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ORIGINAL PAPER

Ligand-assisted click reaction for the synthesis of new hybrid compounds based on 1,2,3-triazoles and 5,5-diphenylimidazolidine-2,4-dione and evaluation of their antibacterial activities

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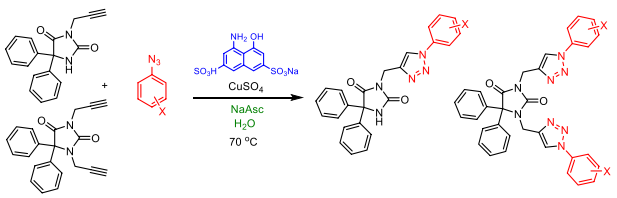
Abstract

The new hybrid compounds based on 1,2,3-triazoles and 5,5-diphenylimidazolidine-2,4-dione were successfully synthesized by copper-catalyzed click reaction in the presence of water-soluble ligand, sodium 4-amino-5-hydroxy-7-sulfonaphthalene-2-sulfonate and copper salt. The click reaction of 5,5-diphenyl-3-(prop-2-yn-1-yl)imidazolidine-2,4-dione and 5,5-diphenyl-1,3-di(prop-2-yn-1-yl)imidazolidine-2,4-dione with aryl azides or sodium azide and benzyl chloride in water produced new 1,2,3-triazoles linked-5,5-diphenylimidazolidine-2,4-dione. The 4-amino-5-hydroxy-7-sulfonaphthalene-2-sulfonate was used as ligand, which enhanced the reactions and reduced the quantity of the toxic copper salt. The in vitro antibacterial activities of the all synthesized compounds were screened against the Gram-positive and Gram-negative bacteria, by the use of well diffusion method. The results showed that all compounds were active against both *M. luteus* and *P. aeruginoasa* bacteria.

Graphic abstract



Keywords Antibacterial activity · Click reaction · Hydantoin · 1,2,3-Triazole · Ligand-assisted

Introduction

1,2,3-Triazoles have occupied an important position in pharmaceutical chemistry due to their convenient preparation by click reaction and attractive features with diverse biological activities [1–3]. The 1,2,3-triazole nucleus is present in the structure of a large number of biologically active molecules that have wide biological activities such as antifungal [4], antibacterial [5, 6], antiallergic [7], anti-HIV [8, 9], antitubercular [10, 11], and anti-inflammatory [12]. Hydantoins, known as 5,5-diphenylimidazolidine-2,4-dione derivatives, contain an active urea moiety with a variety of biological activities, including lowering blood sugar level in mammals [13], aldose reductants [14], anti-inflammatory [15],

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antimycobacterial [16], and antitumor [17, 18]. Also, these compounds have been used for increasing HDL cholesterol concentration [19] and as antiserotoninergic agents [20].

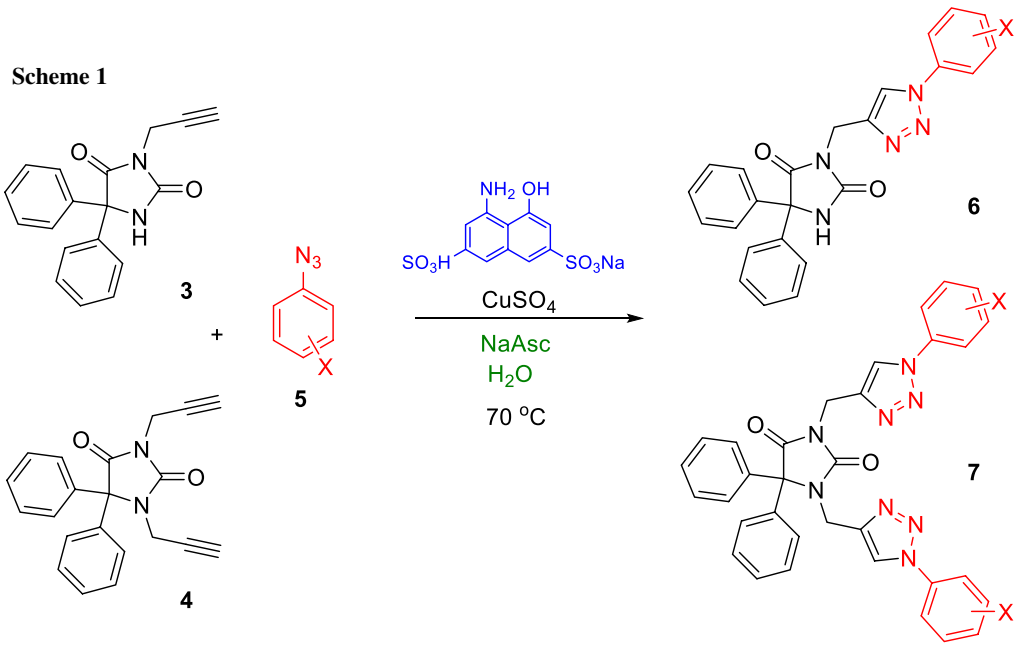
Sharpless and co-workers invented the concept of Click Chemistry [21]. Reactions could be considered as Click if they fulfilled several fundamental requirements: no sensitivity to moisture or oxygen, high to excellent yields and stereospecificity, solventless or use of a green solvent, and easy product separation. Sharpless [22] and Meldal [23] reported separately the effectiveness of Cu(I) salts as catalysts for the cycloaddition of organic azides and terminal acetylenic compounds to produce 1,2,3-triazoles. Frequently, in these conditions, the reactions were totally regioselective and only 1,4-disubstituted triazoles were successfully produced, in comparison with the mixture of regioisomers frequently produced in the thermal conditions. Because of the instability of Cu(I) species, copper(I) catalysts are frequently produced in situ from Cu(II) salts in the presence of reducing agent sodium ascorbate. Recently, several researchers have focused on the rate enhancement of click reaction by the use of ligands [24–27] such as polydentate aza-ligands, including polytriazole and polybenzimidazole ones [28–30]. Synthesis of hybrid compounds based on 1,2,3-triazoles during copper-catalyzed click reaction is a substantial way for the preparation of novel biologically active compounds [31–33]. In continuation of our recent reports on the synthesis of new heterocyclic compounds [34–42], here we explain the use of water-soluble ligand, sodium 4-amino-5-hydroxy-7-sulfonaphthalene-2-sulfonate for construction new hybrid compounds based on 1,2,3-triazoles and 5,5-diphenylimidazolidine-2,4-dione. The novel hybrid compounds were examined for in vitro antibacterial activities.

