

## Efficient Eco-Friendly Solvent-Free Click Synthesis and Antimicrobial Evaluation of New Fluorinated 1,2,3-Triazoles and their Conversion into Schiff Bases

Mohamed R. Aouad<sup>\*,a,b</sup>

<sup>a</sup>Department of Chemistry, Faculty of Sciences, Taibah University,  
30002 Al-Madinah Al-Munawarah, Saudi Arabia

<sup>b</sup>Laboratoire de Chimie & Electrochimie des Complexes Métalliques (LCECM) USTO-MB,  
Department of Chemistry, Faculty of Sciences, University of Sciences and Technology Mohamed  
Boudiaf, B.p. 1505 El M'nouar, 31000 Oran, Algeria

A facile and convenient green click synthesis has been developed for the preparation of new fluorinated 1,2,3-triazoles under solvent-free conditions via a Huisgen 1,3-dipolar cycloaddition reaction between dimethylacetylene dicarboxylate (DMADC) and fluorophenyl azides in excellent yields within 2 min. Treatment of the resulting diesters with hydrazine hydrate furnished the corresponding dihydrazides, which, upon condensation with benzaldehyde derivatives, afforded a new series of bis-hydrazones. All of the synthesized compounds were fully characterized using infrared (IR) spectroscopy, <sup>1</sup>H, <sup>13</sup>C and <sup>19</sup>F nuclear magnetic resonance (NMR), mass spectrometry (MS) and elemental analysis. A preliminary bioassay indicated that some of the tested compounds exhibited significant antimicrobial activity.

**Keywords:** free solvent reaction, click synthesis, 1,2,3-triazoles, Schiff bases, antimicrobial activity

### Introduction

During the last few years, the development of fast, safe and high-yielding click chemistry methodologies have rapidly emerged as one of the most challenging and attractive topics in modern heterocyclic chemistry.<sup>1-6</sup> The most popular example of click chemistry is the synthesis of 1,2,3-triazoles via 1,3-dipolar cycloaddition reactions.<sup>7</sup> The 1,2,3-triazole based derivatives have been employed in various medicinal chemistry applications, such as anti-HIV,<sup>8</sup> antiviral,<sup>9</sup> anticonvulsant,<sup>10</sup> antiallergic,<sup>11</sup> anticancer,<sup>12</sup> and antifungal<sup>13</sup> agents. In addition, several fluorinated drug structures have incorporated a 1,2,3-scaffold.<sup>14</sup> Therefore, considerable attention has been devoted to the synthesis and applications of fluorinated compounds in medicinal chemistry and agrochemistry.<sup>15-20</sup> The incorporation of a fluorine atom into organic molecules results in high thermal stability and enhanced lipophilicity, which can enhance the rate of cell penetration and transport of a drug to an active site.<sup>21-24</sup> 1,3-Dipolar Huisgen cycloaddition of organic azides with alkynes has been

recognized as the most widely reported method for the construction of 1,2,3-triazole scaffold. In addition, the reaction of dimethyl/ethylacetylene dicarboxylate with different organoazides via a 1,3-dipolar cycloaddition has been extensively adopted for the synthesis of 4,5-disubstituted 1,2,3-triazoles. Savin *et al.*<sup>25</sup> was the first to report the efficient microwave solvent-free reaction of dimethylacetylene dicarboxylate (DMADC) with benzyl azide within 1 min. Recently, Shanmugavelan *et al.*<sup>26</sup> reproduce the same synthesis without microwave irradiation via conventional heating of the reactants at 90-120 °C for 1 min. However, few examples for the synthesis of 1-aryl-1,2,3-triazoles have been previously reported.<sup>27</sup> Kamalraj *et al.*<sup>28</sup> developed a one-pot synthesis of 1-aryl-4-acetyl-5-methyl-1,2,3-triazole from organoazide and acetylacetone in the presence of a base under warm conditions in ethanol. Recently, an efficient one-pot copper-catalysed synthesis of 1,4-diaryl-substituted 1,2,3-triazoles was developed using aryldiazonium silica sulfates, sodium azide, terminal alkynes, and sodium ascorbate.<sup>29</sup> Another method is the copper-free synthesis of 1-aryl-1,2,3-triazoles from sodium acetylide and aryl azides at room temperature.<sup>30</sup>

\*e-mail: mr\_aouad@yahoo.fr

To the best of our knowledge, the synthesis of 1-aryl-1,2,3-triazoles under solvent-free conditions has not been previously reported. Inspired by Shanmugavelan *et al.*'s work,<sup>26</sup> we investigated the viability of utilizing the solvent-free conditions as an efficient eco-friendly protocol for the synthesis of 1-aryl-1,2,3-triazoles. Herein, we describe our modified methodology for the quick synthesis of new 1-fluoroaryl-1,2,3-triazole-4,5-diester via 1,3-dipolar cycloaddition of DMADC with different fluorophenyl azides under solvent-free conditions. Moreover, the main purpose of the present study was to design and to synthesize some novel 1-fluoroaryl-1,2,3-triazole-hydrazone hybrids in order to improve the physicochemical properties of 1,2,3-triazole and/or synergistic effect by combining the 1,2,3-triazole nucleus with hydrazone linkage in one scaffold. The synthesized bis-hydrazones were evaluated for their antimicrobial activity against different Gram-negative and Gram-positive bacteria. In addition, the effect of introducing the fluorine substituent on the antimicrobial activity has also been investigated.

## Results and Discussion

### Chemistry

Initially, fluorophenyl azides were synthesized via diazotization of their corresponding fluoroanilines in the presence of a sodium nitrite solution in acidic media followed by the addition of sodium azide according to the method described by Boyer and Canter.<sup>31</sup> 1,3-Dipolar cycloaddition of 2-fluorophenyl azide (**2a**) to dimethylacetylene dicarboxylate (**1**) in the presence of dichloromethane has been previously reported by Bouasla *et al.*<sup>32</sup> under both conventional and microwave heating methods. The resulting dimethyl 1-(2-fluorophenyl)-1,2,3-triazolo-4,5-dicarboxylate (**3a**) was obtained in 68% yield after regular stirring for 24 h and in 88% yield under microwave irradiation (MWI) for 8 min. In the current study, the same reaction was conducted under solvent-free conditions in a sealed tube. The reaction required heating in a water bath for 2 min to afford 1,2,3-triazole **3a** in 96% yield. The promising result obtained from the cycloaddition of 2-fluorophenylazide **2a** with **1** inspired us to extend the

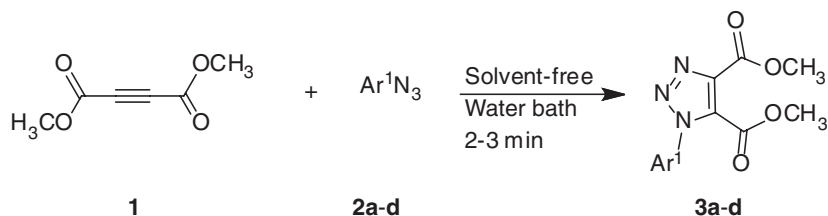
reaction to other fluorophenylazides. Accordingly, new 1-(fluorophenyl)-1,2,3-triazoles **3b-d** were synthesized in 93-96% yield within 2-3 min through the same eco-friendly solvent-free protocol previously described (Scheme 1).

The synthesized 1,2,3-triazole diesters **3a-d** were fully characterized based on their infrared (IR), <sup>1</sup>H and <sup>13</sup>C nuclear magnetic resonance (NMR) and mass spectrometry (MS) spectra. Their IR spectra contained two absorption bands at 1727-1737 and 2923-2988 cm<sup>-1</sup>, which are characteristic of the ester C=O and CH<sub>3</sub> groups, respectively. The <sup>1</sup>H NMR spectra of compounds **3a-d** recorded in CDCl<sub>3</sub> revealed the presence of two characteristic singlets at δ 3.83-3.94 ppm, which confirmed the nonequivalence of the two methyl ester protons. The phenyl protons appeared in the aromatic region at a δ of approximately 7.39-8.09 ppm. In the <sup>13</sup>C NMR spectra, the signal corresponding to the two nonequivalent carbonyl ester groups appeared at 157.56-161.28 ppm, and the two methyl carbons appeared at 52.69-54.83 ppm.

