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Synthesis and anti-HSV-1 activity of new 1,2,3-triazole derivatives

Alessandro K. Jordão [a], Vitor F. Ferreira [a], Thiago M. L. Souza [b], Gabrielle G. de Souza Faria [a], Viviane Machado [b], Juliana L. Abrantes [b,c], Maria C. B. V. de Souza [a], Anna C. Cunha [a,*]

[a] Universidade Federal Fluminense, Departamento de Química Orgânica, Programa de Pós-Graduação em Química, Outeiro de São João Baptista, 24020-141 Niterói, Rio de Janeiro, Brazil

[b] Laboratório de vírus respiratórios e do sarampo/Brazilian National Influenza Center (NIC), Instituto Oswaldo Cruz, FIOCRUZ, Rio de Janeiro, Brazil

[c] Laboratório de Estrutura e Regulação de proteínas, Programa de pós-graduação em Química Biológica, Instituto de Bioquímica Médica, UFRJ, Rio de Janeiro, Brazil

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ABSTRACT

In this work, a new series of arysulfonylhydrazine-1*H*-1,2,3-triazole derivatives were synthesized, and their ability to inhibit the in vitro replication of HSV-1 was evaluated. Among the 1,2,3-triazole derivatives, 1-[(5″-methyl-1″-(4‴-fluorophenylamino)-1*H*-1,2,3-triazol-4″-yl)carbonyl]-2-(4′-meth- ylphenylsulfonyl)hydrazine and 1-[(5′-methyl-1′-(2″,5″-dichlorophenylamino)-1*H*-1,2,3-triazol-4′-yl)carbonyl]-2-(phenylsulfonyl)hydrazine, with IC_{50} values of 1.30 and 1.26 μM, respectively, displayed potent activity against HSV-1. Because these compounds have low cytotoxicity, their selectivity indices are high. Under the assay conditions, they have better performance than does the reference compound acyclovir. The structures of all of the compounds were confirmed by one- and two-dimensional NMR techniques (^{1}H, ^{13}C-APT, COSY-^{1}H × ^{1}H and HETCOR $^1J_{CH}$) and by elemental analysis.

1. Introduction

The *Herpesviridae* is a large family of DNA viruses that cause diseases in animals, including humans. There are 25 types of viruses within this family, and they are currently divided into three subfamilies: *Alphaherpesvirinae*, *Betaherpesvirinae*, and *Gammaherpesvirinae*.[1] In particular, eight or more types of herpes viruses of the subfamily *Alphaherpesvirinae* are known to cause frequent infections in humans. Infection with the herpes virus is categorized into one of several distinct disorders on the basis of the site of infection.[2] For instance, herpes simplex viruses 1 and 2 (HSV-1 and HSV-2), also known as Human herpes viruses 1 and 2 (HHV-1 and HHV-2), commonly cause recurrent infections affecting the skin, the mouth (gingivostomatitis), the lips (herpes labialis), the eyes (herpes keratitis), and the genitals.[2] Although HSV-1 is traditionally associated with orofacial lesions, it may also cause genital infection. HSV-2 also causes genital lesions[1] that are classified as sexually transmitted diseases (STD).[3] Other syndromes related to these viruses include encephalitis, viral meningitis, neonatal herpes, and, in immunocompromised patients, disseminated infection.[4] Herpes virus is generally transmitted by direct contact of the skin or the mucous membranes of the mouth and genitals when the sores are present or just before the sores appear (a process known as viral shedding).[5]

The other viruses of the subfamily *Alphaherpesvirinae*[3,6] include Human herpesvirus 3 (Varicella zoster virus, VZV), Human herpesvirus 4 (Epstein–Barr virus, EBV), Human herpesvirus 5 (Cytomegalovirus, CMV), Human herpesvirus 6 (Roseolovirus), Human herpesvirus 7 (Roseolovirus), and Human herpesvirus 8 (Kaposi's sarcoma-associated herpesvirus, KSHV).