Results and discussion

Synthesis of hybrid compounds based on 1,2,3-triazole moiety has been recently reported but no example concerning the hybrid compounds containing 1,2,3-triazole and 5,5-diphenylimidazolidine-2,4-dione (hydantoin) has yet been reported. In this investigation we describe the synthesis of novel hybrid compounds based on 1,2,3-triazoles and 5,5-diphenylimidazolidine-2,4-dione by reacting of 5,5-diphenyl-3-(prop-2-yn-1-yl)imidazolidine-2,4-dione (**3**) or 5,5-diphenyl-1,3-di(prop-2-yn-1-yl)imidazolidine-2,4-dione (**4**) with azides through copper click reaction in the presence of the sodium 4-amino-5-hydroxy-7-sulfonaphthalene-2-sulfonate (**L3**) as an effective ligand in water (Scheme 1).

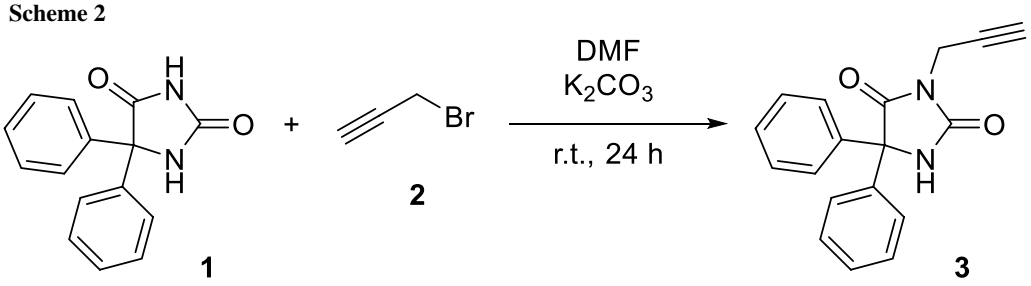
The starting material, 5,5-diphenylimidazolidine-2,4-dione (hydantoin, **1**) was prepared from the reaction of 1,2-diphenylethane-1,2-dione with urea in the basic

Scheme 1



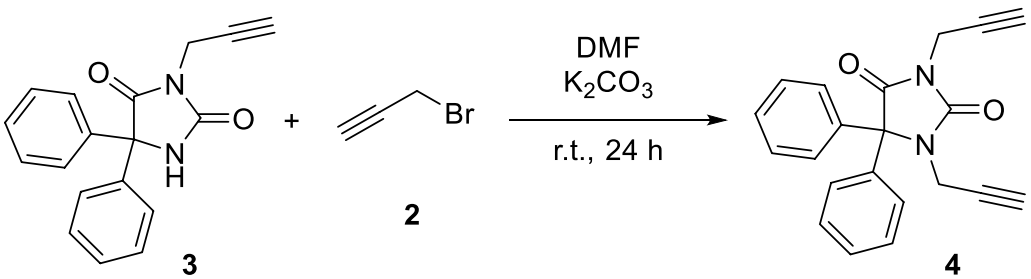
Reaction conditions for **6**: **3** (1.0 mmol), **5** (1.0 mmol), $CuSO_4$ (2 mol%), NaAsc (4 mol%), **L3** (2 mol%), 3 cm^3 H_2O, 70 °C.
Reaction conditions for **7**: **4** (1.0 mmol), **5** (2.0 mmol), $CuSO_4$ (2 mol%), NaAsc (4 mol%), **L3** (2 mol%), 3 cm^3 H_2O, 70 °C.

Scheme 2



Reaction conditions: **1** (1.0 mmol), **2** (1.2 mmol), K_2CO_3 (1.2 mmol), 3 cm^3 DMF, RT.

Scheme 3



Reaction conditions: **3** (1.0 mmol), **2** (1.2 mmol), K_2CO_3 (1.2 mmol), 3 cm^3 DMF, RT.

