 31.60 (CH_2), 46.46 (NCH_2), arom-C: [126.83 (2CH), 126.90 (2CH), 127.24 (2CH), 128.61 (CH), 128.79 (CH), 134.69 (C), 138.16.07 (C), 139.42 (C), 140.83 (C)], 145.62 (triazole-C-3), 154.21 (triazole-C-5), 166.17 (C=O), 182.03 (C=S). *Anal*. Calcd. (%) for $C_{18}H_{17}ClFN_7O_2S$: C, 48.05; H, 3.81; N, 21.79. Found: C, 48.26; H, 3.89; N, 22.01.

1-[4-Amino-3-(4-tolyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetyl-4-(3-florophenyl)thiosemicarbazide (3c). This compound was obtained as colorless needles (yield: 3.72 g, 86.57 %); m.p. 187°C; ir (KBr) (ν, cm^{-1}): 3331-3210 (NH_2), 3155 (3NH), 1722 and 1681 (2C=O), 1613 (C=N), 1198 (C=S); ^{1}H nmr (DMSO-d_6, δ ppm): 2.04 (CH_3), 3.25 (s, benzylic CH_2), 4.61 (s, NCH_2), 5.31 (s, NH_2), 7.17-7.28 (m, 8H, arom-H), 8.87 (bs, NH), 9.41 (bs, NH), 9.75 (s, NH); ^{13}C nmr (DMSO-d_6, δ ppm): 20.13 (CH_3), 32.41 (CH_2), 46.47 (NCH_2), arom-C: [126.17 (CH), 126.68 (2CH), 127.45 (2CH), 127.37 (2CH), 127.74 (CH), 134.16 (C), 138.16.07 (2C), 140.15 (C)], 146.13 (triazole-C-3), 154.62 (triazole-C-5), 166.17 (C=O), 182.05 (C=S). *Anal*. Calcd. (%) for $C_{19}H_{20}FN_7O_2S$: C, 53.14; H, 4.69; N, 22.83. Found: C, 53.39; H, 4.69; N, 22.72.

1-(4-Amino-3-benzyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)acetyl-4-benzyl semicarbazide (4a). This compound was obtained as colorless needles (yield: 2.82 g,71.32 %); m.p. 153°C; ir (KBr) (ν, cm^{-1}): 3314-3207 (NH_2), 3107 (3NH), 1721, 1702 and 1684 (3C=O), 1561 (C=N); ^{1}H nmr (DMSO-d_6, δ ppm): 3.67 (s, benzylic CH_2), 4.61 (s, NCH_2), 4.78 (s, $NHCH_2$), 5.38 (s, NH_2), 7.15-7.43 (m, 10H, arom-H), 8.23 (bs, NH), 9.64 (bs, NH), 11.16 (s, NH); ^{13}C nmr (DMSO-d_6, δ ppm): 33.36 (CH_2), 38.11-40.25 ($NHCH_2$ + DMSO-d_6), 46.75 (NCH_2), arom-C: [125.33 (2CH), 125.89 (2CH), 128.17 (2CH), 128.76 (2CH), 129.84 (2CH), 136.65 (C), 138.56 (C)], 144.64 (triazole-C-3), 154.28 (triazole-C-5), 166.46 and 169.13 (2C=O); ms: *m/z* (%) 395 (M^+, 15), 368 (11), 357 (11), 325 (19), 304 (15), 303 (64), 299 (16), 236 (15), 208 (15), 186 (100). *Anal*. Calcd. (%) for $C_{19}H_{21}N_7O_3$: C, 57.71; H, 5.35; N, 24.80. Found: C, 57.89; H, 5.37; N, 24.80.

1-[4-Amino-3-(4-chlorobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetyl-4-benzyl semicarbazide (4b). This compound was obtained as colorless needles (yield: 3.17 g, 73.75 %); m.p. 173°C; ir (KBr) (ν, cm^{-1}): 3314-3209 (NH_2), 3113 (3NH), 1720, 1702 and 1685 (3C=O), 1584 (C=N); ^{1}H nmr (DMSO-d_6, δ ppm): 3.54 (s, benzylic CH_2), 4.60 (s, NCH_2), 4.74 (s, $NHCH_2$), 5.30 (s, NH_2), 7.18-7.32 (m, 9H, arom-H), 8.61 (bs, NH), 9.36 (bs, NH), 10.71 (s, NH); ^{13}C nmr (DMSO-d_6, δ ppm): 33.39 (CH_2), 38.10-40.27 ($NHCH_2$ + DMSO-d_6), 46.57 (NCH_2), arom-C: [126.25 (CH), 126.13 (3CH), 127.71 (2CH), 128.68 (2CH), 129.76 (CH), 136.65 (C), 138.56 (C), 138.68 (C)], 144.64 (triazole-C-3), 154.31 (triazole-C-5), 166.45 and 168.47 (2C=O); ms: *m/z* (%) 430 (M+1, 31), 376 (20), 299 (26), 297 (74), 252 (19), 237 (34), 225 (22), 157 (94), 130 (100). *Anal*. Calcd. (%) for $C_{19}H_{20}ClN_7O_3$: C, 53.09; H, 4.69; N, 22.81. Found: C, 53.17; H, 4.65; N, 22.70.

