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Benzimidazole-1,2,3-triazole Hybrid Molecules: Synthesis and Evaluation for Antibacterial/Antifungal Activity

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A novel series of hybrid molecules **4a–i** and **5a–i** were prepared by condensation of 4-(trimethylsilylethynyl)benzaldehyde **1** with substituted *o*-phenylenediamines. These in turn were reacted with 2-(azidomethoxy)ethyl acetate in a Cu alkyne–azide cycloaddition (CuAAC) to generate the 1,2,3-triazole pharmacophore under microwave assistance. The newly synthesized compounds were examined for their *in vitro* antimicrobial activities against Gram-positive and Gram-negative bacteria and the phytopathogenic fungi *Verticillium dahliae* and *Fusarium oxysporum* f. sp. *albedinis*. 2-((4-(4-(5-Trifluoromethyl benzimidazol-2-yl)phenyl)-1,2,3-triazol-1-yl)methoxy)ethanol **5e** showed a moderate inhibition of 30% in the Foa sporulation test.

Keywords: Antibacterial activity / Antifungal activity / Hybrid molecules

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Introduction

Infectious diseases have been a serious and growing threat to human health during the past few decades. The decrease of sensitivity to anti-microbial agents in current use has also been increasing for a great variety of pathogens and the resistance to multiple drugs is more and more prevalent for several microorganisms, especially for Gram-positive bacteria and some intractable fungi. The benzimidazole ring is an important nitrogen-containing heterocyclic compound, found in several pharmaceutical, synthetic, and natural products. Benzimidazole-based compounds can exhibit a broad range of biological activities; i.e., they are efficient structures against the human cytomegalovirus (HCMV) [1], they have also been used as antihistaminic [2], antimicrobial [3], antifungal [4], and anti-herpes (HSV-1) [5] agents.

The principal way to prepare benzimidazole derivatives is the condensation of 1,2-phenylenediamines and carbonyl compounds such as aldehydes [6–11] or acid derivatives [12–15]. Quite often this reaction is run using the aldehyde route under mild oxidative conditions.

The 1,2,3-triazole core has been applied in many synthetic organic chemistry approaches. This heterocycle exhibited a broad range of efficient biological activities. Moreover, 1,2,3-triazole derivatives are shown to possess a diversity of interesting biological activities, including anti-HIV and hepatitis C [16–18], anti-allergic [19], antifungal [20–23], anti-tubercular [24, 25], anti-inflammatory agents [26], and antimicrobial [27].

One of the most popular methods to prepare 1,2,3-triazoles is the cycloaddition of alkyl azides with terminal alkynes via 1,3-dipolar cycloaddition reaction – the Huisgen reaction – as

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a regioisomeric mixture of the 1,4- and 1,5-disubstituted ones [28]. This reaction was further developed by Meldal and Sharpless. They discovered that the use of copper(I) as catalyst guarantees a high regioselectivity and excellent yield allowing exclusively the 1,4-regioisomer. The copper-catalyzed azide–alkyne cycloaddition (CuAAC) has thus attracted attention for use in a variety of applications [29–32].

Syntheses of heterocycles have seen impressive improvements in using different synthetic methods. Especially, microwave ovens as the heating source have become a very helpful procedure in their preparation. Microwave irradiation in general is a powerful tool for fast and efficient synthesis of a diversity of organic products [33].

Combining preferred heterocyclic entities to construct hybrid molecules have emerged as an interesting exploratory concept for developing new pharmaceutical compounds. They may provide scaffolds on which pharmacophores can be arranged to yield potent and hopefully selective drugs. The increase in bacterial resistance has attracted considerable interest in the discovery and development of new classes of anti-bacterial agents. The new agents should preferably have chemical characteristics that clearly differ from those of existing agents. The search for efficient antibiotics is growing for the reason that most of antibiotic agents develop resistance in clinical applications. Hybrid molecules remain an active area of research despite their extensive investigation.

Following this concept, we report the synthesis, antibacterial and antifungal evaluation of novel hybrid molecules that covalently connect 1,2,3-triazolide and benzimidazoles via a benzene connector.

Results and discussion

Chemistry

In this report, the hybrid molecules were prepared as illustrated in the schemes below. In the first step, the 4-(trimethylsilylethynyl)benzaldehyde **1** was condensed with *o*-phenylenediamine derivatives in the presence of $Na_2S_2O_5$ [34, 35] in dioxane under microwave irradiation to get 2-(4-(2-(trimethylsilyl)ethynyl)phenyl)benzimidazole derivatives **2a–i** in good yields (Scheme 1).

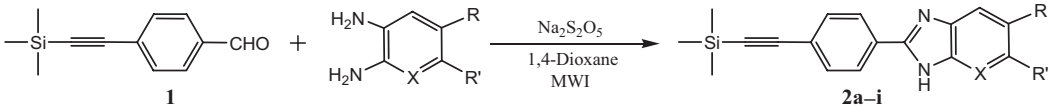
In the second step, the trimethylsilyl group was removed by reacting the products **2a–i** with tetrabutylammonium fluoride in tetrahydrofuran at room temperature [36, 37] to obtain the terminal acetylene linked to the benzimidazole core **3a–i** (Scheme 2).

Next, the resulting compounds **3a–i** with terminal acetylene and the azido substrate were condensed using the Cu alkyne–azide cycloaddition (CuAAC) and triethylamine under microwave irradiation to achieve the new ring 1-substituted 1,2,3-triazole connected via benzene to the benzimidazole nucleus **4a–i** with excellent yields (Table 1, Scheme 3) and in very short reaction time. The next step is cleavage of the acetyl group using potassium carbonate (K_2CO_3) in methanol [38, 39] in order to liberate the hydroxy group of the corresponding hybrid triazolides **5a–h**. The latter were obtained in almost quantitative yields (Table 1, Scheme 3).