Most antiherpetic drugs in clinical use, such as acyclovir (ACV, **1**), penciclovir (**2**), and ribavirin (**3**), are nucleoside analogues (Fig. 1). However, cidofovir (**4**) is a phosphonate molecule derived from cytidine.[5–8] Nucleoside analogues, such as **1** and **2**, are prodrugs, because they need to be phosphorylated before they become effective. These compounds are selectively phosphorylated only within virus-infected cells by viral thymidine kinase (TK).[9,10] Additional phosphorylation by cellular enzymes leads to the production of acyclovir or penciclovir triphosphate, both of which compete with the natural nucleotide, dGTP, resulting in the selective inhibition of viral DNA polymerase. Incorporation of the triphosphate into the growing DNA chain prevents continued extension of the chain.[9,10]

The emergence of virus strains that are resistant to commonly used anti-herpesvirus drugs is a problem in clinical settings, particularly in immunocompromised individuals undergoing HSV-1 infection.[11–13] Alternative approaches, such as the clinical use of non-nucleoside drugs, have been studied.[14–17] Examples of non-nucleoside inhibitors that have been proposed as candidate drugs for the treatment of herpes virus replication have recently been described (Fig. 2).[14–17]

* Corresponding author. Tel.: +55 21 26292148; fax: +55 21 26292145.
E-mail address: annac@vm.uff.br (A.C. Cunha).

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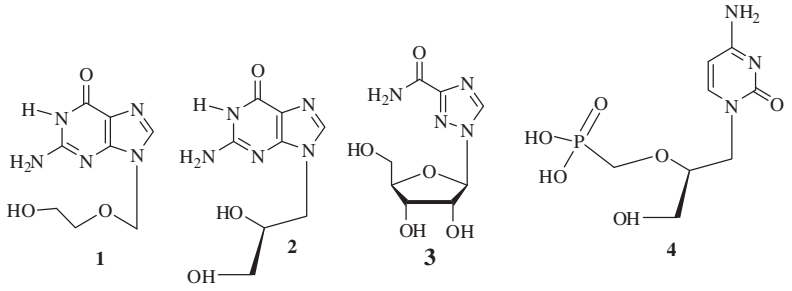


Figure 1. Antiviral drugs in clinical use against herpes virus.

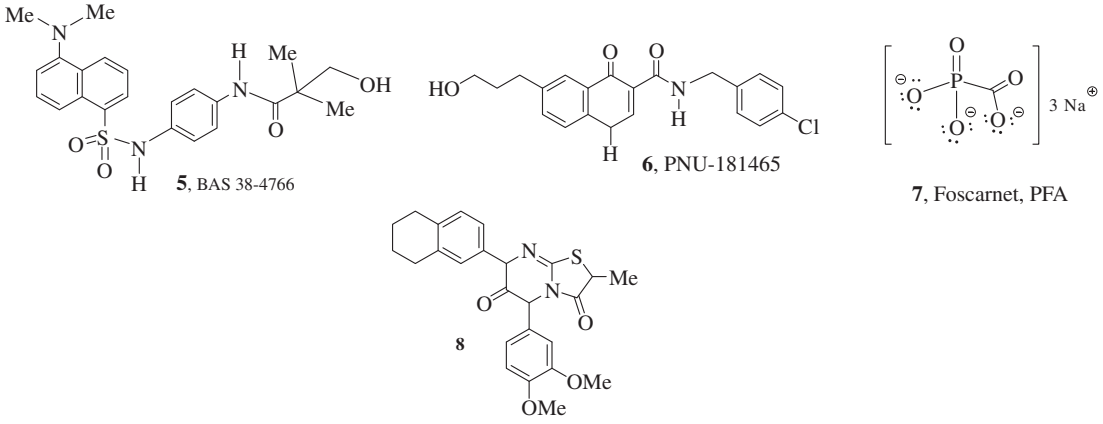


Figure 2. Non nucleoside inhibitors of herpes virus replication.

1,2,3-Triazole derivatives, which belong to an important group of N-heterocyclic compounds, have been the subject of extensive studies, because several biological properties, such as antiplatelet,[18,19] antipsychotic,[20] tuberculostatic,[21] antiophidic,[22] and antiviral[23,24] properties, have been associated with this class of substances.

Two general synthetic methods are available for the construction of 1,2,3-triazole rings: Huisgen's [1,3]-dipolar cycloaddition reactions[25] (in particular, copper(I)-catalyzed cycloaddition[26]) and the intramolecular 1,5-electrocyclization of β-substituted α-diazocarbonyl compounds.[27,28] The latter method is more flexible, because it uses readily available carbonyl compounds. With this methodology, two pathways can be followed: (i) starting from β-amino-α,β-unsaturated ketones or esters,[29,30] followed by a diazo transfer reaction[31,32] (*pathway* **I**) and (ii) starting from α-diazocarbonyl compounds,[18] followed by α-diazoimino formation[29,33] (*pathway* **II**) (Scheme 1). The diazo donor reagents can be 3-diazo-1,3-dihydro-2*H*-indol-2-one[28,34] and sulfonyl azides,[35] such as tosyl azide, *p*-carboxylbenzenesulfonyl azide, and methanesulfonyl azide.