General method for the synthesis of compounds 5, 6 and 7. A solution of corresponding thiosemicarbazide (**2** or **3**) or semicarbazide (**4**) (10 mmol) in 2 *N* NaOH was refluxed for 3 h. The resulting solution was cooled to room temperature and acidified to pH 3-4 with 37% HCl. The precipitate formed was collected by filtration, washed with water and recrystallized from ethanol (**5b, 6a, 6b, 7a**) or dimethyl sulfoxide (1:1) (**5a, 5c, 6c**).

4-Amino-3-benzyl-1-[4-benzyl-5-mercapto-4*H*-1,2,4-triazol-3-yl)methyl]-4,5-dihydro-*1H*-1,2,4-triazol-5-one (5a). This compound was obtained as colorless needles (yield: 2.92 g, 74.11 %); m.p. 235°C; ir (KBr) (ν, cm^{-1}): 3327-3204 (NH_2), 2772 (SH), 1720 and 1682 (2C=O), 1618 (C=N), 1256 (C=S); ^{1}H nmr (DMSO-d_6, δ ppm): 3.64 (s, benzylic CH_2), 4.92 (s, NCH_2), 5.01 (s, NCH_2), 5.22 (s, NH_2), 7.03-7.33 (m, 10H, arom-H), 13.97 (s, SH); ^{13}C nmr (DMSO-d_6, δ ppm): 29.99 (CH_2), 38.49-40.16 (NCH_2+DMSO-d_6), 45.70 (NCH_2), arom-C: [126.14 (2CH), 126.53 (CH), 127.30 (CH), 128.10 (2CH), 128.28 (2CH), 128.65 (2CH), 134.72 (C), 135.37 (C)], 147.37 (triazole-C-3), 147.96 (triazole-C-3'), 152.46 (triazole-C-5), 168.11 (triazole-C-5'); ms: *m/z* (%) 394 (M^+, 28), 354 (19), 152 (22), 130 (19), 129 (100), 104 (22), 103 (31), 102 (34). *Anal*. Calcd. (%) for $C_{19}H_{19}N_7OS$: C, 58.00; H, 4.87; N, 24.92. Found: C, 58.25; H, 4.89; N, 24.76.

4-Amino-3-(4-chlorobenzyl)-1-[(4-benzyl-5-mercapto-4*H*-1,2,4-triazol-3-yl)methyl]-4,5-dihydro-1*H*-1,2,4-triazol-5-one

(5b). This compound was obtained as colorless needles (yield: 3.06 g, 71.34 %); m.p. 252°C; ir (KBr) (ν, cm^{-1}): 3322-3206 (NH_2), 2778 (SH), 1724 and 1682 (2C=O), 1611 (C=N), 1253 (C=S); ^{1}H nmr (DMSO-d_6, δ ppm): 3.56 (s, benzylic CH_2), 4.90 (s, NCH_2), 5.07 (s, NCH_2), 5.34 (s, NH_2), 7.08-7.41 (m, 9H, arom-H), 13.94 (s, SH); ^{13}C nmr (DMSO-d_6, δ ppm): 31.86 (CH_2), 38.50-40.21 (NCH_2+DMSO-d_6), 46.77 (NCH_2), arom-C: [126.11 (2CH), 126.39 (CH), 127.05 (CH), 128.10 (2CH), 128.66 (2CH), 128.75 (CH), 134.72 (C), 135.37 (C), 137.93 (C)], 147.65 (triazole-C-3), 147.81 (triazole-C-3'), 153.07 (triazole-C-5), 167.96 (triazole-C-5'). *Anal.* Calcd. (%) for $C_{19}H_{18}ClN_7OS$: C, 53.33; H, 4.24; N, 22.91. Found: C, 53.64; H, 4.26; N, 22.75.

4-Amino-3-(4-tolyl)-1-[(4-benzyl-5-mercapto-4*H*-1,2,4-triazol-3-yl)methyl]-4,5-dihydro-1*H*-1,2,4-triazol-5-one (5c). This compound was obtained as colorless needles (yield: 2.92 g, 71.65 %); m.p. 260°C; ir (KBr) (ν, cm^{-1}): 3335-3213 (NH_2), 2772 (SH), 1720 and 1685 (2C=O), 1576 (C=N), 1256 (C=S); ^{1}H nmr (DMSO-d_6, δ ppm): 2.27 (s, CH_3), 3.61 (s, benzylic CH_2), 4.92 (s, NCH_2), 5.04 (s, NCH_2), 5.28 (s, NH_2), 7.11-7.37 (m, 9H, arom-H), 13.97 (s, SH); ^{13}C nmr (DMSO-d_6, δ ppm): 20.35 (CH_3), 31.84 (CH_2), 38.53-40.29 (NCH_2+DMSO-d_6), 45.14 (NCH_2), arom-C: [125.68 (2CH), 126.21 (CH), 127.05 (CH), 128.13 (2CH), 128.47 (2CH), 128.66 (CH), 134.70 (C), 135.37 (C), 136.84 (C)], 147.47 (triazole-C-3), 148.21 (triazole-C-3'), 154.19 (triazole-C-5), 167.95 (triazole-C-5'). *Anal.* Calcd. (%) for $C_{20}H_{21}N_7OS$: C, 58.95; H, 5.19; N, 24.06. Found: C, 59.19; H, 5.19; N, 24.00.