The structures of all compounds were characterized by ^{1}H NMR, ^{13}C NMR, mass spectrometry, and HRMS spectra. The structure of **5a** was also confirmed by X-ray diffraction analysis. This structure contains three planar parts: the benzimidazole, the benzene, and the triazole ring. Furthermore, various intermolecular hydrogen bond interactions between the molecules form a three-dimensional network (the hydrogen at N1 with the nitrogens at N4 and N5 as well as the hydrogen at O2 with the nitrogen at N2). The molecular structure of single crystal **5a** is shown in Fig. 1 [40].

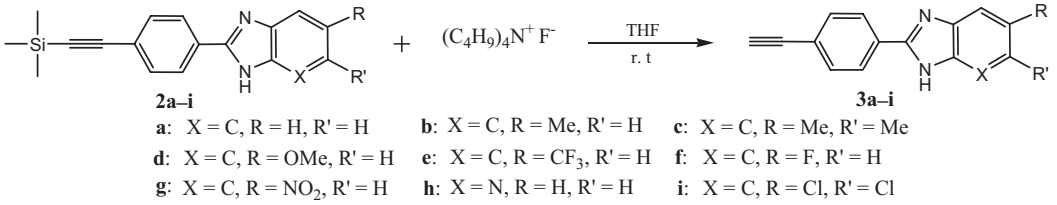
Antibacterial *in vitro* screening of compounds 4a–i and 5a–h

All described compounds (**4a–i**, **5a–h**) were evaluated *in vitro* for their antibacterial activity against the following bacterial strains: *Staphylococcus aureus* (ATCC 13709 *in vivo*, ATCC 25923, Oxford and MRSA *in vivo*), *Enterococcus faecalis* (ATCC 29212 VanS), *Enterococcus faecium* (Van A), *Streptococcus pneumoniae* (VanA, ATCC49619, PenR and Blood effect), *Haemophilus influenzae* (ATCC 31517 MMSA), *Escherichia coli* (ATCC 25922), and *Pseudomonas aeruginosa* (ATCC 27853), using standard techniques and the minimum inhibitory concentration values (MICs) [41]. All products were dissolved in DMSO to have a concentration of 2.56 μg/mL. The MIC of synthesized compounds against Gram-negative and Gram-positive



a: X = C, R = H, R' = H **b**: X = C, R = Me, R' = H **c**: X = C, R = Me, R' = Me
d: X = C, R = OMe, R' = H **e**: X = C, R = CF_3, R' = H **f**: X = C, R = F, R' = H
g: X = C, R = NO_2, R' = H **h**: X = N, R = H, R' = H **i**: X = C, R = Cl, R' = Cl

Scheme 1. Condensation reaction to **2a–i** of 4-(trimethylsilylethynyl)benzaldehyde **1** with substituted *o*-phenylenediamines.

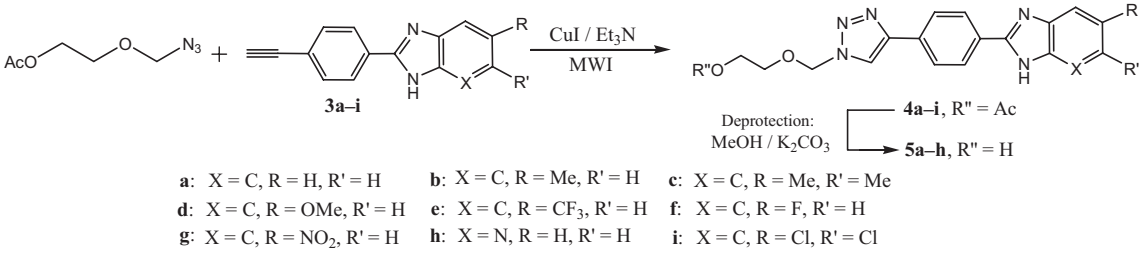


Scheme 2. Deprotection of **2a–i** to obtain the free acetylenic compounds **3a–i**.

Table 1. Results of 1,2,3-triazole-benzimidazole hybrids.

Entry	Product	Yield[a)] (%)	Product	Yield[a)] (%)
1	**4a**	93	**5a**	99
2	**4b**	82	**5b**	98
3	**4c**	75	**5c**	98
4	**4d**	86	**5d**	99
5	**4e**	70	**5e**	95
6	**4f**	80	**5f**	98
7	**4g**	60	**5g**	98
8	**4h**	65	**5h**	95
9	**4i**	67	–	–

[a)] Isolated yields.



Scheme 3. Microwave assisted Cu alkyne–azide cycloaddition to **4a–i** followed by deprotection to **5a–h**.

