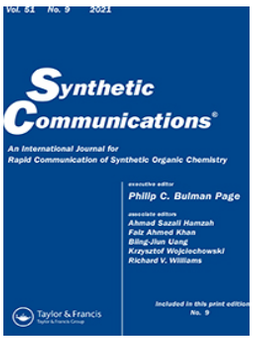

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Facial synthesis of novel 3-(2-methylbenzofuran-3-yl)-5-((4-(phenoxymethyl)-1H-1,2,3-triazole-1-yl)methyl)-1,2,4-oxadiazole derivatives

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Facial synthesis of novel 3-(2-methylbenzofuran-3-yl)-5-((4-(phenoxymethyl)-1H-1,2,3-triazole-1-yl)methyl)-1,2,4-oxadiazole derivatives

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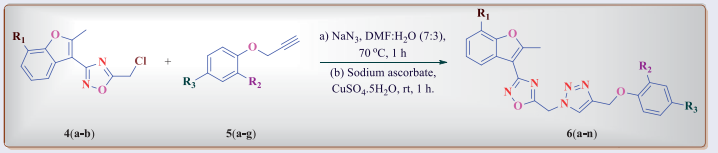
ABSTRACT

An efficient and practical methodology was developed for rapid and green synthesis of novel benzofuran-1,2,4-oxadiazole-1,2,3-triazole hybrids (**6a–n**) from 5-(chloromethyl)-3-(2-methylbenzofuran-3-yl)-1,2,4-oxadiazoles (**4a–b**) by *in situ* generation of 5-(azidomethyl)-3-(2-methylbenzofuran-3-yl)-1,2,4-oxadiazoles followed by 1,3-dipolar cycloaddition with substituted-1-(prop-2-yn-1-yloxy)benzenes (**5a–g**) through Click reaction under mild reaction conditions with good to excellent yields (70–86%).

GRAPHICAL ABSTRACT



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KEYWORDS
Benzofuran; click reaction; 1,3-dipolar cycloaddition; 1,2,4-oxadiazole; 1,2,3-triazole

Introduction

Benzofuran motifs have significant molecules from the last decades attributable to their attentive physiological and chemotherapeutic properties along with their widespread amount in nature.[1] The derivatives of benzofuran containing compounds are significantly distributed in nature and exhibiting physiological and chemotherapeutic properties like anti-hyperglycemic,[2] analgesic,[3] anti-parasitic,[4] anti-microbial,[5] anti-tumor and kinase inhibitor activities.[6,7] Especially benzofurans with substituents at C-2 and C-3 positions have been widely investigated for selective biological and pharmacological properties.[8,9] Recently, benzofuran containing drugs were accepted in U.S. FDA.[10,11] Benzofuran derivatives are innovative biodynamic agents that can be used to design and development of novel potential therapeutic agents for diverse biological activities.[12] 1,2,4-oxadiazoles are promising frameworks of biologically active natural products.[13] The various 3,5 disubsttituted oxadiazole derivatives were reported as anti-cancer,[14] anti-biotic,[15] anti-fungal,[16] anti-oxidant,[17] anti-inflammatory[18] and anti-convulsant