4-Amino-3-benzyl-1-{[(4-(3-florophenyl)-5-mercapto-4*H*-1,2,4-triazol-3-yl]methyl}-4,5-dihydro-1*H*-1,2,4-triazol-5-one (6a). This compound was obtained as colorless needles (yield: 2.47 g, 62.15 %); m.p. 237°C; °C; ir (KBr) (ν, cm^{-1}): 3351-3205 (NH_2), 2774 (SH), 1706 and 1685 (2C=O), 1574, 1517 and 1499 (3C=N), 1228 (C=S); ^{1}H nmr (DMSO-d_6, δ ppm): 3.80 (s, benzylic CH_2), 4.81 (s, NCH_2), 5.18 (s, NH_2), 7.22-7.42 (m, 9H, arom-H), 13.95 (s, SH); ^{13}C nmr (DMSO-d_6, δ ppm): 29.56 (CH_2), 40.19-40.67 (NCH_2+DMSO-d_6), arom-C: [115.88 (CH), 116.74 (CH), 125.84 (CH), 127.62 (C), 128.90 (2CH), 130.54 (2CH), 130.83 (2CH), 134.55 (C), 135.03 (C)], 147.48 (triazole-C-3), 147.65 (triazole-C-3'), 152.24 (triazole-C-5), 168.36 (triazole-C-5'). *Anal.* Calcd. (%) for $C_{18}H_{16}FN_7OS$: C, 54.40; H, 4.06; N, 24.64. Found: C, 54.69; H, 4.12; N, 24.48.

4-Amino-3-(4-chlorobenzyl)-1-{[(4-(3-florophenyl)-5-mercapto-4*H*-1,2,4-triazol-3-yl]methyl}-4,5-dihydro-1*H*-1,2,4-triazol-5-one (6b). This compound was obtained as colorless needles (2.88 g, 66.89 %); m.p. 248°C; ir (KBr) (ν, cm^{-1}): 3357-3192 (NH_2), 2774 (SH), 1703 and 1689 (2C=O), 1574, 1511 and 1493 (3C=N), 1228 (C=S); ^{1}H nmr (DMSO-d_6, δ ppm): 3.80 (s, benzylic CH_2), 4.81 (s, NCH_2), 5.18 (s, NH_2), 7.22-7.42 (m, 9H, arom-H), 13.97 (s, SH); ^{13}C nmr (DMSO-d_6, δ ppm): 29.43 (CH_2), 40.16-40.58 (NCH_2+DMSO-d_6), arom-C: [115.83 (CH), 116.29 (CH), 128.21 (CH), 128.98 (C), 129.92 (2CH), 130.54 (3CH), 131.27 (C), 134.50 (2C)], 147.48 (triazole-C-3), 147.58 (triazole-C-3'), 152.21 (triazole-C-5), 168.41 (triazole-C-5'); ms: *m/z* (%) 432 (M^+, 19), 417 (88), 414 (88), 325 (44), 304 (100), 114 (47). *Anal.* Calcd. (%) for $C_{18}H_{15}ClFN_7OS$: C, 50.06; H, 3.50; N, 22.70. Found: C, 50.24; H, 3.52; N, 22.78.

4-Amino-3-(4-tolyl)-1-{[(4-(3-florophenyl)-5-mercapto-4*H*-1,2,4-triazol-3-yl]methyl}-4,5-dihydro-1*H*-1,2,4-triazol-5-one (6c). This compound was obtained as colorless needles (yield: 2.72 g, 66.11 %); m.p. 275°C; ir (KBr) (ν, cm^{-1}): 3357-3190 (NH_2), 2771 (SH), 1711 and 1685 (2C=O), 1572, 1510 and 1493 (3C=N), 1228 (C=S); ^{1}H nmr (DMSO-d_6, δ ppm): 1.97 (s, CH_3), 3.83 (s, benzylic CH_2), 4.88 (s, NCH_2), 5.24 (s, NH_2), 7.20-7.37 (m, 8H, arom-H), 13.98 (s, SH); ^{13}C nmr (DMSO-d_6, δ ppm): 29.47 (CH_2), 40.14-40.58 (NCH_2+DMSO-d_6), arom-C: [115.83 (CH), 116.34 (CH), 125.64 (2CH), 128.98 (C), 129.67 (2CH), 131.17 (2CH), 131.28 (C), 134.56 (C), 135.68 (C)], 147.48 (triazole-C-3), 147.55 (triazole-C-3'), 153.61 (triazole-C-5), 168.39 (triazole-C-5'). *Anal.* Calcd. (%) for $C_{19}H_{18}FN_7OS$: C, 55.46; H, 4.41; N, 23.83. Found: C, 55.34; H, 4.50; N, 23.79.

4-Amino-3-benzyl-1-[4-benzyl-5-oxo-4*H*-1,2,4-triazol-3-yl)methyl]-4,5-dihydro-1*H*-1,2,4-triazol-5-one (7). This compound was obtained as colorless needles (Yield: 2.63 g, 69.68 %); m.p. 226°C; ir (KBr) (ν, cm^{-1}): 3364-3216 (NH_2), 1720, 1704 and 1682 (3C=O), 1611 (C=N); ^{1}H nmr (DMSO-d_6, δ ppm): 3.67 (s, benzylic CH_2), 4.72 (s, NCH_2), 4.78 (s, NCH_2), 5.05 (s, NH_2), 7.03-7.32 (m, 10H, arom-H), 13.86 (s, NH); ^{13}C nmr (DMSO-d_6, δ ppm): 30.06 (CH_2), 38.48-40.46 (NCH_2+DMSO-d_6): 43.10 (NCH_2), arom-C: [126.10 (2CH), 126.52 (CH), 127.21 (CH), 128.21 (2CH), 128.28 (2CH), 128.63 (2CH), 135.44 (C), 136.04 (C)], 142.92 (triazole-C-3), 147.26 (triazole-C-3'), 152.51 (triazole-C-5), 155.08 (triazole-C-5'). *Anal.* Calcd. (%) for $C_{19}H_{19}N_7O_2$: C, 60.47; H, 5.07; N, 25.98. Found: C, 60.60; H, 5.26; N, 25.77

