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Paper

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Metal-free hypervalent iodine-mediated synthesis and biological evaluation of 2-[(3-aryl-isoxazol-5-yl)methoxy)]benzaldehydes

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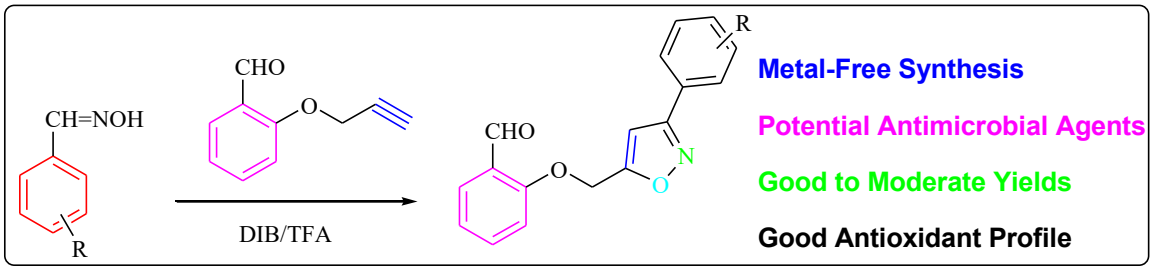
Abstract

A series of 2-[(3-aryl-isoxazol-5-yl)methoxy]benzaldehydes were synthesized through metal-free hypervalent iodine-mediated [3+2]-cycloaddition between 2-(2-propynyloxy)benzaldehyde and aldoximes. All new products were screened for their antibacterial activity against a number of gram-positive and -negative bacterial strains. Further, antifungal activity of these compounds was also evaluated against *C. albicans*. 2-[(3-(3-Tolyl-isoxazol-5-yl)methoxy)]benzaldehyde and 2-[(3-(3-fluorophenyl-isoxazol-5-yl)methoxy)benzaldehyde were found to be the most potent amongst all the synthesized compounds. Antioxidant properties were also evaluated by using DPPH radical scavenger method in which 2-[(3-(3-bromophenylisoxazol-5-yl)methoxy)benzaldehyde showed the highest antioxidant activity. All new products were also screened for their *in vitro* cytotoxicity against mouse fibroblast and plant cell germination cell lines.



Keywords: Metal-free, hypervalent iodine, [3+2]-cyclization, isoxazoles, antimicrobial activity, antioxidants

Introduction

Isoxazole and its derivatives have shown excellent range of biological activity and are well-known synthetic precursors for the synthesis of diverse new compounds. Besides, isoxazoles have been identified as excellent pharmacophores and are widely utilized as vital moiety in drug synthesis.[1-2] The extraordinary architectures associated with functionalized isoxazoles facilitate high-binding affinity to diverse targets or multiple receptors, which aids in the development of pioneering medications with new therapeutic applications. The chemistry of isoxazoles has led to the development of several potential lead compounds with antibacterial,[3] antifungal,[4] antioxidant,[5] antidepressant,[6] anticancer,[7] and antithrombotic activities,[8] etc. The core structure of isoxazoles is present in various marketed drugs e.g. parecoxib (COX2 inhibitor),[9] leflunomide (immunosuppressant agent),[10] muscimol ($GABA_A$),[11] valdecoxib (NSAID),[12] and sulfamethoxazole (antibiotic)[13] as shown in Figure 1. Besides, several daily use goods also contain isoxazole derivatives. The unique and diverse applications associated with these molecules make them ideal candidates for researchers to design and synthesize new compounds bearing isoxazole core structure. Therefore, chemists have always been interested in developing new synthetic pathways to synthesize isoxazole-containing compounds with a variety of medicinal and other benefits. A range of homogeneous as well as heterogeneous catalysts have been reported to access the functionalized isoxazoles.[14-21] Amongst the various synthetic routes, some synthetic methods are: (i) Pd-catalyzed Sonogashira coupling of acid chlorides with terminal alkynes, followed by the 1,3-dipolar cycloaddition with *in-situ* prepared nitrile oxides; (ii) ruthenium-catalyzed synthetic strategy for the synthesis of 3,4 disubstituted isoxazoles; (iii) copper-catalyzed 1,3-dipolar cycloaddition reactions; (iv) condensation, cyclo isomerization, and direct functionalization reactions. As the metal-catalyzed reactions are often associated with certain drawbacks, such as, high costs, toxicity, low abundance, etc., there is a huge demand for the development of new methods or the exploration of developed protocols to access the synthesis of isoxazoles under metal-free conditions. A comprehensive review highlighting the different metal-free synthetic routes to isoxazoles has been recently published by Das and Chanda.[22]