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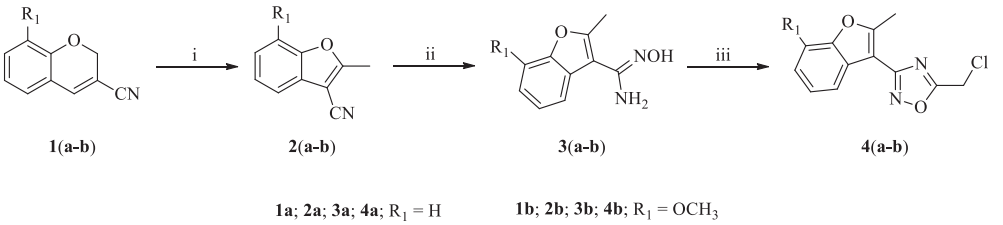
agents.[19] Recently, various 3,5-disubstituted-1,2,4-oxadiazoles were reported as potential anti-cancer agents and apoptosis against various cancer cell lines.[20–24] Furthermore 1,2,4-oxadiazole derivatives are possess hydrolytic, metabolic stability, improved pharmacokinetic properties[25] and also defined as bioisosters of amides and esters.[26] 1,2,3-Triazoles have been established as significant molecules in medicinal chemistry in last decades. 1,2,3-Triazole moiety does not occur in nature although, the basic 1,4-disubstituted-1,2,3-triazole ring itself is a potential pharmacophore that showed interesting biological activities such as anti-bacterial,[27] anti-malarial,[28] anti-fungal,[29] anti-viral,[30] anti-tubercular[31] and anti-cancer activities.[32] 1,2,3-Triazoles can actively involve in dipole-dipole and π-stacking interactions and hydrogen bonding with enhanced binding affinity to target proteins,[33–35] these are considered as peptide and amide bond isosteres.[36,37] Sharpless et al. reported[38] the Cu (I) catalyzed 1,3-dipolar cycloaddition between terminal alkynes and alkyl azides leads regioselectively 1,4-disubstituted-1,2,3-triazoles under Click reaction condition. Furthermore, one-pot 1,3-cycloaddition was earlier reported[39,40] Feldmanin et al. were reported situ azide generated cycloaddition,[41] Pokhodylo et al. were reported one-pot 1,2,3-triazol and 1,3,4/1,2,4-oxadiazole hybrids.[42] Hybrid molecules with two or more diverse heterocyclic pharmacophores having significant results in drug discovery, due to reduce side effects and overcome the drug resistance may also precise action mechanisms.[43,44] Notably heterocyclic hybrids were privileged scaffolds exhibiting several biological activities such as anti-fungal, anti-tuberculosis, anti-malarial, anti-inflammatory, anti-cancer and anti-bacterial activity.[45,46] Recently, various oxygen and nitrogen-containing heterocyclic pharmacophores with 1,2,3-triazole linker were found in the development of novel anti-cancer drugs.[47] These fascinating biological properties enhance our interest toward the synthesis of oxadiazole, 1,2,3-triazole derivatives and their biological activity.

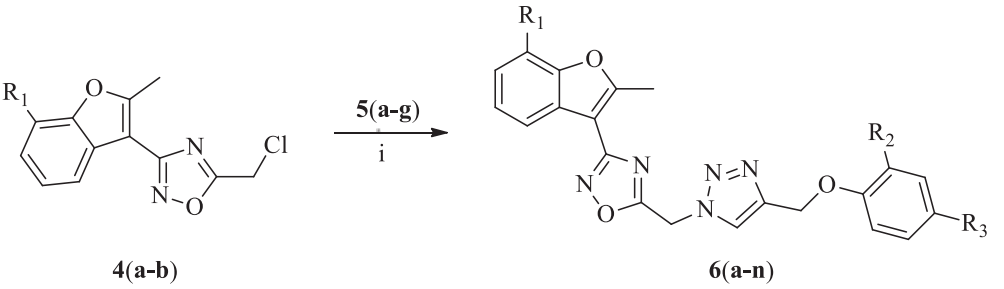
Results and discussion

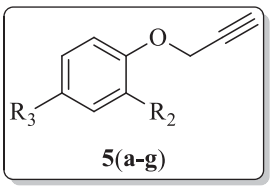
Novel benzofuran-1,2,4-oxadiazole-1,2,3-triazole hybrids (**6a–n**) were synthesized from 2*H*-chromene-3-carbonitriles (**1a–b**). 2*H*-chromene-3-carbonitriles (**1a–b**) were synthesized from the previous reported procedure.[48] Initially, 5-(chloromethyl)-3-(2-methylbenzofuran-3-yl)-1,2,4-oxadiazoles (**4a–b**) were prepared from 2*H*-chromene-3-carbonitriles (**1a-b**) by using my earlier reported method.[49] Catalyst free sodium azide mediated ring retrenchment in pyran ring of compounds **1**(**a–b**) into furan ring in DMSO at 160 °C witch gave 2-methylbenzofuran-3-carbonitriles (**2a–b**), were respectively. Furthermore, hydroxylamine hydrochloride reacted with compounds **2**(**a–b**) using triethylamine in ethanol under reflux gave N-hydroxy-2-methylbenzofuran-3-carboximidamides (**3a–b**) individually. Moreover, compounds **3**(**a–b**) was acetylation followed by condensation with chloroacetyl chloride in THF at reflux, provided 5-(chloromethyl)-3-(2-methylbenzofuran-3-yl)-1,2,4-oxadiazoles (**4a–b**) respectively (Scheme 1).