General method for the synthesis of compounds 8, 9 and 10. A mixture of corresponding thiosemicarbazide (**2b** or **3b**) (10 mmol) or semicarbazide (**4b**), in cold concentrated sulfuric acid (28 mL) was stirred for 10 min. then, the mixture was allowed to reach room temperature. After stirring for an additional 30 min., the resulting solution was poured into ice-cold water and made alkaline to pH 8 with ammonia. The precipitated product was collected by filtration, washed with water and recrystallized from ethanol to afford pure compounds.

4-Amino-3-(4-chlorobenzyl)-1-[(5-benzylamino-1,3,4-thidazol-2-yl)methyl]-4,5-dihydro-1*H*-1,2,4-triazol-5-one (8). This compound was obtained as colorless needles (yield: 3.26 g, 76.24 %); m.p. 228 °C; ir (KBr) (ν, cm^{-1}): 3337-3231 (NH_2+NH), 1720 (C=O), 1655, 1590 and 1566 (3C=N); ^{1}H nmr (DMSO-d_6, δ ppm): 3.05 (s, benzylic CH_2), 3.90 (s, NCH_2), 4.23 (s, $NHCH_2$), 5.25 (s, NH_2), 7.21-7.34 (m, 7H, arom-H), 7.37-7.60 (m, 2H, arom H), 10.41 (s, NH); ^{13}C nmr (DMSO-d_6, δ ppm): 30.01 (CH_2), 42.53 ($NHCH_2$), 44.76 (NCH_2) arom-C: [127.28 (2CH), 127.66 (2CH), 128.12 (2CH), 129.41 (2CH), 131.96 (CH), 133.75 (C), 135.04 (C), 137.41 (C)], 142.49 (triazole-C-3), 154.11 (triazole-C-5), 154.46 (thiadiazole-C-2), 165.27 (thiadiazole-C-5). *Anal.* Calcd. (%) for $C_{19}H_{18}ClN_7OS$: C, 53.33; H, 4.24; N, 22.91. Found: C, 53.33; H, 4.20; N, 22.83.

4-Amino-3-(4-chlorobenzyl)-1-({[(5-(3-florophenyl)amino]-1,3,4-thidazol-2-yl}-methyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (9). This compound was obtained as colorless needles (yield: 3.29 g, 76.24 %); m.p. 198°C; ir (KBr) (ν, cm^{-1}): 3328-3217 (NH_2 + NH), 1721 (C=O), 1655 and 1566 (3C=N); ^{1}H nmr (DMSO-d_6, δ ppm): 3.04 (s, benzylic CH_2), 3.91 (s, NCH_2), 5.14 (s, NH_2), 7.15-7.35 (m, 6H, arom-H), 7.38-7.64 (m, 2H, arom H), 10.40 (s, NH); ^{13}C nmr (DMSO-d_6, δ ppm): 30.04 (CH_2), 44.76 (NCH_2) arom-C: [127.21 (CH), 127.35 (2CH), 128.14 (2CH), 128.67 (2CH), 130.43 (CH), 131.66 (2C), 135.04 (2C)], 144.93 (triazole-C-3), 153.15 (triazole-C-5), 154.17 (thiadiazole-C-2), 165.25 (thiadiazole-C-5); ms: *m/z* (%) 432 (M^+, 53), 415 (22), 376 (25), 359 (23), 305 (22), 304 (81), 303 (22), 282 (20), 225 (28), 281 (20), 207 (39), 154 (31), 149 (31), 136 (24), 125 (34), 117 (66), 115 (100). *Anal.* Calcd. (%) for

$C_{18}H_{15}ClFN_7OS$: C, 50.06; H, 3.50; N, 22.70. Found: C, 50.14; H, 3.51; N, 22.67.

4-Amino-3-(4-chlorobenzyl)-1-{[5-(benzylamino)-1,3,4-oxazol-2-yl]methyl}-4,5-dihydro-1*H*-1,2,4-triazol-5-one (10). This compound was obtained as colorless needles (yield: 2.89 g, 70.36 %); m.p. 223°C; ir (KBr) (ν, cm^{-1}), 3315-3201 (NH_2+ NH), 1699 (C=O), 1573, 1501 and 1498 (3C=N); ^{1}H nmr (DMSO-d_6, δ ppm): 3.21 (s, benzylic CH_2), 4.29 (s, NCH_2), 5.02 (s, $NHCH_2$), 5.31 (s, NH_2), 7.00-7.23 (m, 7H, arom-H), 7.25-7.39 (m, 2H, arom H), 10.42 (s, NH); ^{13}C nmr (DMSO-d_6, δ ppm): 30.21 (CH_2), 43.81 ($NHCH_2$), 45.32 (NCH_2) arom-C: [121.91 (2CH), 123.63 (2CH), 126.58 (2CH), 128.34 (2CH), 129.02 (CH), 133.75 (C), 135.59 (C), 140.37 (C)], 146.80 (triazole-C-3), 152.62 (triazole-C-5), 154.11 (thiadiazole-C-2), 165.31 (thiadiazole-C-5). *Anal.* Calcd. (%) for $C_{19}H_{18}ClN_7O_2$: C, 55.41; H, 4.41; N, 23.81. Found: C, 55.58; H, 4.46; N, 23.69.

