Microwave-assisted one-pot synthesis of novel Phenoxazine-[1,2,3] triazole hybrids and their biological evaluation

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Abstract

A copper-catalyzed one-pot synthesis of phenoxazine-[1,2,3]triazole derivatives from phenoxazine with different aryl azides via an in situ generated 10-(prop-2-yn-1-yl)-10H-phenoxazine intermediate in DMF under microwave irradiation is reported. The reaction provided the desired phenoxazine-[1,2,3]triazole in good to excellent yields. The in vitro cytotoxic examination results revealed that compounds 2d and 2i exhibited good anti-proliferative activity against two cancer cell lines, MCF-7 and HeLa with IC_{50} values ranging from 18.17 ± 0.5 μM to 22.44 ± 0.3 μM which are comparable to the standard drug doxorubicin (2.61 ± 0.2 and 1.23 ± 0.08 μM).

The remaining compounds have shown good to moderate activity against the tested cell lines. In vitro antibacterial results revealed that the compounds 2b and 2i were found to possess an excellent broad spectrum of inhibiting potency against all the tested bacterial strains with minimum inhibitory concentration values ranging from 3.125 to 25 μg mL^{-1}.

Keywords: Phenoxazine, 1,2,3-triazole, MWI, Anticancer activity, Antibacterial activity.

Introduction

The world population has suffered from infectious diseases due to the pathogens resistant to multiple drugs against artificial antibiotics. Among them, bacterial infections due to their rapid spread, toxicity and resistance to existing antibiotics are the second most important diseases in the world after cardiovascular disease.[1] The importance of phenoxazines in biological systems has attracted great interest due to their medicinal and pharmacological characteristics.

Many compounds containing the phenoxazine group have found widespread biological activities including antitumor,[2] antiproliferative,[3] antiviral,[4] antimallaria,[5] antimicrobial.[6] For example, the phenoxazine derivative 2-amino-4,4α-dihydro-4α, 7-dimethyl-3H-phenoxazine-3-one prepared by the reaction of 2-amino-5-methylphenol with bovine hemolysates was reported by Shimmamoto et al[2] to inhibit proliferation and induce apoptosis in human leukemia cell lines K562, HL-60 and HAL-01 in a dose-dependent manner.

Kohno et al[7] have reported 2-amino-3H-phenoxazin-3-one having anti-inflammatory and immune regulatory properties, thus providing a promising therapeutic strategy for the treatment of inflammatory autoimmune disease mediated by T cells, as well as chronic inflammatory disease induced by bacteria.

Likewise, the importance of 1,2,3-triazoles in biological systems has attracted great interest due to their medicinal and pharmacological characteristics.[8-18] Many compounds that contain 1,2,3-triazole moiety have found widespread biological activities including antimicrobials, anticancer agents, antioxidants, anti-HIV, antiinflammatories, antiprotozoals, anticonvulsants, antihistamines and antitubercular properties. Such compounds have also been described as selective β3 adrenergic receptor agonists, kinase inhibitors and other enzyme inhibitors.[19] The present study was conducted to synthesize the highly functionalized active compounds using the two phenoxazine and 1,2,3-triazole pharmacophores to improve the biological activities in the pharmaceutical compounds.

Material and Methods

All reagents and solvents were purchased from Aldrich and Merck and used without further purifications. IR spectra were recorded on a PerkinElmer BX series FT-IR spectrometer in KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance spectrometer (400 and 100 MHz, respectively) in $CDCl_3$ with TMS as internal standard. Mass spectra were recorded on a Jeol JMC-300 spectrometer (ESI, 70 eV). Elemental analyses were performed on Carlo Erba 106 and PerkinElmer model 240 analyzers. Melting points were determined using a Cintex apparatus and are uncorrected. TLC performed using Merck silica gel 60 F254 precoated plates (0.25 mm), silica gel (100–200 mesh) was used for column chromatography. The progress of the reactions as well as purity of the compounds were monitored by TLC, eluent EtOAc–hexane.

Synthesis of 10-((1-(aryl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenoxazine (General method). CuI (10 mol %) was added to a solution of phenoxazine (1) (0.001 mol), propargyl bromide (0.0013 mol), aryl azide (0.0015 mol), t-BuOK (0.002 mol) and DMF (10 mL) in a microwave reactor vessel (30 ml). The mixture was heated at 100 ˚C for

30 min. Progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was extracted with EtOAc (2×15 ml). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. The Na_2SO_4 was filtered off and the residue ionic liquid was washed with water and reused for the further reactions. The crude products were purified by column chromatography, eluent EtOAc–hexane, 2:3.