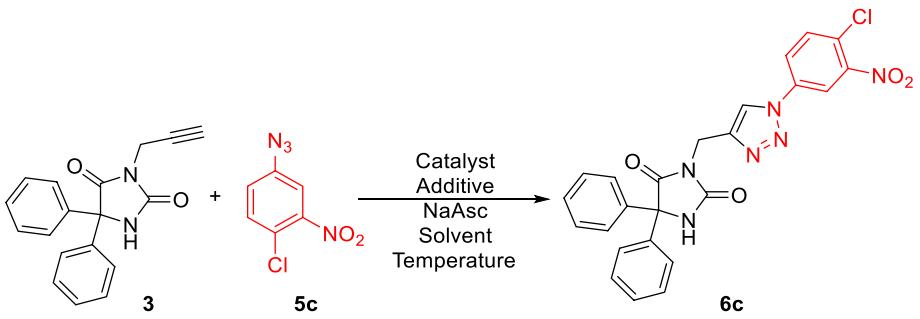
condition [43]. Reaction of 5,5-diphenylimidazolidine-2,4-dione (**1**) with 3-bromoprop-1-yne (**2**) in DMF in the presence of K_2CO_3 as a base produced 5,5-diphenyl-3-(prop-2-yn-1-yl)imidazolidine-2,4-dione (**3**) in good yield (Scheme 2) [44]. Similarly, the reaction of 5,5-diphenyl-3-(prop-2-yn-1-yl)imidazolidine-2,4-dione (**3**) with 3-bromoprop-1-yne (**2**) afforded 5,5-diphenyl-1,3-di(prop-2-yn-1-yl)imidazolidine-2,4-dione (**4**) under the same experimental conditions (Scheme 3) [45, 46].

In order to find the suitable reaction conditions, the reaction of 5,5-diphenyl-3-(prop-2-yn-1-yl)imidazolidine-2,4-dione (**3**) with 4-azido-1-chloro-2-nitrobenzene (**5c**) was utilized as a model reaction. The results obtained from this examination are tabulated in Table 1. We carried out the reaction in a variety of solvents, by using different amounts of catalysts in the presence of ligands at different temperatures. The results displayed that the best reaction conditions were 2 mol% of $CuSO_4$, 4 mol% of sodium ascorbate, and 2 mol% of **L3** in H_2O at 70 °C (Table 1, entry 16). Also, the reaction proceeded in the absence of ligand by the use of a large amount of $CuSO_4$ (10 mol%) in the same conditions and produced the desired product with excellent yield (90%) (Table 1, entry 12). In the classic copper click reactions, a high quantity of a toxic copper catalyst contaminates the biological samples. It is difficult to completely remove the catalyst from the product of the reactions. The use of ligands reduces the required amount of copper catalyst compared to the original copper click reactions [47].

In this study, we used several ligands, including salophen (**L1**), salen (**L2**), 4-amino-5-hydroxy-7-sulfonaphthalene-2-sulfonate (**L3**), and the copper complexes including Cu^{2+}-salen and Cu^{2+}-salophen in the reactions to reduce the quantity of the copper catalyst (Figs. 1, 2). When the sodium 4-amino-5-hydroxy-7-sulfonaphthalene-2-sulfonate (**L3**) was used as an additive, the reaction proceeded more efficiently and was completed in 20 min. In this condition, the desired product was obtained with 95% yield (Table 1, entries 15 and 16). As a result, the optimal reaction conditions include 2 mol% of **L3**, 2 mol% of $CuSO_4$, and 4 mol% of sodium ascorbate at 70 °C in H_2O (Table 1,entry16).

In order to illustrate the versatility of this protocol, we used various aromatic azides for the synthesis of substituted

Table 1 Influence of several catalysts, additives, solvents, and temperature on the reaction of 5,5-diphenyl-3-(prop-2-yn-1-yl)imidazolidine-2,4-dione with 4-azido-1-chloro-2-nitrobenzene[a]



Entry	Copper salt/mol%	Additive/mol%	Solvent	*T*/°C	Time/min	Yield/%
1	$Cu(OAc)_2$ (10)	–	DMF	r.t	120	50
2	$Cu(OAc)_2$ (10)	–	DMF	60	90	80
3	$Cu(OAc)_2$ (10)	–	CH_3CN	r.t	120	60
4	$Cu(OAc)_2$ (10)	–	CH_3CN	60	90	70
5	$Cu(OAc)_2$ (10)	–	EtOH	r.t	70	75
6	$Cu(OAc)_2$ (10)	–	EtOH	50	55	80
7	$Cu(OAc)_2$ (10)	–	EtOH	78	50	93
8	$Cu(OAc)_2$ (10)	–	H_2O	r.t	90	60
9	$Cu(OAc)_2$ (10)	–	H_2O	50	70	70
10	$Cu(OAc)_2$ (10)	–	H_2O	70	60	75
11	$CuCl_2$ (10)	–	H_2O	70	75	60
12	$CuSO_4$ (10)	–	H_2O	70	55	90
13	$CuSO_4$ (5)	–	H_2O	70	60	70
14	$CuSO_4$ (2)	–	H_2O	70	60	60
15	$CuSO_4$ (5)	**L3** (5)	H_2O	70	20	95
16	$CuSO_4$ (2)	**L3** (2)	H_2O	70	20	95
17	$CuSO_4$ (1)	**L3** (1)	H_2O	70	40	80
18	$CuSO_4$ (5)	**L2** (5)	H_2O	70	40	85
19	$CuSO_4$ (5)	**L1** (5)	H_2O	70	60	80
20	–	Cu^{2+}-salophen (5)	H_2O	70	55	70
21	–	Cu^{2+}-salen (5)	H_2O	70	35	75

[a]Reaction conditions: **3** (1 mmol), **5c** (1 mmol), copper salt, additive, and NaAsc (twice the amount of copper salt) in 3 cm^3 solvent

3-[(1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl]-5,5-diphenylimidazolidine-2,4-diones **6a**–**6d** and 1,3-bis[(1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl]-5,5-diphenylimidazolidine-2,4-diones **7a**–**7c** in the optimized reaction conditions. The results are shown in Table 2.