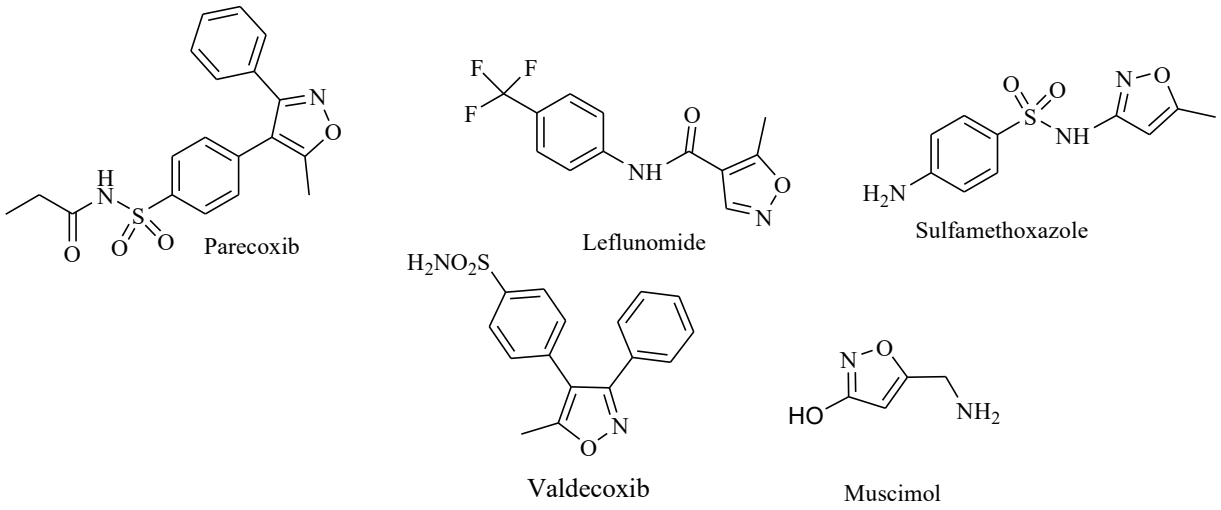


Figure 1. Structure of isoxazole-containing marketed drugs.

One of the most widely utilized synthetic protocols involve the 1,3-dipolar cycloaddition of alkynes as dipolarophiles and nitrile oxides as dipoles.[23] These [3+2]-cycloaddition reactions have been reported to undergo either through a pericyclic reaction *via* concerted mechanism[24] or *via* a step-by-step process involving

diradical formation.[25] Organohypervalent iodine compounds have been well-established oxidants to access diverse oxidative transformations under mild reaction conditions.[26-29] These compounds are excellent alternatives to transition metal reagents/catalysts. Some of the hypervalent iodine mediated oxidative transformations include oxidation of sulfides,[30] C-H functionalization,[31] oxidation of alcohols.[32] Construction of isoxazoles utilizes hypervalent iodine compounds like (diacetoxyiodo)benzene, [hydroxy(tosyloxy)iodo] benzene, iodosylbenzene, [bis(trifluoroacetoxy)iodo]benzene, etc.[33-38] Besides, synthesis of isoxazoles can also be efficiently achieved using only catalytic amount of hypervalent iodine in the presence of an appropriate terminal oxidant.[35-38] Aldoximes on treatment with hypervalent iodine generate nitrile oxides which undergo [3+2]-cycloaddition reaction with an alkyne to afford the corresponding isoxazole derivative. Certain synthetic methodologies developed by different researchers using hypervalent iodine are: di- and tri-substituted isoxazole derivatives by employing (diacetoxyiodo)benzene,[39] coumarin- and flavones based isoxazoles via a one-pot reaction of substituted benzaldehydes, hydroxylamine hydrochloride and *o*-propargyl coumarin/flavones,[40] synthesis of pyrrolo-isoxazoles utilizing 2-iodobenzoic acid in the presence of *m*-CPBA and triflic acid.[41] We recently reported a hypervalent iodine-mediated, metal-free route for the synthesis of a series of di- and trisubstituted pyrazole-tethered isoxazole derivatives in good yields; some of these compounds were associated with good antimicrobial and antioxidant activities.[42] Inspired by our previous results, we herein extend the scope of this study for the synthesis of 2-[(3-aryl-isoxazol-5-yl)methoxy]benzaldehydes (**1a-m**) and evaluated their biological activity. The present study describes the use of hypervalent iodine for the synthesis of 2-[(3-aryl-isoxazol-5-yl)methoxy]benzaldehydes (**1a-m**) (Figure 2) in 49-61% yields via *in-situ* generating nitrile oxides.