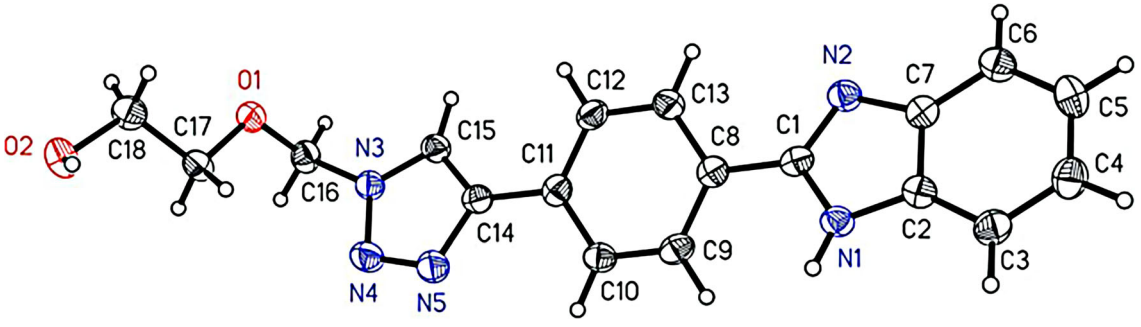


Figure 1. X-ray crystal structure of compound **5a**; displacement ellipsoids are drawn at the 50% probability level.

bacteria were tested using ciprofloxacin and linezolid as standard drugs for comparison. All compounds lacked antibacterial activity with MICs greater than 64 μg/mL, only **5d** showed an activity against *H. influenza* Hi4 at 32 μg/mL.

Screening of antifungal activity *in vitro*

The newly synthesized compounds **5a–h** were screened for antifungal activities *in vitro* against two phytopathogenic fungi *Verticillium dahliae* Kleb (VD) and *Fusarium oxysporum* f. sp.

Table 2. Antifungal activities of compounds **5a–h** at 20 μg/mL.

	Linear growth inhibitory rates (%)[a)]	
Compounds	**VD**	**Foa**
PELT	100 ± 0.1	100 ± 0.14
5a	11.29 ± 0.3	3.02 ± 0.96
5b	13.76 ± 0.6	−1.59 ± 0.05
5c	10.64 ± 0.41	2.7 ± 0.16
5d	7.21 ± 0.84	−0.16 ± 0.02
5e	29.76 ± 0.2	17.01 ± 0.96
5f	−1.69 ± 0.03	2.3 ± 0.29
5g	−7.72 ± 1.03	−1.41 ± 0.3
5h	1.56 ± 0.07	−1.14 ± 0.05

[a)] Linear growth inhibitory rates, showing as mean ± standard error.

Table 3. Title compounds and their sporulation medium.

	Sporulation inhibitory rates (means %)[a)]	
Compounds	**VD**	**Foa**
PELT	100 ± 0.02	100 ± 0.2
5a	−1.88 ± 0.03	−5.85 ± 0.04
5b	−18.87 ± 1.9	16.36 ± 0.2
5c	−2.13 ± 0.83	−34.79 ± 0.72
5d	−14.82 ± 0.97	21.94 ± 0.26
5e	22.04 ± 1.02	30.62 ± 0.5
5f	−0.31 ± 0.4	−77.59 ± 2.64
5g	−12.92 ± 0.6	−61.05 ± 1.34
5h	5.59 ± 0.4	−48.72 ± 2.35

[a)] Shown as mean ± standard error.

albedinis (Foa) by using the mycelia linear growth rate method followed by sporulation test (Table 2). The two tests were carried out as described [42, 43]. All compounds were tested at a concentration of 20 μg/mL (H. B. Lazrek, unpublished results). A positive control is Pelt, which is a systemic fungicide, a benzimidazole precursor (70% of methyl thiophanate). The trial was established as a completely randomized experimental design with five replicates. Data were subjected to analysis of variance using SPSS software V17.0. The mean values among treatments were compared by Duncan's multiple range tests at a 5% ($p < 0.05$) level to determine significant difference between the inhibition rates of various compounds at the same concentration.

The result of the mycelia linear growth rate indicates that some of the compounds show a weak inhibition against the two fungi, the only compound that shows a significantly increased rate is compound **5e** with (29.76%) ($p < 0.05$) against *Verticillium dahliae* (Fig. 2). On the other hand, the sporulation was evaluated in the aim to know their fungicidal or fungistatic effect (Table 2, 3). The structure of this molecule uniquely holds a CF_3 group fixed to the benzimidazole core. Since the trifluoromethyl group due to their lipophilicity is known to modulate absorption and metabolism, it may explain the enhanced activity.

As shown in Table 3, benzimidazole derivatives **5b**, **5d**, and **5e** exhibited a weak inhibition effect on the growth of Foa sporulation.

Conclusion

In summary, we have described the synthesis of a series of hybrid molecules, which combined two "privileged pharmacophore" heterocycles (benzimidazole and 1,2,3-triazole) in excellent yields using simple, efficient, and fast routes. These benzimidazole/triazoles **5a–h** were tested against Gram-negative and Gram-positive bacteria and as antifungal agents,

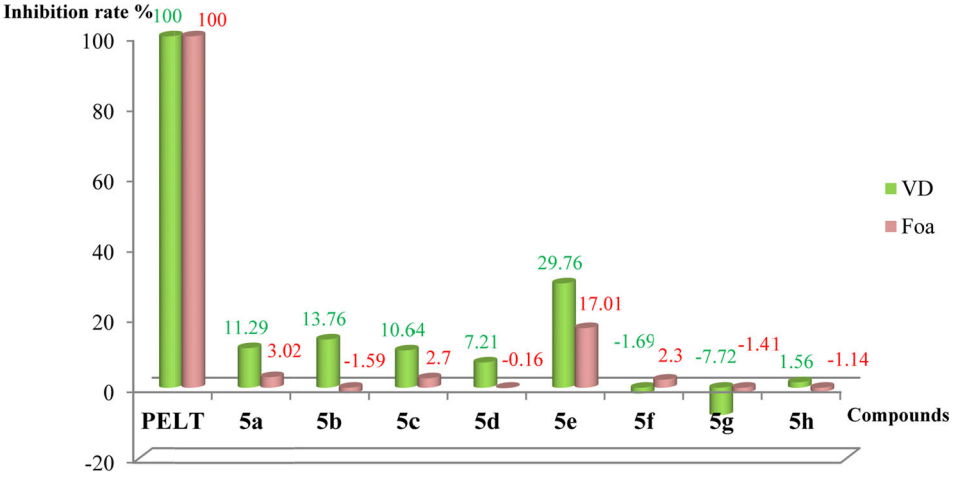


Figure 2. Comparison of the inhibition rate (%) of compounds **5a–h** at the 8th day against VD and Foa at 20 μg/mL.