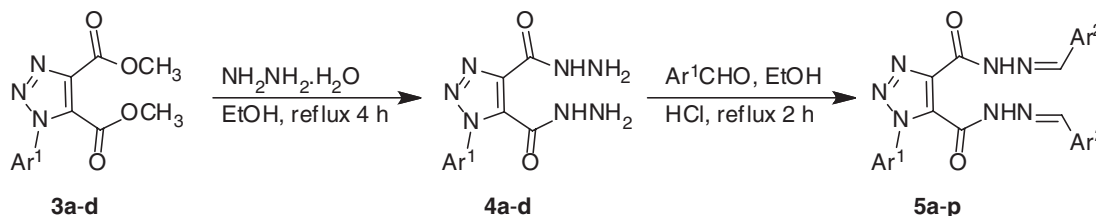
Diesters **3a-d** were refluxed with hydrazine hydrate in ethanol for 4 h to afford corresponding dihydrazides **4a-d** in 88-92% yields. The formation of dihydrazides **4a-d** was confirmed by IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR and MS analyses. Their IR spectra revealed the appearance of characteristic hydrazide NH and NH<sub>2</sub> groups at 3227-3371 cm<sup>-1</sup>. In the <sup>1</sup>H NMR spectra of compounds **4a-d**, the disappearance of the methyl ester signals and appearance of two singlets at δ 4.50-4.79 and 10.34-11.55 ppm due to the NH<sub>2</sub> and NH protons, respectively, confirmed the success of the hydrazinolysis reaction. In addition, carbonyl signals of the amide functionalities in the <sup>13</sup>C NMR spectra appeared at 157.16-163.67 ppm, which supported the proposed structures for dihydrazides **4a-d**.

However, the heating of dihydrazides **4a-d** with benzaldehyde derivatives in the presence of a catalytic amount of hydrochloric acid for 2 h yielded the corresponding bis-hydrazones **5a-p** in 83-91% yields (Scheme 2). The structures of the synthesized bis-hydrazones have been elucidated by IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR and MS analyses.

Hydrazones were reported to exist as *E/Z* geometrical isomers about the imine bond (HC=N) and *cis/trans* conformers to the carbonyl amide linkage.<sup>33-35</sup> These arrangements may be due to the restricted rotation around the C=N bond, which could generate different

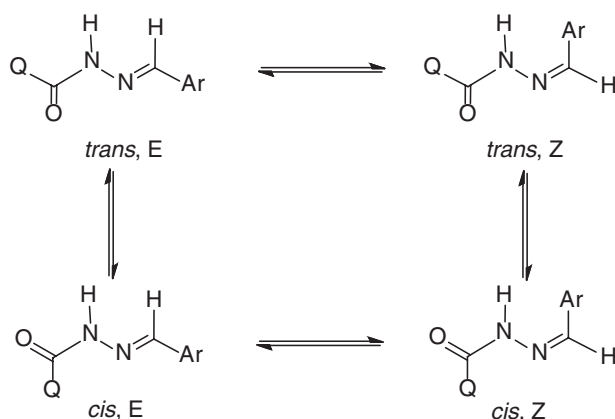


**Scheme 1.** Synthesis of new fluorinated-1,2,3-triazole diesters **3a-d**.



**Scheme 2.** Synthesis of new fluorinated-1,2,3-triazole dihydrazides **4a-d** and bis-hydrazones **5a-p**.

steric rearrangements of the hydrazone functionality in the geometric *syn* and *anti* isomers. In addition, the *E*-geometrical isomer and the *cis/trans* conformers were the more predominant forms in highly polar solvent, such as deuterated dimethylsulfoxide (DMSO-*d*<sub>6</sub>), and the *Z*-isomer was only observed in less polar solvents.<sup>36,37</sup> Scheme 3 summarizes the general *E/Z* geometrical isomers and *cis/trans* conformers (Scheme 3).



**Scheme 3.** *E/Z* geometrical isomers and *cis/trans* conformers.

The <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra of all of the synthesized Schiff bases **5a-p** recorded in DMSO-*d*<sub>6</sub> confirm the existence of a mixture of diastereomers (i.e., *E/cis* and *E/trans*) for each imino-amide moiety.

The <sup>1</sup>H NMR spectrum of bis-hydrazone **5f** derived from *p*-methoxybenzaldehyde contained four different characteristic singlet peaks at  $\delta$  7.95, 8.21, 8.48 and 8.59 ppm with a ratio of 1:1:1:1, which have a total integration of two protons that are related to the two nonequivalent imine protons (HC=N). The spectrum also contained four singlets at  $\delta$  12.25, 12.39, 12.47 and 12.79 ppm that have a total integration of two NH protons with the same ratio. In addition, the two methoxy groups split into four singlets at  $\delta$  3.71, 3.79, 3.80 and 3.81 ppm and have a total integration of six protons. The aromatic protons appeared at their expected chemical shifts and have a total integration of 12 protons. The <sup>13</sup>C NMR spectrum also confirmed the presence of the *E/cis* and *E/trans* isomers due the appearance of three signals at  $\delta$  55.18, 55.25 and 55.29 ppm, which are characteristic of the two methoxy

groups. In addition, the nonequivalent carbonyl (C=O) and imine (C=N) signals resonated in the downfield region between  $\delta$  152.92-161.40 ppm.

The absence of this pairing of signals in the <sup>1</sup>H NMR spectrum of bis-hydrazides **4a-d** compared to bis-hydrazones **5a-p** confirmed the formation these compounds as a mixture of *E/cis* and *E/trans* diastereomers.

To confirm the solvent effect for the isomerism of hydrazones, the <sup>1</sup>H NMR spectrum of compound **5f** was measured in a less polar solvent (chloroform-*d*). Two singlet signals were observed at 12.01 and 14.68 ppm for the NH proton, 8.61 and 8.79 ppm for the HC=N proton and 5.10 and 5.58 ppm for the OCH<sub>3</sub> protons corresponding to the *cis* or *trans* conformers of the *E* isomer.

#### Antimicrobial screening

The synthesized 1,2,3-triazoles were evaluated for their *in vitro* antimicrobial activity against three Gram-positive bacteria, three Gram-negative and two fungal strains. Both microbial screenings were assessed by the minimum inhibitory concentration (MIC) using the broth dilution method.<sup>38,39</sup> The MIC is defined as the minimum concentration of compounds required to completely inhibit bacterial growth. The antibacterial and antifungal screening data expressed as MIC are listed in Table 1. The 1,2,3-triazole diesters **3a-d** exhibit good to moderate antibacterial activity against all of the bacterial strains with a MIC range of 16 to 31.25  $\mu\text{g mL}^{-1}$ . However, a lack of activity was observed against all of the fungal strains. The antimicrobial activity of dihydrazides **4a-d** indicated that compounds **4a** and **4b** possessing 2-F and/or 4-F substitution on the phenyl ring exhibited excellent antibacterial activity against all of the Gram-positive bacteria with a MIC range of 4 to 8  $\mu\text{g mL}^{-1}$  and good activity against all of the Gram-negative bacterial strains at a MIC of 16  $\mu\text{g mL}^{-1}$ . Compound **4d**, which contains both fluoro and iodo substitutions, exhibited excellent antifungal activity at a MIC of 8  $\mu\text{g mL}^{-1}$ . The antimicrobial screening revealed that of the tested bis-hydrazones **5a-p**, compounds **5a**, **5c**, **5e**, **5g**, **5m** and **5o** exhibited excellent activity against all of the tested bacterial strains with a MIC range of 4 to 8  $\mu\text{g mL}^{-1}$ . In addition, the highest antifungal

**Table 1.** Antimicrobial activity expressed as MIC

Compound	Minimum inhibitory concentration / ( $\mu\text{g mL}^{-1}$ )							
	Gram-positive bacteria <sup>a</sup>			Gram-negative bacteria <sup>b</sup>			Fungi <sup>c</sup>	
	Sp	Bs	Sa	Pa	Ec	Kp	Af	Ca
<b>3a</b>	16	16	16	16	16	31.25	125	250
<b>3b</b>	16	31.25	16	16	16	31.25	125	250
<b>3c</b>	16	31.25	31.25	16	31.25	31.25	250	250
<b>3d</b>	16	31.25	16	16	31.25	31.25	125	62.5
<b>4a</b>	8	4	4	16	16	16	16	16
<b>4b</b>	8	4	8	31.25	16	16	16	16
<b>4c</b>	16	16	8	31.25	31.25	31.25	16	16
<b>4d</b>	16	8	8	31.25	31.25	31.25	8	8
<b>5a</b>	4	4	4	8	4	8	16	16
<b>5b</b>	16	8	8	16	8	16	31.25	31.25
<b>5c</b>	8	8	4	8	4	4	4	8
<b>5d</b>	16	16	8	16	8	16	31.25	31.25
<b>5e</b>	4	4	8	8	4	8	16	16
<b>5f</b>	16	16	8	16	8	16	31.25	31.25
<b>5g</b>	8	8	4	8	8	4	8	8
<b>5h</b>	16	16	8	16	8	16	31.25	31.25
<b>5i</b>	8	16	8	16	16	8	31.25	16
<b>5j</b>	16	16	16	16	31.25	31.25	31.25	31.25
<b>5k</b>	16	8	8	8	16	8	16	8
<b>5l</b>	16	16	16	16	31.25	31.25	16	16
<b>5m</b>	8	8	4	8	8	16	8	4
<b>5n</b>	16	16	8	8	16	16	16	16
<b>5o</b>	8	4	4	8	8	8	4	4
<b>5p</b>	16	8	8	8	16	16	16	16
Ciprofloxacin	$\leq 5$	$\leq 1$	$\leq 5$	$\leq 5$	$\leq 1$	$\leq 1$	–	–
Fluconazole	–	–	–	–	–	–	$\leq 1$	$\leq 1$