Recently, we have published the design and synthesis of *N*-amino-1,2,3-triazole derivatives and an evaluation of their antiviral activity against Cantagalo virus (CTGV) replication in cell culture. In this study, it was found that the compound 1-(4-fluorophenylamino)-5-methyl-1*H*-[1,2,3]-triazole-4-carbohydrazide,[24] exhibited a significant effect against CTGV. CTGV was the first sample isolated during a poxvirus outbreak in 1999 in Rio de Janeiro state, and it was characterized as a vaccinia virus (VACV) strain.

As part of an ongoing research program on the synthesis of new bioactive N-heterocycles by using diazocarbonyl compounds,[18–20,22,24] we herein report the synthesis and anti-HSV-1 evaluation of a family of 1,2,3-triazole derivatives **9a–i** bearing an arylsulfonylhydrazide function at position C-4 of the azolic ring. In addition, we investigated the effect of different substituents attached to *N*-phenyl ring on biological activity (Scheme 2).

2. Results and discussion

2.1. Chemistry

The synthesis of new arylsulfonylhydrazide-1,2,3-triazole derivatives **9a–i** is shown in Scheme 1. The ethyl N-substituted-phenylamino-4-carbethoxy-1*H*-1,2,3-triazoles **10a–e** were prepared in moderate yields by the condensation of ethyl 2-diazoacetoacetate with substituted phenylhydrazine hydrochlorides according to the method outlined in our previous report.[23] These compounds were converted into corresponding carbohydrazides **11a–e** on treatment with hydrazine hydrate in refluxing ethanol.[24]

The new class of triazoles **9a–i** was prepared by the condensation of compounds **11a–e** with suitable arylsulfonyl chlorides **12a–c** in pyridine. The yields of these reactions (**9a–i**) are listed in Table 1.

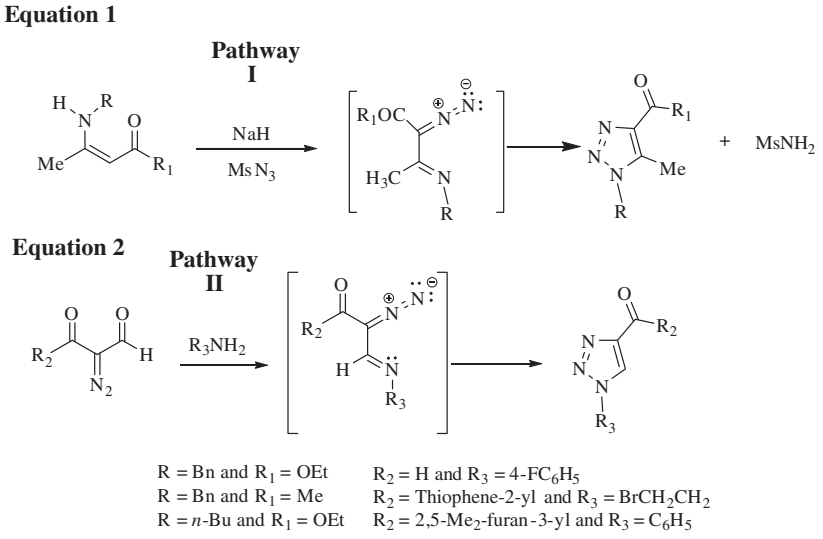
2.2. Materials and methods

2.2.1. Cells and virus

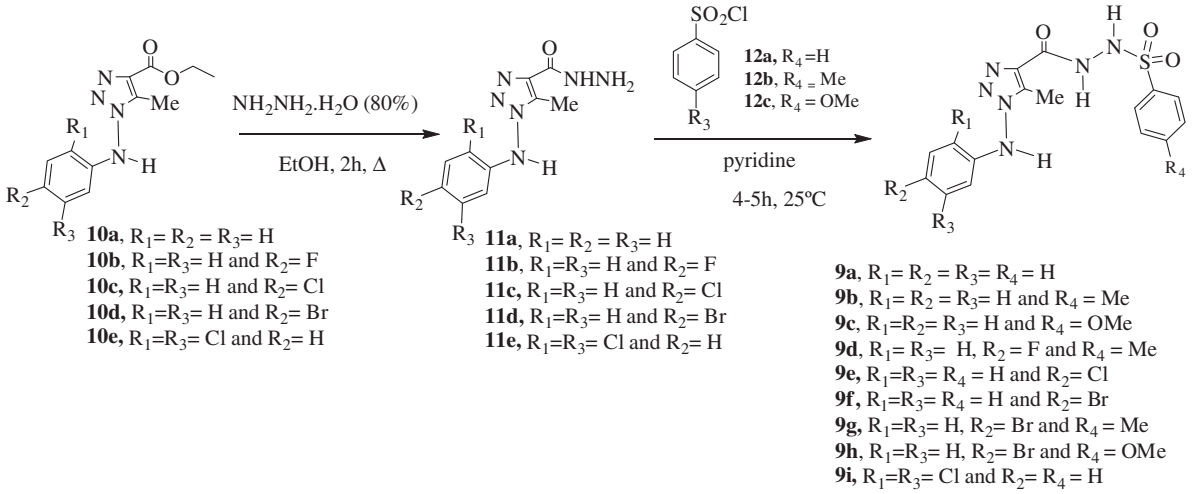
African green monkey kidney cells (Vero) were cultured in Dulbecco's Modified Eagles Medium (DMEM) with 5% fetal bovine serum (FBS), 100 U/mL penicillin and 100 μg/mL streptomycin and then incubated at 37 °C in 5% CO_2. Vero cells were infected with HSV-1 to obtain virus stock at a multiplicity of infection[36] (MOI) of 0.1 at 37 °C for 1 h. At 48 h post-infection (p.i.), cell supernatants were centrifuged and stored at −70 °C.