only very modest inhibition against sporulation of *F. oxysporum* f. sp. *albedinis* (Foa) was observed for some of these analogs and a modest inhibition was found for the CF_3 substituted **5e**.

Experimental

General methods

All starting materials for synthesis were purchased from Alfa Aesar, Fluka, or Sigma–Aldrich; thin-layer chromatography (TLC): aluminum sheets, silica gel 60 F_{254}. Melting points were measured using a Stuart Scientific melting point (SMP1) apparatus. NMR spectra were recorded with a Bruker AC-300 MHz and AC-400 MHz in $CDCl_3$ and DMSO-d_6 with $SiMe_4$ as an internal standard. Chemical shifts are given in ppm and the spin–spin coupling constants, *J*, are given in Hz (s, singlet; d, doublet; t, triplet; m, multiplet, and br, broad); Bzm = benzimidazole and Imzp = imidazo[4,5-*b*]pyridine.

All microwave-assisted syntheses were carried out in a dedicated CEM-Discover mono-mode microwave apparatus. ESI-mass spectrometry was performed on a Fisons instrument equipped with a VG platform II with quadrupole analyzer. High-resolution mass spectrometry (HRMS) was performed with a MALDI Orbitrap LTQ XL instrument (Thermo Fisher).

*General procedure for the synthesis of compounds **4a–h***

A mixture of 4-(trimethylsilylethynyl)benzaldehyde (150 mg, 0.74 mmol), 2 equivalents of the appropriate *ortho*-phenylenediamine and 1.01 equivalents of sodium metabisulfite were dissolved in 1 mL of dioxane and reacted under microwave irradiation for 2 min. The residue was poured in water and extracted with ethyl acetate (3 × 20 mL). The organic extract was dried over Na_2SO_4 and evaporated under reduced pressure. The crude products were purified by column chromatography using a methylene chloride and methanol mixture in 98:2 ratio. The benzimidazole compounds **2a–i** were obtained in good yields (84–95%).

The trimethylsilyl group was cleaved by reaction of tetrabutylammonium fluoride (1 equivalent) with the compounds **2a–i** in tetrahydrofuran (2.5 mL), the reaction was monitored by TLC analysis until complete consumption of the protected product (20–30 min). The resulting products **3a–i** were purified by column chromatography eluting with methylene chloride/methanol (95:5). This reaction is characterized by giving excellent yields.

The terminal alkynes **3a–i**, ethanol 2-(azidomethoxy)acetate (2.5 equivalents), triethylamine (1 equivalent), and copper(I) iodide (0.1 equivalents) were irradiated in a microwave oven using 300 W as power level for 2 min. The crude products **4a–i** were then purified on silica gel column using methylene chloride/methanol (95:5) as eluent to afford the expected compounds.

*Spectral data for selected compounds **4a–h***

*2-((4-(4-(Benzimidazol-2-yl)phenyl)-1,2,3-triazol-1-yl)-methoxy)ethyl acetate (**4a**)*

Yield: 93%; Rf: 0.63; eluent: CH_2Cl_2/MeOH, 95:5 v/v; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.90 (s, 3H, $-CH_3$), 3.75 (m, 4H, $-CH_2-$), 5.78 (s, 2H, $-CH_2-$), 7.26 (m, 2H, Ar–H), 7.64 (m, 3H, Ar–H, CH-triazole), 8.02 (d, 2H, Ar–H, $J = 7.6$ Hz), 8.19 (d, 2H, Ar–H, $J = 7.2$ Hz), 8.71 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 59.71, 67.28 (CH_2), 78.35 (CH_2), 114.96, 122.38 (Bzm-CH), 122.94, 125.94 (phenyl-CH), 127.15 (phenyl-C), 128.79 (triazole-CH), 131.57 (Bzm-C), 146.18 (triazole-C), 151.77 (Bzm-C), 171.12 (CO). ESI-MS *m*/*z* calcd. for $C_{20}H_{19}N_5O_3$ (M+H): 378.40, found: 378.50.

*2-((4-(4-(5-Methyl benzimidazol-2-yl)phenyl)-1,2,3-triazol-1-yl)methoxy)ethyl acetate (**4b**)*

Yield: 82%; Rf: 0.63; eluent: CH_2Cl_2/MeOH, 95:5 v/v; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.89 (s, 3H, $-CH_3$), 2.38 (s, 3H, Ar–CH_3), 3.74 (m, 4H, $-CH_2-$), 5.77 (s, 2H, $-CH_2-$), 7.07 (d, 2H, Ar–H, $J = 8.0$ Hz), 7.43 (s, 1H, CH-triazole), 7.54 (d, 1H, Ar–H, $J = 7.2$ Hz), 7.99 (d, 2H, Ar–H, $J = 8.00$ Hz), 8.17 (d, 2H, Ar–H, $J = 7.6$ Hz), 8.69 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 20.36 (CH_3), 21.08 (Bzm-CH_3), 62.74, 67.33 (CH_2), 78.46 (CH_2), 114.17, 114.97, 122.29 (Bzm-CH), 124.44, 125.82 (phenyl-CH), 126.97 (phenyl-C), 127.16 (triazole-CH), 131.57, 132.67 (Bzm-C), 146.13 (triazole-C), 153.91 (Bzm-C), 171.09 (CO). ESI-MS *m*/*z* calcd. for $C_{21}H_{21}N_5O_3$ (M+H): 392.42, found: 392.40.