<sup>a</sup>Gram-positive bacteria: *Streptococcus pneumonia* (RCMB 010010, Sp), *Bacillus subtilis* (RCMB 010067, Bs), *Staphylococcus aureus* (RCMB 010025, Sa); <sup>b</sup>Gram-negative bacteria: *Pseudomonas aeruginosa* (RCMB 010043, Pa), *Escherichia coli* (RCMB 010052, Ec), *Klebsiella pneumonia* (RCMB 010058, Kp); <sup>c</sup>yeasts: *Aspergillus fumigatus* (RCMB 02568, Af), *Candida albicans* (RCMB 05036, Ca).

activity with a MIC range of 4 to 8  $\mu\text{g mL}^{-1}$  was exhibited by compounds **5c**, **5g**, **5m** and **5o**, possessing  $\text{NO}_2$  and/or iodo substitution. The remaining compounds were found to be more active at higher concentrations (16–31.25  $\mu\text{g mL}^{-1}$ ). Therefore, the antimicrobial activity and structure activity relationship indicated that the higher inhibition exhibited by the bis-hydrazones against all of bacterial and fungal strains is most likely due to the presence of imine linkage in addition to the 1,2,3-triazole moiety. In addition, the incorporation of fluorine, nitro and/or iodo groups increased the antimicrobial activity.

## Conclusions

In conclusion, an eco-friendly, safe, high-yielding and experimentally simple method has been developed for the synthesis of 1-(fluorinated phenyl)-1,2,3-triazole diesters in

shorter reaction times. These reactions were carried out via interaction of fluorophenyl azides with dimethylacetylene dicarboxylate under solvent-free conditions in a water bath. The dihydrazides, which were synthesized through hydrazinolysis of the diesters, were condensed with different benzaldehydes to afford the corresponding bis-hydrazones. Some of the tested 1,2,3-triazoles exhibited significant antibacterial and antifungal activities with a MIC range of 4–16  $\mu\text{g mL}^{-1}$ .

## Experimental

### General procedures

The melting points were determined on a Melt-temp apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed on Merck silica gel 60 F254, and

the spots were visualized by UV light absorption. The IR spectra were measured using potassium bromide pellets on a Perkin-Elmer 1430 series FTIR spectrometer. NMR spectra were recorded on an Avance Bruker-400 MHz spectrometer ( $^1\text{H}$  NMR at 400 MHz,  $^{13}\text{C}$  NMR at 100 MHz and  $^{19}\text{F}$  NMR at 377 MHz) in DMSO- $d_6$  using tetramethylsilane (TMS) as the internal standard. Elemental analyses were performed using an elementary analyser system Elementar-vario EL III element analyzer. The MS spectra were measured on a high-performance liquid chromatographer-mass spectrometer (HPLC-MS) (ion trap) from Thermo Scientific.

General procedure for the synthesis of dimethyl 1-(substituted phenyl)-1*H*-1,2,3-triazole-4,5-dicarboxylate **3a-d**

Dimethyl acetylenedicarboxylate (0.015 mmol) and the appropriate fluorophenyl azide (0.02 mmol) were heated in a water bath for 2-3 min. The reaction mixture was cooled, and then, ether was added to precipitate the product. The solid was filtered and washed with ether to obtain the desired product.

Dimethyl 1-(2-fluorophenyl)-1*H*-1,2,3-triazole-4,5-dicarboxylate (**3a**)

IR (KBr)  $\nu_{\text{max}}$  /  $\text{cm}^{-1}$  3061 (C–H, aromatic), 2946, 2959 (C–H, aliphatic), 1737 (C=O), 1573 (C=C);  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  3.83 (s, 3H, OCH<sub>3</sub>), 3.94 (s, 3H, OCH<sub>3</sub>), 7.52 (dd, 1H, *J* 8, 16 Hz, Ar–H), 7.63 (ddd, 1H, *J* 4, 8, 16 Hz, Ar–H), 7.77 (ddd, 1H, *J* 4, 8, 16 Hz, Ar–H), 7.86 (ddd, 1H, *J* 4, 8, 16 Hz, Ar–H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  52.85 (OCH<sub>3</sub>), 53.77 (OCH<sub>3</sub>), 116.62, 116.80, 122.87, 122.99, 125.59, 125.63, 128.24, 132.02, 133.33, 133.41, 138.67, 153.90, 156.40 (Ar–C), 157.71, 159.70 (C=O);  $^{19}\text{F}$  NMR (377 MHz, DMSO- $d_6$ )  $\delta$  –123.63 to –123.70 (m, 1F, Ar–F); MS (EI) [ $\text{M}^+$ ] 279.10; anal. calcd. (C<sub>12</sub>H<sub>10</sub>FN<sub>3</sub>O<sub>4</sub>): C 51.62%, H 3.61%, N 15.05%; found: C 51.86%, H 3.47%, N 15.19%.

Dimethyl 1-(4-fluorophenyl)-1*H*-1,2,3-triazole-4,5-dicarboxylate (**3b**)

IR (KBr)  $\nu_{\text{max}}$  /  $\text{cm}^{-1}$  3053 (C–H, aromatic), 2951, 2967 (C–H, aliphatic), 1727 (C=O), 1583 (C=C);  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  3.84 (s, 3H, OCH<sub>3</sub>), 3.92 (s, 3H, OCH<sub>3</sub>), 7.51 (dd, 2H, *J* 8, 16 Hz, Ar–H), 7.74 (dd, 2H, *J* 4, 12 Hz, Ar–H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  52.69 (OCH<sub>3</sub>), 53.85 (OCH<sub>3</sub>), 116.56, 116.80, 127.41, 127.50, 131.44, 131.47, 131.86, 138.32 (Ar–C), 158.43, 159.80, 161.61, 164.08 (C=O);  $^{19}\text{F}$  NMR (377 MHz, DMSO- $d_6$ )  $\delta$  –109.89 to –109.96 (m, 1F, Ar–F); MS (EI) [ $\text{M}^+$ ] 279.20; anal. calcd. (C<sub>12</sub>H<sub>10</sub>FN<sub>3</sub>O<sub>4</sub>): C 51.62%, H 3.61%, N 15.05%; found: 51.79%, H 3.75%, N 15.24%.

Dimethyl 1-(3-fluoro-4-methylphenyl)-1*H*-1,2,3-triazole-4,5-dicarboxylate (**3c**)

IR (KBr)  $\nu_{\text{max}}$  /  $\text{cm}^{-1}$  3025 (C–H, aromatic), 2923, 2970 (C–H, aliphatic), 1733 (C=O), 1577 (C=C);  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  3.38 (s, 3H, CH<sub>3</sub>), 3.86 (s, 3H, OCH<sub>3</sub>), 3.92 (s, 3H, OCH<sub>3</sub>), 7.39 (dd, 2H, *J* 4, 12 Hz, Ar–H), 7.53–7.59 (m, 2H, Ar–H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  13.97 (CH<sub>3</sub>), 52.68 (OCH<sub>3</sub>), 53.89 (OCH<sub>3</sub>), 111.99, 112.26, 120.58, 120.61, 127.44, 127.61, 131.79, 132.40, 133.77, 133.66, 138.22, 158.47 (Ar–C), 159.72, 161.28 (C=O);  $^{19}\text{F}$  NMR (377 MHz, DMSO- $d_6$ )  $\delta$  –114.28 to –114.34 (m, 1F, Ar–F); MS (EI) [ $\text{M}^+$ ] 293.29; anal. calcd. (C<sub>13</sub>H<sub>12</sub>FN<sub>3</sub>O<sub>4</sub>): C 53.24%, H 4.12%, N 14.33%; found: C 53.06%, H 4.31%, N 14.16%.