For further investigation, we carried out the reaction in a multi-component approach. The three-component reaction of 5,5-diphenyl-3-(prop-2-yn-1-yl)imidazolidine-2,4-dione (**3**), benzyl chloride (**8**), and sodium azide (**9**) in the presence of $CuSO_4$ and **L3** in H_2O gave the target products **10a**–**10c** in high reaction yields (Scheme 4). The results are shown in Table 3.

The characterizations made for the new structures were based on the NMR spectra and mass analysis. In the ^1H NMR spectrum for **6a**, a singlet at $\delta = 9.76$ ppm, which disappeared by deuteration, was characterized as the NH proton; another singlet at 9.03 ppm was typical of a triazole proton; four aromatic protons of aryl group appeared as four classes: a triplet at 8.73 ppm ($J = 1.8$ Hz), two doublet of doublets at 8.40 ppm ($J = 8.1$ Hz, 1.2 Hz) and 8.32 ppm ($J = 8.1$ Hz, 1.5 Hz), respectively, and a triplet at 7.89 ppm ($J = 8.1$ Hz). A multiplet at 7.35–7.45 ppm was due to the ten aromatic protons of the two phenyl groups.

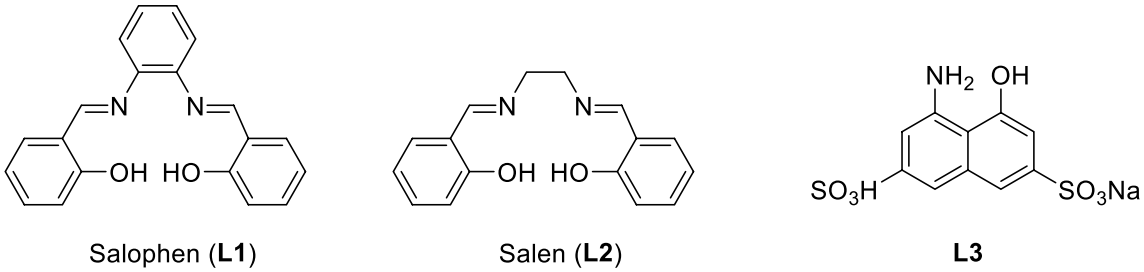
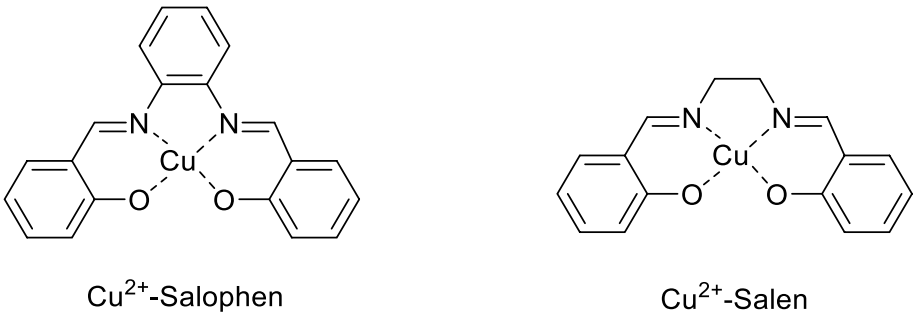


Fig. 1 Ligands utilized for copper-catalyzed click reactions

Fig. 2 Copper(II) complexes utilized for copper-catalyzed click reactions



Finally, the singlet at 4.85 ppm with two proton areas was characterized as the methylene group.

Evaluation of antibacterial activities

The in vitro antibacterial activities of the all synthesized 1,2,3-triazole-linked 5,5-diphenylimidazolidine-2,4-dione were screened against the Gram-positive and Gram-negative bacteria, including *Micrococcus luteus* (*M. luteus*) and *Pseudomonas aeruginosa* (*P. aeruginosa*) by the use of well diffusion method. DMSO and tetracycline were used as the negative and the positive control, respectively. The results are presented in Table 4. The results showed that all compounds were active against both *M. luteus* and *P. aeruginoasa*. Furthermore, compounds **6a**, **6c**, **7a**, and **7b** have better inhibitory activities than the others against *Micrococcus luteus (M. luteus)* and **6a** was the most effective against *P. aeruginosa*.

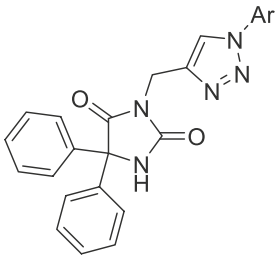
Conclusion

In this investigation, an efficient protocol was established for the synthesis of hybrid compounds based on 1,2,3-triazole and 5,5-diphenylimidazolidine-2,4-dione moieties. The click reaction of 5,5-diphenyl-3-(prop-2-yn-1-yl)imidazolidine-2,4-dione and 5,5-diphenyl-1,3-di(prop-2-yn-1-yl)imidazolidine-2,4-dione with aromatic azides or sodium azide and benzyl chloride in water produced new 1,2,3-triazoles linked-5,5-diphenylimidazolidine-2,4-dione. The 4-amino-5-hydroxy-7-sulfonaphthalene-2-sulfonate was used as ligand, enhanced the reactions, and reduced the amount of the toxic copper salt. Simplicity, short reaction time, high yield, mild and safe experimental conditions, and easy work-up are the major benefits of this protocol. The in vitro antibacterial activities of the all synthesized compounds were screened against the Gram-positive and Gram-negative bacteria, by the use of well diffusion method. The results showed that all compounds were active against both *M. luteus* and *P. aeruginoasa* bacteria.