*2-((4-(4-(5,6-Dimethyl benzimidazol-2-yl)phenyl)-1,2,3-triazol-1-yl)methoxy)ethyl acetate (**4c**)*

Yield: 75%; Rf: 0.64; eluent: CH_2Cl_2/MeOH, 95:5 v/v; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.89 (s, 3H, $-CH_3$), 2.27 (s, 6H, Ar–CH_3), 3.74 (m, 4H, $-CH_2-$), 5.77 (s, 2H, $-CH_2-$), 7.38 (s, 1H, CH-triazole), 7.99 (m, 3H, Ar–H), 8.13 (m, 3H, Ar–H), 8.68 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 19.83 (Bzm-CH_3), 20.37 (CH_3), 62.70, 67.27 (CH_2), 78.33 (CH_2), 114.94 (Bzm-CH), 125.84, 126.71 (phenyl-CH), 129.09 (triazole-CH), 131.12 (phenyl-C), 131.61 (Bzm-C), 146.25 (triazole-C), 151.92 (Bzm-C), 171.16 (CO). ESI-MS *m*/*z* calcd. for $C_{22}H_{23}N_5O_3$ (M−H): 404.45, found: 404.27.

*2-((4-(4-(5-Methoxy benzimidazol-2-yl)phenyl)-1,2,3-triazol-1-yl)methoxy)ethyl acetate (**4d**)*

Yield: 86%; Rf: 0.60; eluent: CH_2Cl_2/MeOH, 95:5 v/v; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.88 (s, 3H, $-CH_3$), 3.72 (m, 4H, $-CH_2-$), 3.74 (s, 3H, $-OCH_3$), 5.75 (s, 2H, $-CH_2-$), 6.83 (dd, 2H, Ar–H, $J = 8.0$ Hz), 7.12 (s, 1H, CH-triazole), 7.54 (d, 1H, Ar–H, $J = 8.0$ Hz), 7.90 (d, 2H, Ar–H, $J = 8.4$ Hz), 8.12 (d, 2H, Ar–H, $J = 8.4$ Hz), 8.61 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 20.35 (CH_3), 55.42 ($-OCH_3$), 62.74, 67.28 (CH_2), 78.33 (CH_2), 97.22, 112.52, 116.15 (Bzm-CH), 125.76, 125.90 (phenyl-CH), 126.82 (triazole-CH), 128.67 (phenyl-C), 131.29 (Bzm-C), 146.14 (triazole-C), 156.13 (Bzm-C), 171.16 (CO). ESI-MS *m*/*z* calcd. for $C_{21}H_{21}N_5O_4$ (M+H): 408.42, found: 408.40.

*2-((4-(4-(5-Trifluoromethyl benzimidazol-2-yl)phenyl)-1,2,3-triazol-1-yl)methoxy)ethyl acetate (**4e**)*

Yield: 70%; Rf: 0.50; eluent: CH_2Cl_2/MeOH, 95:5 v/v; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.90 (s, 3H, $-CH_3$), 3.74 (m, 4H, $-CH_2-$), 5.77 (s, 2H, $-CH_2-$), 7.51 (d, 1H, Ar–H, $J = 8.4$ Hz), 7.76 (d, 1H, Ar–H, $J = 8.4$ Hz), 7.94 (s, 1H, CH-triazole), 8.01 (d, 2H, Ar–H, $J = 8.4$ Hz), 8.17 (m, 3H, Ar–H), 8.70 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 20.35 (CH_3), 62.73, 67.25 (CH_2), 78.32 (CH_2), 119.20, 122.40, 123.43 (Bzm-CH), 123.01 ($-CF_3$), 125.70, 125.92 (phenyl-CH), 127.57 (triazole-CH), 128.30 (phenyl-C), 132.05 (Bzm-C), 146.05 (triazole-C), 153.45 (Bzm-C), 171.09 (CO). ESI-MS *m*/*z* calcd. for $C_{21}H_{18}F_3N_5O_3$ (M+H): 446.39, found: 446.35.

*2-((4-(4-(5-Fluoro benzimidazol-2-yl)phenyl)-1,2,3-triazol-1-yl)methoxy)ethyl acetate (**4f**)*

Yield : 80%; Rf: 0.50; eluent: CH_2Cl_2/MeOH, 95:5 v/v; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.89 (s, 3H, $-CH_3$), 3.74 (m, 4H, $-CH_2-$), 5.76 (s, 2H, $-CH_2-$), 7.02 (m, 1H, Ar–H), 7.36 (d, 1H, Ar–H, $J = 11.6$ Hz), 7.58 (s, 1H, CH-triazole), 7.98 (d, 2H, Ar–H, $J = 8.4$ Hz), 8.12 (m, 3H, Ar–H, $J = 8.4$ Hz), 8.67 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 20.34 (CH_3), 62.73, 67.24 (CH_2), 78.31 (CH_2), 115.64, 122.34 (Bzm-CH), 125.71, 125.99 (phenyl-CH), 127.14 (triazole-CH), 128.55 (phenyl-C), 131.60 (Bzm-C), 146.11 (triazole-C), 157.22, 160.35 (Bzm-C), 171.16 (CO). ESI-MS *m/z* calcd. for $C_{20}H_{18}FN_5O_3$ (M−H): 394.39, found: 394.45.