10-((1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenoxazine(2a) : White solid (89%), mp 188–190 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ : 8.21-8.12 (m, 1H), 8.10-8.09 (m, 1H), 7.80 (s, 1H, triazole), 7.70 (s, 1H), 7.62-7.50 (m, 2H), 7.44-7.34 (m, 2H), 7.33-7.23 (m, 2H), 7.22-7.15 (m, 1H), 7.05-6.95 (m, 2H), 5.61 (s, 2H, N-CH_2), 3.84 (s, 3H, O-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.8, 140.9, 137.7, 133.4, 132.9, 125.1, 123.6, 123.3, 122.5, 121.9, 121.7 116.4, 114.7, 55.6, 45.1. IR (υ, cm^{-1}): 3153, 3011, 1580, 1464, 1278, 1127, 783. ESI-MS m/z: 371 [M+H]. Anal. Cal for $C_{22}H_{18}N_4O_2$: C, 71.34; H, 4.90; N, 15.13; found: C, 71.39; H, 4.83; N, 15.08.

10-((1-(3,5-dimethylphenyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenoxazine (2b) : Pale yellow solid (81%), mp 182–184 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ : 8.20-8.15 (m, 1H), 8.11-8.07 (m, 1H), 7.72 (s, 1H, triazole), 7.64-7.56 (m, 1H), 7.55-7.47 (m, 1H), 7.40-7.20 (m, 6H), 7.04 (s, 1H), 5.62 (s, 2H, N-CH_2), 2.35 (s, 6H, Ar-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ : 145.5, 136.3, 129.9, 127.9, 125.2, 121.5, 119.2, 117.5, 114.8, 45.6, 20.7. IR (υ, cm^{-1}): 3139, 2941, 1583, 1462, 1274, 1164, 754. ESI-MS m/z: 369 [M+H]. Anal. Cal for $C_{23}H_{20}N_4O$: C, 74.98; H, 5.47; N, 15.21; found: C, 74.90; H, 5.55; N, 15.25.

10-((1-(2,3-dimethylphenyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenoxazine (2c) : White solid (78%), mp 151–153 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ : 8.20-8.10 (m, 2H), 7.80 (s, 1H, triazole), 7.70-7.35 (m, 5H), 7.30-6.95 (m, 4H), 5.64 (s, 2H, N-CH_2), 2.64 (s, 3H, Ar-CH_3), 2.31 (s, 3H, Ar-CH_3). IR (υ, cm^{-1}): 3180, 2923, 1603, 1581, 1474, 1266, 1158,753. ESI-MS m/z: 369 [M+H]. Anal. Cal for $C_{23}H_{20}N_4O$: C, 74.98; H, 5.47; N, 15.21; found: C, 74.91; H, 5.54; N, 15.26.

10-((1-(3,5-dichlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenoxazine (2d) : Yellow solid (73%), mp 211–213 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ : 8.20-8.12 (m, 2H), 7.80 (s, 1H, triazole), 7.60-7.50 (m, 4H), 7.40-7.30 (m, 6H), 5.64 (s, 2H, N-CH_2). IR (υ, cm^{-1}): 3090, 2927, 1608, 1585, 1475, 1269, 1153,752. ESI-MS m/z: 409 [M+H]. Anal. Cal for $C_{21}H_{14}Cl_2N_4O$: C, 61.63; H, 3.45; N, 13.69; found: C, 61.68; H, 3.49; N, 13.62.

10-((1-(4-butylphenyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenoxazine (2e) : White solid (69%), mp 157–159 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ : 8.20-8.13 (m, 2H), 7.72 (s, 1H, triazole), 7.63-7.51 (m, 4H), 7.41-7.25 (m, 6H), 5.64 (s, 2H, N-CH_2), 2.65 (t, J= 7.6 Hz, 2H, Ar-CH_2-CH_2-CH_2-CH_3), 1.70-1.40 (m, 4H, Ar-CH_2-CH_2-CH_2-CH_3), 0.93 (t, J= 7.3 Hz, 3H, Ar-CH_2-CH_2-CH_2-CH_3). IR (υ, cm^{-1}): 3161, 2987, 1589, 1472, 1257, 1163,736. ESI-MS m/z: 397 [M+H]. Anal. Cal for $C_{25}H_{24}N_4O$: C, 75.73; H, 6.10; N, 14.13; found: C, 75.77; H, 6.19; N, 14.18.