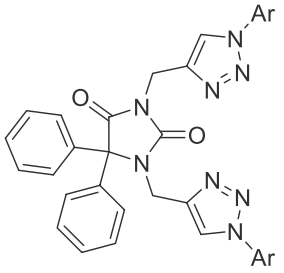
Experimental

All the starting materials and the other reagents used were of the best grade, supplied from Merck, Across, and Fluka, and were used without further purification. The reactions were monitored by TLC using silica gel 60 F-254 plates, and the chromatograms were visualized under UV 254–336 nm or iodine tank. Melting points were obtained on a Bamstead Electrothermal. NMR spectra were recorded on a Bruker A 300 spectrometer with DMSO-d_6 serving as the solvent. Chemical shifts were reported in ppm with the solvent residual peak used as the internal reference [DMSO-d_6: 2.52 ppm (^{1}H), 39.9 ppm (^{13}C)]. Multiplicities were described using the following abbreviations: s = singlet, br = broad, d = doublet,

Table 2 Synthesis of 3-[(1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl]-5,5-diphenylimidazolidine-2,4-diones **6a**–**6d**[a] and 1,3-bis[(1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl]-5,5-diphenylimidazolidine-2,4-diones **7a**–**7c**[b]



6a-6d



7a-7c

Entry	Ar	Product	Time/min	Yield/%
1	3-NO_2–C_6H_4–	**6a**	25	85
2	2-Cl-4-NO_2–C_6H_3–	**6b**	30	88
3	4-Cl-3-NO_2–C_6H_3–	**6c**	20	95
4	4-Cl-2-NO_2–C_6H_3–	**6d**	25	90
5	4-Cl-3-NO_2–C_6H_3–	**7a**	35	82
6	4-NO_2–C_6H_4–	**7b**	30	79
7	2-Cl-4-NO_2–C_6H_3–	**7c**	35	83

[a]Reaction conditions: **3** (1.0 mmol), **5** (1.0 mmol), $CuSO_4$ (2 mol%), NaAsc (4 mol%), **L3** (2 mol%), 3 cm^3 H_2O, 70 °C

[b]Reaction conditions: **4** (1.0 mmol), **5** (2.0 mmol), $CuSO_4$ (2 mol%), NaAsc (4 mol%), **L3** (2 mol%), 3 cm^3 H_2O, 70 °C

t = triplet, and m = multiplet. IR spectra were recorded on a Shimadzo IR-470 (KBr discs).

5,5-Diphenyl-3-(prop-2-yn-1-yl)imidazolidine-2,4-dione (3) 3-Bromoprop-1-yne (**2**, 1.2 mmol) was added slowly to a stirring mixture of 5,5-diphenylimidazolidine-2,4-dione (**1**, 1 mmol) and K_2CO_3 (1.2 mmol) in 3 cm^3 dry DMF at room temperature. Stirring was continued until the disappearance of compound 1 (monitored by TLC). The solvent was evaporated to dryness; the residue was washed with H_2O and dried. White powder solid; yield 87%; m.p.: 136–138 °C (Ref.[44]: 137–138 °C).

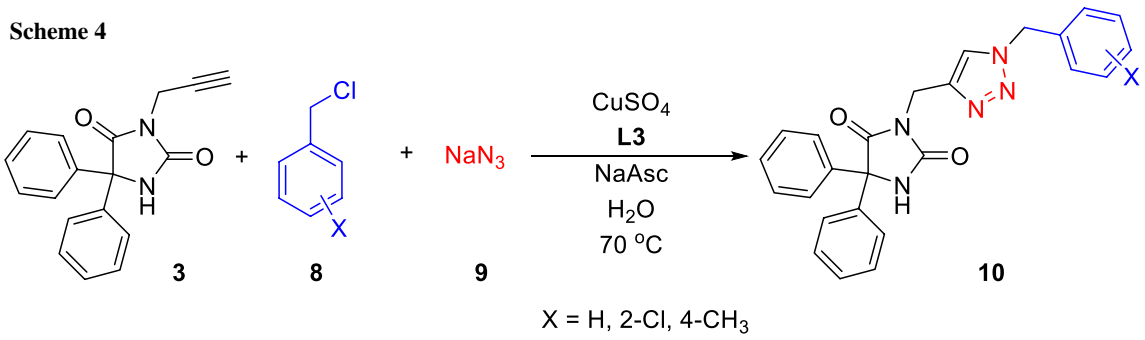
5,5-Diphenyl-1,3-di(prop-2-yn-1-yl)imidazolidine-2,4-dione (4) 3-Bromoprop-1-yne (**2**, 1.2 mmol) was slowly added to a stirring mixture of 5,5-diphenyl-3-(prop-2-yn-1-yl)imidazolidine-2,4-dione (**3**, 1 mmol) and K_2CO_3 (1.2 mmol) in 3 cm^3 dry DMF at room temperature. Stirring was continued until the disappearance of compound **3** (monitored by TLC). The solvent was evaporated to dryness. The residue was washed with H_2O and dried. Yellow powder solid; yield 85%; m.p.: 157–158 °C (Refs. [45, 46]: 157–158 °C).

