Journal of Medicinal Chemistry

ARTICLE

pubs.acs.org/jmc

Novel 1,2,3-Triazole Derivatives for Use against *Mycobacterium tuberculosis* H37Rv (ATCC 27294) Strain

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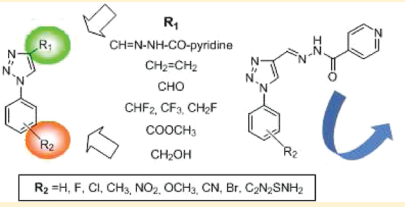
ABSTRACT: The purpose of this study was to prepare various 4-substituted *N*-phenyl-1,2,3-triazole derivatives using click chemistry. The derivatives were screened in vitro for antimicrobial activity against *Mycobacterium tuberculosis* strain H37Rv (ATCC 27294) using the Alamar Blue susceptibility test. The activity was expressed as the minimum inhibitory concentration (MIC) in μg/mL (μM). Derivatives of isoniazid (INH), (*E*)-*N*′-[(1-aryl)-1*H*-1,2,3-triazole-4-yl)methylene] isonicotinoyl hydrazides, exhibited significant activity with MIC values ranging from 2.5 to 0.62 μg/mL. In addition, they displayed low cytotoxicity against liver cells (hepatoma HepG2) and kidney cells (BGM), thereby providing a high therapeutic index. The results demonstrated the potential and importance of developing new INH derivatives to treat mycobacterial infections.



Entry	MIC	IS
Isoniazid	0.06 (0.437)	-----
Rifampicin	1.0 (1.21)	-----
4-Cl	0.62 (1.8)	>1612
3-CH_3	0.62 (2.0)	>422
2-OCH_3	0.62 (1.9)	>1612

INTRODUCTION

Tuberculosis (TB) is an infectious disease that has affected humanity for more than five millennia.[1]The etiologic agent of TB, *Mycobacterium tuberculosis* (or Koch bacillus), is suspected of causing a large number of deaths despite the availability of effective chemotherapy and the Bacille Calmette−Guérin (BCG) vaccine.[2] It is estimated that 70% of the population in poor countries is infected with the Koch bacillus, and 7.5 million new cases and 2.8 million deaths are reported each year. The high rate of disease occurrence in these countries is closely related to the precarious living conditions encountered there. The two factors associated with the spread of TB are human immunodeficiency virus (HIV) infection and the emergence of *M. tuberculosis* strains that are resistant to one or more drugs ("multiple drug resistant" *M. tuberculosis*, MDR-TB). The ever-increasing number of MDR-TB cases has caused great concern because they contribute to an increase in deaths from TB and are often associated with HIV infection. It is estimated that one-third of the 42 million individuals infected with HIV are coinfected with *M. tuberculosis*; most people infected with HIV develop TB as the first manifestation of acquired immunodeficiency syndrome (AIDS).

The presence of MDR-TB reflects a weakness in TB control, but this weakness can be treated with extended chemotherapy (approximately two years). With an extended treatment period, however, patients have an increased risk of toxicity and the treatment costs are approximately 100 times higher than the typical treatment of TB (which is conducted for six to nine months).[3] INH is an active oral drug that exhibits bacteriostatic effects on bacillus and is highly active against *Mycobacterium tuberculosis*.[4] The MIC of INH is notably low (0.02 to 0.06 μg/mL), which contributes to its effectiveness.

The concept of making structural analogues of INH became increasingly important in the 1990s after the discovery of its mechanism of action; INH interferes with the synthesis of mycolic acid, one of the chemical pathways responsible for the production of cell walls in *M. tuberculosis*. Thus, INH inhibits the bacteria from multiplying and causes bacterial death. INH is metabolized in the human liver and forms compounds, such as hydrazine, that are toxic to the organs and the central nervous system.[5−7] Because INH is a critical drug in the therapeutic arsenal[8−11] for TB treatment, efforts are being made to develop of new INH derivatives with greater activity, lower toxicity, and fewer side effects than INH.[12−14]

Received: March 18, 2011
Published: July 21, 2011

dx.doi.org/10.1021/jm2003624 | *J. Med. Chem.* 2011, 54, 5988–5999

The INH molecule was previously incorporated onto aryloxyacetonitriles, giving isonicotinoylhydrazones that showed significant tuberculostatic activity.[12] Bukowski and co-workers prepared isonicotinoyl hydrazides that were active against *M. tuberculosis* H37Rv and *M. tuberculosis* 210 isolated from patients who were resistant to INH, ethambutol, and rifampicin at 3.13 μg/mL.[13] Additionally, other compounds with a halogen-substituted phenyl group showed even greater activity.[14] Therefore, it is possible to attach chemical groups that are important in drug entry to INH and thus make *M. tuberculosis* strains more susceptible to this drug.[15]

We have recently published our findings on the tuberculostatic activity of a series of 1,2,3-triazoles with MIC values of approximately 2.5 μg/mL.[16] These compounds were designed from observations of the antimicrobial activity present in different classes of compounds that contained the basic N1-phenylazole subunit.[17] In continuing the search for new tuberculostatic compounds, the goal was to obtain compounds **3t**, **4a**−**o**, **4r**, **5a**−**o**, **6p**, **7p**, **8c**−**d**, **8p**−**s**, **9d**, **9r**, **9t**, **10a**, **10c**, **10i**−**j**, and **10m**−**o**. In the present study, we evaluated the activity of novel 4-substituted *N*-phenyl-1,2,3-triazole derivatives against *M. tuberculosis* H37Rv as well as their in vitro cytotoxicity.

MATERIALS AND METHODS

Chemistry. When preparing 4-carboxaldehyde-1,2,3-triazoles (**4a**−**o**, **4r**), a synthetic route was utilized that used aromatic azides (**2a**−**o**) previously obtained by a diazotization reaction[18] of corresponding anilines (**1a**−**o**) and further reacted with terminal alkynes.

The methodology for obtaining the triazoles (**3a**−**s**, **6p**, and **7p**) was based on the Huisgen 1,3-dipolar cycloaddition reaction.[19] To obtain only the 1,4-regioisomers, click chemistry reaction conditions using Cu(I) as a catalyst were utilized. In addition to increasing the reaction rate, the copper catalyst provided full control over reaction regioselectivity, which led to the production of only the 1,4-regioisomers.[20]As observed by Sharpless, the speed of the reaction and the yields are much higher in this method than in the traditional method, achieving 80% to 100% regioselectivity.[21] The following 4-carboxaldehyde-1,2,3-triazoles (**4a**−**o**, **4r**) were prepared by oxidation of the products **3a**−**s** using 2-iodoxybenzoic acid (IBX).[22]

The synthesis of isonicotinoyl hydrazide derivatives (**5a**−**o**) was accomplished through a Schiff reaction between the appropriate 4-carboxaldehyde-1,2,3-triazoles (**4a**−**o**, **4r**) and INH, as described in the general procedure (Scheme 1). To obtain derivatives **8c**−**d**, **8p**−**s**, **9d**, and **9r**, fluorination of substrates **3c**−**d**, **3p**−**s**, **4d**, and **4r** with dimethylaminosulfur trifluoride (DAST) was performed. This reagent has been widely used due to its high selectivity for fluorination of alcohols, aldehydes, and ketones.[23]

The derivatives **3t** and **9t** were obtained from substrates substituted with a cyano group (**3r** and **9r**) through reaction with classical thiosemicarbazones in trifluoroacetic acid.[24]

To synthesize the 4-vinyl-1,2,3-triazoles (**10a**, **10c**, **10i**−**j**, **10m**−**o**), the respective aldehydes (**4a**, **4c**, **4i**−**j**, and **4m**−**o**) were treated with methyltriphenylphosphonium bromide and sodium hydride (NaH), leading to the products in good yields. Although 4-vinyl-1,2,3-triazoles have been reported in the literature, the Wittig reaction was used here for the preparation of a series of these compounds.[25]

All of the compounds were obtained with good yields and were fully characterized by ^{1}H nuclear magnetic resonance (^{1}H NMR), ^{13}C NMR, infrared spectroscopy (FTIR), mass spectroscopy, and elemental analysis (CHN).

Minimum Inhibitory Concentration. The tuberculostatic activities of compounds **3t**, **5a**−**o**, **6p**, **7p**, **8c**−**d**, **8p**−**s**, **9d**, **9r**, **9t**, **10a**, **10c**, **10i**−**j**, **10m**−**o**, and their precursors **3a**−**s** and **4a**−**o**, **4r** were assessed against the *M. tuberculosis* H37Rv strain (ATCC 27294), which is susceptible to both rifampin and INH. The biological study was carried out using the Microplate Alamar Blue Assay (MABA), which is nontoxic, uses thermally stable reagents, and shows strong correlation and proportionality with the BACTEC MGIT 960 system (Mycobacterium Growth Indicator Tube, Becton Dickinson Company, MD, USA).[26−28] This colorimetric method uses the Alamar Blue resazurin-based oxidation−reduction indicator to obtain drug susceptibility measurements for bacteria. A blue color in the well was interpreted as indicating no bacterial growth, a pink color was scored as growth, and purple indicated growth inhibition. Compounds showing 90% inhibition in the primary screen were considered active and retested at a lower concentration against *M. tuberculosis* (ATCC 27294 H37Rv) to determine the actual MIC. The MIC was defined as the lowest drug concentration that prevented a change of color from blue to pink. The positive controls used were rifampicin and INH. All determinations were performed in triplicate, and the values shown in Table 1 are the averages.

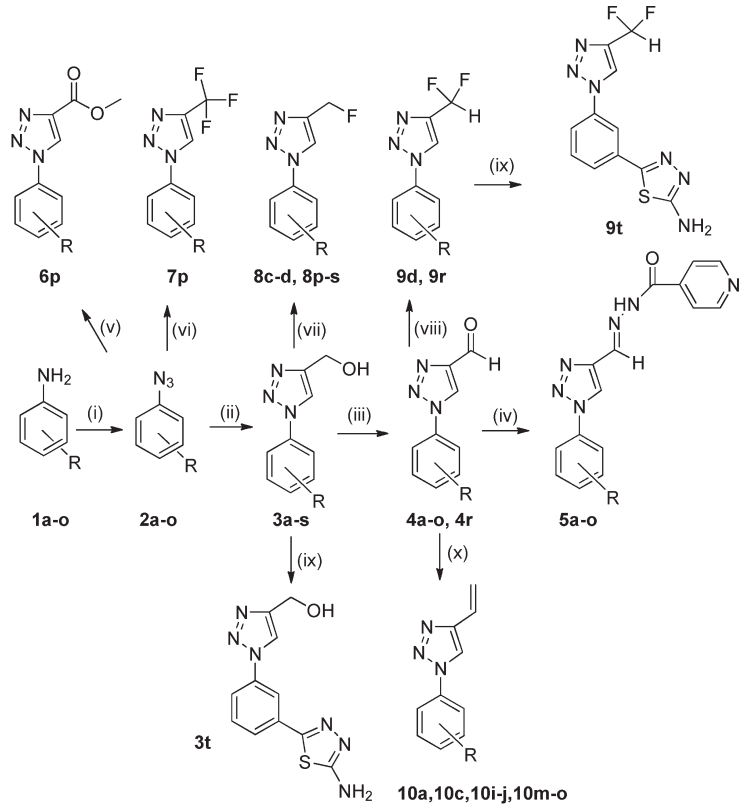
Cytotoxicity. The cytotoxic activity of 1,2,3-triazoles was assayed only on compounds with MIC ≤ 12.5 μg/mL (**4c**, **5a**−**o**, and **10o**). The cytotoxicity was tested against hepatoma cells (HEPG2) and kidney basal cells (BGM) using the MTT ((3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay. The results are summarized in Table 2.

RESULTS AND DISCUSSION

The synthetic route was initiated with the preparation of aromatic azides. Aromatic amines and sodium nitrite were appropriately combined to form diazonium salts, which were subsequently converted into azide (Scheme 1). Aromatic azides were obtained as yellow oils with yields ranging from 63% to 100%. The azides were used directly in the next step without purification to prevent degradation. The chemical structures of the azides were confirmed by analyzing the crude product using FTIR. Analysis showed a strong absorption band at 2099−2100 cm^{-1}, referring to the stretch vibrations of the N_3 bond of the azido group.