10-((1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenoxazine (2f) : Pale yellow solid (71%), mp 161–163 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ : 8.10-7.95 (m, 2H), 7.94 (s, 1H, triazole), 7.63- 7.40 (m, 7H), 7.30-7.20 (m, 3H), 5.78 (s, 2H, N-CH_2). IR (υ, cm^{-1}): 3150, 3028, 1578, 1431, 1044. ESI-MS m/z: 420 [M+2H]. Anal. Cal for $C_{21}H_{15}BrN_4O$: C, 60.16; H, 3.61; N, 13.36; found: C, 60.12; H, 3.68; N, 13.31.

10-((1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenoxazine (2g) : Yellow solid (70%), mp 191–193 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ : 8.54-8.53 (m, 1H), 8.27-8.24 (m, 1H), 7.87 (s, 1H, triazole), 7.71- 7.67 (m, 1H), 7.16- 7.14 (m, 2H), 7.10- 7.08 (m, 2H), 6.95- 6.91 (m, 2H), 6.83- 6.81 (m, 2H), 5.31 (s, 2H, N-CH_2). IR (υ, cm^{-1}): 3130, 3093, 2957, 1588, 1476, 1263, 1151,752. ESI-MS m/z: 386 [M+H]. Anal. Cal for $C_{21}H_{15}N_5O_3$: C, 65.45; H, 3.92; N, 18.17; found: C, 65.41; H, 3.96; N, 18.13.

10-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)-10H-phenoxazine (2h) : Yellow solid (70%), mp 161–163 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ : 8.18-8.13 (m, 1H), 8.10-8.04 (m, 1H), 7.87 (s, 1H, triazole), 7.71- 7.67 (m, 1H), 7.16- 7.16 (m, 2H), 7.10- 7.08 (m, 2H), 6.91- 6.90 (m, 2H), 6.83- 6.81 (m, 2H), 5.36 (s, 2H, N-CH_2). IR (υ, cm^{-1}): 3142, 3014, 1589, 1457, 1219, 1037, 689. ESI-MS m/z: 341 [M+H]. Anal. Cal for $C_{21}H_{16}N_4O$: C, 74.10; H, 4.74; N, 16.46; found: C, 74.19; H, 4.78; N, 16.49.

10-((1-(4-chloro-3,5-dimethoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenoxazine (2i) : White solid (66%), mp 213–215 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ : 8.20-8.15 (m, 1H), 8.11-8.07 (m, 1H), 7.72 (s, 1H, triazole), 7.64-7.56 (m, 1H), 7.50-7.40 (m, 1H), 7.40-7.20 (m, 5H), 7.04 (s, 1H), 5.32 (s, 2H, N-CH_2), 3.931 (s, 3H, O-CH_3), 3.689 (s, 3H, O-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ : 149.5, 144.4, 144.3, 127.3, 127.1, 124.1, 124.1, 123.2, 122.8, 115.5, 115.1, 108.9, 56.9, 56.6, 45.0. IR (υ, cm^{-1}): 3151, 2987, 1582, 1457, 1225, 1044, 694. ESI-MS m/z: 444 [M+H]. Anal. Cal for $C_{23}H_{19}ClN_4O_3$: C, 63.52; H, 4.40; N, 12.88; found: C, 63.48; H, 4.46; N, 12.93.

10-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenoxazine (2j) : Yellow solid (77%), mp 188–190 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ : 8.18-8.11 (m, 2H), 7.72 (s, 1H, triazole), 7.63-7.50 (m, 4H), 7.40-7.20 (m, 6H), 5.61 (s, 2H, N-CH_2). IR (υ, cm^{-1}): 3151, 3021, 2920, 1600, 1472, 1254, 1161,759. ESI-MS m/z: 374 [M+H]. Anal. Cal for $C_{21}H_{15}ClN_4O$: C, 67.29; H, 4.03; N, 14.95; found: C, 67.22; H, 4.06; N, 14.87.