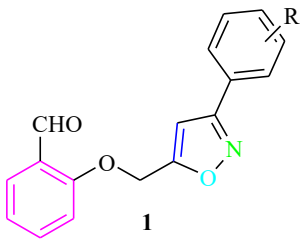


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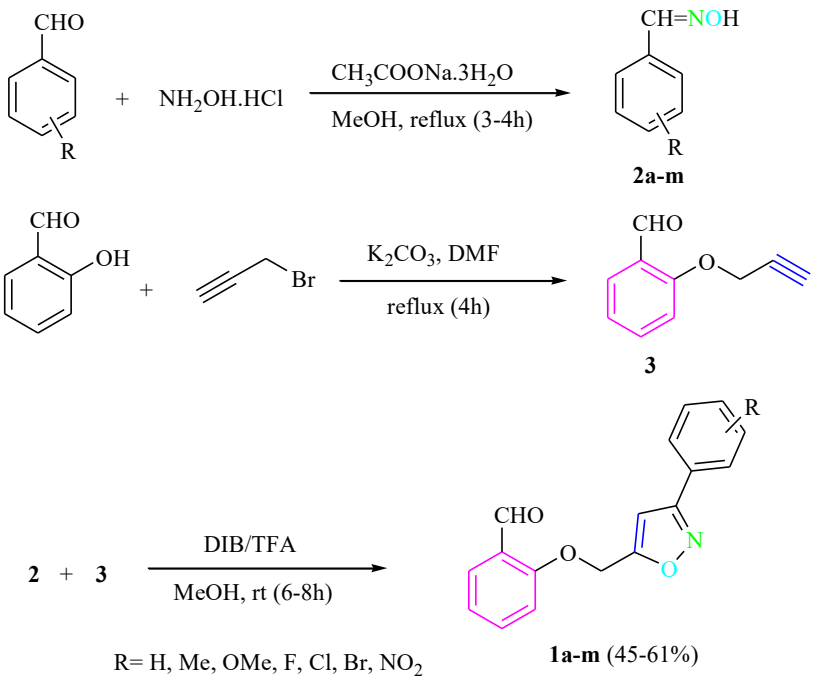
Figure 2. Structure of the title compounds, 2-[(3-aryl-isoxazol-5-yl)methoxy)]benzaldehydes (1a-m).

Results and Discussion

Chemistry

As discussed in the introductory section, hypervalent iodine can be effectively utilized for the [3+2]-cycloaddition of oximes with alkenes/alkynes to afford the corresponding isoxazoles. This synthetic approach was explored for the reaction of aldoximes **2a-m** with 2-(2-propynyloxy)benzaldehyde **(3)** for the synthesis of 2-[(3-aryl-isoxazol-5-yl)methoxy)] benzaldehydes (**1a-m**) (Scheme 1). Structures of these compounds were interpreted based on their spectral data viz., FTIR, ^{1}H NMR, ^{13}C NMR and HRMS. The present study was initiated with the reaction of benzaldehyde oxime **(2a)** and 2-(2-propynyloxy)benzaldehyde **(3)** in presence of (diacetoxy)iodobenzene (DIB) and trifluoroacetic acid (TFA) at room temperature using methanol as the solvent. The *in-situ* generated nitrile oxide by the reaction of oxime with DIB/TFA slowly dimerizes to form oxadiazole-N-oxide.[44] Hence, in order to minimize the possibility of dimerization, addition of DIB/TFA solution was carried out portion wise, so that the nitrile oxide can be captured by compound **3** to form the