2.2.2. Cytotoxicity assay

Monolayers of Vero cells in 96-multiwell plates (10^4 cells/well) were treated with different concentrations of the test compounds



Scheme 1. Methods for preparing triazoles from α-diazoimines.



Scheme 2. Synthetic pathways used for the preparation of **9a–i**.

for 72 h. Then, XTT (2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-2*H*-tetrazolium-5-carboxanilide) was added to each well at a final concentration of 2.5 mg/mL in the presence of phenazine methosulfate (PMS) at 32 μg/mL. After a 4 h incubation period, the optical density was measured using a spectrophotometer with 492-nm test and 620-nm reference wavelengths. For comparison, acyclovir was used as a positive control. The 50% cytotoxic concentration (CC_{50}) was calculated by linear regression analysis of the dose-response curves obtained from the data.

2.2.3. Anti-HSV-1 assays

Vero cells (10^4 cells/well) in 96-well plates were infected with HSV-1 at 100 $CCID_{50}$/well for 1 h. After that, virus inoculum was removed, cells were washed and a medium containing 50 μM of the test compounds was added. After incubation for 72 h, XTT/PMS solution was added to each well to measure the ability of the compounds to inhibit the HSV-1-induced cytopathic effect, as described above.[37]

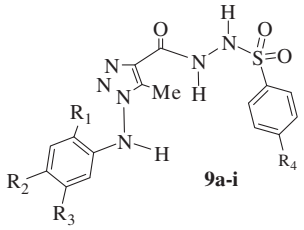
To determine the IC_{50} values of the test compounds, Vero cells in a 6-well plates were infected with HSV-1 at an MOI of 5 for 1 h at 37 °C. After this period of time, cells were washed and treated with different concentrations of the most effect test compounds. After a 24 h incubation period, HSV-1-infected cells were lysed, the supernatant of these cells was harvested and tittered as described in the previous paragraph.[37] Acyclovir was used as a positive control. The 50% inhibitory concentration (CC_{50}) was calculated by linear regression analysis of the dose-response curves obtained from the data.

2.3. Anti-HSV-1 activity

The 1,2,3-triazole derivatives **9a–i** were evaluated for their inhibitory effect on HSV-1 (Table 2). Of the nine tested compounds, five inhibited virus replication by more than 70% at 50 μM after 72 h post-infection. The bioactive compounds **9a** ($R_1 = R_2 = R_3 = R_4 = H$), **9d** ($R_1 = H$, $R_2 = F$, $R_3 = H$ and $R_4 = Me$), **9g** ($R_1 = H$, $R_2 = Br$, $R_3 = H$ and $R_4 = Me$), **9h** ($R_1 = H$, $R_2 = Br$, $R_3 = H$ and $R_4 = OMe$), and **9i** ($R_1 = Cl$, $R_2 = H$, $R_3 = Cl$ and $R_4 = H$) inhibited HSV-1 replication by 79%, 88%, 69%, 77%, and 71%, respectively. The positive control acyclovir (ACV) inhibited 95% of HSV-1 replication under these experimental conditions.