Dimethyl 1-(2-fluoro-4-iodophenyl)-1*H*-1,2,3-triazole-4,5-dicarboxylate (**3d**)

IR (KBr)  $\nu_{\text{max}}$  /  $\text{cm}^{-1}$  3084 (C–H, aromatic), 2942, 2988 (C–H, aliphatic), 1735 (C=O), 1559 (C=C);  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  3.83 (s, 3H, OCH<sub>3</sub>), 3.92 (s, 3H, OCH<sub>3</sub>), 7.62 (dd, 1H, *J* 8, 12 Hz, Ar–H), 7.89 (dd, 1H, *J* 4, 8 Hz, Ar–H), 8.09 (d, 1H, *J* 8 Hz, Ar–H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  52.88 (OCH<sub>3</sub>), 53.81 (OCH<sub>3</sub>), 117.60, 120.62, 124.26, 124.81, 125.08, 125.19, 129.77, 131.30, 132.06, 133.88, 133.92, 137.52, 139.60, 153.54, 154.10, 154.23 (Ar–C), 157.58, 158.55 (C=O);  $^{19}\text{F}$  NMR (377 MHz, DMSO- $d_6$ )  $\delta$  –121.29 to –121.33; MS (EI) [ $\text{M}^+$ ] 404.69; anal. calcd. (C<sub>12</sub>H<sub>9</sub>FIN<sub>3</sub>O<sub>4</sub>): C 35.58%, H 2.24%, N 10.37%; found: C 35.77%, H 2.40%, N 10.21%.

General procedure for the synthesis of 1-(substituted phenyl)-1*H*-1,2,3-triazole-4,5-dicarbohydrazide **4a-d**

A mixture of **3a-d** (0.02 mmol) and hydrazine hydrate (0.04 mmol) in ethanol (50 mL) was heated under reflux for 4 h. After cooling, ethanol was removed under reduced pressure, and the product was recrystallized from ethanol.

1-(2-Fluorophenyl)-1*H*-1,2,3-triazole-4,5-dicarbohydrazide (**4a**)

IR (KBr)  $\nu_{\text{max}}$  /  $\text{cm}^{-1}$  3242–3365 (NH, NH<sub>2</sub>), 3071 (C–H, aromatic), 1697 (C=O), 1562 (C=C);  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  4.55 (bs, 4H, NH<sub>2</sub>), 7.43 (dd, 1H, *J* 8, 12 Hz, Ar–H), 7.51 (dd, 1H, *J* 8, 12 Hz, Ar–H), 7.63–7.70 (m, 2H, Ar–H), 10.61 (bs, 2H, NH);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  115.96, 116.14, 124.80, 124.84, 125.08, 125.21, 128.35, 132.14, 132.28, 132.36, 137.56, 154.31, 154.67 (Ar–C), 157.16, 158.68 (C=O);  $^{19}\text{F}$  NMR (377 MHz, DMSO- $d_6$ )  $\delta$  –122.72 to –122.78 (m, 1F, Ar–F); MS (EI) [ $\text{M}^+$ ] 279.24; anal. calcd. (C<sub>10</sub>H<sub>10</sub>FN<sub>7</sub>O<sub>2</sub>): C 43.01%, H 3.61%, N 35.11%; found: C 43.26%, H 3.44%, N 35.35%.

1-(4-Fluorophenyl)-1*H*-1,2,3-triazole-4,5-dicarbohydrazide (**4b**)

IR (KBr)  $\nu_{\max}$  /  $\text{cm}^{-1}$  3227-3369 (NH, NH<sub>2</sub>), 3076 (C–H, aromatic), 1694 (C=O), 1581 (C=C); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  4.74 (bs, 4H, NH<sub>2</sub>), 7.41-7.45 (m, 2H, Ar–H), 7.63-7.65 (m, 2H, Ar–H), 10.55 (bs, 2H, NH); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  115.92, 116.16, 127.27, 127.70, 132.19, 132.89, 138.39, 155.55 (Ar–C), 158.64, 163.67 (C=O); <sup>19</sup>F NMR (377 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  –111.20 to –111.28 (m, 1F, Ar–F); MS (EI) [M<sup>+</sup>] 279.01; anal. calcd. (C<sub>10</sub>H<sub>10</sub>FN<sub>7</sub>O<sub>2</sub>): C 43.01%, H 3.61%, N 35.11%; found: C 43.33%, H 3.49%, N 35.24%.

1-(2-Fluoro-4-methylphenyl)-1*H*-1,2,3-triazole-4,5-dicarbohydrazide (**4c**)

IR (KBr)  $\nu_{\max}$  /  $\text{cm}^{-1}$  3249-3371 (NH, NH<sub>2</sub>), 3023 (C–H, aromatic), 1688 (C=O), 1560 (C=C); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  2.33 (s, 3H, CH<sub>3</sub>), 4.69 (bs, 4H, NH<sub>2</sub>), 7.33 (dd, 1H, *J* 4, 8 Hz, Ar–H), 7.44-7.51 (m, 2H, Ar–H), 10.34 (s, 1H, NH), 10.96 (s, 1H, NH); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  112.28, 112.54, 120.99, 121.03, 126.40, 126.57, 131.81, 131.86, 132.17, 135.12, 135.23, 138.43, 155.47 (Ar–C), 158.61, 161.04 (C=O); <sup>19</sup>F NMR (377 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  –115.39 to –115.44 (m, 1F, Ar–F); MS (EI) [M<sup>+</sup>] 293.26; anal. calcd. (C<sub>11</sub>H<sub>12</sub>FN<sub>7</sub>O<sub>2</sub>): C 45.05%, H 4.12%, N 33.43%; found: C 44.87%, H 4.28%, N 33.26%.

1-(2-Fluoro-4-iodophenyl)-1*H*-1,2,3-triazole-4,5-dicarbohydrazide (**4d**)

IR (KBr)  $\nu_{\max}$  /  $\text{cm}^{-1}$  3235-3359 (NH, NH<sub>2</sub>), 3086 (C–H, aromatic), 1691 (C=O), 1557 (C=C); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  4.79 (bs, 4H, NH<sub>2</sub>), 7.49 (dd, 1H, *J* 8, 12 Hz, Ar–H), 7.81 (dd, 1H, *J* 4, 8 Hz, Ar–H), 7.99 (d, 1H, *J* 8 Hz, Ar–H), 10.84 (s, 1H, NH), 11.55 (s, 1H, NH); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  117.60, 120.62, 124.81, 125.08, 125.19, 129.77, 132.06, 133.88, 133.92, 137.52, 137.60, 153.54, 154.23 (Ar–C), 157.58, 158.55 (C=O); <sup>19</sup>F NMR (377 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  –120.40 to –120.43; MS (EI) [M<sup>+</sup>] 404.84; anal. calcd. (C<sub>12</sub>H<sub>9</sub>FIN<sub>3</sub>O<sub>4</sub>): C 35.58%, H 2.24%, N 10.37%; found: C 35.39%, H 2.09%, N 10.51%.

General procedure for the synthesis of Schiff bases **5a-q**

A mixture of **4a-d** (0.01 mmol) and the appropriate benzaldehyde derivative (0.02 mmol) was refluxed in ethanol (30 mL) containing HCl (0.5 mL) for 2 h. After cooling, the obtained precipitate was filtered and recrystallized from ethanol to afford the desired product.

1-(2-Fluorophenyl)-N<sup>4</sup>,N<sup>5</sup>-bis(4-fluorobenzylidene)-1*H*-1,2,3-triazole-4,5-dicarbohydrazide (**5a**)

IR (KBr)  $\nu_{\max}$  /  $\text{cm}^{-1}$  3279-3346 (NH), 3047 (C–H, aromatic), 1693 (C=O), 1575 (C=C); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  7.10-7.15 (m, 1H, Ar–H), 7.26-7.37 (m, 3H, Ar–H), 7.43-7.61 (m, 3H, Ar–H), 7.70-7.85 (m, 5H, Ar–H), 7.99 (s, 0.55H, H–C=N), 8.36 (s, 0.5H, H–C=N), 8.50 (s, 0.4H, H–C=N), 8.68 (s, 0.55H, H–C=N), 12.46 (s, 0.7H, NH), 12.79 (bs, 0.6H, NH), 13.27 (s, 0.6H, NH); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  115.88, 116.10, 123.01, 128.33, 128.77, 129.26, 129.74, 136.23, 138.39, 140.19, 140.48, 144.11, 144.79 (Ar–C), 155.40, 155.55, 156.12, 156.56, 156.97, 159.21 (C=O, C=N); <sup>19</sup>F NMR (377 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  –109.76 to –110.41 (4m, 2F, Ar–F), –122.78 to –122.92 (2m, 1F, Ar–F); MS (EI) [M<sup>+</sup>] 491.42; anal. calcd. (C<sub>24</sub>H<sub>16</sub>F<sub>3</sub>N<sub>7</sub>O<sub>2</sub>): C 58.66%, H 3.28%, N 19.95%; found: C 58.85%, H 3.44%, N 19.78%.