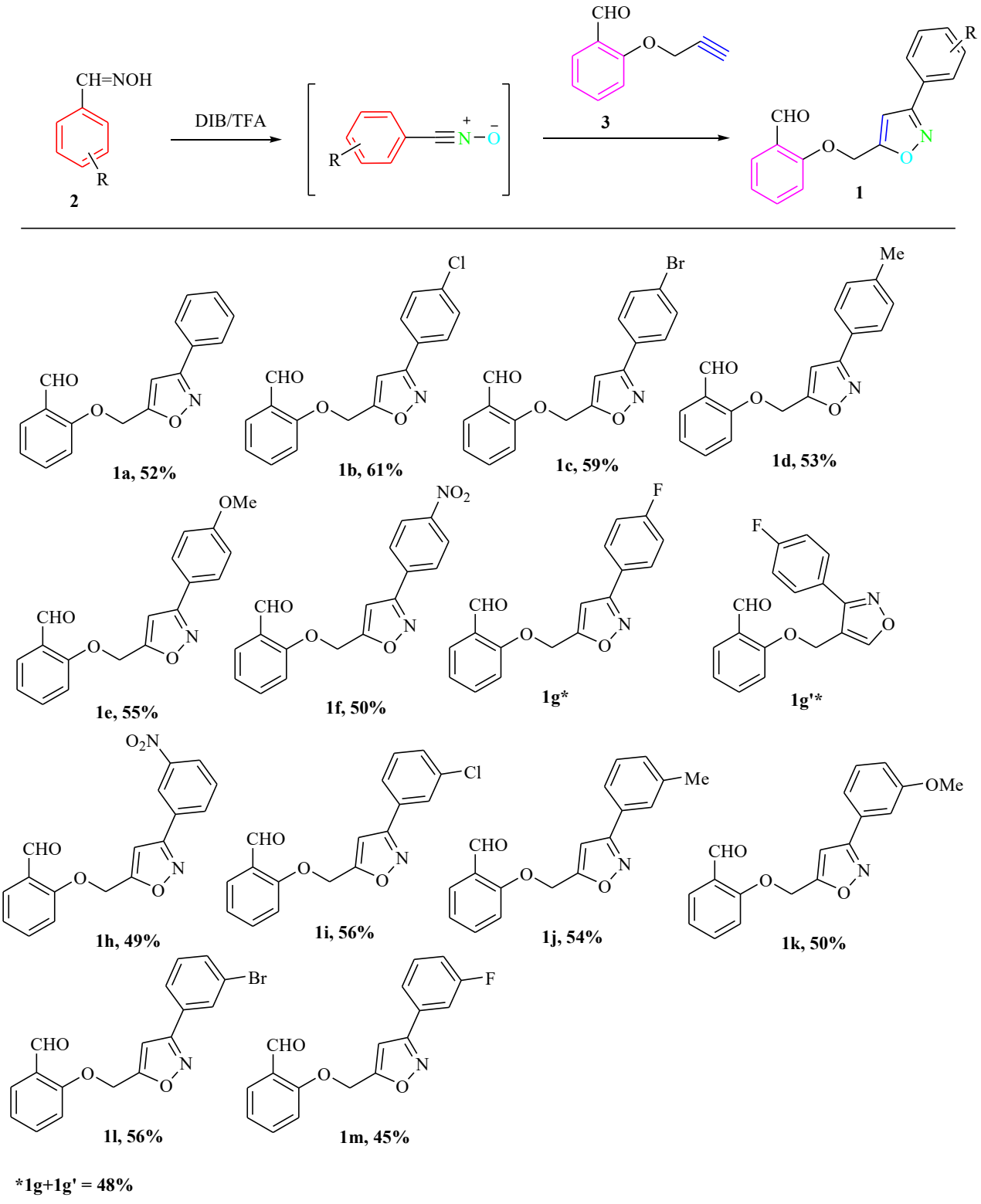
corresponding isoxazole ring **1**.



Scheme 1. DIB-mediated synthesis of 2-[(3-aryl-isoxazol-5-yl)methoxy]benzaldehydes (**1a-m**) through [3+2]-cycloadditon.

The structure of **1a** was confirmed by thoroughly analyzing its spectral data IR, ^{1}H NMR, ^{13}C NMR and HRMS. The IR spectra of **1a** showed a recognizable absorption band between 1620 cm^{-1} corresponding to C=N bond in the isoxazole moiety as well as the C=O bond of -CHO was detected at 1715 cm^{-1}. The formation of **1a** was confirmed by disappearance of the band at 2110 cm^{-1} corresponding to alkyne group. ^{1}H NMR spectra of **1a** showed a singlet at δ 6.694 ppm corresponding to C-H of isoxazole ring while one singlet at δ 5.340 for two protons confirmed the presence of –CH_2 group. In ^{13}C NMR the peak at δ 61.834 ppm appeared due to the carbon of –CH_2. The HRMS data showed *m/z* peak at 280.1019 corresponding to $[M+H]^+$. Using this approach, other isoxazoles **1b-m** bearing electron-donating and electron-withdrawing substituents were synthesized in 45-61% isolated yield by treating appropriate substituted aldoximes **2b-m** with 2-(2-propynyloxy)benzaldehyde **(3)** under similar reaction conditions (Table 1). All the title compounds were fully characterized by analyzing their spectral data. Substrate scope of the [3+2]-cycloaddition to afford title compounds **1a-m** are outlined in Table 1. The reaction led to the isolation of 2-[(3-aryl-isoxazol-5-yl)methoxy)]benzaldehyde in each case, however, in case of aldoxime **2g** bearing 4-fluoro substituent, both the regioisomers **1g** and **1g'** were obtained. These regioisomers were obtained in 59:41 ratio. Aldoximes **2** needed for the synthesis were prepared by the reported procedure.[43] 2-(2-Propynyloxy)benzaldehyde **(3)** was synthesized by refluxing salicylaldehyde with propargylbromide for 4 hours in the presence of potassium carbonate and N,N'- dimethyl formamide (DMF) as solvent.[44]