10-((1-(3-chlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenoxazine (2k) : Yellow solid (70%), mp 187–189 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ : 8.10-7.98 (m, 2H), 7.83 (s, 1H, triazole), 7.80- 7.20 (m, 10H), 5.78 (s, 2H, N-CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ : 145.1, 138.5, 135.1, 134.5, 133.1, 131.2, 129.8, 125.7, 122.6, 121.3, 120.5, 116.4, 44.1. IR (υ, cm^{-1}): 3141, 3022, 1589, 1436, 1039. ESI-MS m/z: 374 [M+H]. Anal. Cal for $C_{21}H_{15}ClN_4O$: C, 67.29; H, 4.03; N, 14.95; found: C, 67.27; H, 4.07; N, 14.88.

In vitro* anti cancer activity*: All synthesized compounds were evaluated for their cytotoxic *in vitro* activity against two different cancer cell lines such as breast cancer cell line (MCF-7) and cervical carcinoma cell line (HeLa). All the cancer cell lines used in this research work were obtained from the National Centre for Cell Sciences (NCCS), Pune, India. Cell viability in the presence of the test samples was measured by MTT microcultured tetrazolium assay. This assay is a quantitative colorimetric method for determining cell cytotoxicity. The assessed parameter is the metabolic activity of living cells. Metabolically active cells reduce bleached yellow tetrazolium salt (MTT) to a dark blue water-insoluble formazan which can be quantified directly after solubilization with DMSO. The absorbance of the formazan directly correlates with the number of viable cells.

MCF- 7 and HeLa were plated into a 96-well plate at a density of 1x10^4 cells/well. Cells were grown overnight in the full medium and then switched to the low serum media. DMSO was used as control. After 48 h of treatment with different concentrations of test compounds, the cells were incubated with MTT (2.5 mg/mL) in the CO_2 chamber for 2h. The medium was then removed and 100 µL of DMSO was added into each well to dissolve formazan crystals. After thoroughly mixing, the plates were read at 570 nm for optical density, which is directly correlated with cell quantity. The results were represented as percentage of cytotoxity/viability. All the experiments were carried out in triplicate. The IC_{50} values were calculated from the percentage of cytotoxicity and compared with the reference drug doxorubicin.

Antibacterial activity: All the synthesized compounds were screened for their *in vitro* antibacterial activity against the two gram-positive and two gram-negative micro-organisms by agar well diffusion method. Streptomycin was used as a standard drug. Serial dilutions of the test compounds as well as standards were performed at concentrations ranging from 150 to 0.97 mg mL^{-1} in a 200 mL culture medium final volume.

Afterwards each well was seeded with a 50 *u*L microbial suspension of 0.5 MacFarland densities. In each test, a microbial culture control and a sterility control (negative) were performed. The plates were incubated for 24 h at 37 ^{o}C. The lowest concentration which inhibited the visible microbial growth was considered the MIC.

Results and Discussion

The synthesis of phenoxazine-[1,2,3]triazole (2a–k) derivatives is outlined in scheme 1. One-pot synthesis of phenoxazine containing 1,2,3-triazole derivatives was performed according to the literature procedure.[20] 1,3-dipolar cycloaddition of phenoxazine (1) with propargyl bromide and different aryl azides in the presence of CuI and t-BuOK in DMF under microwave irradiation yielded 1,4-disubstituted 1,2,3-triazoles. The structures of the newly synthesized compounds 2a-k were confirmed by analytical and spectral data (^{1}H NMR, ^{13}C NMR, ESI-MS) and elemental (CHN) analysis. The structure of the intermediate was confirmed by the spectral (IR, ^{1}H NMR, ^{13}C NMR and EI-MS) studies and elemental analysis (C, H and N).

In the IR spectrum of 2a, the appearance of a broad absorption band and sharp bands at 3153, 1580 and 1464 cm^{-1} are ascribed to C-H (triazole), –C=N and –C=C stretching frequencies respectively. The peaks observed at δ 7.80 (s, 1H, triazole), 8.21–6.95 (m, 12H, Ar-H) in ^{1}H NMR spectrum, the presence of carbon signals at 159.8 ppm (*C*-OCH_3), 140.9 ppm (N=C-N), 55.6 (O-CH_3), 45.1 (N-CH_2) in ^{13}C NMR spectrum and [M+H] ion peak observed at m/z 371 in EI-MS well established the structure of compound 2a. The elemental analysis (C, H and N) data (C, 71.39; H, 4.83; N, 15.08.) confirmed the purity of compound 2a.