*2-((4-(4-(6-Nitrobenzimidazol-2-yl)phenyl)-1H-1,2,3-triazol-1-yl)methoxy)ethyl acetate (**4g**)*

Yield: 60%; Rf: 0.50; eluent: CH_2Cl_2/MeOH, 95:5 v/v; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.90 (s, 3H, $-CH_3$), 3.73 (m, 4H, $-CH_2-$), 5.73 (s, 2H, $-CH_2-$), 7.60 (d, 1H, Ar–H, $J = 8.4$ Hz), 7.86–7.89 (m, 2H, Ar–H, 8.2 Hz), 7.95–8.03 (m, 4H, Ar–H, $J = 8.0$ Hz), 8.30 (s, 1H, CH-triazole), 8.62 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 20.38 (CH_3), 62.75, 67.29 (CH_2), 78.39 (CH_2), 104.51, 114.13, 118.22 (Bzm-CH), 125.82, 127.52 (phenyl-CH), 128.63 (triazole-CH), 132.25, 133.15 (phenyl-C), 145.99, 142.71 (Bzm-C), 150.68 (triazole-C), 155.25 (Bzm-C), 171.12 (CO). ESI-MS *m/z* calcd. for $C_{20}H_{18}N_6O_5$ (M−H): 421.39, found: 421.44.

*2-((4-(4-(Imidazo[4,5-b]pyridin-2-yl)phenyl)-1,2,3-triazol-1-yl)methoxy)ethyl acetate (**4h**)*

Yield: 65%; Rf: 0.60; eluent: CH_2Cl_2/MeOH, 95:5 v/v; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.90 (s, 3H, $-CH_3$), 3.75 (m, 4H, $-CH_2-$), 5.78 (s, 2H, $-CH_2-$), 7.29 (dd, 1H, Ar–H, $J = 12$ Hz), 8.00–8.05 (m, 4H, Ar–H), 8.23 (d, 2H, Ar–H, $J = 12.4$ Hz), 8.33 (s, 1H, CH-triazole), 8.71 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 20.37 (CH_3), 62.74, 67.27 (CH_2), 78.35 (CH_2), 118.70, 122.49 (Imzp-CH), 125.92, 126.02 (phenyl-CH), 127.58 (phenyl-C), 128.49 (triazole-CH), 132.08 (Imzp-CH), 144.07 (Imzp-C), 146.09 (triazole-C), 152.65 (Imzp-C), 171.11 (CO). ESI-MS *m/z* calcd. for $C_{19}H_{18}N_6O_3$ (M+H): 379.38, found: 379.50.

*2-((4-(4-(5,6-Dichlorobenzimidazol-2-yl)phenyl)-1,2,3-triazol-1-yl)methoxy)ethyl acetate (**4i**)*

Yield: 67%; Rf: 0.65; eluent: CH_2Cl_2/MeOH, 95:5 v/v; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.89 (s, 3H, $-CH_3$), 3.74 (m, 4H, $-CH_2-$), 5.76 (s, 2H, $-CH_2-$), 7.77 (m, 2H, Ar–H), 7.95 (s, 1H, CH-triazole), 8.07 (m, 2H, Ar–H, 8.4 Hz), 8.13 (d, 2H, Ar–H, $J = 8.0$ Hz), 8.67 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 20.36 (CH_3), 62.73, 67.24 (CH_2), 78.30 (CH_2), 122.29, 124.86 (Bzm-CH), 125.70, 127.08 (phenyl-CH), 128.10 (Bzm-C), 128.89 (triazole-CH), 131.80, 133.35 (phenyl-C), 137.48 (Bzm-C), 146.03 (triazole-C), 153.15 (Bzm-C), 171.07 (CO). ESI-MS (M−H), *m/z* calcd. for $C_{20}H_{18}N_6O_5$: 446.29, found: 445.40.

*General procedure for the synthesis of compounds **5a–h***

The compounds **4a–h** were reacted at room temperature with K_2CO_3 (2 equivalents) in methanol 2.5 mL. The mixture was stirred for 30 min. The reaction was monitored by TLC analysis. The solvent was evaporated under reduced pressure. Then, the crude compounds **5a–h** were purified by passing through a flash chromatography column using methylene chloride/methanol (95:5) as eluent.

*Spectral data for selected compounds **5a–h***

*2-((4-(4-(Benzimidazol-2-yl)phenyl)-1,2,3-triazol-1-yl)-methoxy)ethanol (**5a**)*

M.p. 229–230 °C; yield: 99%; Rf: 0.40; eluent: CH_2Cl_2/MeOH, 9:1 v/v; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.52 (t, 2H, $-CH_2-$, $J = 4.0$ Hz), 3.55 (t, 2H, $-CH_2-$, $J = 4.0$ Hz), 5.19 (bs, 1H, −OH), 5.76 (s, 2H, $-CH_2-$), 7.21–7.33 (m, 2H, Ar–H), 7.60–7.69 (m, 3H, Ar–H, CH-triazole), 8.01 (d, 2H, Ar–H, $J = 8.4$ Hz), 8.17 (d, 2H, Ar–H, $J = 8.4$ Hz), 8.64 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 59.71, 70.90 (CH_2), 78.56 (CH_2), 122.25, 122.77 (Bzm-CH), 125.90 (phenyl-CH), 127.07 (phenyl-C), 128.94 (triazole-CH), 131.46 (Bzm-C), 146.15 (triazole-C), 151.73 (Bzm-C). ESI-MS *m/z* calcd. for $C_{18}H_{17}N_5O_2$ (M+H): 336.36, found: 336.4. HRMS (M+H): calcd. for $C_{18}H_{17}N_5O_2$: 336.14550, found: 336.14574.