1-(2-Fluorophenyl)-N<sup>4</sup>,N<sup>5</sup>-bis(4-methoxybenzylidene)-1*H*-1,2,3-triazole-4,5-dicarbohydrazide (**5b**)

IR (KBr)  $\nu_{\max}$  /  $\text{cm}^{-1}$  3268-3360 (NH), 3079 (C–H, aromatic), 1687 (C=O), 1562 (C=C); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  3.94 (s, 1.4H, OCH<sub>3</sub>), 4.02 (s, 0.4H, OCH<sub>3</sub>), 4.04 (s, 0.9H, OCH<sub>3</sub>), 4.06 (s, 1.65H, OCH<sub>3</sub>), 4.07 (s, 1.65H, OCH<sub>3</sub>), 7.03-7.17 (m, 1H, Ar–H), 7.24-7.32 (m, 3H, Ar–H), 7.65-7.87 (m, 4H, Ar–H), 7.93-8.04 (m, 4H, arH), 8.18 (s, 0.5H, H–C=N), 8.55 (s, 0.6H, H–C=N), 8.71 (s, 0.4H, H–C=N), 8.88 (s, 0.5H, H–C=N), 12.54 (s, 0.7H, NH), 12.88 (s, 0.6H, NH), 13.51 (s, 0.6H, NH); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  55.39, 55.51, 55.55, 55.57 (OCH<sub>3</sub>), 114.18, 114.38, 114.53, 114.64, 114.67, 124.53, 124.66, 125.46, 125.15, 126.31, 126.66, 126.85, 128.08, 128.57, 128.91, 129.34, 129.42, 134.22, 135.10, 138.53, 140.79, 145.98, 148.83, 149.84, 150.57, 152.28, 154.67, 155.66 (Ar–C), 156.72, 157.16, 159.24, 161.05, 161.16, 161.47, 161.54 (C=O, C=N); <sup>19</sup>F NMR (377 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  –122.47 to –122.60, –122.74 to –122.81 (2m, 1F, Ar–F); MS (EI) [M<sup>+</sup>] 515.49; anal. calcd. (C<sub>26</sub>H<sub>22</sub>FN<sub>7</sub>O<sub>4</sub>): C 60.58%, H 4.30%, N 19.02%; found: C 60.74%, H 4.46%, N 19.34%.

1-(2-Fluorophenyl)-N<sup>4</sup>,N<sup>5</sup>-bis(4-nitrobenzylidene)-1*H*-1,2,3-triazole-4,5-dicarbohydrazide (**5c**)

IR (KBr)  $\nu_{\max}$  /  $\text{cm}^{-1}$  3255-3339 (NH), 3086 (C–H, aromatic), 1698 (C=O), 1559 (C=C); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  7.10-7.19 (m, 1H, Ar–H), 7.29-7.37 (m, 3H, Ar–H), 7.67-7.89 (m, 4H, Ar–H), 7.97-8.07 (m, 4H, Ar–H), 8.16 (s, 0.5H, H–C=N), 8.58 (s, 0.6H, H–C=N), 8.74 (s, 0.4H, H–C=N), 8.84 (s, 0.6H, H–C=N), 12.51 (s, 0.7H, NH), 12.84 (s, 0.6H, NH), 13.58 (s, 0.6H, NH); <sup>13</sup>C NMR

(100 MHz, DMSO- $d_6$ )  $\delta$  114.52, 114.66, 114.89, 123.02, 123.77, 124.81, 125.24, 125.63, 126.12, 126.77, 127.58, 128.23, 128.67, 129.06, 129.58, 133.12, 134.68, 137.95, 139.68, 144.36, 145.89, 148.30, 150.89, 152.16, 154.94, 155.72 (Ar-C), 156.12, 157.28, 159.09, 160.99, 162.28, 162.63 (C=O, C=N);  $^{19}\text{F}$  NMR (377 MHz, DMSO- $d_6$ )  $\delta$  -122.65 to -122.74, -123.02 to -123.08 (2m, 1F, Ar-F); MS (EI) [ $\text{M}^+$ ] 545.43; anal. calcd. ( $\text{C}_{24}\text{H}_{16}\text{FN}_9\text{O}_6$ ): C 52.85%, H 2.96%, N 23.11%; found: C 52.61%, H 2.74%, N 23.35%.

1-(2-Fluorophenyl)- $\text{N}^4, \text{N}^5$ -bis(benzylidene)-1*H*-1,2,3-triazole-4,5-dicarbohydrazide (**5d**)

IR (KBr)  $\nu_{\text{max}}$  /  $\text{cm}^{-1}$  3261-3382 (NH), 3019 (C-H, aromatic), 1683 (C=O), 1583 (C=C);  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  7.31-7.34 (m, 1H, Ar-H), 7.43-7.60 (m, 8H, Ar-H), 7.65-7.80 (m, 5H, Ar-H), 8.01 (s, 0.55H, H-C=N), 8.35 (s, 0.5H, H-C=N), 8.53 (s, 0.4H, H-C=N), 8.69 (s, 0.55H, H-C=N), 12.49 (s, 0.7H, NH), 12.80 (bs, 0.6H, NH), 13.27 (s, 0.6H, NH);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  116.59, 116.87, 117.48, 125.22, 126.99, 127.12, 127.35, 127.45, 127.73, 128.81, 128.87, 128.94, 130.22, 130.66, 130.79, 133.31, 133.94, 134.04, 138.43, 140.45, 145.91, 148.75, 149.67 (Ar-C), 150.22, 154.00, 154.39, 155.53, 156.55, 159.27 (C=O, C=N);  $^{19}\text{F}$  NMR (377 MHz, DMSO- $d_6$ )  $\delta$  -122.70 to -122.76, -122.88 to -122.93 (2m, 1F, Ar-F); MS (EI) [ $\text{M}^+$ ] 455.02; anal. calcd. ( $\text{C}_{24}\text{H}_{18}\text{FN}_7\text{O}_2$ ): C 63.29%, H 3.98%, N 21.53%; found: C 63.14%, H 3.86%, N 21.70%.

1-(4-Fluorophenyl)- $\text{N}^4, \text{N}^5$ -bis(4-fluorobenzylidene)-1*H*-1,2,3-triazole-4,5-dicarbohydrazide (**5e**)

IR (KBr)  $\nu_{\text{max}}$  /  $\text{cm}^{-1}$  3285-3357 (NH), 3078 (C-H, aromatic), 1679 (C=O), 1568 (C=C);  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  7.20 (dd, 1H,  $J$  8, 12 Hz, Ar-H), 7.27-7.36 (m, 3H, Ar-H), 7.43-7.51 (m, 3H, Ar-H), 7.67-7.76 (m, 3H, Ar-H), 7.79-7.85 (m, 2H, Ar-H), 8.03 (s, 0.6H, H-C=N), 8.31 (s, 0.45H, H-C=N), 8.56 (s, 0.5H, H-C=N), 8.68 (s, 0.45H, H-C=N), 12.40 (s, 0.55H, NH), 12.66 (bs, 1.45H, NH);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  115.73, 115.77, 115.85, 115.95, 115.98, 116.06, 116.41, 116.64, 116.83, 117.07, 126.31, 126.40, 127.32, 127.41, 129.08, 129.24, 129.33, 129.42, 129.65, 129.74, 130.16, 130.69, 131.78, 132.24, 133.78, 134.48, 139.06, 139.90, 145.01, 147.68, 148.40, 148.58 (Ar-C), 153.22, 155.39, 156.12, 160.06, 161.37, 161.43, 161.88, 162.06, 162.19, 164.35 (C=O, C=N);  $^{19}\text{F}$  NMR (377 MHz, DMSO- $d_6$ )  $\delta$  -109.50 to -109.58, -109.94 to -110.04, -110.26 to -110.33, -110.48 to -110.55 (4m, 3F, Ar-F); MS (EI) [ $\text{M}^+$ ] 491.36; anal. calcd. ( $\text{C}_{24}\text{H}_{16}\text{F}_3\text{N}_7\text{O}_2$ ): C 58.66%, H 3.28%, N 19.95%; found: C 58.79%, H 3.12%, N 20.21%.