General method for the synthesis of compounds 11, 12 and 13. 4-Chlorophenacylbromide (2.33 g, 10 mmol) and sodium acetate (16.4 g 200 mmol) were added to the solution of corresponding thiosemicarbazide (**2a-c** or **3c**) or semicarbazide (**4b**) (10 mmol) in ethanol and the reaction mixture allowed to reflux for 8 h. Then, the mixture was cooled to room temperature, poured into ice-cold water while stirring and left overnight in cold. The formed solid was collected by filtration, washed with water three times and recrystallized from ethanol-water (1:1) (**11a, 11b, 12**) or dimethyl sulfoxide-water (1:1) (**11c** and **13**) to afford pure compounds.

2-(4-Amino-3-benzyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-*N*'-[4-(4-chloro-phenyl)-3-benzyl-1,3-thiazol-2(3*H*)-yliden]-acetohydrazide (11a). This compound was obtained as colorless powder (yield: 3.64 g, 66.66 %); m.p. 163°C; ir (KBr) (ν, cm^{-1}): 3320-3210 (NH_2+ NH), 1713 and 1673 (2C=O), 1588 and 1640 (2C=N); ^{1}H nmr (DMSO-d_6, δ ppm): 3.68 (s, benzylic CH_2), 4.89 (s, NCH_2), 5.03 (s, NCH_2 + thiazole C-5-H), 5.24 (s, NH_2), 6.96 (bs, 2H, arom H), 7.03-7.29 (m, 8H, arom-H), 7.50 (d, 2H, arom H, *J*= 8 Hz), 8.03 (d, 2H, arom H, *J*= 8.4 Hz), 13.95 (s, NH); ^{13}C nmr (DMSO-d_6, δ ppm): 30.01 (CH_2), 38.09-40.58 (NCH_2+DMSO-d_6), 46.46 (NCH_2), arom-C: [125.94 (2CH+ thiazole-C-5), 126.51 (CH), 127.57 (CH), 128.27 (2CH), 128.37 (2CH), 128.64 (2CH), 128.79 (2CH), 130.19 (2CH), 133.81 (C), 134.69 (C), 135.43 (C), 138.51 (C)], 147.26 (triazole-C-3), 150.48 (thiazole-C-4), 151.59 (triazole-C-5), 152.45 (thiazole-C-2), 192.06 (C=O); ms: *m/z* (%) 546 (M^+, 3), 157 (22), 156 (38), 135 (50), 129 (100), 104 (56). *Anal.* Calcd. (%) for $C_{27}H_{24}ClN_7O_2S$: C, 59.39; H, 4.43; N, 17.96. Found: C, 59.45; H, 4.47; N, 17.76.

2-[4-Amino-3-(4-chlorobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-*N*'-[4-(4-chlorophenyl)-3-benzyl-1,3-thiazol-2(3*H*)-yliden]acetohydrazide (11b). This compound was obtained as colorless powder (yield: 3.87 g, 66.72 %); m.p. 158°C; ir (KBr) (ν, cm^{-1}): 3334-3212 (NH_2+ NH), 1717 and 1674 (2C=O), 1633 and 1587 (2C=N); ^{1}H nmr (DMSO-d_6, δ ppm): 3.68 (s, benzylic CH_2), 4.90 (s, NCH_2), 5.01 (s, NCH_2+thiazole C-5-H), 5.25 (s, NH2), 6.96 (bs, 2H, arom H), 7.18-7.36 (m, 7H, arom-H), 7.61 (d, 2H, arom H, *J*= 8 Hz), 7.65 (d, 2H, arom H, J= 8.4 Hz), 13.95 (s, NH); ^{13}C nmr (DMSO-d_6, δ ppm): 29.42 (CH_2), 38.08-40.58 (NCH_2+DMSO-d_6), 46.46 (NCH_2), arom-C: [124.14 (CH+ thiazole-C-5), 127.59 (CH), 128.19 (2CH), 128.39 (CH), 128.62 (2CH), 128.81 (2CH), 130.22 (2CH), 130.58 (2CH), 131.24 (C), 133.83 (C), 134.38 (C), 134.71 (C), 138.53 (C)], 146.57 (triazole-C-3), 150.48 (thiazole-C-4), 150.51 (triazole-C-5), 151.55 (thiazole-C-2), 192.08 (C=O); ms: *m/z* (%) 580 (M^+, 100), 582 (66), 290 (16), 124 (22), 104 (28). *Anal.* Calcd. (%) for $C_{27}H_{23}Cl_2N_7O_2S$: C, 55.86; H, 3.39; N, 16.89. Found: C, 56.04; H, 3.26; N, 16.72.