*2-((4-(4-(5-Methyl benzimidazol-2-yl)phenyl)-1,2,3-triazol-1-yl)methoxy)ethanol (**5b**)*

M.p. 203–204 °C; yield: 98%; Rf: 0.40; eluent: CH_2Cl_2/MeOH, 9:1 v/v; ^{1}H NMR (400 MHz,DMSO-d_6) δ (ppm): 2.34 (s, 3H, Ar–CH_3), 3.52 (t, 2H, $-CH_2-$, $J = 3.6$ Hz), 3.54 (t, 2H, $-CH_2-$, $J = 3.6$ Hz), 5.26 (bs, 1H, −OH), 5.75 (s, 2H, $-CH_2-$), 7.00 (d, 2H, Ar–H, $J = 8.0$ Hz), 7.37 (s, 1H, CH-triazole), 7.49 (d, 1H, Ar–H, $J = 7.6$ Hz), 7.95 (d, 2H, Ar–H, $J = 8.00$ Hz), 8.14 (d, 2H, Ar–H, $J = 6.4$ Hz), 8.64 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 21.08 (Bzm-CH_3), 59.71, 70.89 (CH_2), 78.54 (CH_2), 114.21, 122.15, 124.17 (Bzm-CH), 125.83 (phenyl-CH), 126.88 (phenyl-C), 129.04 (triazole-CH), 131.25, 132.21 (Bzm-C), 146.18 (triazole-C), 150.44 (Bzm-C). ESI-MS *m/z* calcd. for $C_{19}H_{19}N_5O_2$ (M+H): 350.39, found: 350.1. HRMS (M+H): calcd. for $C_{19}H_{19}N_5O_2$: 350.16115, found: 350.16114.

*2-((4-(4-(5,6-Dimethyl benzimidazol-2-yl)phenyl)-1,2,3-triazol-1-yl)methoxy)ethanol (**5c**)*

M.p. 233–234 °C; yield: 98%; Rf: 0.45; eluent: CH_2Cl_2/MeOH, 9:1 v/v; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.26 (s, 6H, Ar–CH_3), 3.51 (t, 2H, $-CH_2-$, $J = 3.6$ Hz), 3.55 (t, 2H, $-CH_2-$, $J = 3.6$ Hz), 5.19 (bs, 1H, −OH), 5.76 (s, 2H, $-CH_2-$), 7.36 (s, 1H, CH-triazole), 7.96–7.99 (m, 3H, Ar–H), 8.11–8.14 (m, 3H, Ar–H), 8.66 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 19.83 (Bzm-CH_3), 59.70, 70.89 (CH_2), 78.55 (CH_2), 122.17 (Bzm-CH), 126.79 (phenyl-CH), 129.18 (phenyl-C), 131.09 (triazole-CH), 131.50 (Bzm-C), 146.21 (triazole-C), 149.87 (Bzm-C). ESI-MS *m/z* calcd. for $C_{20}H_{21}N_5O_2$ (M+H): 364.41, found: 364.5. HRMS (M+H): calcd. for $C_{20}H_{21}N_5O_2$: 364.17680, found: 364.17704.

*2-((4-(4-(5-Methoxy benzimidazol-2-yl)phenyl)-1,2,3-triazol-1-yl)methoxy)ethanol (**5d**)*

M.p. 172–173 °C; yield: 99%; Rf: 0.40; eluent: CH_2Cl_2/MeOH, 9:1 v/v; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.48 (t, 2H, $-CH_2-$, $J = 3.6$ Hz), 3.52 (t, 2H, $-CH_2-$, $J = 4$ Hz), 3.74 (s, 3H, $-OCH_3$), 5.16 (bs, 1H, −OH), 5.74 (s, 2H, $-CH_2-$), 6.81–6.84 (dd, 2H, Ar–H, $J = 11.6$ Hz), 7.09 (s, 1H, CH-triazole), 7.47 (d, 1H, Ar–H, $J = 11.6$ Hz), 7.96 (d, 2H, Ar–H, $J = 11.2$ Hz), 8.08 (d, 2H, Ar–H, $J = 10.8$ Hz), 8.64 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 55.39 ($-OCH_3$), 59.68, 70.86 (CH_2), 78.33 (CH_2), 112.29, 122.16 (Bzm-CH), 125.84, 125.91 (phenyl-CH), 126.70 (phenyl-C), 129.05 (triazole-CH), 131.14 (Bzm-C), 146.16 (triazole-C), 155.99 (Bzm-C). ESI-MS *m/z* calcd. for $C_{19}H_{19}N_5O_3$ (M+H): 366.39, found: 366.3. HRMS (M+H): calcd. for $C_{19}H_{19}N_5O_3$: 366.15607, found: 366.15583.