The synthesis of triazoles **3a**−**s** involved the 1,3-dipolar cycloaddition reaction between propargyl alcohol and aromatic azides catalyzed by Cu(I). Copper sulfate ($CuSO_4$) and sodium ascorbate guided the regioselectivity. To obtain derivatives **6p** and **7p**, cycloadditions were conducted using methyl propiolate and 3,3,3-trifluoro-1-propyne. Reactions were performed under magnetic stirring at room temperature and were protected from light due to the photosensitivity of the aromatic azides. After purification in a flash-type column, triazole compounds were obtained as white or yellow crystals with yields ranging from 30% to 82%. Triazoles (**3a**−**s**, **6p**, **7p**) were identified using FTIR and showed the absence of stretching vibrations of the azide group and the presence of bands related to axial deformation of the OH bond. In the ^{1}H NMR spectra, the signals of the respective protons of the synthesized compounds were verified on the basis of their chemical shifts, multiplicities, and coupling constants. The triazole protons were observed as a singlet at

Scheme 1. Synthetic Route for the Preparation of 1,2,3-Triazole Derivatives[a]



	a	b	c	d	e	f	g	h	i	j	l	m	n	o
R	H	4-F	4-Cl	3-Cl	2-Cl	4-CH_3	3-CH_3	2-CH_3	4-NO_2	4-OCH_3	3-OCH_3	2-OCH_3	3,4-diCl	2,5-diCl

	p	q	r	s	t
	3,5-diCl	4-CN	3-CN	4-Br	$C_2N_2SNH_2$

[a] Reagents and conditions: (i) $NaNO_2$, HCl 10%; NaN_3, 2−4 h, rt. (ii) propargyl alcohol, $CuSO_4$, sodium ascorbate, H_2O:*t*-butanol, 3 h, rt; (iii) IBX/DMSO, 3 h, rt; (iv) $NH_2NHC(O)C_5H_4N$, MeOH, 48 h, rt; (v) methyl propiolate, $CuSO_4$, sodium ascorbate, H_2O:*t*-butanol, 24 h, rt; (vi) 3,3,3-trifluoro-1-propyne, $CuSO_4$, sodium ascorbate, H_2O:*t*-butanol, 4 days, rt; (vii) DAST, CH_2Cl_2, 4 days, rt; (viii) DAST, CH_2Cl_2, 24 h, rt; (ix) thiosemicarbazide, CF_3COOH, 24 h, 60 °C; (x) methyltriphenylphosphonium bromide, NaH, THF, 3−4 hours, rt.

7.96 to 8.05 ppm, whereas the CH_2 group was a doublet at 4.57−5.46 ppm. The **6p** derivative showed characteristic ^1H and ^{13}C NMR signals at 3.90 and 160.2 ppm, respectively; these signals corresponded to the methyl group and the ester carbonyl. Compound **7p** was confirmed by ^{19}F NMR and showed a characteristic signal at −59.9 ppm that confirmed the presence of the trifluoromethyl group.

1,2,3-Triazole alcohols (**3a**−**o**, **3r**) were further oxidized to aldehydes (**4a**−**o**, **4r**) using IBX in dimethyl sulfoxide (DMSO). Compounds were purified by silica gel flash-type column chromatography, and the triazole aldehydes were obtained as white or light-yellow crystals in yields ranging from 55% to 100%. Structures were confirmed by FTIR, ^1H NMR, and ^{13}C NMR. The FTIR showed no bands relating to axial deformation of the OH bond and contained characteristic bands of carbonyl group stretching from the aldehydes between 1690 and 1704 cm^{-1}. The ^1H NMR spectra showed singlet signals between 10.0 and 9.9 ppm, corresponding to the aldehyde hydrogens. Signals between 8.00 and 8.10 ppm were assigned to the triazole hydrogens. ^{13}C NMR spectra also showed signals in the region of 185.0 ppm, corresponding to the carbonyl carbons.

For the preparation of fluorinated derivatives **8c**−**d**, **8p**−**s**, **9d**, and **9r**, DAST was used as the fluorinating agent. The reaction was carried out under magnetic stirring at room temperature and led to the formation of products in good yields. The ^{19}F NMR spectra of monofluoro products showed characteristic signals between −207 and −206 ppm. The ^{13}C NMR spectra showed signals between 75.2 and 76.1 ppm with fluorine coupling constants in the range of 160 Hz. These signals confirmed the presence of one fluorine atom. The preparation of compounds **3t** and **9t** was performed by reacting aromatic nitrile derivatives with thiosemicarbazide in boiling trifluoroacetic acid to give 2-amino-5-aryl-1,3,4-thiadiazoles.[24] Good yields were obtained, although an extended reaction time was required. Spectroscopic analysis confirmed the formation of these products. Amine (NH_2) protons were observed as a singlet at 7.56 ppm, and elemental analyses were consistent with the structures.

The syntheses of the isonicotinoyl hydrazide derivatives (**5a**−**o**) were performed with the appropriate aldehyde 1,2,3-triazoles (**4a**−**o**) and INH, as described in the general procedure. Reaction mixtures were maintained at room temperature, leading to desired compounds **5a**−**o** in 52−99% yield. The FTIR spectra

dx.doi.org/10.1021/jm2003624 |*J. Med. Chem.* 2011, 54, 5988–5999

Table 1. The in Vitro Activity Expressed by MIC in μg/mL (μM) of Compounds 3a−t, 4a−o, 4r, 5a−o, 6p, 7p, 8c−d, 8p−s, 9d, 9r, 9t, 10a, 10c, 10i−j, and 10m−o against *M. tuberculosis* H37Rv (ATCC-27294) Strain

entry	MIC	entry	MIC
isoniazid	0.06 (0.437)	**4o**	> 100
rifampicin	1.0 (1.21)	**5a**	2.5 (8.5)
3a	>100	**5b**	1.25 (4.0)
3b	>100	**5c**	0.62 (1.8)
3c	>100	**5d**	0.62 (1.8)
3d	>100	**5e**	1.25 (3.8)
3e	>100	**5f**	1.25 (4.0)
3f	>100	**5g**	0.62 (2.0)
3g	>100	**5h**	2.5 (8.1)
3h	>100	**5i**	0.62 (1.8)
3i	>100	**5j**	2.5 (7.7)
3j	>100	**5l**	1.25 (3.8)
3l	>100	**5m**	0.62 (1.9)
3m	>100	**5n**	2.5 (6.9)
3n	>100	**5o**	1.25 (3.4)
3o	>100	**6p**	>100
3p	>100	**7p**	50.0 (177.2)
3q	>100	**8c**	100.0 (472.5)
3r	>100	**8d**	100.0 (472.5)
3s	>100	**8p**	100.0 (406.3)
3t	>100	**8q**	>100
4a	25.0 (144.5)	**8r**	>100
4b	25.0 (130.7)	**8s**	100.0 (390.5)
4c	12.5 (60.2)	**9d**	>100
4d	25.0 (120.7)	**9r**	25.0 (113.6)
4e	50.0 (240.8)	**9t**	100.0 (340.0)
4f	12.5 (66.7)	**10a**	>100
4g	25.0 (133.5)	**10c**	50.0 (243.1)
4h	50.0 (267.1)	**10i**	>100
4i	25.0 (114.6)	**10j**	50.0 (243.5)
4j	25.0 (123.0)	**10m**	>100
4l	25.0 (123.0)	**10n**	>100
4m	50.0 (246.0)	**10o**	3.12 (13.0)
4n	50.0 (206.6)		

showed the carbonyl peaks at 1651−1703 cm^{-1}, and the NH stretching vibrations at 3013−3213 cm^{-1}. The ^{1}H NMR spectra displayed the hydrazide (NH) protons as singlets between 12.40 and 11.94 ppm, and the hydrazone protons (H−C═N−N) between 8.91 and 8.55 ppm. The ^{13}C NMR spectra showed C═O signals at 162.0−163.4 ppm and C═N signals at 142.6−143.0 ppm.

The Wittig reaction was used to synthesize the 4-vinyl compounds (**10a**, **10c**, **10i**−**j**, and **10m**−**o**).[25] Most of the Wittig reagents used were prepared with ultrasound in situ using a mixture of the appropriate phosphonium salt and base. In the work presented, the reaction of the corresponding aldehydes (**4a**, **4c**, **4i**−**j**, and **4m**−**o**) with methyl(triphenyl1)phosphonium bromide in the presence of NaH gave only the 4-vinyl-1,2,3-triazoles (**10a**, **10c**, **10i**−**j**, and **10m**−**o**). The FTIR spectra showed C═C peaks at 1485 to 1505 cm^{-1}. The ^{1}H NMR spectra showed CH═CHH′ protons as doublets from 5.44 to 6.02 and from 6.76 to 6.80 ppm. The ^{13}C NMR showed characteristic signals from 115.2 to 117.4 and from 117.9 to 127.2 ppm, corresponding to $CH{=}CH_2$ moieties.

Table 2. The Cytotoxicity of the Compounds Is Expressed by MDL_{50} in μg/mL (μM), and Selectivity Index Calculated Using Two Cells Lines

	MDL_{50} μg/mL mean ± SD		selectivity index	
compd	HepG2	BGM	HepG2	BGM
4c	71 ± 1	97 ± 18	6	8
5h	314 ± 0.5	>1000	126	400
5m	>1000	>1000	>1612	>1612
5b	>1000	>1000	>800	>800
5c	>1000	>1000	>1612	>1612
5j	>1000	>1000	>400	>400
10o	>1000	>1000	>321	>321
5l	NT[a]	>1000	NT[a]	>800
5g	124 ± 21	262 ± 25	200	422
5i	>1000	>1000	>1612	>1612
5n	>1000	>1000	>400	>400
5f	118 ± 14	>1000	94	>800
5e	263 ± 75	>1000	210	>800
5o	>1000	>1000	>800	>800
5a	>1000	>1000	>400	>400
5d	>1000	>1000	>1612	>1612

[a] NT = not tested.

All of the compounds showed mass spectra with molecular ions characteristic of their chemical structure.

Following the presented methodology, we synthesized an extensive set of 4-substituted *N*-phenyl-1,2,3-triazole derivatives. Cytotoxicity studies were done only on the most active compounds using the MTT assay. The ratios between cytotoxicity and tuberculostatic activities in vitro enabled the determination of the selectivity index (SI). Compounds that exhibited SI values greater than 10 were considered nontoxic.[29] Comparing the toxicity exhibited by the compounds using the two cell lines, compounds **4c**, **5h**, **5g**, **5e**, and **5f** showed lower SI values for the HepG2 cell line while the remaining compounds showed no toxicity. In some cases, the selectivity index for these compounds was higher than 1612. These results demonstrated that only compound **4c** was toxic with an SI value lower than 10.

All of the compounds were evaluated against *M. tuberculosis* H37Rv ATCC 27294, and the principal results are reported in Table 1. The tested compounds showed antimycobacterial activity with most of their MIC values between 267.1 and 1.8 μM. However, the test compounds **3a**−**s** were ineffective at inhibiting the growth of the *M. tuberculosis* H37Rv ATCC 27294 strain (MICs ≥ 100 mg/L). It is possible that failure of mycolic acid synthesis upon cell wall formation in this strain could prevent penetration of this group of substances into the mycobacteria.

In our previous work,[16] we synthesized the derivatives **4c**−**d**, **4f**, **4i**−**j**, **4m**, **4r**, **9d**, and **9r** using diazomalonaldehyde, which was added to aniline hydrochlorides through cycloaddition. Diazomalonaldehyde was obtained from a relatively complex four-step synthetic route.[16] As expected, the synthesis of 1,2,3-triazole derivatives using click chemistry proved to be more effective than using diazomalonaldehyde.

dx.doi.org/10.1021/jm2003624 |*J. Med. Chem.* 2011, 54, 5988–5999

CONCLUSIONS

In summary, this study showed that 1,2,3-triazole derivatives exhibited antimycobacterial activity in the same range as INH for the susceptible H37Rv strain. Several synthesized compounds displayed MIC values below the 6.25 μg/mL value postulated by the Global Program for the Discovery of New Anti-Tuberculosis Drugs as an upper threshold for the evaluation of new *M. tuberculosis* therapies. We believe that the isonicotinoyl hydrazide unit in compounds **5a**−**o** plays an important role in its antibacterial activity but is not the only pharmacophore involved. We observed that phenyl triazoles with various substituents exhibited notably different activities. Specifically, the substituent at the 4-position on the triazole was much more influential on inhibitory activity than other positions. We could therefore conclude that the reactivity order of compounds having substituent at the 4-position on the triazole was isonicotinoyl hydrazide > vinyl > CHO > CHF_2 > CF_3 ≫ CH_2F ≫ $COOCH_3$ ≫ CH_2OH. Moreover, it is expected that isonicotinoyl hydrazide derivatives **5a**−**o** could exhibit lower toxicity and fewer side effects than INH itself because the highly reactive hydrazine group in INH is protected in the isonicotinoyl hydrazide derivatives.[30] Whereas there are no new options for treating TB, we envision the possibility of using INH derivatives, such as the ones reported here, as suitable lead compounds for further development. The results reported in this study should be useful in guiding future efforts to discover new compounds with increased tuberculostatic activity.