2-[4-Amino-3-(4-tolyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-*N*'-[4-(4-chlorophenyl)-3-benzyl-1,3-thiazol-2(3*H*)-yliden]acetohydrazide (11c). This compound was obtained as colorless powder (yield: 2.80 g, 50.00 %); m.p. 165°C; ir (KBr) (ν, cm^{-1}), 3305-3199 (NH_2+ NH), 1682 (2C=O), 1571 (2C=N); ^{1}H nmr (DMSO-d_6, δ ppm): 2.25 (s, CH_3), 3.83 (s, benzylic CH_2), 4.29 (s, NCH_2), 4.97 (s, thiazole C-5-H), 5.05 (s, NCH_2), 5.25 (s, NH_2), 6.93 (bs, 1H, arom H), 7.11-7.64 (m, 10H, arom-H), 8.03 (d, 2H, arom H, J= 10 Hz), 13.97 (s, NH); ^{13}C nmr (DMSO-d_6, δ ppm): 20.50 (CH_3), 29.84 (CH_2), 40.01-40.59 (NCH_2+DMSO-d_6), 46.51 (NCH_2), arom-C: [125.96 (CH+ thiazole-C-5), 126.41 (2CH), 127.03 (2CH), 127.50 (CH), 128.40 (CH), 128.55 (CH), 128.85 (CH), 130.21 (CH), 130.36 (CH), 132.30 (CH), 132.66 (CH), 133.85 (C), 135.52 (C), 138.55 (C), 146.50 (C), 147.47 (C)], 150.05 (triazole-C-3), 151.80 (thiazole-C-4), 153.80 (triazole-C-5), 152.50 (thiazole-C-2), 192.12 (C=O); ms: *m/z* (%) 560 (M^+, 69), 582 (100), 306 (22), 217 (16), 104 (28). *Anal.* Calcd. (%) for $C_{28}H_{26}ClN_7O_2S$: C, 60.05; H, 4.68; N, 17.51. Found: C, 59.89; H, 4.68; N, 17.36.

2-[4-Amino-3-(4-tolyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-*N*'-[4-(4-chlorophenyl)-3-(3-florophenyl)-1,3-thiazol-2(3*H*)-yliden]acetohydrazide (12). This compound was obtained as colorless powder (yield: 2.90 g, 51.41 %); m.p. 165°C; ir (KBr) (ν, cm^{-1}), 3363-3263 (NH_2+ NH), 1694 (2C=O), 1633 and 1503 (2C=N); ^{1}H nmr (DMSO-d_6, δ ppm): 2.18 (s, CH_3), 3.64 (s, benzylic CH_2), 4.38 (s, NCH_2), 4.75 (s, oxazole C-5-H), 4.87 (s, NCH_2), 5.36 (s, NH_2), 7.18-7.64 (m, 10H, arom-H), 8.03 (d, 2H, arom H, *J*= 8.4 Hz), 13.65 (s, NH); ^{13}C nmr (DMSO-d_6, δ ppm): 20.47 (CH_3), 30.37 (CH_2), 46.55 (NCH_2), arom-C: [126.14 (CH+thiazole-C-5), 126.78 (3CH), 127.36 (3CH), 128.61 (3CH), 129.98 (2CH), 130.62 (2C), 134.57 (C), 131.24 (C), 140.30 (2C)], 150.05 (triazole-C-3), 152.50 (thiazole-C-2), 152.80 (thiazole-C-4), 154.27 (triazole-C-5), 192.12 (C=O); ms: *m/z* (%) 582 (M+H_2O, 100), 564 (M^+, 69), 411 (16), 302 (24), 217 (16), 129 (16). *Anal.* Calcd. (%) for: $C_{27}H_{23}ClFN_7O_2S$: C, 59.89; H, 4.11; N, 17.38. Found: C, 59.80; H, 4.03; N, 17.22.

2-[4-Amino-3-(4-chlorobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-*N*'-[4-(4-chlorophenyl)-3-benzyl-1,3-oxazol-2(3*H*)-yliden]acetohydrazide (13). This compound was obtained as colorless powder (yield: 3.11 g, 55.11%); m.p. 220°C; ir (KBr) (ν, cm^{-1}): 3314-3207 (NH_2+ NH), 1702 and 1683 (2C=O), 1562 and 1492 (2C=N); ^{1}H nmr (DMSO-d_6, δ ppm): 3.40 (s, benzylic CH_2), 3.87 (s, NCH_2), 4.22 (s, NCH_2), 4.62 (s, oxazole-C-5-H), 5.29 (s, NH_2), 7.03 (bs, 1H, arom H), 7.20-7.38 (m, 10H, arom-H), 7.98 (s, 1H, arom H), 9.81 (s, NH); ^{13}C nmr (DMSO-d_6, δ ppm): 29.58 (CH_2), 42.37 (NCH_2), 46.30 (NCH_2), 96.47 (oxazole-C-5), arom-C: [126.38 (2CH), 126.70 (2CH), 127.97 (3CH), 128.18 (3CH), 130.57 (3CH), 131.20 (2C), 134.64 (arom-C+oxazole C-4), 131.24 (C), 140.30 (C)], 146.53 (triazole-C-3), 152.55 (triazole-C-5), 157.29 (oxazole-C-2), 166.54 (C=O); ms: *m/z* (%) 566 (M+1, 53), 564 (M^+, 67), 509 (19), 452 (94), 430 (29), 376 (22), 297 (33), 237 (18), 159 (15), 156 (94), 132 (40), 130 (100). *Anal.* Calcd. (%) for: $C_{27}H_{23}Cl_2N_7O_2S$: C, 55.86; H, 3.99; N, 16.89. Found: C, 56.04; H, 4.12; N, 16.72.