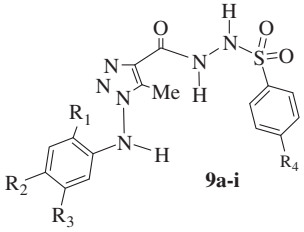
The cytotoxicity and antiviral potency of the most-active triazoles **9a**, **9b**, **9d**, **9h**, and **9i** were evaluated (Table 3). These azo-compounds were less cytotoxic (CC_{50} = 1512, 863, 1266, 971, and

Table 1
Yields and mp for arylsulfonylhydrazide-1,2,3-triazoles **9a–i**



Compounds	R_1	R_2	R_3	R_4	Mp (°C)	Yield (%)
9a	H	H	H	H	180–182	87
9b	H	H	H	Me	207–215	73
9c	H	H	H	OMe	187–190	67
9d	H	F	H	Me	208–210	60
9e	H	Cl	H	H	188–191	47
9f	H	Br	H	H	185–193	69
9g	H	Br	H	Me	207–208	78
9h	H	Br	H	OMe	167–169	93
9i	Cl	H	Cl	H	235–238	83

Table 2
Antiviral activity for 1,2,3-triazole derivatives **9a–i**



Compounds	R_1	R_2	R_3	R_4	% of inhibition of virus yield[a] (HSV-1)
9a	H	H	H	H	79 ± 2.3
9b	H	H	H	Me	37 ± 1.2
9c	H	H	H	OMe	54 ± 3.2
9d	H	F	H	Me	88 ± 2.0
9e	H	Cl	H	H	57 ± 4.3
9f	H	Br	H	H	31 ± 1.5
9g	H	Br	H	Me	69 ± 2.2
9h	H	Br	H	OMe	77 ± 4.5
9i	Cl	H	Cl	H	71 ± 3.9
ACV	—	—	—	—	95 ± 1.2

[a] The experimental concentrations of triazole derivatives **9a–i** were 50 μM and ACV concentration was 50 μM. Results are presented as means of triplicate experiments. ACV-acyclovir has been included for comparison purposes.

1174 μM) than was acyclovir, which presented a CC_{50} of 860 ± 54 μM, under our assay conditions.[38] Only two of these compounds, **9d** and **9i**, with IC_{50} values of 1.30 and 1.26 μM, respectively, displayed potent activity against HSV-1. Selective index (SI) values, which represent the in vitro antiviral potency and safety of a candidate antiviral drug, of **9d** and **9i** are comparable to the ACV SI (Table 3). The antiviral activity of these compounds is comparable to that of other molecules studied by our group[36] and described elsewhere.[37]

These results strongly suggest that compounds **9d** and **9i** could be considered as promising candidates for the development of new derivatives with anti-HSV-1 activity and for additional studies concerning the antiviral activity of this group of compounds.

3. Conclusion

In summary, a new series of arysulfonylhydrazide-1,2,3-triazoles, **9a–i**, have been synthesized and evaluated for their antiviral activities against HSV-1 replication in cell culture. Among these N-heterocyclic derivatives, compounds **9d** and **9i** were the most promising molecules with potent anti-HSV-1 activity. These compounds exhibited lower cytotoxicity and higher selectivity indices than did the reference compound acyclovir.

These 1,2,3-triazole analogues, **9d** and **9i**, represent promising structures for the development of new compound analogues with anti-HSV-1 activity and for future in vivo analysis.

Table 3
Cytotoxicity, anti-HSV-1 activity, and selectivity index in Vero cells for triazole derivatives **9a**, **9d**, **9h**, and **9i**

Compounds	R_1	R_2	R_3	R_4	CC_{50}[a] (μM)	IC_{50}[b] (μM)	SI[c]
9a	H	H	H	H	1512 ± 34	19 ± 0.02	80
9d	H	F	H	Me	1266 ± 62	1.3 ± 0.04	974
9h	H	Br	H	OMe	971 ± 23	37 ± 3.0	26
9i	Cl	H	Cl	H	1174 ± 52	1.26 ± 0.03	932
ACV	—	—	—	—	860 ± 25	0.99 ± 0.02	869

Acyclovir was used as a positive control. The mean values ± standard deviations are representative of three independent experiments.

[a] CC_{50}: cytotoxic concentration (μM) or concentration required to reduce the viability of host cells by 50%. The cytotoxicity was determined by XTT assay and the anti-HSV-1 activity by viral plaque number reduction assay.

[b] IC_{50}: 50% inhibitory concentration, defined as the concentration (μM) that inhibited 50% of viral plaque formation when compared to untreated controls.

[c] SI: selectivity index is the ratio between CC_{50} and IC_{50} values.