The preparation of new compounds (**3t**, **4e**, **4h**, **4n**, **4o**, **5a**−**o**, **6p**, **7p**, **8c**−**d**, **8p**−**s**, **9t**, **10c**, **10i**−**j**, and **10m**−**o**) was performed with robust yields from commercially available materials. The synthesis of the new 1,2,3-triazole derivatives described in this work took advantage of azide and alkyne reactivity in the Huisgen cycloaddition. The methodology utilized was a simple way to obtain 4-substituted *N*-phenyl-1,2,3-triazoles using $CuSO_4$ and sodium ascorbate. Several of the 1,2,3-triazole derivatives synthesized using this technology exhibited strong activity when compared with first-line drugs, such as INH and rifampicin.

EXPERIMENTAL SECTION

1. Chemistry. Reagents were purchased from Aldrich or Acros Chemical Co. and used without further purification. Column chromatography was performed with Silica Gel 60 (Merck 70−230 mesh). Analytical thin-layer chromatography was performed with silica gel plates (Merck, thin layer chromatography (TLC) Silica Gel 60 F254), and the spots were visualized using ultraviolet (UV) light or aqueous solutions of ammonium sulfate. Yields refer to chromatographically and spectroscopically homogeneous materials. Melting points were obtained on a Fischer−Johns apparatus and are uncorrected. Infrared spectra were measured using potassium bromide (KBr) pellets on a Perkin-Elmer model 1420 FT-IR spectrophotometer, which was calibrated relative to the 1601.8 cm^{-1} absorbance of polystyrene. The NMR spectra were recorded on a Varian Unity Plus VXR (300 MHz) instrument and Bruker Avance instruments (400 and 500 MHz) in DMSO-d_6, deuterochloroform ($CDCl_3$), or acetone-d_6 (CD_3COCD_3) solutions. The chemical shift data are reported in units of δ (ppm) downfield from tetramethylsilane (TMS) or the solvent, which was used as an internal standard. Coupling constants (*J*) are reported in hertz and refer to apparent peak multiplicities. Mass spectra were acquired on a Shimadzu model QP5050A instrument coupled to GC model 17A (Shimadzu). Elemental analysis was used to ascertain purity > (95%) of all compounds for which biological data were determined. The CHN elemental analyses were performed on a Perkin-Elmer 2400 CHN elemental analyzer (São Paulo University, USP/Brazil) and within 0.4% of theoretical values.

*General Procedure for Preparation of **2a**−**o***. In a round-bottom flask equipped with a magnetic stirring bar, substituted aniline was dissolved (10 mmol) with HCl 6N (10 mL) in an ice bath at 0−5 °C. Next, $NaNO_2$ (15 mmol in 25 mL of H_2O) was added dropwise. The reaction mixture was stirred for 30 min at 0−5 °C. Next, a solution of sodium azide (40 mmol in 50 mL of H_2O) was added dropwise. After addition, the system was stirred for another hour. Next, the mixture was extracted with ethyl acetate and the combined organic extracts were washed with H_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residual crude product was used directly without purification.

*General Procedure for Preparation of **3a**−**s***. In a round-bottom flask equipped with a magnetic stirring bar, sodium azide (0.83 mmol) was added, along with propargyl alcohol (0.75 mmol), *tert*-butanol (0.7 mL), $CuSO_4$ pentahydrate (0.04 mmol), sodium ascorbate (0.11 mmol), and H_2O (0.7 mL). The reaction mixture was stirred for 48−72 h at room temperature and subsequently extracted with ethyl acetate. The combined organic extracts were washed with H_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residual crude product was purified via silica gel column chromatography using a gradient mixture of hexane−ethyl acetate to obtain the pure derivatives **3a**−**s**.

*1-(Phenyl)-1H-1,2,3-triazole-4-yl-methanol (**3a**)*. White solid, mp = 109−110 °C. IR ν_{max} (cm^{-1}): 3379, 3138, 1594, 1501, 1465, 1349, 1238, 1176, 1012, 819, 758, 684. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 4.73 (1H, d, *J* = 5.6, OH), 5.46 (2H, td, *J* = 5.6 and 1.7, C$\underline{H_2}$OH), 7.56−7.62 (1H, m, H-4′), 7.68−7.73 (2H, m, H-3′ and H-5′), 8.00−8.03 (2H, m, H-2′ and H-6′), 8.77 (1H, s, H-5). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 55.7 (C$\underline{H_2}$OH), 120.6 (C-4′), 121.6 (C-5), 129.1 (C-3′ and C-5′), 130.5 (C-2′and C-6′), 137.4 (C-1′), 149.8 (C-4).

*1-(4-Fluorophenyl)-1H-1,2,3-triazole-4-yl)methanol (**3b**)*. White solid, mp = 133−134 °C. IR ν_{max} (cm^{-1}): 3397, 3230, 3066, 1575, 1494, 1290, 1250, 1060, 824, 685. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 4.90 (2H, d, *J* = 5.8, C$\underline{H_2}$OH), 5.50 (1H, t, *J* = 5.8, OH), 7.72 (2H, d, *J* = 9.3, H-3′ and H-5′), 8.03 (2H, d, *J* = 9.3, H-2′ and H-6′), 8.80 (1H, s, H-5). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 56.0 (C$\underline{H_2}$OH), 121.3 (C-5), 121.8 (C-2′ and C-6′), 130.2 (C-2′ and C-6′), 141.6 (C-1′), 142.4 (C-4), 160.8 (C-4′).

*1-(4-Chlorophenyl)-1H-1,2,3-triazole-4-yl)methanol (**3c**)*. White solid, mp = 144−145 °C. IR ν_{max} (cm^{-1}): 3320, 3113, 3071, 2930, 2867, 2826, 1500, 1433, 1411, 1239, 1184, 1092, 1061, 1039, 1014, 836, 774, 703, 676. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 4.61 (2H, d, *J* = 5.6, C$\underline{H_2}$OH), 5.35 (1H, t, *J* = 5.6, OH), 7.66 (2H, d, *J* = 9.1, H-3′ and H-5′), 7.95 (2H, d, *J* = 9.1, H-2′ and H-6′), 8.71 (1H, s, H-5). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 55.0 (C$\underline{H_2}$OH), 121.1 (C-5), 121.6 (C-2′ and C-6′), 129.9 (C-3′ and C-5′), 132.8 (C-4′), 135.6 (C-1′), 149.4 (C-4).

*1-(3-Chlorophenyl)-1H-1,2,3-triazole-4-yl)methanol (**3d**)*. White solid, mp = 95−97 °C. IR ν_{max} (cm^{-1}): 3263, 3090, 1593, 1487, 1464, 1236, 1043, 871, 784, 671. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 4.61 (2H, d, *J* = 4.7, C$\underline{H_2}$OH), 5.36 (2H, t, *J* = 5.5, OH), 7.54−7.56 (1H, m, H-4′), 7.62 (1H, t, *J* = 8 Hz, H-5′), 7.91−7.94 (1H, m, H-6′), 8.04−8.06 (1H, m, H-2′), 8.77 (1H, s, H-5). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 54.9 (CH_2OH), 118.4 (C-5′), 119.6 (C-4′), 121.1 (C-5), 128.2 (C-2′), 131.6 (C-6′), 134.1 (C-3′), 137.7 (C-1′), 149.3 (C-4).

*1-(2-Chlorophenyl)-1H-1,2,3-triazole-4-yl)methanol (**3e**)*. White solid, mp = 86−87 °C. IR ν_{max} (cm^{-1}): 3266, 3112, 3072, 2988, 2935, 2868, 1498, 1467, 1420, 1380, 1341, 1227, 1181, 1122, 1041, 1012, 947, 882, 765, 675. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 4.62 (2H, d, *J* = 5.6, C$\underline{H_2}$OH), 5.32 (1H, t, *J* = 5.6, OH), 7.55−7.67 (3H, m, H-3′, H-4′ and H-5′), 7.76 (1H, dd, *J* = 1.95 and 1.22), 8.40 (1H, s, H-5). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 128.4 (C-2′), 124.8 (C-5), 131.4 (C-3′), 130.5 (C-4′), 128.3 (C-5′), 128.2 (C-6′), 54.8 (C-6), 135.0 (C-1′), 148.0 (C-4).

*1-(4-Methylphenyl)-1H-1,2,3-triazole-4-yl)methanol (**3f**).* White solid, mp = 124−125 °C. IR ν_{max} (cm^{-1}): 3426, 3221, 3117, 1517, 1239, 1187, 1042, 1013, 824, 772, 714, 686. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.28 (3H, s, CH_3), 4.66 (2H, d, J = 5.2, CH_2OH), 5.48 (1H, s, OH), 7.65 (2H, d, J = 9.5, H-3′ and H-5′), 7.99 (2H, d, J = 9.5, H-2′ and H-6′), 8.89 (1H, s, H-5). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 21.1 (CH_3), 59.0 (CH_2OH), 120.0 (C-5), 121.6 (C-2′ and C-6′), 130.9 (C-2′ and C-6′), 132.7 (C-4′), 135.3 (C-1′), 150.4 (C-4).

*1-(3-Methylphenyl)-1H-1,2,3-triazole-4-yl)methanol (**3g**).* White solid, mp = 94−95 °C. IR ν_{max} (cm^{-1}): 3257, 3128, 3089, 1611, 1488, 1232, 1055, 1017, 851, 786, 688. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.87 (3H, s, CH_3), 3.09 (1H, t, J = 4.8, OH), 4.89 (2H, d, J = 4.8, CH_2OH), 7.23−7.27 (1H, m, H-4′), 7.36−7.41 (1H, m, H-5′), 7.47−7.50 (1H, m, H-6′), 7.55−7.56 (1H, m, H-2′), 7.98 (1H, s, H-5). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 21.2 (CH_3), 56.0 (CH_2OH), 117.4 (C-6′), 120.2 (C-5), 121.0 (C-4′ and C-5′), 129.4 (C-2′), 136.7 (C-3′), 139.8 (C-1′), 148.4 (C-4).

*1-(2-Methylphenyl)-1H-1,2,3-triazole-4-yl)methanol (**3h**).* White solid, mp = 58−59 °C. IR ν_{max} (cm^{-1}): 3266, 3112, 3072, 2988, 2935, 2868, 1498, 1467, 1420, 1380, 1341, 1227, 1181, 1122, 1041, 1012, 947, 882, 765, 710, 675, 643. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.24 (3H, s, CH_3), 4.61 (2H, d, J = 5.4, CH_2OH), 5.45 (1H, s, OH), 7.37−7.49 (4H, m, H-3′, H-4′, H-5′ and H-6′), 8.23 (1H, s, H-5). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 17.6 (CH_3), 55.1 (C-2′), 124.6 (C-5), 126.2 (C-3′), 127.3 (C-4′), 130.0 (C-5′), 131.6 (C-6′), 133.3 (C-6), 136.6 (C-1′), 148.2 (C-4).

*1-(4-Nitrophenyl)-1H-1,2,3-triazole-4-yl)methanol (**3i**).* White solid, mp = 201−202 °C. IR ν_{max} (cm^{-1}): 3283, 3138, 3080, 2934, 1583, 1484, 1452, 1369, 1237, 1094, 1054, 1022, 844, 808. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 4.63 (2H, s, CH_2OH), 5.39 (1H, s, OH), 8.23 (1H, d, J = 9.1, H-2′), 8.44 (1H, d, J = 9.1, H-3′), 8.23 (1H, d, J = 9.1, H-5′), 8.44 (1H, d, J = 9.1, H-6′). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 54.2 (CH_2OH), 120.7 (C-5), 119.7 (C-2′), 119.7 (C-6′), 140.3 (C-4′), 124.9 (C-3′), 124.9 (C-5′), 145.9 (C-1′), 149.2 (C-4).

*1-(4-Methoxyphenyl)-1H-1,2,3-triazole-4-yl)methanol (**3j**).* White solid, mp = 127−129 °C. IR ν_{max} (cm^{-1}): 3421, 3145, 3093, 1584, 1488, 1400, 1225, 1140, 1061, 703, 676. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 4.57 (2H, d, J = 5.5, CH_2OH), 5.4 (1H, t, J = 5.5, OH), 7.74 (1H, d, J = 9.1, H-6′), 7.09 (1H, d, J = 9.1, H-5′), 7.09 (1H, d, J = 9.1, H-3′), 7.74 (1H, d, J = 9.1, H-2′), 8.45 (1H, s, H-5). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 55.1 (CH_2OH), 115.1 (C-5′), 121.2 (C-5), 121.9 (C-2′), 130.3 (C-4′), 121.9 (C-6′), 115.1 (C-3′), 149.0 (C-1′), 159.4 (C-4).