Compounds **4**(**a–b**) were treated with sodium azide provided, *in situ* 5-(azidomethyl)-3-(2-methylbenzofuran-3-yl)-1,2,4-oxadiazoles subsequently, 1,3-dipolar cycloaddition with substituted-1-(prop-2-yn-1-yloxy)benzenes (**5a–g**) using sodium ascorbate and $CuSO_4.5H_2O$ in DMF:H_2O (7:3) under Click reaction gave corresponding



Scheme 1. Synthesis of compounds **4(a–b)**, reagents and conditions: (i) NaN_3, DMSO, 160 °C, 30 min; (i) $NH_2OH.HCl$, TEA, EtOH, reflux, 6 h; (iii) Chloroacetylchloride, THF, reflux, 6 h.





5a; $R_2 = H$, $R_3 = H$
5b; $R_2 = H$, $R_3 = CH_3$
5c; $R_2 = H$, $R_3 = OCH_3$
5d; $R_2 = Cl$, $R_3 = H$
5e; $R_2 = H$, $R_3 = Cl$
5f; $R_2 = H$, $R_3 = Br$
5g; $R_2 = H$, $R_3 = NO_2$

6a; $R_1 = H$, $R_2 = H$, $R_3 = H$
6b; $R_1 = H$, $R_2 = H$, $R_3 = CH_3$
6c; $R_1 = H$, $R_2 = H$, $R_3 = OCH_3$
6d; $R_1 = H$, $R_2 = Cl$, $R_3 = H$
6e; $R_1 = H$, $R_2 = H$, $R_3 = Cl$
6f; $R_1 = H$, $R_2 = H$, $R_3 = Br$
6g; $R_1 = H$, $R_2 = H$, $R_3 = NO_2$
6h; $R_1 = OCH_3$, $R_2 = H$, $R_3 = H$
6i; $R_1 = OCH_3$, $R_2 = H$, $R_3 = CH_3$
6j; $R_1 = OCH_3$, $R_2 = H$, $R_3 = OCH_3$
6k; $R_1 = OCH_3$, $R_2 = Cl$, $R_3 = H$
6l; $R_1 = OCH_3$, $R_2 = H$, $R_3 = Cl$
6m; $R_1 = OCH_3$, $R_2 = H$, $R_3 = Br$
6n; $R_1 = OCH_3$, $R_2 = H$, $R_3 = NO_2$

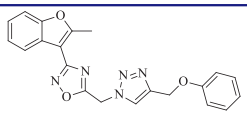
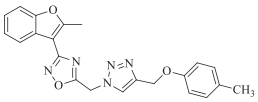
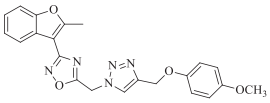
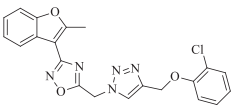
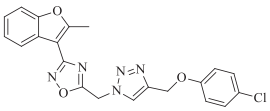
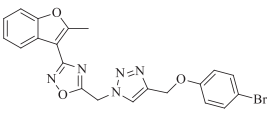
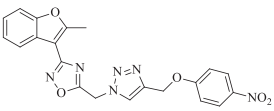
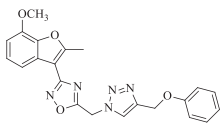
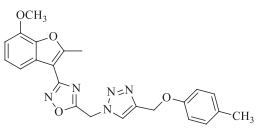
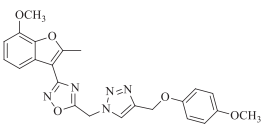
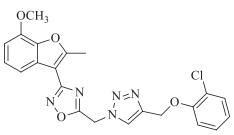
Scheme 2. Synthesis of compounds **6(a–n)**, reagents and conditions: (i) (a) NaN_3, DMF:H_2O (7:3), 70 °C, 1 h; (b) Sodium ascorbate, $CuSO_4.5H_2O$, rt, 1 h.

3-(2-methylbenzofuran-3-yl)-5-((4-(phenoxymethyl)-1H-1,2,3-triazole-1-yl)methyl)-1,2,4-oxadiazole derivatives (**6a–n**) with good yields (Scheme 2; Table 1).