4. Experimental section

Melting points were determined with a Fisher-Johns instrument and are uncorrected. Infrared (IR) spectra were recorded on an ABB FTLA2000-100 spectrophotometer in KBr pellets. NMR spectra, unless otherwise stated, were obtained in Me_2SO-d_6 or $CDCl_3$ by using a Varian Unity Plus 300 MHz spectrometer. Chemical shifts (δ) are expressed in ppm and the coupling constants (J) in Hertz. Column chromatography purification was performed on silica gel flash from Across. Reactions were routinely monitored by thin-layer chromatography (TLC) on Silica Gel pre-coated F_{254} by using Merck plates. Microanalyses were performed on a Perkin–Elmer Model 2400 instrument, and all values were within ±0.4% of the calculated compositions.

4.1. Chemistry

4.1.1. General procedure for the preparation of the 1,2,3-triazole derivatives 9a–i

To a stirred solution of 4-carbohydrazide-1,2,3-triazole derivatives **10a–e** (1 mmol) in pyridine (10 mL), the desired aryl sulfonylchlorides (1.2 mmol) were added at 0 °C. The resulting mixture was stirred at room temperature for 4–5 h. After this period, the reaction mixture was diluted with 1 M HCl and extracted with ethyl acetate (4 × 25 mL). The combined layers were washed with sodium bicarbonate solution, filtered, and dried over anhydrous Na_2SO_4. Evaporation of the solvent under vacuum produced the crude products that were purified by column chromatography employing EtOAc/hexane mixture as eluent giving:

4.1.1.1. 1-[(5′-Methyl-1′-(phenylamino)-1*H*-1,2,3-triazol-4′-yl)-carbonyl]-2-(phenylsulfonyl)hydrazine 9a. As a white solid by condensation of **11a** with benzenesulfonyl chloride. IR (KBr) ν_{max} (cm^{-1}) 3248 (N–H), 1685 (C=O); ^1H NMR (300.00 MHz, DMSO-d_6) δ 2.38 (s, 3H, CH_3), 6.42–6.45 (m, 2H), 6.89–6.94 (m, 1H), 7.21–7.27 (m, 2H), 7.54–7.59 (m, 2H), 7.65–7.68 (m, 1H), 7.84–7.87 (m, 2H), 10.12 (br s, 1H, N–H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ 8.0 (CH_3), 112.9 (C-2′ and C-6′), 121.2 (C-4′), 127.6 (C-3′ and C-5′), 128.9 (C-2″ and C-6″), 129.5 (C-3″ and C-5″),

133.0 (C-4″), 135.6 (C-4 or C-5), 138.1 (C-4 or C-5), 146.1 (C-1′), 159.9 (C=O) ppm. Anal. Calcd for $C_{16}H_{16}N_6O_2S$: C, 51.60; H, 4.33; N, 22.57. Found: C, 51.57; H, 4.67; N, 21.48.

4.1.1.2. 1-[(5″-Methyl-1″-(phenylamino)-1*H*-1,2,3-triazol-4″-yl)-carbonyl]-2-(4′methylphenylsulfonyl)hydrazine 9b. As a white solid by condensation of **11a** with *p*-tolylsulfonyl chloride chloride. IR (KBr) ν_{max} (cm^{-1}) 3306 (N–H); 1685 (C=O); ^1H NMR (300.00 MHz, DMSO-d_6) δ 2.28 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 6.43–6.46 (m, 2H), 6.90–6.95 (m, 1H), 7.22–7.27 (m, 2H), 7.36 (d, 2H, J = 8.2), 7.74 (d, 2H, J = 8.5), 10.12 (br s, 1H, N–H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.9 (CH_3), 20.9 (CH_3), 112.8 (C-2′ and C-6′), 121.4 (C-4′), 127.6 (C-2" and C-6"), 129.2 (C-3′ and C-5′), 129.4 (C-3″ and C-5″), 135.5 (C-1″), 136.4 (C-4 or C-5), 137.8 (C-4 or C-5), 143.2 (C-4″), 145.9 (C-1′), 146.1 (C-3" and C-5"), 159.8 (C=O) ppm. Anal. Calcd for $C_{17}H_{18}N_6O_3S$: C, 52.84; H, 4.70; N, 21.75. Found: C, 53.55; H, 5.09; N, 20.98.