General method for the synthesis of compounds 14, 15 and 16. The mixture of corresponding thiosemicarbazide (**2a,b,c or 3b**) (10 mmol) or semicarbazide (**4a** or **4b**), chloroacetic acid (0.94 g, 10 mmol) and sodium acetate (16.4 g, 200 mmol) in

ethanol was refluxed for 8 h. Then, the mixture was cooled to room temperature, poured into ice-cold water while stirring and left overnight in cold. The formed solid was collected by filtration, washed with water three times and recrystallized from ethanol-water (1:1) to afford pure compounds.

2-(4-Amino-3-benzyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-*N*'-(3-benzyl-4-oxo-1,3-thiazolidin-2-yliden)-acetohydrazide (14a). This compound was obtained as colorless powder (yield: 2.45 g, 54.32 %); m.p. 155°C; ir (KBr) (ν, cm^{-1}): 3318-3206 (NH_2+ NH), 1692 (2C=O), 1576 and 1540 (2C=N); ^{1}H nmr (DMSO-d_6, δ ppm): 3.39 (s, thiazole C-5-H), 3.64 (s, benzylic CH_2), 4.91 (s, NCH_2), 5.21 (s, NCH_2), 5.32 (s, NH_2), 7.03-7.32 (m, 10H, arom-H), 13.95 (s, NH); ^{13}C nmr (DMSO-d_6, δ ppm): 29.98 (CH_2), 38.50-40.17 (NCH_2 + DMSO-d_6 + thiazole-C-5), 45.68 (NCH_2), arom-C: [126.13 (2CH), 126.52 (CH), 127.29 (CH), 128.09 (2CH), 128.27 (2CH), 128.64 (2CH), 134.72 (C), 135.37 (C)], 147.36 (triazole-C-3), 147.92 (thiazole-C-2), 152.45 (triazole-C-5), 168.09 (thiazole-C-4), 189.98 (C=O); ms: *m/z* (%) 451 (M^+, 13), 416 (44), 394 (47), 218 (19), 156 (28), 153 (31), 131 (22), 129 (100), 118 (34). *Anal*. Calcd. (%) for: $C_{21}H_{21}N_7O_3S$: C, 55.86; H, 4.69; N, 21.72. Found: C, 56.11; H, 4.57; N, 21.48.

2-[4-Amino-3-(4-chlorobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-*N*'-(3-benzyl-4-oxo-1,3-thiazolidin-2-yliden)-aceto-hydrazide (14b). This compound was obtained as colorless powder (yield: 2.63 g, 54.12 %); m.p. 188°C; ir (KBr) (ν, cm^{-1}): 3324-3209 (NH_2+ NH), 1698 (2C=O), 1640 and 1581 (2C=N); ^{1}H nmr (DMSO-d_6, δ ppm): 3.39 (s, thiazole C-5-H), 3.63 (s, benzylic CH_2), 4.85 (s, NCH_2), 4.91 (s, NCH_2), 5.20 (s, NH_2), 7.06-7.36 (m, 9H, arom-H), 13.96 (s, NH); ^{13}C nmr (DMSO-d_6, δ ppm): 29.36 (CH_2), 38.50-40.58 (NCH_2 + DMSO-d_6 + thiazole-C-5), 45.67 (NCH_2), arom-C: [126.48 (2CH), 127.30 (2CH), 128.10 (2CH), 128.19 (2CH), 130.57 (CH), 134.33 (C), 134.73 (2C)], 147.92 (triazole-C-3), 147.05 (thiazole-C-2), 152.45 (triazole-C-5), 168.09 (thiazole-C-4), 190.50 (C=O); ms: *m/z* (%) 486 (M^+, 28), 451 (25), 450 (56), 430 (38), 428 (100), 377 (22), 359 (38), 304 (47), 252 (22), 208 (34), 186 (22), 141 (22), 140 (44), 118 (38), 100 (50). *Anal*. Calcd. (%) for: $C_{21}H_{20}ClN_7O_3S$: C, 51.90; H, 4.15; N, 20.18. Found: C, 52.24; H, 4.26; N, 20.04.

2-[4-Amino-3-(4-tolyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-*N*'-(3-benzyl-4-oxo-1,3-thiazolidin-2-yliden)-aceto-hydrazide (14c). This compound was obtained as colorless powder (yield: 2.69 g, 57.72 %); m.p. 210°C; ir (KBr) (ν, cm^{-1}): 3310-3186 (NH_2+ NH), 1678 (2C=O), 1575 and 1489 (2C=N); ^{1}H nmr (DMSO-d_6, δ ppm): 2.50 (s, CH_3), 3.50 (s, thiazole C-5-H), 3.58 (s, benzylic CH_2), 4.89 (s, NCH_2), 4.96 (s, NCH_2), 5.20 (s, NH_2), 7.20 (bs, 5H, arom-H), 7.27 (m, 4H, arom-H), 13.94 (s, NH); ^{13}C nmr (DMSO-d_6, δ ppm): 20.50 (CH_3), 29.61 (CH_2), 38.07-40.58 (NCH_2 + DMSO-d_6 + thiazole-C-5), 45.70 (NCH_2), arom-C: [124.14 (2CH), 127.30 (CH), 128.10 (2CH), 128.53 (2CH), 128.83 (2CH), 132.22 (C), 134.72 (C), 135.59 (C)], 147.54 (triazole-C-3), 147.94 (thiazole-C-2), 152.73 (triazole-C-5), 168.31 (thiazole-C-4), 190.15 (C=O); ms: *m/z* (%) 466 (M^+, 25), 448 (25), 408 (28), 169 (22), 158 (28), 156 (81), 131 (66), 129 (100). *Anal*. Calcd. (%) for: $C_{22}H_{23}N_7O_3S$: C, 56.76; H, 4.98; N, 21.05. Found: C, 57.04; H, 4.84; N, 21.09.