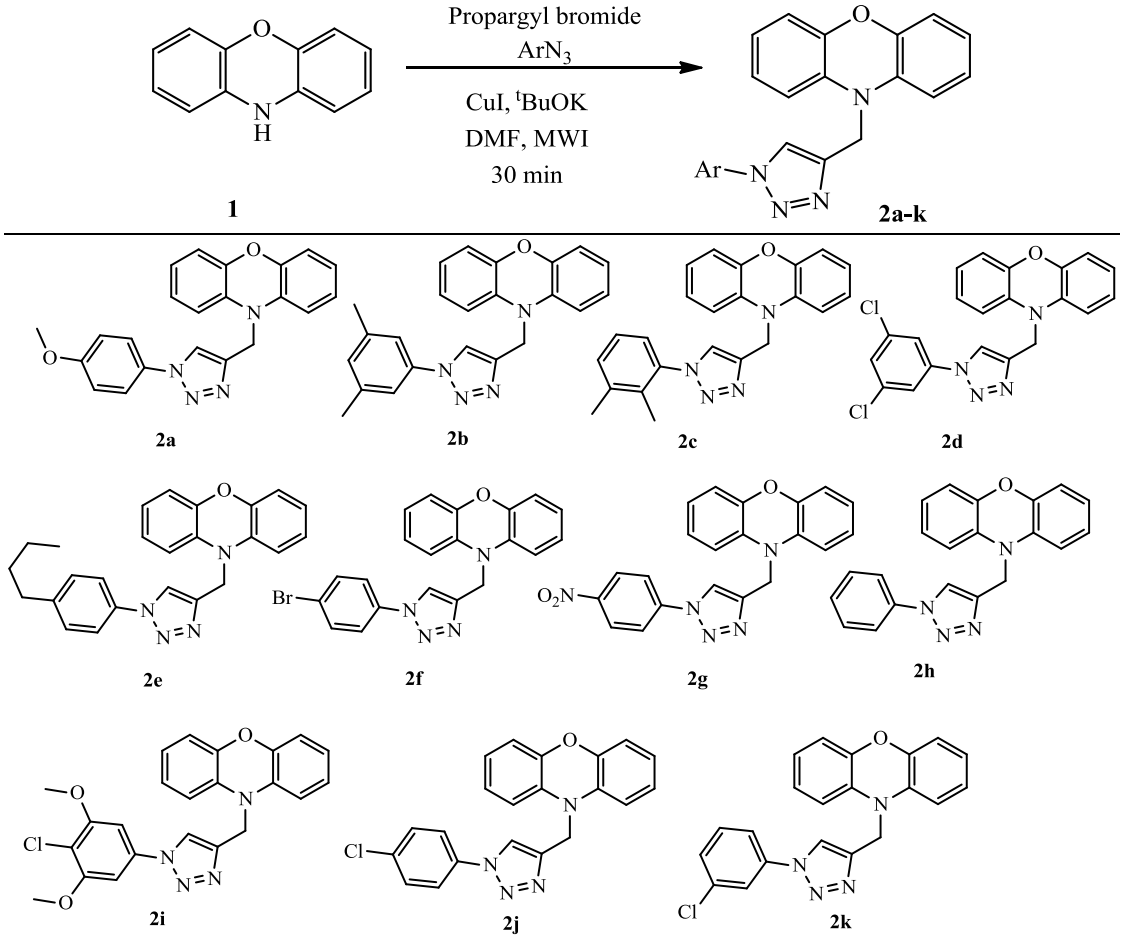
***In vitro* proliferative activity:** An *in vitro* cytotoxic activity assay was performed against cultures of human cells such as MCF-7 (breast) and HeLa (cervical) using the microcultivated tetrazolium assay MTT.[21] The IC_{50} values corresponding to the concentration required for a 50% inhibition. % of the cell viability of compounds (2a-2k) were presented in (Table 1). The results of detection of cytotoxic activity in vitro revealed that compound 2i has shown a broad spectrum activity against three MCF-7 and HeLa cell lines with IC_{50} values of 20.11 ± 1.0 and 21.02 ± 0, 7 μM respectively; HeLa and MCF-7 with IC_{50} values of 18.17 ± 0.5 and 22.44 ± 0.3 μM respectively.