*2-((4-(4-(5-Trifluoromethyl benzimidazol-2-yl)phenyl)-1,2,3-triazol-1-yl)methoxy)ethanol (**5e**)*

M.p. 150–151°C; yield: 95%; Rf: 0.30; eluent: CH_2Cl_2/MeOH, 9:1 v/v; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.52 (m, 4H, $-CH_2-$), 5.16 (bs, 1H, –OH), 5.72 (s, 2H, $-CH_2-$), 7.41 (d, 1H, Ar–H, $J = 11.2$ Hz), 7.70 (d, 1H, Ar–H, $J = 11.2$ Hz), 7.86 (s, 1H, CH-triazole), 7.94 (d, 2H, Ar–H, $J = 10.0$ Hz), 8.10 (m, 3H, Ar–H), 8.63 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 59.68, 62.46 (CH_2), 78.52 (CH_2), 119.08, 122.26, 122.90 (Bzm-CH), 123.32 ($-CF_3$) 125.64, 125.84 (phenyl-CH), 127.30 (triazole-CH), 128.16 (phenyl-C), 131.96 (Bzm-C), 145.99 (triazole-C), 153.33 (Bzm-C). ESI-MS *m/z* calcd. for $C_{19}H_{16}F_3N_5O_2$ (M+H): 404.36, found: 404.5. HRMS (M+H): calcd. for $C_{19}H_{16}F_3N_5O_2$: 404.13289, found: 404.13232.

*2-((4-(4-(5-Fluorobenzimidazol-2-yl)phenyl)-1,2,3-triazol-1-yl)methoxy)ethanol (**5f**)*

M.p. 220–222°C; yield: 98%; Rf: 0.30; eluent: CH_2Cl_2/MeOH, 9:1 v/v; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.52 (m, 4H, $-CH_2-$), 5.17 (bs, 1H, –OH), 5.73 (s, 2H, $-CH_2-$), 6.99 (m, 1H, Ar–H, $J = 11.2$ Hz), 7.30 (d, 1H, Ar–H, $J = 12$ Hz), 7.52 (s, 1H, CH-triazole), 7.94 (d, 2H, Ar–H, $J = 11.6$ Hz), 8.07 (m, 3H, Ar–H, $J = 11.2$ Hz), 8.62 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 59.69, 70.87 (CH_2), 78.52 (CH_2), 110.54, 110.86, 122.19 (Bzm-CH), 125.80, 125.81 (phenyl-CH), 126.94 (triazole-CH), 128.50 (phenyl-C), 131.50 (Bzm-C), 146.07 (triazole-C), 157.18, 160.36 (Bzm-C). ESI-MS *m/z* calcd. for $C_{18}H_{16}FN_5O_2$ (M+H): 353.35, found: 354.4. HRMS (M+H): calcd. for $C_{18}H_{16}FN_5O_2$: 354.13608, found: 354.13594.

*2-((4-(4-(6-Nitrobenzimidazol-2-yl)phenyl)-1,2,3-triazol-1-yl)methoxy)ethanol (**5g**)*

M.p. 223–225°C; yield: 98%; Rf: 0.30; eluent: CH_2Cl_2/MeOH, 9:1 v/v; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.52 (t, 2H, $-CH_2-$, $J = 3.2$ Hz), 3.55 (t, 2H, $-CH_2-$, $J = 3.6$ Hz), 5.19 (bs, 1H, –OH), 5.77 (s, 2H, $-CH_2-$), 7.66 (d, 2H, Ar–H, $J = 8.8$ Hz), 7.94–7.98 (m, 1H, Ar–H), 8.03 (d, 2H, Ar–H, $J = 8.0$ Hz), 8.10 (d, 2H, Ar–H, $J = 8.0$ Hz), 8.39 (s, 1H, CH-triazole), 8.64 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 59.70, 70.90 (CH_2), 78.57 (CH_2), 104.51, 118.20, 122.44 (Bzm-CH), 125.88, 127.53 (phenyl-CH), 128.64 (triazole-CH), 132.28, 133.13 (phenyl-C), 142.71 (Bzm-C), 145.97 (triazole-C), 150.72 (Bzm-C). ESI-MS *m/z* calcd. for $C_{18}H_{16}N_6O_4$ (M–H): 379.36, found: 379.4. HRMS (M+H): calcd. for $C_{18}H_{16}N_6O_4$: 381.13058, found: 381.13046.

*2-((4-(4-(Imidazo[4,5-b]pyridin-2-yl)phenyl)-1,2,3-triazol-1-yl)methoxy)ethanol (**5h**)*

M.p. 274–276°C; yield: 95%; Rf: 0.40; eluent: CH_2Cl_2/MeOH, 9:1 v/v; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.52 (t, 2H, $-CH_2-$, $J = 4.0$ Hz), 3.56 (t, 2H, $-CH_2-$, $J = 4.0$ Hz), 5.18 (bs, 1H, –OH), 5.77 (s, 2H, $-CH_2-$), 7.29 (dd, 1H, Ar–H, $J = 8.0$ Hz), 8.00–8.10 (m, 4H, Ar–H), 8.23 (d, 2H, Ar–H, $J = 8.4$ Hz), 8.33 (s, 1H, CH-triazole), 8.71 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 59.70, 70.90 (CH_2), 78.58 (CH_2), 122.35, 122.54 (Imzp-CH), 125.84, 126.05 (phenyl-CH), 127.63 (phenyl-C), 128.44 (triazole-CH), 132.12 (Imzp-CH), 146.04 (triazole-C), 146.02, 152.67 (Imzp-C). ESI-MS *m/z* calcd. for $C_{17}H_{16}N_6O_2$ (M+H): 337.35, found: 337.3. HRMS (M+H): calcd. for $C_{17}H_{16}N_6O_2$: 337.14075, found: 337.14084.

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