2-[4-Amino-3-(4-chlorobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-*N*'-{[3-(3-florophenyl)]-4-oxo-1,3-thiazolidin-2-yliden}-acetohydrazide (15). This compound was obtained as colorless powder (yield: 2.64 g, 53.87 %); m.p. 154°C; ir (KBr) (ν, cm^{-1}): 3326-3218 (NH_2+ NH), 1703 and 1692 (2C=O), 1642 and 1580 (2C=N); ^{1}H nmr (DMSO-d_6, δ ppm): 3.37 (s, thiazole C-5-H), 3.62 (s, benzylic CH_2), 4.82 (s, NCH_2), 5.32 (s, NH_2), 7.13-7.38 (m, 8H, arom-H), 13.93 (s, NH); ^{13}C nmr (DMSO-d_6, δ ppm): 30.17 (CH_2), 41.21 (thiazole-C-5), 45.69 (NCH_2), arom-C: [126.49 (2CH), 127.32 (2CH), 128.43 (2CH), 128.67 (CH), 130.11 (CH), 134.33 (C), 134.58 (C), 134.73 (2C)], 147.02 (thiazole-C-2), 147.90 (triazole-C-3), 152.45 (triazole-C-5), 168.17 (thiazole-C-4), 190.52 (C=O). *Anal*. Calcd. (%) for: $C_{20}H_{17}ClN_7O_3S$: C, 49.03; H, 3.50; N, 20.01. Found: C, 48.86; H, 3.71; N, 19.85.

2-[4-Amino-3-benzyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-*N*'-(3-benzyl-4-oxo-1,3-oxazolidin-2-yliden)-acetohydrazide (16a). This compound was obtained as colorless powder (yield: 0.261 g, 59.94%); m.p. 206°C; ir (KBr) (ν, cm^{-1}), 3314-3206 (NH_2+NH), 1721, 1702 and1682 (3C=O), 1651 and 1568 (2C=N); ^{1}H nmr (DMSO-d_6, δ ppm): 3.40 (s, benzylic CH_2), 3.66 (bs, oxazole C-5-H), 4.72 (s, NCH_2), 4.86 (s, NCH_2), 5.32 (s, NH_2), 7.08 (bs, 2H, arom-H), 7.20-7.32 (m, 7H, arom H), 7.84 (s, 1H, arom H), 9.85 (s, NH); ^{13}C nmr (DMSO-d_6, δ ppm): 30.22 (CH_2), 42.35 (NCH_2), 46.27 (NCH_2), 61.10 (oxazole C-5), arom-C: [126.40 (CH), 126.52 (2CH), 126.71 (2CH), 128.01 (2CH), 128.31 (2CH), 128.69 (CH), 134.66 (2C), 135.79 (C)], 140.39 (triazole-C-3), 146.85 (triazole-C-5), 157.85 (oxazole-C-2), 157.93 (C=O), 166.64 (oxazole-C-4); ms: *m/z* (%) ($M+H_2O$, 11), 419 (26), 418 (100), 285 (13), 263 (24), 236 (20). *Anal*. Calcd. (%) for: $C_{21}H_{21}N_7O_4$: C, 57.92; H, 4.86; N, 22.52. Found: C, 58.13; H, 4.84; N, 22.50.

2-[4-Amino-3-(4-chlorobenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-*N*'-(3-benzyl-4-oxo-1,3-oxazolidin-2-yliden)-acetohydrazide (16b). This compound was obtained as colorless powder (yield: 2.58 g, 54.90 %); m.p. 220°C; ir (KBr) (ν, cm^{-1}), 3314-3206 (NH_2+ NH), 1721, 1702 and1682 (3C=O), 1651 and 1568 (2C=N); ^{1}H nmr (DMSO-d_6, δ ppm): 3.40 (s, benzylic CH_2), 3.87 (bs, oxazole C-5-H), 4.22 (s, NCH_2), 4.36 (s, NCH_2), 5.29 (s, NH_2), 7.05 (bs, 1H, arom-H), 7.22-7.38 (m, 7H, arom H), 7.99 (s, 1H, arom H), 9.82 (s, NH); ^{13}C nmr (DMSO-d_6, δ ppm): 29.61 (CH_2), 42.40 (NCH_2), 46.31 (NCH_2), 61.10 (oxazole C-5), arom-C: [126.41 (CH), 126.73 (2CH), 128.00 (2CH), 128.21 (2CH), 130.59 (2CH), 131.23 (C), 134.66 (2C)], 140.32 (triazole-C-3), 146.55 (triazole-C-5), 153.30 (oxazole-C-2), 157.83 (C=O), 166.58 (oxazole-C-4); *m/z* (%) 470 (M^+, 53), 301 (12), 286 (11), 159 (100), 158 (45), 157 (40), 131 (20), 130 (35), 118 (11). *Anal*. Calcd. (%) for: $C_{21}H_{20}ClN_7O_4$: C, 53.68; H, 4.29; N, 20.87. Found: C, 53.83; H, 4.34; N, 21.27.

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