



Synthesis And Biological Evaluation of New Triazolyl Analogues Derived From 1-Oxaspiro[4.4]nona-3,6-Dien-6-Ylmethanol

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ABSTRACT

A series of 4-[(1-oxaspiro[4.4]nona-3,6-dien-6-ylmethoxy)methyl]-1-phenyl-1H-1,2,3-triazolyl congeners have been designed and synthesized in an attempt to develop potent antimicrobial and antifungal agents. A regioselective approach using Huisgen 1,3-dipolar cycloaddition reaction of 1-oxaspiro[4.4]nona-3,6-dien-6-ylmethanol-alkyne derivative with various aromatic azides was employed to target an array of triazolyl derivatives in an efficient manner. Their structures were confirmed by using proton, ¹³C NMR and ESI-MS spectral analysis. All the compounds were evaluated for the antimicrobial and antifungal activity by disc diffusion method. The antibacterial and antifungal activity was evaluated against, *A. niger*, *C. albicans* (fungal strains), *E. coli* and *P. aeruginosa* (Gram negative bacteria), *S. aureus* and *S. pyogenes* (Gram positive bacteria) using Nystatin (for fungi) and ciprofloxacin (for bacteria) as the standard drugs. The pharmacological results showed that some of the compounds displayed high level of antimicrobial and antifungal activity compared with parent compound. Compounds **8b**, **8c**, **8f** and **8g** were found to be the most potent compounds in this study.

Keywords: 1-oxaspiro[4.4]nona-3,6-dien-6-ylmethanol, Huisgen 1,3-dipolar cycloaddition, regioselective approach, antimicrobial activity, antifungal activity.

INTRODUCTION

Compounds containing furo-furanone scaffolds (1- 4, Figure 1) have found widespread application as neurotropic factor enhancing agents [1], antimicrobial [2,3], antifungal [3], antileukemic [3], and cytotoxic [3] agents. While working on the synthesis of these compounds [4-7] we decided to screen the intermediate compounds for different biological properties. Among the intermediates, compound 6 exhibited promising antibacterial and antifungal activities. Keeping in view the broad spectrum potential of triazoles in general a library of 1-oxaspiro[4.4]nona-3,6-dien-6-ylmethanol triazolyl derivatives has been synthesized by employing click chemistry protocol as potential antimicrobial and antifungal compounds. Click chemistry enables a modular approach to generate these novel pharmacophores utilizing a collection of reliable chemical reactions [8]. All the

triazolyl derivatives were screened for anti-bacterial and antifungal activity against *E. coli* and *P. aeruginosa* (Gram negative bacteria), *S. aureus* and *S. pyogenes* (Gram positive bacteria) and *A. niger*, *C. albicans* (fungal strains), using Nystatin (for fungi) and ciprofloxacin (for bacteria) as the standard drugs. To our delight, it was observed that some of the compounds exhibited promising activity against the tested bacterial and fungal strains. It has been found from the data that some compounds exhibited better antibacterial and anti-fungal potential than the parent compound 6 and standard drugs used in this study. A close inspection of the results confirmed that the triazolyl derivatives of compound 6 with *o*-bromo, *o*-trifloro methyl, *o*-chloro and *o*-floro substitution at aromatic ring were found to be the most promising compounds.