Similarly, compound 2b has shown good activity against MCF-7 (IC_{50}: 26.41 ± 0.8 μM) and moderate activity against HeLa (IC_{50}: 31.17 ± 0.5 μM). Compounds 2j have shown good activity against HeLa with an IC_{50} value of 24.17 ± 0.8 μM. The rest of the compounds have shown moderate activity with IC_{50} values ranging from 30.49 ± 1.1 to 131.24 ± 1.7 μM.

Antibacterial activity: All the synthesized compounds were examined for their antibacterial activity *in vitro* against two gram-positive bacteria such as *Staphylococcus aureus* and *Bacillus subtilis* and two gram-negative bacteria such as *Escherichia coli* and *Proteus vulgaris.* Streptomycin was used as a standard drug (positive control) for comparison. The minimum inhibitory concentrations (MIC = lower concentration that inhibit visible microbial growth) for synthesized compounds 2a-2k were determined (Table 2) by the broth dilution method recommended by the European

Society of Clinical Microbiology and Infectious Diseases (ESCMID).[22,23]

The antibacterial activity screening results revealed that compound 2i has shown excellent inhibition against *S. aureus* and *B. Subtilis* with MIC values 3.125 μgmL^{-1} and moderate activity against *E. coli* and *P. vulgaris* with MIC values 12.5 and 6.25 μgmL^{-1} respectively. Similarly, compound 2b against *S. aureus* has shown good inhibition with MIC values 3.125 μgmL^{-1} and moderate activity against *E. coli* and *P. vulgaris* with MIC values 12.5 and 6.25 μgmL^{-1} respectively.



Scheme 1: Microwave-assisted one-pot synthesis of novel Phenoxazine-[1,2,3]triazoles

Table 1
Cytotoxic activity of potential Phenoxazine derived 1,2,3-triazole derivatives (2a-2k) on human cancer cell lines [*in vitro*[a] (IC_{50} μM/mL)]

S.N.	Product	MCF-7	HeLa
1	2a	30.49 ± 1.1	30.90 ± 0.6
2	2b	**26.41 ± 0.8**	31.17 ± 0.5
3	2c	38.19 ± 1.3	29.67 ± 1.1
4	**2d**	**22.44 ± 0.3**	**18.17 ± 0.5**
5	2e	69.47 ± 1.2	56.93 ± 1.5
6	2f	70.69 ± 1.0	76.64 ± 1.3
7	2g	110.69 ± 1.8	116.29 ± 1.3
8	2h	122.71 ± 1.3	131.24 ± 1.7
9	**2i**	**20.11 ± 1.0**	**21.02 ± 0.7**
10	2j	41.82 ± 1.0	**24.17 ± 0.8**
11	2k	68.08 ±1.3	70.54 ± 1.2
12	**Doxorubicin**	**2.61 ± 0.2**	**1.23 ± 0.08**

[a] Values are expressed as mean ± SEM. Cytotoxicity as IC_{50} for each cell line, is the concentration of compound which reduced by 50% the optical density of treated cells with respect to untreated cells using the MTT assay.

Table 2
***In vitro*, MICs of synthesized compounds 2a-2k**

Compound	MIC (µg/ml)			
	E.coli	***S.aureus***	***P.vulgaris***	***B.Subtilis***
2a	50	50	>100	>100
2b	**12.5**	**3.125**	**6.25**	25
2c	25	**12.5**	**12.5**	50
2d	25	50	50	25
2e	50	50	25	25
2f	>100	>100	>100	>100
2g	>100	>100	>100	>100
2h	>100	>100	>100	>100
2i	**12.5**	**3.125**	**6.25**	**3.125**
2j	>100	>100	>100	>100
2k	>100	>100	>100	>100
Streptomycin	**6.25**	**6.25**	**3.125**	**6.25**

Conclusion

In conclusion, a novel series of phenoxazine-[1,2,3]triazole derivatives (2a-2i) was synthesized by using copper-catalyzed [3+2]cycloaddition of *in situ* generated 10-(prop-2-yn-1-yl)-10H-phenoxazine and aryl azides in a one pot method under microwave irradiation. In this pure reaction, 1,2,3-triazole derivatives were synthesized as preferred target products. The advantages of this process include high yields, easy processing and short reaction times. The newly synthesized compounds (2a-2k) were screened for their *in vitro* anti-cancer and antibacterial activities. The compounds 2d and 2i have shown better cytotoxic activity than the remaining compounds as compared with the standard drug doxorubicin.