Conclusion

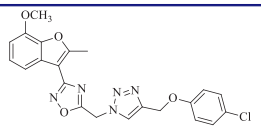
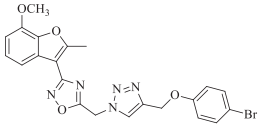
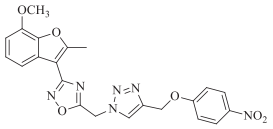
In conclusion, we established an efficient methodology for rapid and green synthesis of novel benzofuran-1,2,4-oxadiazole-1,2,3-triazole hybrids (**6a–n**) from 5-(chloromethyl)-3-(2-methylbenzofuran-3-yl)-1,2,4-oxadiazoles (**4a–b**) by *in situ* construction of

Table 1. Synthesis of 3-(2-methylbenzofuran-3-yl)-5-((4-(phenoxymethyl)-1H-1,2,3-triazole-1-yl)methyl)-1,2,4-oxadiazole derivatives (**6a–n**).

Entry	Product	Yield (%)	mp (°C)
6a		80	220–222
6b		78	217–219
6c		82	214–216
6d		76	221–223
6e		79	224–226
6f		83	228–230
6g		70	213–215
6h		82	213–215
6i		82	210–212
6j		85	216–218
6k		79	224–226

(*continued*)

Table 1. Continued.

Entry	Product	Yield (%)	mp (°C)
6l		86	227–229
6m		80	229–231
6n		74	223–225

5-(azidomethyl)-3-(2-methylbenzofuran-3-yl)-1,2,4-oxadiazoles followed by 1,3-dipolar cycloaddition with substituted-1-(prop-2-yn-1-yloxy)benzenes (**5a–g**) through Click reaction using DMF:H_2O (7:3). The reaction, with this catalyst was carried out under mild reaction conditions with good to excellent yields (70–86%). Further studies aimed at broadening the panel of application of these highly stable, active, inexpensive, heterogeneous and easily prepared heterogeneous metal catalysts are in progress.

General experimental methods

All solvents and reagents were obtained from commercial suppliers. All reactions were performed under nitrogen atmosphere unless otherwise noted. Column chromatography was performed using Merck silica gel 60–120 mesh. ^{1}H NMR and ^{13}C NMR spectra were recorded on bruker spectrometer at 400 MHz and 101 MHz, tetramethylsilane (TMS) as internal standard, chemical shift (δ) are reported in parts per million (ppm). Multiplicity (singlet (s), doublet (d), doublet of doublet (dd), triplet of doublet (td) and multiplet (m)) coupling constant (J in Hz). Mass spectral analysis was accomplished using electro spray ionization (ESI) techniques.

General procedure for synthesis of 3-(2-methylbenzofuran-3-yl)-5-((4-(phenoxymethyl)-1H-1,2,3-triazol-1-yl)methyl)-1,2,4-oxadiazole derivatives (6a–n)

Sodium azide (0.043 g, 0.663 mmol) was added to a stirred solution of 5-(chloromethyl)-3-(2-methylbenzofuran-3-yl)-1,2,4-oxadiazole (**4a**) (0.150 g, 0.603 mmol) in 5 mL of DMF: H_2O (7:3) stirred 70 °C for 1 h. The progress of reaction was monitored by TLC. After the completion of the reaction, reaction mixture was cooled to room temperature then add (prop-2-yn-1-yloxy)benzene (**5a**) (0.079 g, 0.603 mmol), sodium ascorbate (0.02 mmol) and $CuSO_4.5H_2O$ (0.02 mmol) at room temperature stirred for 1 h. After the completion of the reaction. The reaction mixture was poured in ice cold water and extracted with ethyl acetate. Organic layer was separated and dried over anhydrous

Na_2SO_4 then filtered and evaporated. The crude compound was subjected to column purification with n-hexane in ethyl acetate (8:2) to yield compound (**6a**).

3-(2-Methylbenzofuran-3-yl)-5-((4-(phenoxymethyl)-1H-1,2,3-triazol-1-yl)methyl)-1,2,4-oxadiazole (6a)

Yield: 80%, Off white solid, mp: 220–222 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07–8.01 (m, 1H), 7.94 (s, 1H), 7.48–7.44 (m, 1H), 7.34–7.27 (m, 4H), 7.02–6.96 (m, 3H), 5.91 (s, 2H), 5.27 (s, 2H), 2.78 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.17, 164.75, 159.11, 158.07, 154.05, 145.54, 129.62, 125.82, 124.66, 123.75, 123.52, 121.57, 121.42, 114.73, 110.84, 103.79, 61.86, 45.24, 14.33. ESI-HRMS *m/z* calcd for $C_{21}H_{17}N_5O_3$ 388.1409 $[M+H]^+$, found 388.1404.

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