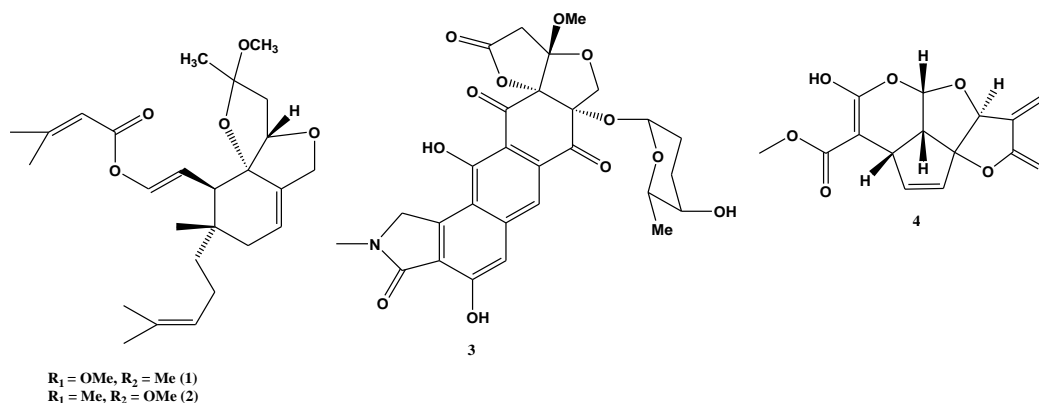


Figure 1. Compounds containing furo-furanone scaffold

MATERIALS AND METHODS

Chemical and solvents used were purchased either from Sigma-Aldrich or Merck. All the reagents were of analytical grade. Thin-layer chromatography (TLC) was performed on E. Merck AL silica gel 60 F254 plates and eluants were visualized under UV light. The $^1\text{H-NMR}$ spectra were recorded in CDCl_3 on a Bruker spectrometer (400MHz). The $^{13}\text{CNMR}$ spectra were recorded in CDCl_3 on a Bruker spectrometer operating at 100MHz. All the chemical shifts were reported in δ (ppm) using TMS as an internal standard.

Synthesis of compound 6: To a solution of compound 5 (300 mg) in THF (5 ml) was added TBAF (200 mg, 1 mmol) and the reaction mixture was stirred at room temperature for 1h. On completion, the solvent was evaporated and the crude product was purified by column chromatography (v/v 1:1 ethylacetate:hexane) to obtain the alcohol 6 (112 mg) in 96% yield.

Synthesis of compound 7: To a solution of 6 (100 mg, 1 mmol) in dry THF (5 ml), sodium hydride (25 mg, 1.6 mmol) and propargyl bromide (298 μl , 5 mmol) were added and the reaction mixture was stirred at room temperature for 4 h. After completion, the solvent was evaporated and the crude product was subjected to column chromatography to afford 7 (115 mg) in 92% yield. ^{13}C NMR (100 MHz, CDCl_3): 141.9, 132.4, 131.1, 126.7, 101.0, 98.1, 80.0, 74.7, 74.4, 65.6, 57.4, 37.3, 29.7; ESI-MS: m/z 191.1 ($M + 1$)

General procedure for the synthesis of triazolyl derivatives 8a-8j: To a solution of compound 7 (15 mg, 0.03 mmol) in $t\text{-BuOH} : \text{H}_2\text{O}$ (2:1, 2 ml), sodium ascorbate (1.2 mg, 0.006 mmol) and CuSO_4 (1.2 mg, 0.0045 mmol) were added at room temperature. To this mixture, aryl azide (0.06 mmol) was added and the reaction mixture was sonicated at room temperature till completion (2-6h). The reaction mixture was extracted with ethylacetate (3 x 10 ml) and the combined organic

layer was dried over sodium sulfate and purified by column chromatography to give pure 8a-8j in 75-96% yield.

1-(4-bromophenyl)-4-[(1-oxaspiro[4.4]nona-3,6-dien-6-ylmethoxy)methyl]-1H-1,2,3-triazole: Yield: 91%; ¹H NMR (400 MHz, CDCl₃): δ 7.9 (s, 1H), 7.6 (bs, 4H), 5.9 (m, 2H), 5.7 (m, 1H), 4.7 (s, 2H), 4.6 (s, 2H), 4.0 (d, *J* = 8 Hz, 2H), 2.4-2.1 (m, 2H), 2.0 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): 146.5, 142.1, 136.0, 132.9, 131.9, 131.2, 126.5, 122.3, 121.9, 120.4, 101.0, 74.6, 66.5, 63.6, 37.1, 29.5; ESI-MS: *m/z* 390.0 (M + 1).