*1-(3-Methoxyphenyl)-1H-1,2,3-triazole-4-yl)methanol (**3l**).* White solid, mp = 100−102 °C. IR ν_{max} (cm^{-1}): 3256, 3110, 3070, 2987, 2930, 2868, 1488, 1447, 1419, 1380, 1351, 1227, 1171, 1112, 1041, 1012, 947, 892, 766, 709, 665, 643. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.87 (3H, s, CH_3), 4.88 (2H, d, J = 5.7, CH_2OH), 2.9 (1H, t, J = 5.7, OH), 7.32 (1H, dd, J = 2.3 H-2′), 6.97 (1H, ddd, J = 8.1, J = 2.3, J = 0.9, H-4′), 7.40 (1H, dd, J = 8.1, H-5′), 7.23 (1H, ddd, J = 8.1, J = 2.3, J = 0.9, H-6′), 7.97 (1H, s, H-5). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 55.5 (OCH_3), 56.1 (CH_2), 112.3 (C-4′), 114.6 (C-6′), 120.2 (C-5), 121.9 (C-2′), 130.4 (C-5′), 137.9 (C-1′), 148.4 (C-4), 160.5 (C-3′).

*1-(2-Methoxyphenyl)-1H-1,2,3-triazole-4-yl)methanol (**3m**).* White solid, mp = 116−117 °C. IR ν_{max} (cm^{-1}): 3276, 3123, 3078, 2954, 1603, 1509, 1472, 1286, 1250, 1180, 1122, 1016, 861, 761, 715, 682. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.58 (3H, s, CH_3), 4.95 (2H, d, J = 5.4, CH_2OH), 2.82 (1H, t, J = 5.4, OH), 7.40−7.49 (4H, m, H-3′, H-4′, H-5′ and H-6′), 8.15 (1H, s, H-5). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 59.8 (C-2′), 59.9 (OCH_3), 126.6 (C-5), 127.2 (C-3′), 128.3 (C-4′), 131.0 (C-5′), 131.9 (C-6′), 133.8 (C-6), 137.6 (C-1′), 150.2 (C-4).

*1-(3,4-Dichlorophenyl)-1H-1,2,3-triazole-4-yl)methanol (**3n**).* White solid, mp = 122−123 °C. IR ν_{max} (cm^{-1}): 3421, 3145, 3093, 1584, 1488, 1400, 1225, 1140, 1061, 992, 872, 832, 804. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 4.60 (2H, d, J = 4.9, CH_2OH), 5.37 (1H, t, J = 4.9, OH), 7.86 (1H, d, J = 8.9, H-6′), 7.96 (1H, dd, J = 8.9 and 2.4, H-5′), 8.26 (1H, d, J = 2.4, H-2′), 8.78 (1H, s, H-5). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 55.0 (CH_2OH), 120.0 (C-5′), 121.3 (C-5), 121.6 (C-2′), 130.9 (C-4′), 131.8 (C-6′), 132.5 (C-3′), 136.3 (C-1′), 149.6 (C-4).

*1-(2,5-Dichlorophenyl)-1H-1,2,3-triazole-4-yl)methanol (**3o**).* White solid, mp = 114−116 °C. IR ν_{max} (cm^{-1}): 3283, 3138, 3080, 2934, 1583, 1484, 1452, 1369, 1237, 1094, 1054, 1022, 844, 808. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 4.62 (2H, s, CH_2OH), 5.36 (1H, s, OH), 7.71 (1H, dd, J = 8.8 and 2.7, H-4′), 7.80 (1H, d, J = 8.8, H-3′), 7.86 (1H, d, J = 2.7, H-6′), 8.42 (1H, s, H-5). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 54.5 (CH_2OH), 124.8 (C-5), 127.4 (C-2′), 128.0 (C-6′), 131.2 (C-4′), 131.8 (C-3′), 132.3 (C-5′), 135.5 (C-1′), 148.1 (C-4).

*1-(3,5-Dichlorophenyl)-1H-1,2,3-triazole-4-yl)methanol (**3p**).* Brown solid, mp = 145−146 °C. IR ν_{max} (cm^{-1}): 3244, 3113, 3074, 2935, 1585, 1474, 1438, 1238, 1060, 1026, 860, 802. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 4.61 (2H, d, J = 5.5 Hz, CH_2OH), 5.38 (1H, t, J = 5.5 Hz, OH), 7.74 (1H, s, H-4′), 8.07 (2H, d, J = 1.5 Hz, H-2′ and H-6′), 8.83 (1H, s, H-5). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 54.8 (CH_2OH), 118.5 (C-4′), 121.3 (C-5), 127.8 (C-2′ and C-6′), 135.2 (C-3′ and C-5′), 138.3 (C-1′), 149.5 (C-4). Anal. Calcd for $C_9H_7Cl_2N_3O$: C, 44.29; H, 2.89; N, 17.22. Found: C, 44.53; H, 3.08; N, 15.30.

*4-(4-(Hydroxymethyl)-1H-1,2,3-triazole-1-yl)benzonitrile (**3q**).* Yellow solid, mp = 165−166 °C. IR ν_{max} (cm^{-1}): 3282, 3140, 2615, 2229, 1951, 1824, 1604, 1516, 1365, 1246, 1029, 856, 563. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 4.62 (2H, d, J = 5.5 Hz, CH_2OH), 5.42 (1H, t, J = 5.5 Hz, OH), 8.10−8.08 (2H, m, H-3′ and H-5′), 8.17−8.15 (2H, m, H-2′ and H-6′), 8.86 (1H, s, H-5). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 54.9 (CH_2OH), 110.8 (C-4′), 118.2 (CN), 120.2 (C-2′ and C-6′), 121.2 (C-5), 134.3 (C-3′ and C-5′), 139.6 (C-1′), 149.7 (C-4).

*3-(4-(Hydroxymethyl)-1H-1,2,3-triazole-1-yl)benzonitrile (**3r**).* White solid, mp = 125.2−126.3 °C. IR ν_{max} (cm^{-1}): 3286, 3132, 3089, 2881, 2237, 1720, 1585, 1500, 1446, 1246, 1049, 1018, 883. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 4.62 (2H, d, J = 5.5 Hz, CH_2OH), 5.37 (1H, t, J = 5.5 Hz, OH), 7.80 (1H, t, J = 8.0 Hz, H-4′), 7.96−7.94 (1H, m, H-5′), 8.29 (1H, dd, J = 1.2 and 8.2 Hz, H-6′), 8.44 (1H, s, H-2′), 8.79 (1H, s, H-5). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 54.8 (CH_2OH), 112.7 (C-4′), 117.8 (CN), 121.1 (C-5), 123.2 (C-2′), 124.5 (C-6′), 131.2 (C-3′) 132.0 (C-5′), 137.1 (C-1′), 149.5 (C-4).

*1-(4-Bromophenyl)-1H-1,2,3-triazole-4-yl)methanol (**3s**).* Brown solid, mp = 134.0−137.1 °C. IR ν_{max} (cm^{-1}): 3232, 3120, 2927, 2666, 1913, 1550, 1500,1404, 1242, 1184, 1060, 1037, 991, 833. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 4.60 (2H, s, CH_2OH), 7.80−7.78 (2H, m, H-3′ and H-5′), 7.89−7.88 (2H, m, H-2′ and H-6′), 8.73 (1H, s, H-5). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 54.9 (CH_2OH), 121.0 (C-5), 121.1 (C-4′), 121.8 (C-2′ and C-6′), 132.8 (C-3′ and C-5′), 135.9 (C-1′), 149.3 (C-4). Anal. Calcd for $C_9H_8BrN_3O$: C, 42.54; H, 3.17; N, 16.54. Found: C, 42.33; H, 3.24; N, 16.16.

*General Procedure for Preparation of **4a**−**o**, **4r**.* In a round-bottom flask equipped with a magnetic stirring bar, IBX (11 mmol) and 10 mmol of general 1,2,3-triazole of type **3** was added to DMSO (27.5 mL) and stirred at room temperature for 4 h. Then, H_2O (20 mL) was added to precipitate IBX crystals, and these crystals were decanted. The mother liquor was extracted with ethyl acetate, washed with $NaHCO_3$ solution, and dried over $MgSO_4$ to obtain pure aldehydes.

*1-(Phenyl-1H-1,2,3-triazole-4-carbaldehyde (**4a**).* White solid, mp = 95−96 °C. IR ν_{max} (cm^{-1}): 3431, 3131, 1691, 1529, 1209, 1168, 990, 853, 782, 761, 683. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.50−7.79 (4H, m, H-2′, H-3′, H-5′ and H-6′), 8.54 (1H, s, H-5), 10.23 (1H, s, H-6). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 120.8 (C-2′ and C-6′), 123.1 (C-5), 129.7 (C-4′), 130.0 (C-3′ and C-5′), 136.1 (C-1′), 148.0 (C-4), 185.0 (C-6), MS (ESI) m/z 173 $(M)^+$.

*1-(4-Fluorophenyl)-1H-1,2,3-triazole-4-carbaldehyde (**4b**).* Yellow solid, mp = 127−128 °C. IR ν_{max} (cm^{-1}): 3382, 3116, 3046, 1702, 1513, 1231, 1214, 1009, 837, 780, 613. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.80 (2H, d, J = 9.5, H-3′ and H-5′), 8.10 (2H, d, J = 9.5, H-2′ and H-6′),

8.85 (1H, s, H-5), 10,20 (1H, s, H-6). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 119.8 (C-2′ and C-6′), 121.1 (C-5), 129.7 (C-4′), 131.0 (C-3′ and C-5′), 140.1 (C-1′), 150.0 (C-4), 183.0 (C-6). MS (ESI) m/z 191 $(M)^+$.

*1-(2-Chlorophenyl)-1H-1,2,3-triazole-4-carbaldehyde (**4e**).* Yellow solid, mp = 76−77 °C. IR ν_{max} (cm^{-1}): 3138, 3092, 2860, 1704, 1573, 1529, 1487, 1402, 1371, 1261, 1199, 1170, 1142, 1100, 1075, 1042, 982, 857, 816, 698, 649. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.52−7.82 (4H, m, C-3′,C-4′,C-5′ and C-6′), 9.34 (1H, s, H-5), 10.13 (1H, s, CHO). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 131.8 (C-2′), 126.6 (C-6′), 128.6 (C-5), 126.7 (C-5′), 128.7 (C-4′), 130.4 (C-3′), 126.8 (C-1′), 144.9 (C-4), 182.9 (C-6).

*1-(3-Methylphenyl)-1H-1,2,3-triazole-4-carbaldehyde (**4g**).* White solid, mp = 90−92 °C. IR ν_{max} (cm^{-1}): 3433, 3459, 1457, 1158, 1025, 857, 759. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.48 (3H, s, CH_3), 7.32−7.61 (4H, m, H-2′, H-4′, H-5′ and H-6′), 8.52 (1H, s, H-5), 10.22 (1H, s, H-6). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 21.3 ($\underline{C}H_3$), 117.8 (C-6′), 121.4 (C-5′), 123.1 (C-5), 129.7 (C-4′), 130.4 (C-2′), 136.0 (C-1′), 140.3 (C-3′), 147.9 (C-4), 184.9 (C-6).

*1-(2-Methylphenyl)-1H-1,2,3-triazole-4-carbaldehyde (**4h**).* White solid, mp = 71−72 °C. IR ν_{max} (cm^{-1}): 3428, 3104, 1691, 1530, 1200, 1045, 996, 874, 773. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.28 (3H, s, CH_3), 7.42−7.61 (4H, m, H-2′, H-4′, H-5′ and H-6′), 8.55 (1H, s, H-5), 10.18 (1H, s, H-6). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 19.8 ($\underline{C}H_3$), 119.8 (C-6′), 121.6 (C-5′), 124.1 (C-5), 130.7 (C-4′), 130.1 (C-2′), 137.0 (C-1′), 145.3 (C-3′), 146.9 (C-4), 182.9 (C-6).

*1-(3-Methoxyphenyl)-1H-1,2,3-triazole-4-carbaldehyde (**4l**).* White solid, mp = 106−107 °C. IR ν_{max} (cm^{-1}): 3427, 3106, 3038, 2998, 1690, 1607, 1503, 1259, 1169, 1042, 845, 773, 677. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.90 (3H, s, OCH_3), 7.88−7.95 (4H, m, H-2′, H-4′, H-5′ and H-6′), 9.65 (1H, s, H-5), 10.30 (1H, s, H-6). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 56.8 (CH_3), 121.3 (C-2′), 122.3 (C-6′), 125.0 (C-5), 115.8 (C-5′), 148.0 (C-4′), 114.8 (C-3′), 130.2 (C-1′), 160.8 (C-4), 185.8 (C-6).

*1-(3,4-Dichlorophenyl)-1H-1,2,3-triazole-4-carbaldehyde (**4n**).* Yellow solid, mp = 168−169 °C. IR ν_{max} (cm^{-1}): 3127, 3088, 2924, 2873, 1693, 1531, 1487, 1437, 1404, 1261, 1206, 1172, 1139, 1034, 990, 857, 822, 771. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.02 (1H, d, J = 8.9, H-6′), 8.14 (1H, dd, J = 8.9 and 2.4, H-5′), 8.46 (1H, d, J = 2.7, H-2′), 9.73 (1H, s, H-5), 10.23 (1H, s, CHO). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 120.9 (C-2′), 122.7 (C-6′), 125.0 (C-5), 132.0 (C-5′), 132.2 (C-4′), 132.6 (C-3′), 135.6 (C-1′), 147.7 (C-4), 183.8 (C-6). MS (ESI) m/z 241 $(M)^+$.