1-(4-Fluorophenyl)- $\text{N}^4, \text{N}^5$ -bis(4-methoxybenzylidene)-1*H*-1,2,3-triazole-4,5-dicarbohydrazide (**5f**)

IR (KBr)  $\nu_{\text{max}}$  /  $\text{cm}^{-1}$  3253-3339 (NH), 3062 (C-H, aromatic), 1695 (C=O), 1571 (C=C);  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  3.71 (s, 1.5 H,  $\text{OCH}_3$ ), 3.79 (s, 1.5 H,  $\text{OCH}_3$ ), 3.80 (s, 1.5 H,  $\text{OCH}_3$ ), 3.81 (s, 1.5 H,  $\text{OCH}_3$ ), 6.87-6.90 (m, 1H, Ar-H), 6.99-7.05 (m, 3H, Ar-H), 7.34-7.37 (m, 1H, Ar-H), 7.45-7.51 (m, 2H, Ar-H), 7.61-7.74 (m, 5H, Ar-H), 7.95 (s, 0.5H, H-C=N), 8.21 (s, 0.5H, H-C=N), 8.48 (s, 0.5H, H-C=N), 8.59 (s, 0.5H, H-C=N), 12.25 (s, 0.5H, NH), 12.39 (s, 0.5H, NH), 12.47 (s, 0.5H, NH), 12.79 (s, 0.5H, NH);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  55.18, 55.25, 55.29 ( $\text{OCH}_3$ ), 114.24, 114.29, 114.38, 116.39, 116.62, 116.83, 117.07, 125.86, 126.00, 126.24, 126.34, 126.54, 126.63, 127.33, 127.43, 128.53, 128.76, 128.95, 129.14, 131.81, 132.28, 133.72, 134.49, 139.04, 139.93, 145.92, 148.63, 149.30, 149.59 (Ar-C), 152.92, 155.22, 155.95, 159.82, 160.88, 161.08, 161.26, 161.33, 161.40 (C=O, C=N);  $^{19}\text{F}$  NMR (377 MHz, DMSO- $d_6$ )  $\delta$  -110.30 to -110.37, -110.51 to -110.58 (2m, 1F, Ar-F); MS (EI) [ $\text{M}^+$ ] 515.31; anal. calcd. ( $\text{C}_{26}\text{H}_{22}\text{FN}_7\text{O}_4$ ): C 60.58%, H 4.30%, N 19.02%; found: C 60.40%, H 4.39%, N 19.21%.

1-(4-Fluorophenyl)- $\text{N}^4, \text{N}^5$ -bis(4-nitrobenzylidene)-1*H*-1,2,3-triazole-4,5-dicarbohydrazide (**5g**)

IR (KBr)  $\nu_{\text{max}}$  /  $\text{cm}^{-1}$  3248-3350 (NH), 3092 (C-H, aromatic), 1688 (C=O), 1579 (C=C);  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  7.42-7.53 (m, 2H, Ar-H), 7.56-7.76 (m, 3H, Ar-H), 7.90 (d, 1H,  $J$  8 Hz, Ar-H), 8.03 (dd, 2H,  $J$  8, 12 Hz, Ar-H), 8.13-8.16 (m, 2H, Ar-H), 8.26-8.33 (m, 2.6H, Ar-H, H-C=N), 8.39 (s, 0.45H, H-C=N), 8.62 (s, 0.5H, H-C=N), 8.75 (s, 0.45H, H-C=N), 12.73 (s, 0.6H, NH), 12.86 (s, 1.45H, NH), 12.92 (s, 0.45H, NH), 13.05 (s, 0.45H, NH);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  116.57, 116.80, 116.87, 117.10, 123.95, 124.02, 124.05, 124.12, 126.47, 126.56, 127.25, 127.34, 127.88, 128.02, 128.20, 128.44, 131.66, 131.93, 133.80, 134.17, 139.16, 139.38, 139.67, 140.00, 140.25, 144.12, 146.47, 147.32, 147.85, 148.03, 148.21 (Ar-C), 153.63, 155.73, 156.23, 160.24, 161.42, 163.90 (C=O, C=N);  $^{19}\text{F}$  NMR (377 MHz, DMSO- $d_6$ )  $\delta$  -110.05 to -110.11, -110.17 to -110.23 (2m, 1F, Ar-F); MS (EI) [ $\text{M}^+$ ] 545.28; anal. calcd. ( $\text{C}_{24}\text{H}_{16}\text{FN}_9\text{O}_6$ ): C 52.85%, H 2.96%, N 23.11%; found: C 52.67%, H 2.82%, N 23.27%.

1-(4-Fluorophenyl)- $\text{N}^4, \text{N}^5$ -bis(benzylidene)-1*H*-1,2,3-triazole-4,5-dicarbohydrazide (**5h**)

IR (KBr)  $\nu_{\text{max}}$  /  $\text{cm}^{-1}$  3258-3337 (NH), 3064 (C-H, aromatic), 1682 (C=O), 1565 (C=C);  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  7.33 (dd, 2H,  $J$  4, 8 Hz, Ar-H), 7.41-7.52 (m, 7H, Ar-H), 7.66-7.71 (m, 2H, Ar-H), 7.73-7.77 (m, 3H,

Ar-H), 8.04 (s, 0.6H, H-C=N), 8.29 (s, 0.45H, H-C=N), 8.57 (s, 0.5H, H-C=N), 8.66 (s, 0.45H, H-C=N), 12.44 (s, 0.6H, NH), 12.56 (s, 0.5H, NH), 12.64 (s, 0.45H, NH), 12.88 (s, 0.45H, NH);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  116.45, 116.68, 116.87, 117.10, 126.30, 126.39, 126.89, 127.12, 127.27, 127.33, 127.43, 128.45, 128.77, 128.87, 128.89, 129.89, 130.20, 130.29, 130.42, 130.68, 131.74, 131.77, 132.17, 132.20, 133.30, 133.50, 133.79, 134.04, 134.11, 134.53, 139.11, 139.91, 144.89, 145.85, 146.14, 148.81, 149.50, 149.70 (Ar-C), 153.20, 155.39, 156.10, 159.44, 160.11, 161.37, 161.44, 163.84, 163.91 (C=O, C=N);  $^{19}\text{F}$  NMR (377 MHz, DMSO- $d_6$ )  $\delta$  -110.21 to -110.28, -110.40 to -110.47 (2m, 1F, Ar-F); MS (EI) [ $\text{M}^+$ ] 455.30; anal. calcd. ( $\text{C}_{24}\text{H}_{18}\text{FN}_7\text{O}_2$ ): C 63.29%, H 3.98%, N 21.53%; found: C 63.11%, H 3.85%, N 21.73%.

1-(2-Fluoro-4-methylphenyl)- $\text{N}^4, \text{N}^5$ -bis(4-fluorobenzylidene)-1*H*-1,2,3-triazole-4,5-dicarbohydrazide (**5i**)

IR (KBr)  $\nu_{\text{max}}$  /  $\text{cm}^{-1}$  3272-3341 (NH), 3038 (C-H, aromatic), 1690 (C=O), 1572 (C=C);  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  2.29 (s, 1.5H,  $\text{CH}_3$ ), 2.34 (s, 1.5H,  $\text{CH}_3$ ), 7.10 (dd, 1H,  $J$  8, 12 Hz, Ar-H), 7.27-7.37 (m, 4H, Ar-H), 7.46-7.59 (m, 3H, Ar-H), 7.71-7.83 (m, 3H, Ar-H), 8.01 (s, 0.55H, H-C=N), 8.28 (s, 0.45H, H-C=N), 8.54 (s, 0.55H, H-C=N), 8.65 (s, 0.45H, H-C=N), 12.44 (s, 0.7H, NH), 12.64 (s, 0.8H, H-C=N), 12.84 (s, 0.4H, NH);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  13.55, 13.93, 14.00 ( $\text{CH}_3$ ), 111.18, 11.45, 111.86, 111.98, 115.80, 115.90, 116.02, 116.12, 119.53, 120.63, 127.20, 127.42, 128.85, 128.99, 129.19, 129.19, 129.35, 129.51, 129.68, 129.76, 130.71, 132.39, 133.72, 134.28, 139.14, 139.94, 145.03, 147.69, 148.41, 148.61 (Ar-C), 153.21, 155.34, 156.70, 158.98, 160.03, 161.32, 161.45 (C=O, C=N);  $^{19}\text{F}$  NMR (377 MHz, DMSO- $d_6$ )  $\delta$  -109.48 to -110.46 (4m, 2F, Ar-F), -114.02 to -114.61 (2m, 1F, Ar-F); MS (EI) [ $\text{M}^+$ ] 505.34; anal. calcd. ( $\text{C}_{25}\text{H}_{18}\text{F}_3\text{N}_7\text{O}_2$ ): C 59.41%, H 3.59%, N 19.40%; found: C 59.58%, H 3.67%, N 19.29%.