1-(2-bromophenyl)-4-[(1-oxaspiro[4.4]nona-3,6-dien-6-ylmethoxy)methyl]-1H-1,2,3-triazole: Yield: 90%; ¹H NMR (400 MHz, CDCl₃): δ 7.97 (d, 1H, *J* = 4 Hz), 7.94 (d, 1H, *J* = 4 Hz), 7.81 (s, 1H), 7.41-7.18 (m, 2H), 5.93 (m, 2H), 5.71 (t, 1H, *J* = 4 Hz), 4.70 (s, 2H), 4.63 (s, 2H), 4.1 (m, 2H), 2.47 (m, 1H), 2.32 (m, 1H), 2.10 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): 142.2, 132.2, 131.9, 131.4, 131.2, 130.5, 130.4, 127.8, 126.7, 123.9, 123.5, 119.1, 118.5, 101.0, 74.6, 66.6, 63.8, 37.2, 29.7; ESI-MS: *m/z* 412.0 (M + Na).

4-[(1-oxaspiro[4.4]nona-3,6-dien-6-ylmethoxy)methyl]-1-[2-(trifluoromethyl)phenyl]-1H-1,2,3-triazole: Yield: 87%; ¹H NMR (400 MHz, CDCl₃): δ 8.08 (s, 1H), 7.96 (d, 1H), 7.85 (d, 1H), 7.57 (m, 1H), 7.43 (m, 1H), 5.97 (d, 1H, *J* = 12 Hz), 5.78 (m, 1H), 5.59 (t, 1H, *J* = 4 Hz), 4.60 (s, 2H), 4.48-4.38 (m, 2H), 4.07 (s, 2H), 2.33-2.23 (m, 2H), 1.98 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): 152.5, 138.2, 136.0, 134.5, 134.5, 132.8, 129.3, 129.0, 128.4, 127.2, 123.6, 121.5, 120.5, 71.1, 68.9, 60.4, 36.1, 31.5; ESI-MS: *m/z* 378.1 (M + 1).

1-(3-nitrophenyl)-4-[(1-oxaspiro[4.4]nona-3,6-dien-6-ylmethoxy)methyl]-1H-1,2,3-triazole: Yield: 85%; ¹H NMR (400 MHz, CDCl₃): δ 8.61 (s, 1H), 8.31 (s, 1H), 8.19 (m, 2H), 7.76 (m, 1H), 5.95 (m, 2H), 5.72 (t, 1H, *J* = 12 Hz), 4.73 (s, 2H), 4.64 (s, 2H), 4.12 (m, 2H), 2.48-2.05 (m, 4H); ¹³C NMR (100 MHz, CDCl₃): 148.9, 142.2, 137.8, 132.2, 131.2, 130.9, 126.5, 125.6, 122.9, 115.3, 101.0, 74.6, 66.7, 63.6, 37.0, 29.7; ESI-MS: *m/z* 377.1 (M + Na).

1-(3,4-dimethylphenyl)-4-[(1-oxaspiro[4.4]nona-3,6-dien-6-ylmethoxy)methyl]-1H-1,2,3-triazole: Yield: 87%; ¹H NMR (400 MHz, CDCl₃): δ 7.92 (s, 1H), 7.52 (s, 1H), 7.41-7.26 (m, 2H), 5.95 (m, 2H), 5.91 (t, 1H, *J* = 12 Hz), 4.70 (s, 2H), 4.62 (s, 2H), 4.09 (m, 2H), 2.47 (m, 1H), 2.32 (m, 2H), 2.09 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): 145.9, 142.2, 138.3, 137.5, 135.0, 131.7, 131.4, 130.5, 126.2, 121.8, 120.6, 117.7, 100.9, 74.6, 66.5, 63.8, 37.1, 29.7, 19.7, 19.3; ESI-MS: *m/z* 339.2 (M + 1).