*1-(2,5-Dichlorophenyl)-1H-1,2,3-triazole-4-carbaldehyde (**4o**).* Yellow solid, mp = 163−164 °C. IR ν_{max} (cm^{-1}): 3138, 3092, 2860, 1704, 1573, 1529, 1487, 1456, 1402, 1371, 1261, 1199, 1170, 1142, 1100, 1075, 1042, 982, 857, 816, 765, 698, 649. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.78 (1H, dd, J = 8.7 and 2.4, H-4′), 7.85 (1H, d, J = 8.7, H-3′), 8.02 (1H, d, J = 2.4, H-6′), 9.36 (1H, s, H-5), 10.13 (1H, s, H-6). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 128.1 (C-2′), 128.7 (C-6′), 130.8 (C-5), 132.2 (C-4′), 132.4 (C-3′), 132.8 (C-5′), 134.9 (C-1′), 146.7 (C-4), 184.7 (C-6).

*General Procedure for Preparation of **5a**−**o**.* The isonicotinoyl hydrazide derivatives **5a**−**o** were prepared by the reaction of triazole (**4a**−**o**) (1.0 mmol) with INH (1.0 mmol) in ethanol/H_2O (10 mL) by initially dissolving the INH in H_2O and adding the respective solution to a solution of the respective triazole (**4a**−**o**) in ethanol. After stirring for 1−3 h at room temperature, the resulting mixture was concentrated under reduced pressure. The residue was purified by washing with cold ethanol and ethyl ether to obtain the pure derivatives **5a**−**o**.

*(E)-N′-[(1-Phenyl-1H-1,2,3-triazole-4-yl)methylene]isonicotinoyl hydrazide (**5a**).* White solid, mp = 212−213 °C. IR ν_{max} (cm^{-1}): 3097, 3034, 1668, 1493, 1424, 1165, 854, 655. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.50−7.59 (5H, m, H-2′, H-3′, H-4′, H-5′ and H-6′), 7.82 (2H, d, J = 8.0), 8.55 (1H, s, H-5), 8.75 (1H, s, N═C−H), 8.95 (2H, d, J = 8.0), 12.23 (1H, s, N−H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 120.5 (C-2′ and C-6′), 121.1 (C-5 and C-3 INH ring), 123.3 (C-5), 128.7 (C-4′), 130.0 (C-3′ and C-5′), 136.6 (C-1′), 140.0 (C═N), 152.0 (C-2 and C-6 INH ring), 168.0 (C═O). MS (ESI) m/z 292 $(M)^+$. Anal. Calcd for $C_{15}H_{12}N_6O$: C, 61.64; H, 4.14; N, 28.75. Found: C, 61.47; H, 4.08; N, 28.68.

*(E)-N′-[(1-(4-Fluorophenyl)-1H-1,2,3-triazole-4-yl)methylene]-isonicotinoyl hydrazide (**5b**).* White solid, mp = 254−255 °C. IR ν_{max} (cm^{-1}): 3454, 3232, 3131, 3080, 1693, 1515, 1284, 1232, 837, 620. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.20 (2H, d, J = 9.5, H-3′ and H-5′), 7.65 (2H, d, J = 9.5, H-2′ and H-6′), 7.83 (2H, d, J = 8.0, INH ring), 8.60 (1H, s, H-5), 8.77 (1H, s, N═C−H), 8.90 (2H, d, J = 8.0, INH ring), 11.23 (1H, s, N−H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 115.5 (C-2′ and C-6′), 121.0 (C-5 and C-3 INH ring), 124.3 (C-5), 124.5 (C-3′ and C-5′), 132.6 (C-1′), 141.0 (C═N), 152.7 (C-2 and C-6 INH ring), 162.0 (C-4′), 168.8 (C═O). MS (ESI) m/z 310 $(M)^+$. Anal. Calcd for $C_{15}H_{11}FN_6O$: C, 58.06; H, 3.57; N, 27.08. Found: C, 58.47; H, 3.99; N, 28.58.

*(E)-N′-[(1-(4-Chlorophenyl)-1H-1,2,3-triazole-4-yl)methylene]-isonicotinoyl Hydrazide (**5c**).* White solid, mp = 267−269 °C. IR ν_{max} (cm^{-1}): 3444, 3246, 1693, 1560, 1499, 1280, 1053, 829, 687. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.25 (2H, d, J = 9.7, H-3′ and H-5′), 7.67 (2H, d, J = 9.7, H-2′ and H-6′), 7.82 (2H, d, J = 8.1, INH ring), 8.62 (1H, s, H-5), 8.70 (1H, s, N═C−H), 8.91 (2H, d, J = 8.1, INH ring), 11.25 (1H, s, N−H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 116.5 (C-2′ and C-6′), 122.0 (C-5 and C-3 INH ring), 124.9 (C-5), 125.5 (C-3′ and C-5′), 131.6 (C-1′), 141.8 (C═N), 152.8 (C-2 and C-6 INH ring), 160.0 (C-4′), 167.0 (C═O). MS (ESI) m/z 326 $(M)^+$. Anal. Calcd for $C_{15}H_{11}ClN_6O$: C, 55.14; H, 3.39; N, 25.72. Found: C, 55.47; H, 3.72; N, 25.63.

*(E)-N′-[(1-(3-Chlorophenyl)-1H-1,2,3-triazole-4-yl)methylene]-isonicotinoyl Hydrazide (**5d**).* White solid, mp = 206−207 °C. IR ν_{max} (cm^{-1}): 3399, 3237, 3066, 1617, 1575, 1290, 1060, 790, 751,684. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.40 (1H, dd, J = 8.0 and 7.9, H-5′), 7.46 (d, 1H, J = 8.0, H-4′), 7.51 (1H, d, J = 7.9, H-6′), 7.80 (1H, s, H-2′), 7.91 (2H, d, J = 8.1, INH ring), 8.51 (1H, s, H-5), 8.79 (1H, s, N═C−H), 8.92 (2H, d, J = 8.1, INH ring), 11.04 (1H, s, N−H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 125.6 (C-2′), 127.0 (C-6′), 128.4 (C-4′), 134.2 (C-5′), 134 (C-3′), 137.5 (C-1′), 123.7 (C-5 and C-3 INH ring), 124.6 (C-5), 141.4 (C═N), 152.2 (C-2 and C-6 INH ring), 142.0 (C-4), 166.7 (C═O). MS (ESI) m/z 326 $(M)^+$. Anal. Calcd for $C_{15}H_{11}ClN_6O$: C, 55.14; H, 3.39; N, 25.72. Found: C, 55.25; H, 3.41; N, 25.79.

*(E)-N′-[(1-(2-Chlorophenyl)-1H-1,2,3-triazole-4-yl)methylene]-isonicotinoyl Hydrazide (**5e**).* White solid, mp = 204−206 °C. IR ν_{max} (cm^{-1}): 3432, 3300, 3126, 1667, 1560, 1493, 1276, 1052, 848, 762. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.41 (1H, dd, J = 8.0 and 7.5, H-4′), 7.47 (1H, dd, J = 8.0 and 7.5, H-5′), 7.49 (1H, d, J = 7.5, H-3′), 7.57 (1H, d, J = 8.0, H-6′), 7.81 (2H, d, J = 8.5, INH ring), 8.64 (1H, s, H-5), 8.72 (1H, s, N═C−H), 8.93 (2H, d, J = 8.5, INH ring), 11.31 (1H, s, N−H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 132.2 (C-1′ and C-2′), 128.9 (C-6′), 130.1 (C-5′), 130.4 (C-4′), 132.3 (C-3′), 121.7 (C-5 and C-3 INH ring), 124.8 (C-5), 142.2 (C═N), 152.1 (C-2 and C-6 INH ring), 142.3 (C-4), 166.9 (C═O). MS (ESI) m/z 326 $(M)^+$. Anal. Calcd for $C_{15}H_{11}ClN_6O$: C, 55.14; H, 3.39; N, 25.72. Found: C, 55.03; H, 3.21; N, 25.63.

*(E)-N′-[(1-(4-Methylphenyl)-1H-1,2,3-triazole-4-yl)methylene]-isonicotinoyl Hydrazide (**5f**).* White solid, mp = 230−234 °C. IR ν_{max} (cm^{-1}): 3467, 3218, 3135, 1675, 1563, 1284, 1052, 823, 683. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.38 (3H, s, CH_3), 7.29 (2H, d, J = 9.3, H-3′ and H-5′), 7.69 (2H, d, J = 9.3, H-2′ and H-6′), 7.80 (2H, d, J = 8.0, INH ring), 8.65 (1H, s, H-5), 8.74 (1H, s, N═C−H), 8.88 (2H, d, J = 8.0, INH ring), 11.00 (1H, s, N−H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 117.5 (C-2′ and C-6′), 120.0 (C-5 and C-3 INH ring), 125.3 (C-5), 125.9 (C-3′ and C-5′), 131.8 (C-1′), 142.0 (C═N), 153.8 (C-2 and C-6 INH ring), 164.0 (C-4′), 168.0 (C═O). MS (ESI) m/z 306 $(M)^+$. Anal. Calcd for $C_{16}H_{14}N_6O$: C, 62.74; H, 4.61; N, 27.44. Found: C, 62.56; H, 4.69; N, 27.32.

*(E)-N′-[(1-(3-Methylphenyl)-1H-1,2,3-triazole-4-yl)methylene]-isonicotinoyl Hydrazide (**5g**).* White solid, mp = 170−172 °C. IR ν_{max} (cm^{-1}): 3386, 3218, 3135, 1686, 1568, 1294, 1051, 852, 777, 685. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.30 (s, CH3), 7.23 (d, 1H, J = 8.0, H-4′), 7.34 (1H, dd, J = 8.0 and 7.9, H-5′), 7.48 (1H, d, J = 7.9, H-6′), 7.50 (1H, s, H-2′), 7.93 (2H, d, J = 8.2, INH ring), 8.45 (1H, s, H-5), 8.77 (1H, s, N═C−H), 8.90 (2H, d, J = 8.2, INH ring), 11.07 (1H, s, N−H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 130.6 (C-2′), 127.2 (C-6′), 128.2 (C-4′), 128.5.2 (C-5′), 138.0 (C-3′), 128.5 (C-1′), 123.6 (C-5 and C-3 INH ring), 124.9 (C-5), 142.4 (C═N), 152.9 (C-2 and C-6 INH ring), 142.7 (C-4), 166.6 (C═O). MS (ESI) m/z 306 $(M)^+$. Anal. Calcd for $C_{16}H_{14}N_6O$: C, 62.74; H, 4.61; N, 27.44. Found: C, 62.70; H, 4.89 N, 27.43.

*(E)-N′-[(1-(2-Methylphenyl)-1H-1,2,3-triazole-4-yl)methylene]-isonicotinoyl Hydrazide (**5h**).* White solid, mp = 185−186 °C. IR ν_{max} (cm^{-1}): 3437, 3281, 3089, 1661, 1550, 1281, 1054, 785, 613. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.93 (1H, s, CH3), 7.32 (1H, dd, J = 8.0 and 7.5, H-4′), 7.38 (1H, dd, J = 8.0 and 7.5, H-5′), 7.47 (1H, d, J = 7.5, H-3′), 7.30 (1H, d, J = 8.0, H-6′), 7.80 (2H, d, J = 8.4, INH ring), 8.60 (1H, s, H-5), 8.71 (1H, s, N═C−H), 8.90 (2H, d, J = 8.4, INH ring), 12.0 (1H, s, N−H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 17.3 (CH_3), 127.2 (C-1′), 140.0 (C-2′), 120.2 (C-6′), 126.1 (C-5′ and C-3′), 131.4 (C-4′), 122.7 (C-5 and C-3 INH ring), 124.9 (C-5), 142.4 (C═N), 152.5 (C-2 and C-6 INH ring), 142.0 (C-4), 166.4 (C═O). MS (ESI) m/z 306 $(M)^+$. Anal. Calcd for $C_{16}H_{14}N_6O$: C, 62.74; H, 4.61; N, 27.44. Found: C, 62.27; H, 4.09; N, 26.99.