4.1.1.3. 1-[(5″-Methyl-1″-(phenylamino)-1*H*-1,2,3-triazol-4″-yl)-carbonyl]-2-(4′methoxylphenylsulfonyl)hydrazine 9c. As a white solid by condensation of **11a** with *p*-methoxybenzenesulfonyl chloride. IR (KBr) ν_{max} (cm^{-1}) 3236 (N–H); 1675 (C=O); ^1H NMR (300.00 MHz, DMSO-d_6) δ 2.28 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 6.42–6.45 (m, 2H), 6.89–6.94 (m, 1H), 7.08 (d, 2H, J = 8.9), 7.21–7.27 (m, 2H), 7.78 (d, 2H, J = 8.9), 9.81 (br s, 1H, N–H), 10.12 (br s, 1H, N–H), 10.56 (br s, 1H, N*H*–C) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ 8.0 (CH_3), 55.6 (OCH_3), 112.6 (C-2″ and C-6″), 114.0 (C-3″ and C-5″), 121.5 (C-4′), 129.4 (C-2′ and C-6′), 129.9 (C-3′ and C-5′), 130.7 (C-1″), 135.6 (C-4 or C-5), 137.9 (C-4 or C-5), 146.1 (C-1′), 159.8 (C-4″), 162.6 (C=O) ppm. Anal. Calcd for $C_{17}H_{18}N_6O_4S$: C, 50.74; H, 4.51; N, 20.88. Found: C, 50.15; H, 4.80; N, 19.92.

4.1.1.4. 1-[(5″-Methyl-1″-(4‴-fluorophenylamino)-1*H*-1,2,3-triazol-4″-yl)carbonyl]-2-(4′methylphenylsulfonyl)hydrazine 9d. As a white solid by condensation of **11b** with *p*-tolylsulfonyl chloride. IR (KBr) ν_{max} (cm^{-1}) 3218 (N–H); 1679 (C=O); ^1H NMR (300.00 MHz, DMSO-d_6) δ 2.30 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 6.49 (dd, 2H, J = 9.0; 4.6), 7.08 (dd, 2H, J = 8.9; 8.8), 7.36 (d, 2H, J = 8.1), 7.74 (d, 2H, J = 8.3), 10.10 (br s, 1H, N–H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.8 (CH_3), 20.9 (CH_3), 114.6 (J = 8.3; C-2′ and C-6′), 115.9 (J = 8.3; C-3′ and C-5′), 127.5 (C-2″ and C-6″), 129.2 (C-3″ and C-5″), 135.6 (C-1″), 136.4 (C-4 or C-5), 137.7 (C-4 or C-5), 142.4 (J = 2.3; C-1′), 157.2 (J = 237.4; C-4′), 159.7 (C=O) ppm. Anal. Calcd for $C_{17}H_{17}FN_6O_3S$: C, 50.49; H, 4.24; N, 20.78. Found: C, 50.26; H, 4.54; N, 20.15.

4.1.1.5. 1-[(5′-Methyl-1′-(4″-chlorophenylamino)-1*H*-1,2,3-triazol-4′-yl)carbonyl]-2-(phenylsulfonyl)hydrazine 9e. As a white solid by condensation of **11c** with benzenesulfonyl chloride. IR (KBr) ν_{max} (cm^{-1}) 3310 (N–H); 1677 (C=O); ^1H NMR (300.00 MHz, DMSO-d_6) δ 2.28 (s, 3H, CH_3), 6.47 (d, 2H, J = 8.9), 7.28 (d, 2H, J = 8.9), 7.54–7.59 (m, 2H), 7.62–7.69 (m, 1H), 7.84–7.87 (m, 2H), 9.97 (br s, 1H, N–H), 10.12 (br s, 1H, N–H), 10.61 (br s, 1H, N–H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.8 (CH_3), 114.5 (C-2′ and C-6′), 125.1 (C-4′), 127.5 (C-3′ and C-5′), 128.8 (C-2″ and C-6″), 129.2 (C-3″ and C-5″), 132.8 (C-4″), 135.6 (C-4 or C-5), 137.8 (C-4 or C-5), 139.4 (C-1″), 144.9 (C-1′), 159.7 (C=O) ppm.

4.1.1.6. 1-[(5′-Methyl-1′-(4″-bromophenylamino)-1*H*-1,2,3-triazol-4′-yl)carbonyl]-2-(phenylsulfonyl)hydrazine 9f. As a white solid by condensation of **11d** with benzenesulfonyl chloride. IR (KBr) ν_{max} (cm^{-1}) 3311 (N–H); 1677 (C=O); ^1H NMR (300,00 MHz, DMSO-d_6) δ 2.27 (s, 3H, CH_3), 6.42 (d, 2H, J = 9.0), 7.41 (d, 2H, J = 9.0), 7.56–7.59 (m, 2H), 7.62–7.67 (m, 1H), 7.84–7.87 (m, 2H), 10.30 (br s, 1H, N–H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.8 (CH_3), 112.7 (C-4′), 115.0 (C-2′ and C-6′), 127.5 (C-3′ and C-5′), 128.8 (C-2″ and C-6″), 132.1 (C-3″ and C-5″), 135.6 (C-4″), 137.9 (C-4 or C-5), 139.3 (C-4 or C-5), 139.3 (C-1″), 145.3 (C-1′), 159.7 (C=O) ppm.