1-(2-chlorophenyl)-4-[(5R)-1-oxaspiro[4.4]nona-3,6-dien-6-ylmethoxy)methyl]-1H-1,2,3-triazole: Yield: 89%; ¹H NMR (400 MHz, CDCl₃): δ 8.08 (s, 1H), 7.74 (m, 1H), 7.43-7.26 (m, 3H), 5.97 (d, 1H, *J* = 12 Hz), 5.78 (m, 1H), 5.59 (t, 1H, *J* = 4 Hz), 4.61 (s, 2H), 4.48-4.38 (m, 2H), 4.04 (s, 2H), 2.33-2.23 (m, 3H), 1.98 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): 152.5, 138.2, 138.1, 134.5, 134.5, 131.2, 130.8, 129.3, 127.6, 127.5, 126.9, 121.5, 71.1, 68.9, 60.4, 36.1, 31.5; ESI-MS: *m/z* 342.1 (M - 1).

1-(2-fluorophenyl)-4-[(5R)-1-oxaspiro[4.4]nona-3,6-dien-6-ylmethoxy)methyl]-1H-1,2,3-triazole: Yield: 86%; ¹H NMR (400 MHz, CDCl₃): δ 8.08 (s, 1H), 7.64 (m, 1H), 7.28 (m, 2H), 7.14 (m, 1H), 5.98 (d, 1H, *J* = 12 Hz), 5.78 (m, 1H), 5.59 (t, 1H, *J* = 4 Hz), 5.60 (s, 2H), 4.36-4.50 (m, 2H), 4.04 (s, 1H), 2.36-2.20 (m, 3H), 1.98 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): 161.5, 152.5, 138.2, 134.5, 134.5, 129.3, 128.0, 127.7, 125.7, 125.7, 121.5, 117.9, 71.1, 68.9, 60.4, 36.1, 31.5; ESI-MS: *m/z* 328.1 (M + 1).

1-(2-nitrophenyl)-4-[[5R]-1-oxaspiro[4.4]nona-3,6-dien-6-ylmethoxy)methyl]-1H-1,2,3-triazole:

Yield: 87%; ¹H NMR (400 MHz, CDCl₃): δ 8.10 (s, 1H), 7.85-7.65 (m, 4H), 5.95 (m, 2H), 5.73 (t, 1H, *J* = 12 Hz), 4.75 (s, 2H), 4.65 (s, 2H), 4.12 (m, 2H), 2.49-2.06 (m, 4H); ¹³C NMR (100 MHz, CDCl₃): 147.9, 142.7, 136.2, 131.8, 131.5, 130.7, 126.8, 125.9, 123.9, 118.3, 101.6, 74.8, 66.9, 64.1, 37.5, 29.9; ESI-MS: *m/z* 355.2 (M + 1).

1-(2,5-dimethylphenyl)-4-[(1-oxaspiro[4.4]nona-3,6-dien-6-ylmethoxy)methyl]-1H-1,2,3-triazole:

Yield: 89%; ¹H NMR (400 MHz, CDCl₃): δ 8.08 (s, 1H), 7.57 (s, 1H), 7.21 (d, 1H), 7.08 (d, 1H), 5.97-5.78 (m, 2H), 5.59 (t, 1H, *J* = 12 Hz), 4.56 (s, 2H), 4.48-4.38 (m, 2H), 4.01 (s, 2H), 2.37 (s, 3H), 2.35 (s, 3H), 2.33 (m, 3H), 1.98 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): 151.9, 141.5, 136.7, 135.9, 135.3, 134.3, 130.7, 129.7, 128.8, 126.3, 124.3, 122.0, 70.6, 68.9, 60.5, 36.4, 30.7, 21.2, 17.2; ESI-MS: *m/z* 338.1 (M + 1).