Similarly, the compounds 2b and 2i were found to possess an excellent broad spectrum of inhibiting potency against all the tested bacterial strains with minimum inhibitory concentration values ranging from 3.125 to 25 μg mL^{-1}. The result of this activity suggests that it can generate a good modification in the structure and potent anticancer and good antibacterial agents can be generated with good efficacy.

References

1. Muroi H., Nihei K., Tsujimoto K. and Kubo I., Synergistic effects of anacardic acids and methicillin against methicillin resistant Staphylococcus aureus, *Bioorg. Med. Chem*., **12(3)**, 583-587 **(2004)**

2. Shimamoto T., Yamaguchi T., Sato K., Izumi R. and Tomoda A., Antitumor Effects of a Novel Phenoxazine Derivative on Human Leukemia Cell Lines in Vitro and in Vivo, *Clin. Cancer Rev*., **7(3)**, 704–708 **(2001)**

3. Prinz H., Chamasmani B., Vogel K., Böhm K.J., Aicher B., Gerlach M., Günther E.G., Amon P., Ivanov I. and Müller K., N-benzoylated phenoxazines and phenothiazines: synthesis, antiproliferative activity and inhibition of tubulin polymerization, *J. Med. Chem*., **54(12)**, 4247-4263 **(2011)**

4. Iwata A., Yamagushi I., Sato K., Izumi R. and Tomoda A., Antiviral Activity of 2-Amino-4, 4a-Dihydro-. 40-7-Dimethyl-3H-Phenoxazine-3-One on Poliovirus, *Yohoku J. Exp. Med*., **200**, 161-165 **(2013)**

5. Mizukawa Y., Ge J.F., Bakar M.A., Itoh I., Scheurer C., Wittlin S., Brun R., Matsuoka H. and Ihara M., Novel synthetic route for antimalarial benzo[a]phenoxazine derivative SSJ-183 and two active metabolites, *Bioorg. Med. Chem*., **22(14)**, 3749-3752 **(2014)**

6. Mickevičienė K., Baranauskaitė R., Kantminienė K., Stasevych M., Komarovska Porokhnyavets O. and Novikov V., Synthesis and Antimicrobial Activity of N-Substituted-β-amino Acid Derivatives Containing 2-Hydroxyphenyl, Benzo[b]phenoxazine and Quinoxaline Moieties, *Molecules*, **20(2)**, 3170-3189 **(2015)**

7. Kohno K., Miyake M., Sano O., Tanaka-Kataoka M., Yamamoto S., Koya-Miyata S., Arai N., Fujii M., Watanabe H., Ushio S., Iwaki K. and Fukuda S., Anti-inflammatory and immunomodulatory properties of 2-amino-3H-phenoxazin-3-one, *Biol. Pharm. Bull*. **31(10),** 1938-1945 **(2008)**

8. Narsimha S., Kumaraswamy B., Kumar N.S., Ramesh G., Narasimha R.Y. and Vasudeva R.N., One-pot synthesis of fused benzoxazino[1,2,3] triazolyl[4,5-c]quinolinone derivatives and their anticancer activity, *RSC Adv*., **6**, 74332-74339 **(2016)**

9. Narsimha S., Kumar T.R., Kumar N.S., Yakub S. and Reddy N.V., Synthesis and antibacterial activity of (1-aryl-1, 2, 3-triazol-4-yl) methyl esters of morpholine-3-carboxylic acid, *Med. Chem. Res*., **23**, 5321–5327 **(2014)**

10 Narsimha S., Kumar N.S., Swamy B.K., Reddy N.V., Althaf Hussain S.K. and Rao M.S., Indole-2-carboxylic acid derived mono and bis 1,4-disubstituted 1,2,3-triazoles: Synthesis, characterization and evaluation of anticancer, antibacterial and DNA-cleavage activities, *Bioorg. Med. Chem. Lett*., **26**, 1639–1644 **(2016)**