General procedure for synthesis of 3-[(1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl]-5,5-diphenylimidazolidine-2,4-diones 6a–6d

To a mixture of 5,5-diphenyl-3-(prop-2-yn-1-yl)imidazolidine-2,4-dione (**3**, 1 mmol) and an aromatic azide (**5**, 1 mmol) in 3 cm^3 H_2O were added **L3** (2 mol%), $CuSO_4$ (2 mol%), and NaAsc (4 mol%). The mixture obtained was stirred at 70 °C until the disappearance of compound **3** (monitored by TLC). After completion of the reaction, the solvent was evaporated to dryness. The crude product was washed with ammonia (1/1) and then H_2O and dried, and the crude product was purified by recrystallization from ethanol.

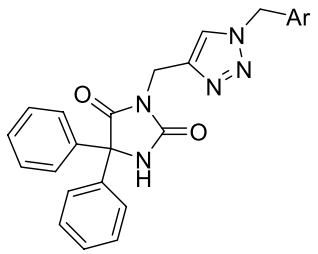
3-[[1-(3-Nitrophenyl)-1H-1,2,3-triazol-4-yl]methyl]-5,5-diphenylimidazolidine-2,4-dione (6a, $C_{24}H_{18}N_6O_4$) Yellow powder solid; yield 85%; m.p.: 249–250 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.86 (s, 2H, CH_2), 7.35–7.45 (m, 10H, ArH), 7.89 (t, J = 8.2 Hz, 1H, ArH), 8.32 (dd, J = 8.1, 1.5 Hz, 1H, ArH), 8.40 (dd, J = 8.1, 1.2 Hz, 1H, ArH), 8.73–8.74 (br, 1H, ArH), 9.03 (s, 1H, CH triazole), 9.77 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 33.9, 69.8, 115.3, 122.5, 123.6, 126.6, 127.3, 128.7, 129.0, 132.0, 137.5, 140.0, 144.0,

Scheme 4



Reaction conditions: **3** (1.0 mmol), **8** (1.2 mmol), **9** (1.2 mmol), $CuSO_4$ (2 mol%), NaAsc (4 mol%), **L3** (2 mol%), 3 cm^3 H_2O, 70 °C.

Table 3 Synthesis of 3-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-5,5-diphenylimidazolidine-2,4-diones **10a**–**10c**[a]



10a-10c

Entry	Ar	Product	Time/min	Yield/%
1	C_6H_5–	**10a**	210	90
2	2-Cl–C_6H_4–	**10b**	210	87
3	4-Me–C_6H_4–	**10c**	210	88

[a]Reaction conditions: **3** (1.0 mmol), **8** (1.2 mmol), **9** (1.2 mmol), $CuSO_4$ (2 mol%), NaAsc (4 mol%), **L3** (2 mmol), 3 cm^3 H_2O, 70 °C

Table 4 Antibacterial activities of selected compounds (1000 μg cm^{-3}) as an inhibition zone in mm

Entry	Compound	*M. luteus*	*P. aeruginosa*
1	**6a**	49	20
2	**6b**	41	15
3	**6c**	48	16
4	**6d**	42	13
5	**7a**	51	17
6	**7b**	52	16
7	**7c**	41	12
8	**10a**	38	14
9	**10b**	40	12
10	**10c**	31	14
11	DMSO	–	–
12	Tetracycline	41	13

149.0, 155.3, 173.3 ppm; IR (KBr): $\overline{\nu}$ = 3296, 1772, 1712, 1595, 1532, 1491, 1446, 1344, 1257, 1200, 1139, 1113, 1040, 873, 771 cm^{-1}; MS: *m/z* = 454 (M^+).

3-[[1-(2-Chloro-4-nitrophenyl)-1H-1,2,3-triazol-4-yl]-methyl]-5,5-diphenylimidazolidine-2,4-dione (6b, $C_{24}H_{17}ClN_6O_4$) Dark orange powder solid; yield 88%; m.p.: 235–236 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.87 (s, 2H, CH_2), 7.35–7.45 (m, 10H, ArH), 8.03 (d, *J* = 9 Hz, 1H, ArH), 8.40 (dd, *J* = 8.7, 2.2 Hz, 1H, ArH), 8.63 (s, 2H, CH of triazole and ArH), 9.77 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 33.9, 69.8, 124.0, 125.9, 126.3, 127.2, 128.7, 129.0, 129.6, 129.7, 139.5, 140.0, 142.9, 148.7, 155.2, 173.3 ppm; IR (KBr): $\overline{\nu}$ = 3298, 1775, 1712, 1599, 1530, 1491, 1447, 1350, 1235, 1138, 1048, 820, 769 cm^{-1}; MS: *m/z* = 488 (M^+).

3-[[1-(4-Chloro-3-nitrophenyl)-1H-1,2,3-triazol-4-yl]-methyl]-5,5-diphenylimidazolidine-2,4-dione (6c, $C_{24}H_{17}ClN_6O_4$) Dark yellow powder solid; yield 95%; m.p.: 220–221 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.84 (s, 2H, CH_2), 7.35–7.45 (m, 10H, ArH), 8.03 (d, *J* = 8.7 Hz, 1H, ArH), 8.30 (dd, *J* = 9, 2.5 Hz, 1H, ArH), 8.72 (d, 1H, *J* = 2.4 Hz, ArH), 8.96 (s, 1H, CH of triazole), 9.76 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 33.9, 69.8, 117.6, 122.5, 125.0, 125.2, 127.2, 128.7, 129.0, 133.6, 136.1, 140.0, 144.0, 148.5, 155.3, 173.3 ppm; IR (KBr): $\overline{\nu}$ = 3300, 1772, 1712, 1600, 1533, 1491, 1445, 1345, 1235, 1201, 1139, 1113, 873, 771 cm^{-1}; MS: *m/z* = 488 (M^+).