1-(naphthalen-1-yl)-4-[(1-oxaspiro[4.4]nona-3,6-dien-6-ylmethoxy)methyl]-1H-1,2,3-triazole:

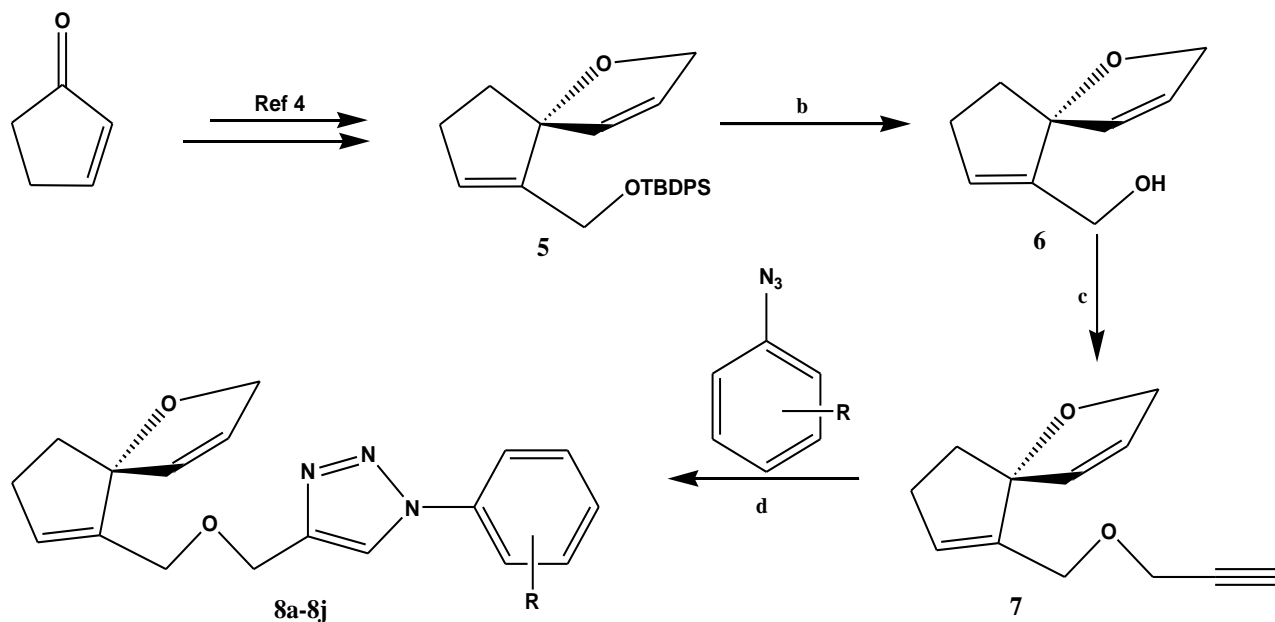
Yield: 83%; ¹H NMR (400 MHz, CDCl₃): δ 8.02 (s, 1H), 7.97-7.92 (m, 2H), 7.58 (m, 5H), 5.98-5.92 (m, 2H), 5.73 (t, 1H, *J* = 12 Hz), 4.79 (s, 2H), 4.64 (s, 2H), 4.16-4.11 (m, 2H), 2.48-2.02 (m, 4H); ¹³C NMR (100 MHz, CDCl₃): 142.4, 134.3, 133.9, 132.2, 131.4, 130.5, 128.7, 128.4, 128.0, 127.2, 126.7, 125.3, 125.1, 123.7, 122.5, 100.9, 74.7, 66.5, 64.0, 37.2, 29.5; ESI-MS: *m/z* 359.2 (M - 1).