*(E)-N′-[(1-(4-Nitrophenyl)-1H-1,2,3-triazole-4-yl)methylene]-isonicotinoyl Hydrazide (**5i**).* White solid, mp = 230−232 °C. IR ν_{max} (cm^{-1}): 3437, 3299, 3092, 1662, 1584, 1525, 1345, 1276, 1049, 853, 749. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.35 (2H, d, J = 9.7, H-3′ and H-5′), 7.75 (2H, d, J = 9.7, H-2′ and H-6′), 7.81 (2H, d, J = 8.2, INH ring), 8.67 (1H, s, H-5), 8.75 (1H, s, N═C−H), 8.89 (2H, d, J = 8.2, INH ring), 12.00 (1H, s, N−H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 119.5 (C-2′), 120.0 (C-6′), 121.2 (C-5 and C-3 INH ring), 126.6 (C-5), 125.9 (C-3′), 130.0 (C-5′), 132.8 (C-1′), 142.6 (C═N), 153.0 (C-2 and C-6 INH ring), 163.0 (C-4′), 169.2 (C═O). MS (ESI) m/z 337 $(M)^+$. Anal. Calcd for $C_{15}H_{11}N_7O_3$: C, 53.41; H, 3.29; N, 29.07. Found: C, 53.56; H, 3.19; N, 29.09.

*(E)-N′-[(1-(4-Methoxyphenyl)-1H-1,2,3-triazole-4yl)methylene]-isonicotinoyl Hydrazide (**5j**).* White solid, mp = 235−236 °C. IR ν_{max} (cm^{-1}): 3435, 3298, 3088, 1662, 1517, 1277, 1251, 1037, 832, 758. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.10 (2H, d, J = 9.1, H-3′ and H-5′), 7.77 (2H, d, J = 9.1, H-2′ and H-6′), 7.88 (2H, d, J = 8.4, INH ring), 8.45 (1H, s, H-5), 8.77 (1H, s, N═C−H), 8.90 (2H, d, J = 8.4, INH ring), 12.05 (1H, s, N−H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 119.7 (C-2′), 121.4 (C-6′), 120.2 (C-5 and C-3 INH ring), 122.6 (C-5), 114.9 (C-3′), 115.0 (C-5′), 148.8 (C-1′), 143.6 (C═N), 154.0 (C-2 and C-6 INH ring), 130,2 (C-4′), 170.2 (C═O). MS (ESI) m/z 322 $(M)^+$. Anal. Calcd for $C_{16}H_{14}N_6O_2$: C, 59.62; H, 4.38; N, 26.07. Found: C, 59.31; H, 4.39; N, 25.95.

*(E)-N′-[(1-(3-Methoxyphenyl)-1H-1,2,3-triazole-4yl)methylene]-isonicotinoyl Hydrazide (**5l**).* White solid, mp = 190−192 °C. IR ν_{max} (cm^{-1}): 3421, 3258, 1670, 1574, 1501, 1295, 1166, 1047, 844, 688. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.85 (s, OCH3), 6.93 (s, 1H, H-2′), 7.11 (1H, d, J = 8.1, H-4′), 7.18 (1H, d, J = 7.5, H-6′), 7.34 (1H, dd, J = 8.1 and 7.5, H-5′), 7.90 (2H, d, J = 8.0, INH ring), 8.42 (1H, s, H-5), 8.76 (1H, s, N═C−H), 8.92 (2H, d, J = 8.0, INH ring), 11.05 (1H, s, N−H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 55.8 (OCH_3), 107.6 (C-2′), 121.2 (C-6′), 114.2 (C-4′), 145.5.2 (C-5′), 168.0 (C-3′), 128.7 (C-1′), 123.7 (C-5 and C-3 INH ring), 125.0 (C-5), 142.7 (C═N), 152.2 (C-2 and C-6 INH ring), 142.4 (C-4), 165.6 (C═O). MS (ESI) m/z 322 $(M)^+$. Anal. Calcd for $C_{16}H_{14}N_6O_2$: C, 59.62; H, 4.38; N, 26.07. Found: C, 59.69; H, 4.38; N, 26.10.

*(E)-N′-[(1-(2-Methoxyphenyl)-1H-1,2,3-triazole-4yl)methylene]-isonicotinoyl Hydrazide (**5m**).* White solid, mp = 194−195 °C. IR ν_{max} (cm^{-1}): 3423, 3158, 1675, 1504, 1500, 1297, 1184, 1049, 852, 712, 689. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.84 (s, OCH_3), 7.00 (d, 1H, J = 8.0, H-3′), 7.12 (dd, 1H, J = 8.0 and 6.5, H-5′), 7.30 (dd, 1H, J = 8.0 and 6.5, H-4′), 7.47 (d, 1H, J = 8.0 Hz, H-6′), 7.89 (2H, d, J = 8.0, INH ring), 8.48 (1H, s, H-5), 8.70 (1H, s, N═C−H), 8.92 (2H, d, J = 8.0, INH ring), 11.05 (1H, s, N−H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 57.9 (CH_3), 112.5 (C-5′ and C-6′), 125.8 (C-3′), 122.3 (C-4′), 119.9 (C-2′), 121.2 (C-5 and C-3 INH ring), 122.9 (C-5), 123.6 (C-5′), 129.3 (C-1′), 143.8 (C═N), 154.7 (C-2 and C-6 INH ring), 171.2 (C═O). MS (ESI) m/z 322 $(M)^+$. Anal. Calcd for $C_{16}H_{14}N_6O_2$: C, 59.62; H, 4.38; N, 26.07. Found: C, 59.89; H, 4.01; N, 26.16.

*(E)-N′-[(1-(3,4-Dichlorophenyl)-1H-1,2,3-triazole-4-yl)methylene]-isonicotinoyl Hydrazide (**5n**).* White solid, mp = 244−246 °C. IR ν_{max} (cm^{-1}): 3416, 3229, 3045, 1668, 1559, 1485, 1285, 1037, 819, 751, 683. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.95 (1H, d, J = 9.0, H-6′), 7.99 (1H, dd, J = 9.0 and 2.0 H-5′), 7.82 (2H, d, J = 8.1, INH ring), 8.44 (1H, d, J = 2.0, H-2′), 9.65 (1H, s, H-5), 8.73 (1H, s, N═C−H), 8.89 (2H, d, J = 8.1, INH ring), 11.05 (1H, s, N−H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 119.5 (C-2′ and C-6′), 122.2 (C-5 and C-3 INH ring), 125.0 (C-5), 130.9 (C-3′ and C-5′), 135.8 (C-1′), 142.5 (C═N), 153.9 (C-2 and C-6 INH ring), 132.7.0 (C-4′), 169.1 (C═O). MS (ESI) m/z 360 $(M)^+$. Anal. Calcd for $C_{15}H_{10}Cl_2N_6O$: C, 49.88; H, 2.79; N, 23.27. Found: C, 49.77; H, 2.73; N, 23.28.

*(E)-N′-[(1-(2,5-Dichlorophenyl)-1H-1,2,3-triazole-4-yl)methylene]-isonicotinoyl Hydrazide (**5o**).* White solid, mp = 246−247 °C. IR ν_{max} (cm^{-1}): 3428, 3289, 3140, 1659, 1485, 1285, 1044, 818, 761, 682. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.78 (1H, dd, J = 8.1 and 1.9, H-4′), 7.80 (1H, d, J = 8.1, H-3′), 7.89 (2H, d, J = 8.3, INH ring), 8.01 (1H, d, J = 1.9, H-6′), 8.46 (1H, s, H-5), 8.79 (1H, s, N═C−H), 8.91 (2H, d, J = 8.3, INH ring), 12.08 (1H, s, N−H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 129.7 (C-2′), 129.9 (C-6′), 121.2 (C-5 and C-3 INH ring), 130.6 (C-5), 132.2 (C-4′), 132.9 (C-3′), 133.0 (C-5′), 133.8 (C-1′), 143.7 (C═N), 154.1 (C-2 and C-6 INH ring), 146,2 (C-4), 185.2 (C═O). MS (ESI) m/z 360 $(M)^+$. Anal. Calcd for $C_{15}H_{10}Cl_2N_6O$: C, 49.88; H, 2.79; N, 23.27. Found: C, 49.53; H, 2.11; N, 23.26.

*Procedure for Preparation of **6p**.* In a round-bottom flask equipped with a magnetic stirring bar, sodium azide (7.5 mmol), methyl propiolate (11.2 mmol), *tert*-butanol (5 mL), $CuSO_4$ pentahydrate (0.075 mmol), sodium ascorbate (0.75 mmol), and H_2O (5 mL) were added. The resulting mixture was stirred for 24 h at room temperature. Next, the mixture was extracted with CH_2Cl_2, and the combined organic extracts were washed with H_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residual crude product was purified via silica gel column chromatography using a gradient mixture of $CHCl_3$−CH_3OH to obtain pure **6p**.

*Methyl 1-(3,5-Dichlorophenyl)-1H-1,2,3-triazole-4-carboxylate (**6p**).* White solid, mp = 188.1−190.4 °C. IR ν_{max} (cm^{-1}): 3132, 3105, 3086, 1708, 1589, 1546, 1481, 1438, 1400, 1342, 1276, 1195, 1161, 1037, 875, 852, 817, 775. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.90 (3H, s, OCH_3), 7.81 (1H, t, J = 3.6 Hz, H-4′), 8.15 (2H, d, J = 1.8 Hz, H-2′ and H-6′), 9.62 (1H, s, H-5). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 119.3 (C-4′), 127.8 (C-5), 128.6 (C-2′ and C-6′), 135.2 (C-3′ and C-5′), 137.6 (C-1′), 139.6 (C-4), 160.2 (C═O). MS (ESI) m/z 272 $(M)^+$. Anal. Calcd for $C_{10}H_7Cl_2N_3O_2$: C, 44.14; H, 2.59; N, 15.44. Found: C, 44.07; H, 2.64; N, 15.17.

*Procedure for Preparation of **7p**.* In a round-bottom flask equipped with a magnetic stirring bar, sodium azide (7.5 mmol), 3,3,3-trifluoro-1-propyne (11.2 mmol), *tert*-butanol (5 mL), $CuSO_4$ pentahydrate (0.075 mmol), sodium ascorbate (0.75 mmol), and H_2O (5 mL) were added. Next, the reaction mixture was stirred for 4 days at room temperature, the mixture was extracted with CH_2Cl_2, and the combined organic extracts were washed with H_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residual crude product was purified via silica gel column chromatography using a gradient mixture of $CHCl_3$−CH_3OH to obtain pure **7p**.

*1-(3,5-Dichlorophenyl)-4-(trifluoromethyl)-1H-1,2-triazole (**7p**).* Yellow oil. IR ν_{max} (cm^{-1}): 3097, 2931, 2357, 2330, 1743, 1585, 1570, 1477, 1442, 1396, 1373, 1261, 1145, 1045, 1026, 983, 856, 790, 740, 725. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.86 (1H, t, J = 1.6 Hz, H-4′), 8.13 (2H, d, J = 1.6 Hz, H-2′ and H-6′), 9.69 (1H, s, H-5). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 119.7 (C-4′), 120.4 (q, J = 267 Hz, $\underline{C}F_3$), 124.9 (d, J = 2.5 Hz, C-5), 129.0 (C-2′ and C-6′), 135.2 (C-3′ and C-5′), 137.4 (C-1′), 137.6 (q, J = 115.1 Hz, C-4). ^{19}F NMR (DMSO-d_6, 376 MHz): δ −59.9. MS (ESI) m/z 281 $(M)^+$. Anal. Calcd for $C_9H_4Cl_2F_3N_3$: C, 38.33; H, 1.43; N, 14.90. Found: C, 38.52; H, 1.63; N, 14.32.

*Procedure for Preparation of **8c**−**d**, **8p**−**s**.* In a round-bottom flask equipped with a drying tube, alcohol derivative (1 mmol), DAST (1 mmol), and CH_2Cl_2 (20 mL) were mixed. The reaction mixture was stirred for 1−4 days at room temperature and was washed with water, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residual crude product was purified via silica gel column chromatography using a gradient mixture of $CHCl_3$−CH_3OH to obtain the pure derivatives **8c**−**d**, **8p**−**s**.

*1-(4-Chlorophenyl)-4-(fluoromethyl)-1H-1,2,3-triazole (**8c**).* White solid, mp = 154.4−156.3 °C. IR ν_{max} (cm^{-1}): 3128, 3089, 2966, 2927, 1732, 1500, 1238, 1026, 968, 829. ^{1}H NMR (acetone-d_6, 400 MHz): δ 5.55 (2H, d, J = 48.8 Hz, $C\underline{H}_2F$), 7.65 (2H, d, J = 8.8 Hz, H-3′ and H-5′), 7.95 (2H, d, J = 8.4 Hz, H-2′ and H-6′), 8.77 (1H, d, J = 2.8 Hz, H-5). ^{13}C NMR (acetone-d_6, 100 MHz): δ 76.2 (d, J = 162.3 Hz, $\underline{C}H_2F$), 122.9 (C-2′and C-6′), 124.0 (C-5), 130.8 (C-3′ and C-5′), 134.8 (C-1′), 136.8 (C-4′), 144.6 (d, J = 20.4 Hz, C-4). ^{19}F NMR (acetone-d_6, 376 MHz): δ −206.2. MS (ESI) m/z 211 $(M)^+$. Anal. Calcd for $C_9H_7ClFN_3$: C, 51.08; H, 3.33; N, 19.86 Found: C, 51.46; H, 3.36; N, 19.34.