1-(2-Fluoro-4-methylphenyl)- $\text{N}^4, \text{N}^5$ -bis(4-methoxybenzylidene)-1*H*-1,2,3-triazole-4,5-dicarbohydrazide (**5j**)

IR (KBr)  $\nu_{\text{max}}$  /  $\text{cm}^{-1}$  3253-3324 (NH), 3027 (C-H, aromatic), 1690 (C=O), 1569 (C=C);  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  2.30 (s, 1.5H,  $\text{CH}_3$ ), 2.34 (s, 1.5H,  $\text{CH}_3$ ), 3.70 (s, 0.2H,  $\text{OCH}_3$ ), 3.72 (s, 0.4H,  $\text{OCH}_3$ ), 3.76 (s, 0.3H,  $\text{OCH}_3$ ), 3.80 (s, 1.3H,  $\text{OCH}_3$ ), 3.81 (s, 2.8H,  $\text{OCH}_3$ ), 6.89 (d, 1H,  $J$  8 Hz, Ar-H), 7.00-7.06 (m, 3H, Ar-H), 7.35-7.42 (m, 2H, Ar-H), 7.46-7.63 (m, 3H, Ar-H), 7.72 (dd, 2H,  $J$  8, 12 Hz, Ar-H), 7.95 (s, 0.55H, H-C=N), 8.22 (s, 0.5H, H-C=N), 8.48 (s, 0.45H, H-C=N), 8.58 (s, 0.5H, H-C=N), 11.89 (s, 0.6H, NH), 12.50 (brs, 1.3H, NH);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  13.95, 13.98, 14.00, 14.03 ( $\text{CH}_3$ ),

55.19, 55.26, 55.30 ( $\text{OCH}_3$ ), 110.83, 111.26, 112.36, 112.86, 114.24, 114.30, 114.38, 119.48, 120.73, 120.87, 125.86, 126.07, 126.57, 126.93, 128.54, 128.74, 128.91, 129.12, 132.25, 132.73, 134.36, 134.52, 134.79, 139.09, 139.95, 146.28, 148.60, 149.25, 149.47 (Ar-C), 155.14, 155.85, 158.78, 159.84, 160.87, 161.06, 161.23, 161.45 (C=O, C=N);  $^{19}\text{F}$  NMR (377 MHz, DMSO- $d_6$ )  $\delta$  -114.02 to -114.08, -114.73 to -114.78 (2m, 1F, Ar-F); MS (EI) [ $\text{M}^+$ ] 529.52; anal. calcd. ( $\text{C}_{27}\text{H}_{24}\text{FN}_7\text{O}_4$ ): C 61.24%, H 4.57%, N 18.52%; found: C 61.41%, H 4.35%, N 18.69%.

1-(2-Fluoro-4-methylphenyl)- $\text{N}^4, \text{N}^5$ -bis(4-nitrobenzylidene)-1*H*-1,2,3-triazole-4,5-dicarbohydrazide (**5k**)

IR (KBr)  $\nu_{\text{max}}$  /  $\text{cm}^{-1}$  3260-3337 (NH), 3090 (C-H, aromatic), 1678 (C=O), 1567 (C=C);  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  2.30 (s, 1.7H,  $\text{CH}_3$ ), 2.34 (s, 1.3H,  $\text{CH}_3$ ), 7.37-7.43 (m, 1H, Ar-H), 7.49-7.55 (m, 2H, Ar-H), 7.68 (d, 1H,  $J$  8 Hz, Ar-H), 7.91 (d, 1H,  $J$  8 Hz, Ar-H), 7.98-8.08 (m, 2H, Ar-H), 8.13-8.16 (m, 2H, Ar-H), 8.27-8.34 (m, 2.6H, H-C=N, Ar-H), 8.40 (s, 0.45H, H-C=N), 8.63 (s, 0.5H, H-C=N), 8.75 (s, 0.45H, H-C=N), 12.75 (s, 0.7H, NH), 12.96 (brs, 1.2H, H-C=N);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  13.97, 14.00, 14.04 ( $\text{CH}_3$ ), 111.09, 11.16, 112.48, 112.86, 119.59, 121.29, 123.95, 124.05, 124.15, 127.89, 128.02, 128.18, 128.42, 134.08, 134.33, 139.42, 140.02, 140.26, 140.73, 141.01, 144.08, 146.45, 147.28, 147.89, 148.16 (Ar-C), 155.66, 156.16, 157.34, 157.59, 160.30, 161.09, 161.47 (C=O, C=N);  $^{19}\text{F}$  NMR (377 MHz, DMSO- $d_6$ )  $\delta$  -113.95 to -114.02, -114.44 to -114.50 (2m, 1F, Ar-F); MS (EI) [ $\text{M}^+$ ] 558.96; anal. calcd. ( $\text{C}_{25}\text{H}_{18}\text{FN}_9\text{O}_6$ ): C 53.67%, H 3.24%, N 22.53%; found: C 53.81%, H 3.10%, N 22.62%.

1-(2-Fluoro-4-methylphenyl)- $\text{N}^4, \text{N}^5$ -bis(benzylidene)-1*H*-1,2,3-triazole-4,5-dicarbohydrazide (**5l**)

IR (KBr)  $\nu_{\text{max}}$  /  $\text{cm}^{-1}$  3277-3369 (NH), 3052 (C-H, aromatic), 1690 (C=O), 1576 (C=C);  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  2.29 (s, 1.7H,  $\text{CH}_3$ ), 2.34 (s, 1.3H,  $\text{CH}_3$ ), 7.33-7.37 (m, 2H, Ar-H), 7.41-7.59 (m, 8H, Ar-H), 7.66-7.68 (m, 1H, Ar-H), 7.73-7.77 (m, 2H, Ar-H), 8.03 (s, 0.6H, H-C=N), 8.28 (s, 0.45H, H-C=N), 8.56 (s, 0.5H, H-C=N), 8.66 (s, 0.45H, H-C=N), 12.44 (s, 0.7H, NH), 12.67 (s, 1.2H, NH);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  13.96, 13.99, 14.00, 14.03 ( $\text{CH}_3$ ), 110.90, 111.16, 112.04, 112.25, 119.54, 120.65, 126.89, 127.12, 127.25, 127.43, 128.77, 128.82, 128.89, 130.67, 131.14, 132.32, 132.75, 132.81, 133.27, 133.53, 133.80, 134.04, 134.08, 134.35, 139.16, 139.94, 146.15, 148.82, 149.50, 149.60 (Ar-C), 153.31, 155.34, 155.98, 158.81, 159.08, 160.09, 161.36 (C=O, C=N);  $^{19}\text{F}$  NMR (377 MHz, DMSO- $d_6$ )  $\delta$  -114.02 to -114.03, -114.61 to -114.66 (2m, 1F, Ar-F); MS (EI)



[M<sup>+</sup>] 469.26; anal. calcd. (C<sub>25</sub>H<sub>20</sub>FN<sub>7</sub>O<sub>2</sub>): C 63.96%, H 4.29%, N 20.88%; found: C 63.77%, H 4.43%, N 20.62%.

1-(2-Fluoro-4-iodophenyl)-N<sup>4</sup>,N<sup>5</sup>-bis(4-fluorobenzylidene)-1*H*-1,2,3-triazole-4,5-dicarbohydrazide (**5m**)

IR (KBr)  $\nu_{\max}$  / cm<sup>-1</sup> 3258-3326 (NH), 3068 (C–H, aromatic), 1683 (C=O), 1564 (C=C); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  7.11-7.15 (m, 1H, Ar–H), 7.27-7.37 (m, 3H, Ar–H), 7.49-7.58 (m, 2H, Ar–H), 7.64-7.72 (m, 1H, Ar–H), 7.82-7.88 (m, 3H, Ar–H), 8.00 (s, 0.45H, H–C=N), 8.04-8.08 (m, 1H, Ar–H), 8.38 (s, 0.6H, H–C=N), 8.49 (s, 0.4H, H–C=N), 8.69 (s, 0.55H, H–C=N), 12.45 (s, 0.7H, NH), 12.80 (s, 0.6H, NH), 13.37 (s, 0.6H, NH); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  115.62, 115.76, 115.89, 115.94, 116.11, 116.16, 125.25, 125.45, 129.29, 129.58, 129.67, 129.78, 129.92, 130.20, 130.49, 130.62, 130.70, 133.89, 134.31, 134.50, 138.30, 140.71, 144.96, 147.63, 148.83, 149.42 (Ar–C), 152.17, 153.89, 155.50, 156.64, 159.04, 161.28, 162.22, 163.36, 163.77 (C=O, C=N); <sup>19</sup>F NMR (377 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  –109.35 to –110.40 (4m, 2F, Ar–F), –120.46 to –120.83 (2m, 1F, Ar–F); MS (EI) [M<sup>+</sup>] 617.21; anal. calcd. (C<sub>24</sub>H<sub>15</sub>F<sub>3</sub>IN<sub>7</sub>O<sub>2</sub>): C 46.69%, H 2.45%, N 15.88%; found: C 46.48%, H 2.39%, N 15.81%.