3-[[1-(4-Chloro-2-nitrophenyl)-1H-1,2,3-triazol-4-yl]-methyl]-5,5-diphenylimidazolidine-2,4-dione (6d, $C_{24}H_{17}ClN_6O_4$) Yellow powder solid; yield 90%; m.p.: 224–225 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.84 (s, 2H, CH_2), 7.34–7.45 (m, 10H, ArH), 8.01 (d, *J* = 8.7 Hz, 1H, ArH), 8.29 (dd, *J* = 9, 2.5 Hz, 1H, ArH), 8.71 (d, *J* = 2.4 Hz, 1H, ArH), 8.96 (s, 1H, CH of triazole), 9.77 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 33.9, 69.8, 117.6, 122.5, 125.0, 125.2, 127.2, 128.7, 129.0, 133.6, 136.1, 140.0, 144.0, 148.5, 155.3, 173.3 ppm; IR (KBr): $\overline{\nu}$ = 3298, 1772, 1712, 1598, 1532, 1495, 1446, 1344, 1235, 1140, 1115, 1040, 880, 771 cm^{-1}; MS: *m/z* = 488 (M^+).

General procedure for synthesis of 1,3-bis[(1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl]-5,5-diphenyl-imidazolidine-2,4-diones 7a-7c

To a mixture of 5,5-diphenyl-1,3-di(prop-2-yn-1-yl)imidazolidine-2,4-dione (**4**, 1 mmol) and an aromatic azide (**5**, 2 mmol) in 3 cm^3 H_2O were added **L3** (2 mol%), $CuSO_4$ (2 mol%), and NaAsc (4 mol%). The mixture obtained was stirred at 70 °C until the disappearance of compound **4** (monitored by TLC). After completion of the reaction, the solvent was evaporated to dryness, the solid obtained was washed ammonia (1/1) and then H_2O and dried. The crude product was purified by recrystallization from ethanol.

1,3-Bis[[1-(4-chloro-3-nitrophenyl)-1H-1,2,3-triazol-4-yl]-methyl]-5,5-diphenylimidazolidine-2,4-dione (7a, $C_{33}H_{22}C_{l2}N_{10}O_6$) Yellow powder solid; yield 82%; m.p.: 170–171 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.74 (s, 2H, CH_2), 4.97 (s, 2H, CH_2), 7.34–7.36 (m, 10H, ArH), 7.98–8.06 (m, 4H, ArH), 8.28 (d, *J* = 8.4 Hz, 1H, ArH), 8.43 (s, 1H, CH of triazole), 8.69 (d, *J* = 1.8 Hz, 1H, ArH), 8.97 (s, 1H, CH triazole) ppm; ^{13}C NMR (75 MHz, DMSO-d_6):

δ = 34.6, 36.8, 75.0, 117.2, 117.5, 122.1, 122.4, 124.9, 125.0, 125.1, 125.2, 129.0, 129.1, 129.2, 133.6, 133.7, 135.9, 136.1, 136.6, 143.8, 148.4, 148.5, 155.3, 173.0 ppm; IR (KBr): $\overline{\nu}$ = 1769, 1712, 1600, 1536, 1491, 1449, 1350, 1235, 1132, 1040, 998, 876, 825, 771, 720, 697 cm^{-1}; MS: *m/z* = 724 (M^+).

1,3-Bis[[1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl]-methyl]-5,5-diphenylimidazolidine-2,4-dione (7b, $C_{33}H_{24}N_{10}O_6$) Orange powder solid; yield 79%; m.p.: 258–259 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.76 (s, 2H, CH_2), 4.99 (s, 2H, CH_2), 7.35–7.37 (m, 10H, ArH), 7.96 (d, *J* = 8.7 Hz, 2H, ArH), 8.01 (s, 1H, CH of triazole), 8.23 (d, *J* = 8.7 Hz, 2H, ArH), 8.43–8.48 (m, 4H, ArH), 9.01 (s, 1H, CH triazole) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 34.6, 36.8, 74.9, 120.8, 121.1, 122.0, 122.4, 126.0, 126.1, 129.0, 129.1, 129.3, 136.7, 140.9, 141.1, 144.0, 147.1, 147.2, 155.3, 173.0 ppm; IR (KBr): $\overline{\nu}$ = 1769, 1718, 1596, 1520, 1440, 1340, 1107, 1043, 985, 937, 851, 774, 745 cm^{-1}; MS: *m/z* = 656 (M^+).