*1-(3-Chlorophenyl)-4-(fluoromethyl)-1H-1,2,3-triazole (**8d**).* Brown solid, mp = 95.0−96.0 °C. IR ν_{max} (cm^{-1}): 3140, 3089, 3059, 2978, 2449, 1955, 1882, 1732, 1597, 1554, 1498,1438, 1226, 1103, 1037, 968, 786. ^{1}H NMR (acetone-d_6, 400 MHz): δ 5.56 (2H, d, J = 48.8 Hz, $C\underline{H}_2F$), 7.54 (1H, d, J = 8.0 Hz, H-6′), 7.64 (1H, t, J = 8.0 Hz, H-5′), 7.91 (1H, d, J = 8.0 Hz, H-4′), 7.99 (1H, s, H-2′), 8.82 (1H, d, J = 3.2 Hz, H-5). ^{13}C NMR (acetone-d_6, 100 MHz): δ 76.2 (d, J = 161.5 Hz, $\underline{C}H_2F$), 119.8 (C-5′), 121.3(C-4′), 124.1 (d, J = 3.0 Hz, C-5), 129.6 (C-2′), 132.3 (C-6′), 135.8 (C-3′), 139.0 (C-1′), 144.7 (d, J = 20.5 Hz, C-4). ^{19}F NMR (acetone-d_6, 376 MHz): δ −206.3. MS (ESI) m/z 211 $(M)^+$. Anal. Calcd for $C_9H_7ClFN_3$: C, 51.08; H, 3.33; N, 19.86 Found: C, 51.08; H, 3.39; N, 19.20.

*1-(3,5-Dichlorophenyl)4-(fluoromethyl)-1H-1,2,3-triazole (**8p**).* White solid, mp = 112−114 °C. IR ν_{max} (cm^{-1}): 3126, 3086, 2976, 1587, 1475, 1438, 1390, 1228, 1116, 983, 850. ^{1}H NMR (acetone-d_6, 400 MHz): δ 5.59 (2H, d, J = 48.4 Hz, $C\underline{H}_2F$), 7.64 (1H, s, H-4′), 8.01 (2H, s, H-2′and H-6′), 8.89 (1H, d, J = 2.8 Hz, H-5). ^{13}C NMR (acetone-d_6, 100 MHz): δ 75.6 (d, J = 162.3 Hz, $\underline{C}H_2F$), 120.0 (C-4′), 124.2 (C-5), 129.2 (C-2′and C-6′), 136.8 (C-3′ and C-5′), 139.6 (C-1′), 144.9 (d, J = 21.0 Hz, C-4). ^{19}F NMR (acetone-d_6, 376 MHz): δ −207.0. MS (ESI) m/z 246 $(M)^+$. Anal. Calcd for $C_9H_7Cl_2FN_3$: C, 43.93; H, 2.46; N, 17.08 Found: C, 43.77; H, 2.49; N, 16.24.

*4-(4-(Fluoromethyl)-1H-1,2,3-triazole-1-yl)benzonitrile (**8q**).* White solid, mp = 145−147 °C. IR ν_{max} (cm^{-1}): 3132, 3089, 2974, 2924, 2229, 1708, 1608, 1566, 1516, 1373, 1242, 1056, 1018, 979, 844, 759. ^{1}H NMR (acetone-d_6, 400 MHz): δ 5.58 (2H, d, J = 48.8 Hz, $C\underline{H}_2F$), 8.05 (2H, d, J = 8.8 Hz, H-3′ and H-5′), 8.18 (2H, d, J = 8.8 Hz, H-2′ and H-6′), 8.90 (1H, d, J = 2.8 Hz, H-5). ^{13}C NMR (acetone-d_6, 100 MHz): δ 76.1 (d, J = 162.1 Hz, $\underline{C}H_2F$), 113.1 (C-4′), 118.5 (CN), 121.8 (C-2′and C-6′), 124.1 (d, J = 3.8 Hz, C-5), 135.0 (C-3′ and C-5′), 140.8 (C-1′), 145.0 (d, J = 20.4 Hz, C-4). ^{19}F NMR (acetone-d_6, 376 MHz): δ −206.9. MS (ESI) m/z 202 $(M)^+$. Anal. Calcd for $C_{10}H_7FN_4$: C, 59.40; H, 3.49; N, 27.71. Found: C, 59.34; H, 3.76; N, 26.05.

*(4-(Fluoromethyl)-1H-1,2,3-triazole-1-yl)benzonitrile (**8r**).* White solid, mp = 112.5−112.9 °C. IR ν_{max} (cm^{-1}): 3140, 3097, 2233, 1732, 1589, 1562, 1500, 1489, 1381, 1350, 1257, 1230, 1049, 1006, 975, 948, 833, 794, 678. ^{1}H NMR (acetone-d_6, 400 MHz): δ 5.58 (2H, d, J = 48.4 Hz, $C\underline{H}_2F$), 7.87 (1H, t, J = 8.0 Hz, H-4′), 7.94 (1H, dt, J = 1.2, 2.5, and 7.7 Hz H-6′), 8.31 (1H, ddd, J = 1.1, 2.2, and 8.2 Hz, H-2′), 8.37 (1H, t, J = 1.6 Hz, H-5′), 8.88 (1H, d, J = 3.0 Hz, H-5). ^{13}C NMR (acetone-d_6, 100 MHz): δ 76.1 (d, J = 161.1 Hz, $\underline{C}H_2F$), 114.6 (C-4′), 118.2 (CN), 124.1 (C-5), 124.6 (C-2′), 125.7 (C-6′), 132.1 (C-3′), 133.1 (C-5′), 138.5 (C-1′), 144.8 (d, J = 20.4 Hz, C-4). ^{19}F NMR (acetone-d_6, 376 MHz): δ −206.8. MS (ESI) m/z 202 $(M)^+$. Anal. Calcd for $C_{10}H_7FN_4$: C, 59.40; H, 3.49; N, 27.71. Found: C, 58.97; H, 3.52; N, 26.50.

*(1-(4-Bromophenyl)-4-(fluoromethyl)-1H-1,2,3-triazole (**8s**).* White solid, mp = 168−171 °C. IR ν_{max} (cm^{-1}): 3124, 3089, 2970, 1558, 1500, 1377, 1234, 1026, 964, 825, 767, 690, 513. ^{1}H NMR (acetone-d_6, 400 MHz): δ 5.55 (2H, d, J = 48.4 Hz, $C\underline{H}_2F$), 7.80 (2H, dt, J = 2.4, 4.8, and 9.4 Hz, H-3′ and H-5′), 7.90 (2H, dt, J = 2.8, 4.8, and 9.6 Hz, H-2′ and H-6′), 8.77 (1H, d, J = 3.2 Hz, H-5). ^{13}C NMR (acetone-d_6, 100 MHz): δ 76.1 (d, J = 160.4 Hz, $\underline{C}H_2F$), 122.6 (C-5), 122.7 (C-4′), 123.1 (C-2′ and C-6′), 123.9 (d, 2.75 Hz, $\underline{C}H_2F$), 133.7 (C-3′ and C-5′), 137.1 (C-1′), 144.6 (d, J = 20.4 Hz, C-4). ^{19}F NMR (acetone-d_6, 376 MHz): δ −206.2. MS (ESI) m/z 256 $(M)^+$. Anal. Calcd for $C_9H_7BrFN_3$: C, 42.21; H, 2.76; N, 16.41 Found: C, 42.50; H, 2.99; N, 15.72.

*Procedure for Preparation of **9d** and **9r**.* In a round-bottom flask equipped with a drying tube, alcohol derivative (1 mmol), DAST (10 mmol), and CH_2Cl_2 (20 mL) were mixed. The reaction mixture was stirred for 24 h at room temperature and washed with water, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residual crude product was purified via silica gel column chromatography using a gradient mixture of $CHCl_3$−CH_3OH to obtain the pure derivatives **9d** and **9r**.

*Procedure for Preparation of **3t** and **9t**.* In a round-bottom flask equipped with a condenser, cyano derivative (**3r** and **9r**) (1 mmol) and thiosemicarbazone (1 mmol) were dissolved in CF_3COOH (5 mmol). The reaction mixture was stirred for 24 h at 60 °C and cooled in an ice bath and adjusted to pH 7−8 with NH_4OH. Precipitate was removed by vacuum filtration and washed with H_2O. The residual crude product was purified via silica gel column chromatography using a gradient mixture of $CHCl_3$−CH_3OH to obtain the pure derivatives **3t** and **9t**.

*(1-(3-(5-Amino-1,3,4-thiadiazol-2-yl)phenyl)-1H-1,2,3-triazole-4-yl)methanol (**3t**).* Yellow solid, mp = 150.1−152.0 °C. IR ν_{max} (cm^{-1}): 3441, 3263, 3101, 2727, 2623, 1647, 1519, 1056, 1029, 1010, 821, 794. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 4.63 (2H, d, J = 5.5 Hz, $C\underline{H}_2OH$), 5.36 (1H, t, J = 5.5 Hz, $O\underline{H}$), 7.56 (2H, s, $N\underline{H}_2$) 7.68 (1H, t, J = 8.0 Hz, H-4′), 7.84 (1H, d, J = 7.9 Hz, H-3′), 7.97 (1H, dd, J = 1.2 and 8.0 Hz, H-6′), 8.25 (1H, s, H-2′), 8.84 (1H, s, H-5). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 54.9 ($\underline{C}H_2$), 117.0 (C-5), 120.6 (C-2′ and C-4′), 121.2 (C-1′), 126.1 (C-5′), 130.8 (C-6′), 132.5 (C-3′), 137.2 (C-4), 149.2 (C-3″). MS (ESI) m/z 274 $(M)^+$. Anal. Calcd for $C_{11}H_{10}N_6OS$: C, 48.17; H, 3.67; N, 30.64. Found: C, 48.92; H, 3.35; N, 30.17.

*5-(3-(4-(Difluoromethyl)-1H-1,2,3-triazole-1-yl)phenyl)-1,3,4-thiadiazol-2-amine (**9t**).* White solid, mp = 131.0−132.3 °C. IR ν_{max} (cm^{-1}): 3383, 3305, 3109, 1678, 1662, 1643, 1508,1411, 1357, 1248, 1188, 1103, 1041, 802. ^{1}H NMR (acetone-d_6, 400 MHz): δ 4.57 (2H, bs, NH_2), 7.18 (1H, t, J = 54.4 Hz, $C\underline{H}F_2$), 7.73 (1H, t, J = 8.0 Hz, H-5′), 7.93 (1H, d, J = 6.8 Hz, H-6′), 8.04 (1H, d, J = 7.9 Hz, H-4′), 8.35 (1H, s, H-5), 9.10 (1H, s, H-2′). ^{13}C NMR (acetone-d_6, 100 MHz): δ 111.3 (t, J = 234.0 Hz, $\underline{C}HF_2$), 119.1 (C-5), 122.5 (C-2′), 123.1 (C-4′), 128.0 (C-1′), 131.7 (C-5′), 134.1 (C-6′), 138.3 (C-3′), 144.1 (C-4, t, J = 28 Hz), 157.0 ($\underline{C}$-NH_2), 170.0 (C-3″). ^{19}F NMR (acetone-d_6, 376 MHz): δ −113.6. MS (ESI) m/z 294 $(M)^+$. Anal. Calcd for $C_{11}H_8F_2N_6S$: C, 44.89; H, 2.74; N, 28.56. Found: C, 44.74; H, 3.02; N, 28.51.

*General Procedure for Preparation of **10a**, **10c**, **10i**−**j**, **10m**−**o**.* In a suspension of anhydrous THF (50 mL) and NaH (2.0 equiv), methyltriphenylphosphonium bromide (7.42 mmol) under argon was

added. The mixture was stirred for 15 min in an ultrasound bath, acquiring a yellow color. The agitation was maintained for 2 h at room temperature, and triazole aldehyde (1.45 mmol) was subsequently added. After 1−2 h, the reaction mixture was dropped to freeze distilled H_2O. Next, this mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic phases were washed with distilled H_2O (2 × 50 mL) and dried with anhydrous Na_2SO_4. The crude product was purified by flash column chromatography using a gradient mixture of hexane-ethyl acetate.