4.1.1.7. 1-[(5″-Methyl-1″-(4‴-bromophenylamino)-1*H*-1,2,3-triazol-4″-yl)carbonyl]-2-(4′-methylphenylsulfonyl)hydrazine 9g. As a white solid by condensation of **11d** with *p*-tolylsulfonyl chloride. IR (KBr) ν_{max} (cm^{-1}) 3301 (N–H); 1678 (C=O); ^1H NMR (300.00 MHz, DMSO-d_6) δ 2.28 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 6.42 (d, 2H, J = 8.9), 7.36 (d, 2H, J = 8.2), 7.41 (d, 2H, J = 8.9), 7.74 (d, 2H, J = 8.2), 10.28 (br s, 1H, N–H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.8 (CH_3), 20.9 (CH_3), 112.7 (C-4′), 114.9 (C-2′ and C-6′), 127.5 (C-2″ and C-6″), 129.2 (C-3″ and C-5″), 132.1 (C-3′ and C-5′), 135.6 (C-1″), 136.4 (C-4 or C-5), 137.8 (C-4 or C-5), 143.1 (C-4″), 145.3 (C-1′), 159.7 (C=O) ppm. Anal. Calcd for $C_{17}H_{17}BrN_6O_3S$: C, 43.88; H, 3.68; N, 18.06. Found: C, 44.07; H, 4.01; N, 17.40.

4.1.1.8. 1-[(5″-Methyl-1″-(4‴-bromophenylamino)-1*H*-1,2,3-triazol-4″-yl)carbonyl]-2-(4′-methoxylphenylsulfonyl)hydrazine 9h. As a white solid by condensation of **11d** with *p*-methoxybenzenesulfonyl chloride. IR (KBr) ν_{max} (cm^{-1}) 3231 (N–H); 1684 (C=O); ^1H NMR (300.00 MHz, DMSO-d_6) δ 2.28 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 6.42 (d, 2H, J = 8.8), 7.08 (d, 2H, J = 9.0), 7.41 (d, 2H, J = 8.8), 7.78 (d, 2H, J = 9.0), 9.81 (br s, 1H, N–H), 10.31 (br s, 1H, N–H), 10.57 (br s, 1H, N–HC) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.9 (CH_3), 55.6 (CH_3), 112.8 (C-4′), 114.0 (C-2′ and C-6′), 115.0 (C-3″ and C-5″), 129.9 (C-2″ and C-6″), 130.7 (C-1″), 132.1 (C-3′ and C-5′), 135.7 (C-4 or C-5), 137.8 (C-4 or C-5), 145.3 (C-1′), 159.7 (C-4″), 162.6 (C=O) ppm. Anal. Calcd for $C_{17}H_{17}BrN_6O_4S$: C, 42.42; H, 3.56; N, 17.46. Found: C, 42.97; H, 3.84; N, 17.70.

4.1.1.9. 1-[(5′-Methyl-1′-(2″,5″-dichlorophenylamino)-1*H*-1,2,3-triazol-4′-yl)carbonyl]-2-(phenylsulfonyl)hydrazine 9i. As a white solid by condensation of **11e** with benzenesulfonyl chloride. IR (KBr) ν_{max} (cm^{-1}) 3248 (N–H); 1685 (C=O); ^1H NMR (300.00 MHz, DMSO-d_6) δ 2.28 (s, 3H, CH_3), 6.02 (d, 1H, J = 2.5), 7.03 (dd, 1H, J = 2.5, 8.3), 7.49–7.58 (m, 3H), 7.63–7.68 (m, 1H), 7.86 (dd, 2H, J = 1.5, 7.3), 10.01 (br s, 1H, N–H), 10.24 (br s, 1H, N–H), 10.68 (br s, 1H, N*H*–C) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.9 (CH_3), 113.1 (C-6′), 116.7 (C-5′), 122.1 (C-4′), 127.5 (C-2″ and C-6″), 128.5 (C-3″ and C-5″), 131.4 (C-3′), 132.7 (C-2′), 132.8 (C-4″), 135.7 (C-4 or C-5), 138.2 (C-4 or C-5), 139.2 (C-1′), 142.8 (C-1″), 159.7 (C=O) ppm. Anal. Calcd for $C_{16}H_{14}Cl_2N_6O_3S$: C, 43.55; H, 3.20; N, 19.04. Found: C, 43.37; H, 3.50; N, 19.36.

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