1-(2-Fluoro-4-iodophenyl)-N<sup>4</sup>,N<sup>5</sup>-bis(4-methoxybenzylidene)-1*H*-1,2,3-triazole-4,5-dicarbohydrazide (**5n**)

IR (KBr)  $\nu_{\max}$  / cm<sup>-1</sup> 3261-3350 (NH), 3070 (C–H, aromatic), 1696 (C=O), 1584 (C=C); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  3.68 (s, 0.5H, OCH<sub>3</sub>), 3.79 (s, 0.5H, OCH<sub>3</sub>), 3.81 (s, 2.5H, OCH<sub>3</sub>), 3.84 (s, 2.5H, OCH<sub>3</sub>), 6.79-6.92 (m, 1H, Ar–H), 6.98-7.07 (m, 3H, Ar–H), 7.40-7.61 (m, 3H, Ar–H), 7.70-7.75 (m, 2H, Ar–H), 7.83-7.87 (m, 1H, Ar–H), 7.94 (s, 0.55H, H–C=N), 8.05-8.08 (m, 1H, Ar–H), 8.31 (s, 0.6H, H–C=N), 8.44 (s, 0.4H, H–C=N), 8.63 (s, 0.45H, H–C=N), 12.49 (s, 0.7H, NH), 12.66 (s, 0.6H, NH), 13.37 (s, 0.6H, NH); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  55.14, 55.26, 55.31, 55.33 (OCH<sub>3</sub>), 114.11, 114.27, 114.40, 124.37, 124.59, 125.88, 126.08, 126.39, 128.75, 129.09, 129.17, 129.48, 129.68, 133.84, 134.26, 134.41, 138.21, 145.86, 148.56, 149.74 (Ar–C), 150.50, 151.85, 153.95, 155.30, 156.50, 158.81, 160.80, 160.93, 161.24, 161.31 (C=O, C=N); <sup>19</sup>F NMR (377 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  –120.45 to –120.49, –120.66 to –120.70 (2m, 1F, Ar–F); MS (EI) [M<sup>+</sup>] 641.22; anal. calcd. (C<sub>26</sub>H<sub>21</sub>FIN<sub>7</sub>O<sub>4</sub>): C 48.69%, H 3.30%, N 15.29%; found: C 48.93%, H 3.19%, N 15.42%.

1-(2-Fluoro-4-iodophenyl)-N<sup>4</sup>,N<sup>5</sup>-bis(4-nitrobenzylidene)-1*H*-1,2,3-triazole-4,5-dicarbohydrazide (**5o**)

IR (KBr)  $\nu_{\max}$  / cm<sup>-1</sup> 3273-3342 (NH), 3058 (C–H, aromatic), 1697 (C=O), 1577 (C=C); <sup>1</sup>H NMR (400 MHz,

DMSO-*d*<sub>6</sub>)  $\delta$  7.55-7.60 (m, 1H, Ar–H), 7.69-7.78 (m, 1H, Ar–H), 7.81-7.89 (m, 2H, Ar–H), 8.00-8.14 (m, 4.55H, H–C=N, Ar–H), 8.23-8.26 (m, 1H, Ar–H), 8.31-8.38 (m, 2H, Ar–H), 8.50 (s, 0.55H, H–C=N), 8.55 (s, 0.45H, H–C=N), 8.79 (s, 0.45H, H–C=N), 12.73 (s, 0.5H, NH), 12.78 (s, 0.4H, NH), 13.08 (s, 0.5H, NH), 13.41 (s, 0.5H, NH); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  123.79, 123.97, 124.06, 124.16, 125.57, 127.96, 128.31, 128.45, 128.59, 129.19, 129.62, 133.98, 134.11, 134.39, 138.52, 139.45, 139.74, 140.11, 140.89, 144.03, 146.38, 147.64, 147.74, 147.88, 147.92, 148.13, 148.23 (Ar–C), 152.64, 155.85, 156.75, 159.28, 159.43, 162.27 (C=O, C=N); <sup>19</sup>F NMR (377 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  –120.50 to –120.55, –120.85 to –120.92 (2m, 1F, Ar–F); MS (EI) [M<sup>+</sup>] 671.18; anal. calcd. (C<sub>24</sub>H<sub>15</sub>FIN<sub>9</sub>O<sub>6</sub>): C 42.94%, H 2.25%, N 18.78%; found: C 42.87%, H 2.36%, N 18.64%.

1-(2-Fluoro-4-iodophenyl)-N<sup>4</sup>,N<sup>5</sup>-bis(benzylidene)-1*H*-1,2,3-triazole-4,5-dicarbohydrazide (**5p**)

IR (KBr)  $\nu_{\max}$  / cm<sup>-1</sup> 3255-3356 (NH), 3087 (C–H, aromatic), 1686 (C=O), 1569 (C=C); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  7.24-7.39 (m, 2H, Ar–H), 7.43-7.59 (m, 6H, Ar–H), 7.64-7.67 (m, 1H, Ar–H), 7.75-7.88 (m, 3H, Ar–H), 8.01 (s, 0.45H, H–C=N), 8.04-8.08 (m, 1H, Ar–H), 8.37 (s, 0.6H, H–C=N), 8.52 (s, 0.4H, H–C=N), 8.70 (s, 0.55H, H–C=N), 12.47 (s, 0.7H, NH), 12.79 (s, 0.6H, NH), 13.36 (s, 0.6H, NH); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  125.25, 125.38, 125.79, 125.91, 127.01, 127.12, 127.39, 127.46, 128.66, 128.79, 128.88, 128.94, 129.12, 129.67, 130.23, 130.62, 130.73, 133.29, 133.56, 133.88, 134.01, 134.32, 134.61, 138.34, 140.67, 146.00, 146.08, 148.36, 148.81, 149.91 (Ar–C), 150.53, 153.52, 153.93, 155.47, 156.63, 159.10 (C=O, C=N); <sup>19</sup>F NMR (377 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  –120.44 to –120.49, –120.72 to –120.81 (2m, 1F, Ar–F); MS (EI) [M<sup>+</sup>] 580.88; anal. calcd. (C<sub>24</sub>H<sub>17</sub>FIN<sub>7</sub>O<sub>2</sub>): C 49.58%, H 2.95%, N 16.87%; found: C 49.73%, H 2.88%, N 16.73%.

## Biological Assays

### Cells

The newly synthesized compounds (**3a-d**, **4a-d** and **5a-p**) were tested to determine their *in vitro* growth inhibitory activity against standard pathogenic strains from the Regional Center for Mycology and Biotechnology (RCMB), i.e., *Streptococcus pneumonia* RCMB 010010, *Bacillus subtilis* RCMB 010067, *Staphylococcus aureus* RCMB 010025 (Gram-positive bacteria), *Pseudomonas aeruginosa* RCMB 010043, *Escherichia coli* RCMB 010052, *Klebsiella pneumonia* RCMB 010058 (Gram-negative bacteria), and the yeast-like

pathogenic fungi *Aspergillus fumigatus* RCMB 02568 and *Candida albicans* RCMB 05036.

#### Antibacterial and antifungal assays

The preliminary antimicrobial activities of the newly synthesized compounds (**3a-d**, **4a-d** and **5a-p**) were tested using the broth microdilution method.<sup>33-35</sup> The MIC determination of the synthesized compounds was carried out in a side-by-side comparison with ciprofloxacin against Gram-positive (*S. pneumonia*, *B. subtilis*, *S. aureus*) and Gram-negative (*P. aeruginosa*, *E. coli*, *K. pneumoniae*) bacteria. The antifungal activity was assayed against yeasts (i.e., *A. fumigatus*, *C. albicans*). The minimum inhibitory concentrations of the compounds were recorded as the lowest concentration of each chemical compound in the tubes with no turbidity (i.e., no growth) of inoculated bacteria/fungi. The test compounds (10 mg) were dissolved in DMSO (1 mL) and then diluted in culture medium (Mueller-Hinton broth for bacteria and Sabouraud liquid medium for fungi). Further progressive dilutions were made to obtain final concentrations of 1, 2, 4, 8, 16, 31.25, 62.5, 125, 250 and 500 mg mL<sup>-1</sup>. The DMSO content never exceeded 1% v/v. The tubes were inoculated with 10<sup>5</sup> colony forming unit mL<sup>-1</sup> (cfu mL<sup>-1</sup>) and incubated at 37 °C for 24 h. The growth control consisting of media and media with DMSO at the same dilutions as used in the experiments was employed.

#### Supplementary Information

Supplementary data are available free of charge at <http://jbcs.sbq.org.br> as PDF file.

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