*1-Phenyl-4-vinyl-1H-1,2,3-triazole (**10a**).* Yield 68%, white solid, mp = 81−85 °C. IR ν_{max} (cm^{-1}): 3430, 3134, 1502, 1235, 1045, 997, 927, 759, 679. ^1H NMR ($CDCl_3$, 500 MHz): δ δ 5.42 (1H, dd, J = 11.0 and 1.2, −CH=CHH′), 6.02 (1H, dd, J = 17.8 and 1.2, −CH=CHH′), 6.80 (1H, dd, J = 17.6 and 11.0, −CH=CHH′), 7.41−7.75 (5H, m, H-2′, H-3′, H-4′, H-5′, H-6′), 7.95 (1H, s, H-5). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 117.1 (−CH=CHH′), 118.6 (−CH=CHH′), 120.8 (C-2′ e C-6′), 125.6 (C-5), 129.1 (C-3′ e C-5′), 130.1 (C-4′), 137.3 (C-1′), 147.3 (C-4). MS (ESI) m/z 172 $(M)^+$.

*1-(4-Chlorophenyl)-4-vinyl-1H-1,2,3-triazole (**10c**).* Yield 99%, white solid, mp = 85−91 °C. IR ν_{max} (cm^{-1}): 3121, 1498, 1237, 1092, 1025, 986, 913, 830. ^1H NMR ($CDCl_3$, 500 MHz): δ 5.44 (1H, dd, J = 11.2 and 1.2 Hz, −CH=CHH′), 6.02 (1H, dd, J = 17.8 and 1.2 Hz, −CH=CHH′), 6.78 (1H, dd, J = 17.8 and 11.2 Hz, −CH=CHH′), 7.48−7.52 (2H, m, H-3′ and H-5′), 7.67−7.72 (2H, m, H-2′ and H-6′), 7.92 (1H, s, H-5). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 116.9 (−CH=CHH′), 117.9 (−CH=CHH′), 121.4 (C-2′ and C-6′), 124.9 (C-5), 129.7 (C-3′ and C-5′), 134.3 (C-4′), 135.3 (C-1′), 147.0 (C-4). MS (ESI) m/z 206 $(M)^+$. Anal. Calcd for $C_{10}H_8ClN_3$: C, 58.41; H, 3.92; N, 20.43. Found: C, 58.71; H, 4.11; N, 20.28. HRMS (ESMS) calcd for $C_{10}H_9ClN_3$ $[M + H]^+$, 206.0479; found, 206.0531.

*1-(4-Nitrophenyl)-4-vinyl-1H-1,2,3-triazole (**10i**).* Yield 60%, yellow solid, mp = 172−177 °C. IR ν_{max} (cm^{-1}): 3102, 3083, 2989, 2945, 2879, 1493, 1184, 1129, 1039, 1010, 947, 872, 759, 710, 680, 653, 758, 711, 670. ^1H NMR ($CDCl_3$, 500 MHz): δ 5.44 (1H, dd, J = 11.2 and 1.5 Hz, −CH=CHH′), 5.99 (1H, dd, J = 17.8 and 1.5 Hz, CH=CHH′), 6.77 (1H, dd, J =11.2 and 17.8 Hz, −CH=CHH′), 8.14−8.19 (2H, m, H-2′ and H-6′), 8.40−8.45 (2H, m, H-3′ and H-5′), 9.02 (1H, s, H-5). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 115.2 (−CH=CHH′), 118.2 (−CH=CHH′), 118.4 (C-2′ and C-6′), 123.0 (C-5), 123.5 (C-3′ and C-5′), 144.5 (C-4′), 138.6 (C-1′), 144.6 (C-4). MS (ESI) m/z 217 $(M)^+$. Anal. Calcd for $C_{10}H_8N_4O_2$: C, 55.55; H, 3.73; N, 25.91. Found: C, 56.87; H, 4.20; N, 24.59. HRMS (ESMS) calcd for $C_{10}H_9N_4O_2$ $[M + H]^+$, 217.0720; found, 217.0726.

*1-(4-Methoxyphenyl)-4-vinyl-1H-1,2,3-triazole (**10j**).* Yield 71%. white solid. mp = 72−76 °C. IR ν_{max} (cm^{-1}): 3102, 3092, 2978, 2935, 2868, 1498, 1191, 1122, 1041, 1012, 947, 882, 765, 710, 675, 643, 748, 715, 670. ^1H NMR ($CDCl_3$, 500 MHz): δ 3.93 (3H, s, OCH_3), 5.45 (1H, dd, J = 11.2 and 1.5 Hz, −CH=CHH′), 5.98 (1H, dd, J = 17.8 and 1.5 Hz, CH=CHH′), 6.76 (1H, dd, J = 11.2 and 17.8 Hz, −CH=CHH′), 9.17 (1H, d, J = 9.3 Hz, H-2′ and H-6′), 8.52 (1H, d, J = 9.0 Hz, H-3′ and H-5′), 10.1 (1H, s, H-5). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 55.8 (OCH_3), 114.8 (C-3′ and C-5′), 116.3 (−CH=CHH′), 119.9 (−CH=CHH′), 121.7 (C-2′ and C-6′), 125.6 (C-5), 129.9 (C-1′), 146.1 (C-4′), 159.3 (C-4). MS (ESI) m/z 202 $(M)^+$. Anal. Calcd for $C_{11}H_{11}N_3O$: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.58; H, 5.79; N, 20.77. HRMS (ESMS) calcd for $C_{11}H_{12}N_3O$ $[M + H]^+$, 202.0975; found, 202.0968.

*1-(2-Methoxyphenyl)-4-vinyl-1H-1,2,3-triazole (**10m**).* Yield 75%, white solid, mp = 72−73 °C. IR ν_{max} (cm^{-1}): 3128, 1601, 1505, 1469, 1289, 1247, 1048, 1013, 908, 748, 695. ^1H NMR ($CDCl_3$, 500 MHz): δ 3.89 (3H, s, OCH_3), 5.36−5.40 (1H, m, −CH=CHH′), 5.95−6.02 (1H, m, −CH=CHH′), 6.75−6.85 (1H, m, −CH=CHH′), 7.07−7.79 (4H, m, Ar), 8.06 (1H, s, H-5). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 55.9 (OCH_3), 112.2 (C-5′), 115.9 (−CH=CHH′), 121.2 (C-6′), 122.4 (C-5), 125.4 (−CH=CHH′), 125.9 (C-3′), 126.2 (C-1′), 130.0 (C-4′), 145.7 (C-2′), 151.1 (C-4). MS (ESI) m/z 202 $(M)^+$. Anal. Calcd for $C_{11}H_{11}N_3O$: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.87; H, 5.60; N, 20.79.

*1-(3,4-Dichlorophenyl)-4-vinyl-1H-1,2,3-triazole (**10n**).* Yield 75%, white solid, mp = 130−131 °C. IR ν_{max} (cm^{-1}): 3133, 1485, 1437, 1237, 1031, 988, 917, 879, 812, 676. ^1H NMR ($CDCl_3$, 500 MHz): δ 5.45 (1H, dd, J = 11.2 and 1.2 Hz, −CH=CHH′), 6.03 (1H, dd, J = 17.7 and 1.2 Hz, −CH=CHH′), 6.77 (1H, dd, J = 11.2 and 17.8 Hz, −CH=CHH′), 7.61−7.62 (2H, m, H-5′ and H-6′), 7.89−7.90 (1H, m, H-2′), 7.92 (1H, s, H-5). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 117.4 (−CH=CHH′), 117.9 (−CH=CHH′), 119.3 (C-2′), 122.0 (C-6′), 124.8 (C-5), 131.4 (C-5′), 132.8 (C-4′), 134.0 (C-3′), 135.9 (C-2′), 147.3 (C-4). MS (ESI) m/z 240 $(M)^+$. Anal. Calcd for $C_{10}H_7Cl_2N_3$: C, 50.03; H, 2.94; N, 17.50. Found: C, 51.01; H, 3.36; N, 16.97.

*1-(2,5-Dichlorophenyl)-4-vinyl-1H-1,2,3-triazole (**10o**).* Yield 75%, white solid, mp = 56−57 °C. IR ν_{max} (cm^{-1}): 3098, 1582, 1483, 1449, 1245, 1097, 1016, 985, 922, 867, 809. ^1H NMR ($CDCl_3$, 500 MHz): δ 5.44 (1H, dd, J = 11.2 and 1.2 Hz, −CH=CHH′), 6,04 (1H, dd, J = 17.8 and 1.2 Hz, −CH=CHH′), 6.79 (1H, dd, J = 11.2 and 17.8 Hz, −CH=CHH′), 7.43 (1H, dd, J = 8.5 and 2.4 Hz, H-3′), 7.52 (1H, d, J = 8.5 Hz, H-4′), 7.68 (1H, d, J = 2.4 Hz, H-6′), 7.97 (1H, s, H-5). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 116.7 (−CH=CHH′), 121.5 (C-5), 124.4 (C-6′), 126.2 (C-5′), 127.2 (−CH=CHH′), 130.2 (C-4′), 131.2 (C-3′), 133.2 (C-2′), 135.0 (C-1′),145.8 (C-4). MS (ESI) m/z 240 $(M)^+$. Anal. Calcd for $C_{10}H_7Cl_2N_3$: C, 50.03; H, 2.94; N, 17.50. Found: C, 50.55; H, 3.18; N, 17.43.

2. Mycobacterial Growth Assay. The *M. tuberculosis* H37Rv ATCC 27294 was grown in 100 mL of Middlebrook 7H9 broth (Difco Laboratories, Detroit, MI, USA) supplemented with 10% (v/v) OADC (oleic acid, albumin, dextrose and catalase; Difco). Cultures were incubated on a rotary shaker at 150 rpm and 37 °C for 24 h. After the bacteria were washed, they were suspended in 10 mL of 7H9 broth and adjusted to 0.1 Mc on the Farland scale, and they were diluted 1:25. Subsequent 2-fold dilutions were performed in 100 μL of 7H9 broth in microplates according to Franzblau et al. (1998).[31]

Briefly, 200 μL of sterile deionized water was added to all outer-perimeter wells of sterile 96-well plates (Falcon, 3072; Becton Dickinson, Lincoln Park, NJ) to minimize evaporation of the medium in the test wells during incubation. The final drug concentrations tested were 0.01−10.0 μg/mL. Plates were covered, sealed with parafilm, and incubated at 37 °C for 5 days. After this time, 25 μL of a freshly prepared 1:1 mixture of Alamar Blue (Accumed International, Westlake, Ohio) reagent and 10% Tween 80 was added to the plate and incubated for 24 h. A blue color in the well was interpreted as no bacterial growth, a pink color was scored as growth, and purple indicated growth inhibition. The MIC was defined as the lowest drug concentration that prevented a change of color from blue to pink.

3. Cell Cultures and Cytotoxicity Test. The human hepatoma cell line (HepG2) was cultured in 75 cm^2 sterile RPMI 1640 medium supplemented with 10% heat-inactivated fetal calf serum and 40 mg/L gentamicin in a 5% CO_2 atmosphere at 37 °C. For in vitro cytotoxicity experiments, the cell monolayer was trypsinized, washed with culture medium, distributed in a flat-bottomed 96-well plate (5 × 10^3 cells/well), and incubated for 18 h at 37 °C for cell adherence. MTT ((3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) was employed, as described in the literature.[32]

The HepG2 cell line was incubated with 20 μL of sample compounds at different concentrations (200−25 μg/mL) for 24 h in an atmosphere of 5% CO_2 at 37 °C. For the MTT assay, which evaluates mitochondrial viability, 20 μL of MTT solution (5 mg/mL) was added, and the plates were incubated for an additional 3 h. After incubation, the supernatant was carefully removed from the wells followed by the addition of 100 μL DMSO with thorough mixing. The optical density at 570 and 630 nm (background) was determined on an ELISA reader. The cell viability was

expressed as the percentage of control absorbance obtained in untreated cells after subtracting the absorbance from an appropriate background. Last, the minimum lethal dose for 50% of the cells (MLD_{50}) was determined, as previously described in the literature.[33]

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ACKNOWLEDGMENT

We are grateful for fellowships granted by the Foundation for Research of the State of Rio de Janeiro (FAPERJ) and the Coordination of the Improvement of Higher Education (CAPES) and the National Council of R&D (CNPq). This study is a part of the Platform for Bioassays number II-RPT11B of the Program of Technological Development in Health Products of the Oswaldo Cruz Foundation (PDTIS-FIOCRUZ).

TB, tuberculosis; BCG, bacille Calmette−Guérin; HIV, human immunodeficiency virus; MDR-TB, "multiple drug resistant" *M. tuberculosis*; INH, isoniazid; MIC, minimum inhibitory concentration; BGM, kidney cells; IBX, 2-iodoxybenzoic acid; DAST, dimethylaminosulfur trifluoride; NMR, nuclear magnetic resonance; FTIR, infrared spectroscopy; CHN, elemental analysis; MABA, microplate Alamar Blue assay; MTT, ((3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay; SI, selectivity index; TLC, thin layer chromatography; UV, ultraviolet; VXR, Varian Unity Plus; TMS, tetramethylsilane; MLD_{50}, minimum lethal dose for 50% of the cells

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