Antimicrobial and Antifungal Bioassay: The measured quantities of the test compounds 8a–8j was dissolved in dimethyl sulphoxide (DMSO) in a final concentration of 50 µg mL⁻¹. The disc diffusion method [9] was used for the evaluation of antibacterial and antifungal activity of these synthesized compounds 8a-8j. The bacterial (24 h) and fungal (48 h) cultures from the slants were diluted with sterile water and mixed thoroughly to prepare a clear homogeneous suspension. These suspensions were spread on solidified agar, potato dextrose agar for fungi and nutrient agar for bacteria medium. The filter paper disks prepared by only DMSO (as a negative control) and with solution of 50 µg/L concentrations of test compounds 8a–8j as well as standard compounds (Ciprofloxacin and Nystatin as positive control) were carefully placed over the spread cultures and incubated at 37 °C for 24 h for bacteria and at 28–30 °C for 48 h for fungi. After the incubation period, the plates were examined for the zone of inhibition. The diameter for the zones of inhibition was measured including the diameter of disk also. All determinations were made in triplicate for each of the compounds and the average value was taken. The antibacterial and antifungal activity was evaluated against *E. coli* and *P. aeruginosa* (Gram negative bacteria), *S. aureus* and *S. pyogenes* (Gram positive bacteria), *A. niger* and *C. albicans* (fungal strains) using ciprofloxacin (for bacteria) and Nystatin (for fungi) as the standard drugs.

RESULTS AND DISCUSSION

The compound 5 was synthesized using our previously developed protocol [4], which on deprotection using TBAF in THF yielded 1-oxaspiro[4.4]nona-3,6-dien-6-ylmethanol 6. Propargylation of the hydroxyl group of hydroxymethyl arm 6 was carried out with NaH in dry THF to deliver the well poised alkyne derivative 7 in excellent yield. On the other hand, aromatic azides were prepared from their respective anilines by diazotization with sodium nitrite in acidic conditions followed by displacement with sodium azide in good to excellent yield. 1,3-dipolar cycloaddition reaction of 7 with aromatic azides in presence of CuSO₄·5H₂O and sodium ascorbate in t-BuOH:H₂O (2:1) resulted into the formation of 1,4 substituted-triazolyl derivatives 8a-8j regioselectively in excellent yields (Scheme 1). All the reactions were carried out at room temperature under ultra-sonication and completed within 1 to 6h. The products were confirmed by ¹H NMR, ¹³C NMR, and ESI-MS analysis. In ¹H NMR cyclization of azides to form triazoles was confirmed by resonance of H-5 of triazole ring in aromatic region as well as by other proton

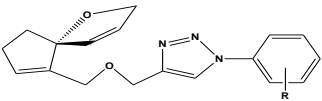
absorptions in aromatic region. By employing the above reaction conditions, a series of 1-oxaspiro[4.4]nona-3,6-dien-6-ylmethanol triazolyl derivatives that vary at substitutions on aromatic ring has been synthesized from a range of aromatic azides. It was observed that all the reactions worked smoothly under ultra-sonication conditions, the reaction time and yields are reported in table 1.

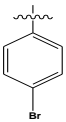



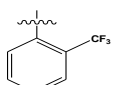
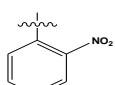
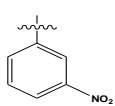
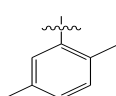
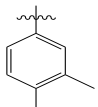
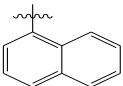


Scheme 1: a) ref 4, b) TBAF, THF, rt, 96%, c) propargyl bromide, NaH, THF, rt, 92%, (d) sodium ascorbate, CuSO₄, t-BuOH: H₂O (2:1), rt, sonication, 75-97%.

Antibacterial and Antifungal Activity: The antibacterial and antifungal activity of the synthesized triazolyl derivatives **8a-8j** (50 $\mu\text{g mL}^{-1}$ concentration) was compared with the standard drug Ciprofloxacin and the results of the investigation have been presented in **table 2**. In general it is observed that the compounds **8b** (R = 2-bromo), **8c** (R = 2-tri-floro methyl), **8f** (R = 2-chloro) and **8g** (R = 2-floro) displayed good antibacterial activity (zone of inhibition: 16-21 mm) with reference to the Ciprofloxacin drug (zone of inhibition: 21-28 mm) when tested against all the bacterial strains (viz., *E. coli*, *P. aeruginosa*, *S. aureus*, *S. pyogenes*), while the compounds **8a** (R = 4-Br), **8d** (R = 3-nitro), **8e** (R = 3, 4-dimethyl), **8h** (R = 2-nitro), **8i** (R = 2,5-dimethyl), and **8j** (R = naphthyl) did not display any significant antibacterial activity (zone of inhibition: 21-29 mm).