1,3-Bis[[1-(2-chloro-4-nitrophenyl)-1H-1,2,3-triazol-4-yl]-methyl]-5,5-diphenylimidazolidine-2,4-dione (7c, $C_{33}H_{22}C_{l2}N_{10}O_6$) Dark orange powder solid; yield 83%; m.p.: 202–204 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.78 (s, 2H, CH_2), 4.98 (s, 2H, CH_2), 7.33–7.40 (m, 10H, ArH), 7.75 (d, *J* = 9 Hz, 1H, ArH), 7.80 (s, 1H, CH triazole), 8.03 (d, *J* = 8.7 Hz, 1H, ArH), 8.37–8.43 (m, 4H, ArH), 8.58 (d, *J* = 2.4 Hz, 1H, ArH), 8.62 (d, *J* = 2.4 Hz, 1H, ArH), 8.64 (s, 1H, CH of triazole) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 34.6, 36.8, 75.0, 124.0, 124.1, 125.2, 125.6, 126.3, 126.4, 128.9, 129.0, 129.1, 129.2, 129.3, 129.6, 129.7, 136.7, 139.3, 139.5, 142.8, 143.9, 148.6, 148.7, 155.3, 173.1 ppm; IR (KBr): $\overline{\nu}$ = 1770, 1715, 1600, 1533, 1443, 1340, 1235, 1107, 1045, 980, 851, 770 cm^{-1}; MS: *m/z* = 724 (M^+).

General procedure for synthesis of 3-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-5,5-diphenylimidazolidine-2,4-diones 10a-10c

To a mixture of benzyl chloride (**8**, 1.2 mmol) and sodium azide (**9**, 1.2 mmol) in 3 cm^3 H_2O were added 5,5-diphenyl-3-(prop-2-yn-1-yl)imidazolidine-2,4-dione (**3**, 1 mmol), **L3** (2 mol%), $CuSO_4$ (2 mol%), and NaAsc (4 mol%). The resulting mixture was stirred at 70 °C until the disappearance of compound **3** (monitored by TLC). After completion of the reaction, the solvent was evaporated to dryness. The solid obtained was washed with ammonia (1/1) and then H_2O and dried. The crude product was purified by recrystallization from ethanol.

3-[(1-Benzyl-1H-1,2,3-triazol-4-yl)methyl]-5,5-diphenylimidazolidine-2,4-dione (10a, $C_{25}H_{21}N_5O_2$) White powder solid; yield 90%; m.p.: 207 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.72 (s, 2H, CH_2), 5.59 (s, 2H, CH_2), 7.28–7.44 (m, 15H, ArH), 8.08 (s, 1H, CH triazole), 9.71 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 34.0, 53.2, 69.7, 123.8, 127.2, 128.4, 128.6, 128.7, 129.0, 129.2, 136.5, 140.0, 142.7, 155.3, 173.3 ppm; IR (KBr): $\overline{\nu}$ = 3310, 1771, 1712, 1596, 1490, 1445, 1330, 1252, 1209, 1120, 1046, 940, 707, 700 cm^{-1}; MS: *m/z* = 423 (M^+).

3-[[1-(2-Chlorobenzyl)-1H-1,2,3-triazol-4-yl]methyl]-5,5-diphenylimidazolidine-2,4-dione (10b, $C_{25}H_{20}ClN_5O_2$) White powder solid; yield 87%; m.p.: 160–161 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.74 (s, 2H, CH_2), 5.71 (s, 2H, CH_2), 7.19 (dd, *J* = 7.2, 1.6 Hz, 1H, ArH), 7.34–7.44 (m, 12H, ArH), 7.53 (dd, *J* = 7.8, 1.2 Hz, 1H, ArH), 8.04 (s, 1H, CH of triazole), 9.72 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 34.0, 51.1, 69.7, 124.2, 127.2, 128.2, 128.7, 129.0, 130.1, 130.7, 130.9, 133.1, 133.7, 140.0, 142.5, 155.3, 173.3 ppm; IR (KBr): $\overline{\nu}$ = 3312, 1766, 1702, 1600, 1446, 1411, 1337, 1216, 1110, 1052, 940, 915, 828, 758, 732, 694, 668 cm^{-1}; MS: *m/z* = 457 (M^+).

3-[[1-(4-Methylbenzyl)-1H-1,2,3-triazol-4-yl]methyl]-5,5-diphenylimidazolidine-2,4-dione (10c, $C_{25}H_{20}ClN_5O_2$) White powder solid; yield 88%; m.p.: 169–170 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.30 (s, 3H, CH_3), 4.70 (s, 2H, CH_2), 5.52 (s, 2H, CH_2), 7.16–7.22 (m, 4H, ArH), 7.33–7.43 (m, 10H, ArH), 8.02 (s, 1H, CH of triazole), 9.70 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.2, 34.0, 53.0, 69.7, 123.6, 127.2, 128.4, 128.7, 129.0, 129.7, 133.5, 137.9, 140.0, 142.6, 155.3, 173.3 ppm; IR (KBr): $\overline{\nu}$ = 3312, 1769, 1712, 1600, 1488, 1446, 1331, 1254, 1209, 1120, 1046, 940 cm^{-1}; MS: *m/z* = 437 (M^+).

Antibacterial assay

The evaluation of antibacterial activities of new 1,2,3-triazole-linked 1,2,4-triazino[5,6-*b*]indole was performed by using a well-diffusion method against *Micrococcus luteus* (*M. luteus*) and *Pseudomonas aeruginosa* (*P. aeruginosa*). The nutrient agar and broth cultures were prepared and incubated at 37 °C. To the nutrient agar plates, a suspension of 40 mm^3 of each bacterium was added. Cups (5 mm in diameter) were cut at the end to each well. Besides, 30 mm^3 of the test compounds at a concentration of 1000 μg cm^{-3} was added in DMSO. The plates were incubated at 37 °C for 24 h, and the inhibition zone was measured in mm. Results were reported as the inhibition zone in mm. The anti-bacterial activities were compared with tetracycline as the standard drug. DMSO was applied as a negative control.

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