11. Reddy N.V., Kumar N.S., Narsimha S., Swamy B.K., Jyotsna T.S. and Reddy Y.N., Synthesis, characterization and biological evaluation of 7-substituted4-((1-aryl-1H-1,2,3-triazol-4-yl) methyl)-2H-benzo[b][1,4]oxazin3(4H)-ones as anticancer agents, *Med. Chem. Res.*, **25**, 1781–1793 **(2016)**

12. Reddy N.V., Narsimha S., Sudhakar L., Swamy B.K. and Althaf Hussain S.K., N,N′-(hexane-1,6-diyl)bis(N-((1-aryl/ alkyl-

1H-1,2,3-triazol-4-yl)methyl)-4-methyl benzene sulfonamide): Synthesis, antibacterial, antioxidant and DNA-cleavage activities, *Phosphorus, Sulfur Silicon Relat. Elem.*, **191(8)**, 1118-1122 **(2016)**

13. Kumar T.R., Narsimha S., Swamy B.K., Chary V.R., Estari M. and Reddy N.V., Synthesis, anticancer and antibacterial evaluation of novel (isopropylidene)uridine-[1,2,3]triazole hybrids, *J. Saudi Chem. Soc*., **21**, 795–802 **(2017)**

14. Swamy B.K., Narsimha S., Reddy N.V., Priyanka B., Rao M.S., Synthesis and antimicrobial evaluation of some novel thiomorpholine derived 1,4-disubstituted 1,2,3-triazoles, *J. Serb. Chem. Soc*., **81(3)**, 233–242 **(2016)**

15. Reddy N.V., Narsimha S., Swamy B.K., Lavudya S. and Thatipamula R.K., Synthesis, cytotoxic and antibacterial activities of 6bromobenzo[d]thiazol-2(3H)-one-[1,2,3] triazole hybrids, *Org. Commun*., **9(2)**, 32-41 **(2016)**

16. Swamy B.K., Narsimha S., Kumar T.R., Reddy Y.N. and Reddy N.V., Synthesis and Biological Evaluation of Novel Thiomorpholine 1,1-Dioxide Derived 1,2,3-Triazole Hybrids as Potential Anticancer Agents, *Chemistry Select*, **2**, 4001–4005 **(2017)**

17. Swamy B.K., Narsimha S., Kumar T.R., Reddy Y.N. and Reddy N.V., Synthesis and Biological Evaluation of (N-(3-methoxyphenyl)-4-((aryl-1H-1,2,3-triazol-4-yl)methyl) thiomorpholine-2-carboxamide 1,1-Dioxide Hybrids as Antiproliferative Agents, *Chemistry Select*, **2**, 9595–9598 **(2017)**

18. Narsimha S., Kumara S.B. and Vasudeva R.N., One-pot synthesis of novel 1,2,3-triazole-pyrimido[4,5-c] isoquinoline hybrids and evaluation of their antioxidant activity, *Synth. Commun*., **48(10)**, 1220–1226 **(2018)**

19. Holla B.S., Mahalinga M., Karthikeyan M.S., Poojary B., Akberali P.M. and Kumari N.S., Synthesis, characterization and antimicrobial activity of some substituted 1,2,3-triazoles, *Eur. J. Med. Chem*., **40**, 1173-1178 **(2005)**

20. Prasad A., Wim D., Valery V.F. and Erik V.E., A microwave-assisted click chemistry synthesis of 1,4-disubstituted 1,2,3-triazoles via a copper(I)-catalyzed three-component reaction, *Org. Lett*., **6(23)**, 4223-4225 **(2004)**

21. Denizot F. and Lang R., Rapid colorimetric assay for cell growth and survival, Modifications to the tetrazolium dye procedure giving improved sensitivity and reliability, *J. Immunol. Methods*, **89(2)**, 271-277 **(1986)**

22. Narsimha S., Kumaraswamy B. and Nagavelli V.R., Design, synthesis and biological evaluation of novel substituted imidazo[2,1-a]isoindole derivatives as antibacterial agents, *Syn. Commun*., **47(9)**, 928–933 **(2017)**

23. Swamy B.K., Narsimha S., Reddy N.V. and Rao M.S., Synthesis and biological evaluation of ss(3-arylisoxazol-5-yl)methyl 6-fluoro-4-oxo-4H-chro- mene-2-carboxylates as antioxidant and antimicrobial agents, *J. Serb. Chem. Soc*., **82(1)**, 1–12 **(2017)**.

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