The results of the antifungal activities of synthesized compounds **8a-8j** are as follows: Compounds **4c** (R = tri-floromethyl) and **4g** (R = 2-floro) displayed good antifungal activity (zone of inhibition: 15-21 mm), while the compounds **8b** (R = 2-Br) and **8f** (R = 2-chloro) showed moderate antifungal activity (zone of inhibition: 18-23 mm) in comparison with standard antifungal drug (Nystatin, 50 $\mu\text{g L}^{-1}$ concentration). Therefore, the present study is valuable for finding the new drugs against bacterial and fungal diseases.

Table 1: 4-[(1-oxaspiro[4.4]nona-3,6-dien-6-ylmethoxy)methyl]-1-phenyl-1H-1,2,3-triazolyl derivatives varying at aromatic ring


Compd	R	Time (h)	Yield ^a	Compd	R	Time (h)	Yield ^a
8a		2h	91	8f		2.5h	89
8b		2h	90	8g		3h	86
8c		3h	87	8h		2.5h	87
8d		3.5h	85	8i		4h	89
8e		4h	87	8j		6h	83

^a Yields reported are isolated yields in percentage .**Table 2:** Results of Antibacterial and Antifungal activity of Compounds 8a-8j

Compound No.	Gram positive bacteria		Gram negative bacteria		Fungi	
	S. aureus	S. pyogenes	E. coli	P.aeruginosa	C. albicans	A. niger
	MTCC 96	MTCC 442	MTCC 443	MTCC 424	MTCC 227	MTCC 282
Zone of inhibition expressed in mm						
5	26	25	23	21	23	26
8a	29	28	26	26	28	28
8b	18	17	19	19	23	20
8c	17	16	19	17	15	19

8d	26	23	21	28	24	29
8e	27	29	23	21	23	31
8f	18	20	18	17	19	18
8g	17	21	19	18	21	18
8h	27	29	25	25	26	23
8i	28	23	19	23	28	23
8j	27	23	23	21	28	31
SD*	28	24	21	21		
SD*					24	24

SD*: Standard drug: Ciprofloxacin (Conc. 50 $\mu\text{g mL}^{-1}$) was used as a standard drug for activity; Nystatin (Conc. 50 $\mu\text{g mL}^{-1}$) was used as a standard drug for antifungal activity.

APPLICATIONS

The results of the antibacterial and anti-fungal activity of the synthesized triazolyl analogues **8a-8j**, of 1-oxaspiro[4.4]nona-3,6-dien-6-ylmethanol **6** revealed that the triazolyl analogues possessing aromatic ring with ortho-bromo **8b**, ortho-trifloro methyl **8c**, ortho-chloro **8f** and ortho-fluoro **8g** substitution are most potent antibacterial and antifungal agents.

CONCLUSIONS

The present study describes the synthesis of a wide range of triazolyl derivatives of terminal alkyne derivative of 1-oxaspiro[4.4]nona-3,6-dien-6-ylmethanol employing Cu(I) catalyzed Huisgen 1,3-dipolar cycloaddition reaction with various aromatic azides. All the compounds synthesized were screened for antibacterial activity and antifungal activity against a panel of four bacterial strains (viz., *E. coli*, *P. aeruginosa*, *S. aureus*, *S. pyogenes*) and two fungal strains (*C. albicans*, *A. niger*). From the data, it was evident that some of the compounds exhibited better antibacterial and antifungal activity against all the tested bacterial and fungal strains compared to Nystatin (for fungi) and ciprofloxacin (for bacteria) used in this study. Compounds **8b**, **8c**, **8f** and **8g** with o-bromo, o-trifloro methyl, o-chloro and o-fluoro substitutions were found to be the most promising derivatives and their detailed mechanistic studies are currently underway in our laboratory.

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