Table 1. Substrate scope for DIB-mediated synthesis of **1**



Pharmacology

Antimicrobial Activity. All the synthesized compounds 1a-m were screened for antibacterial activity against three gram-positive bacteria (*Bacillus cereus ATCC 11770, Staphylococcus aureus ATCC 6538P*, *Listeria monocytogenes MTCC 657)* and four gram-negative bacteria (*Shigella flexneri ATCC9199, Pseudomonas aeruginosa ATCC 15442*, *Salmonella typhi MTCC 73309, Escherichia coli MTCC 733).* In addition, these

compounds were also evaluated for their antifungal activity against the fungal strain, *Candida albicans MTCC 183.* Results of antimicrobial study are shown in Table 2. Amoxycillin and fluconazole were taken as reference drugs for comparing the antibacterial and antifungal properties respectively. It was observed from the MIC values that all the synthesized compounds are either equivalent or better inhibitor than the standard drug, fluconazole, against pathogenic fungal strain *(C. albicans)*. Further, these compounds have MIC value equal to standard drug fluconazole (6.25) or two-fold MIC value (3.125). In case of antibacterial screening, compounds **1e, 1j, 1m** were found equipotent to amoxycillin against all the bacterial strains.

Table 2. MIC values (Minimum inhibitory concentration) of target compounds 1a-m against tested microbes[#]

Compound	Minimum inhibitory concentration (ug/mL)							
	P. aeruginosa	*E. coli*	*S. typhi*	*S. aureus*	*L. monocytogenes*	*B. cereus*	*S. flexneri*	*C. albicans*
1a	3.125	3.125	3.125	6.25	3.125	6.25	3.125	3.125
1b	6.25	3.125	3.125	3.125	3.125	3.125	6.25	6.25
1c	3.125	3.125	3.125	3.125	3.125	6.25	6.25	3.125
1d	6.25	3.125	3.125	3.125	3.125	6.25	6.25	3.125
1e	3.125	3.125	3.125	3.125	3.125	3.125	3.125	6.25
1f	3.125	6.25	3.125	3.125	6.25	6.25	3.125	3.125
1g	6.25	3.125	3.125	3.125	3.125	6.25	6.25	3.125
1h	3.125	3.125	6.25	3.125	3.125	3.125	3.125	6.25
1i	3.125	3.125	6.25	3.125	3.125	3.125	3.125	6.25
1j	3.125	3.125	3.125	3.125	3.125	3.125	3.125	3.125
1k	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25
1l	3.125	3.125	3.125	3.125	3.125	6.25	3.125	3.125
1m	3.125	3.125	3.125	3.125	3.125	3.125	3.125	3.125
Amoxycillin	3.125	3.125	3.125	3.125	3.125	3.125	3.125	0
Fluconazole	0	0	0	0	0	0	0	6.25

[#]Antimicrobial assay conditions are given in the supporting information, ref. SI [1]

Antioxidant Activity. Antioxidants can quench free radicals and protect living beings against damage caused by them. Isoxazole derivatives have been reported as versatile antioxidants. Keeping in view the antioxidant properties associated with isoxazoles, the antioxidant activity of the synthesized compounds **1a-m** was also evaluated in terms of %age radical scavenging activity (% RSA) values using 2,2-diphenyl-1-picrylhydrazyl (DPPH) method. For the comparative purposes, ascorbic acid was used as reference compound. Results of the antioxidant study are presented in Table 3. These results indicated that the synthesized compounds **1a-m** exhibited moderate to excellent antioxidant activity.

Table 3. Radical scavenging activity of the compounds **3a-m**[##]

Compound	Scavenging activity% (RSA)
1a	73.4
1b	45.34
1c	82.67
1d	82.35
1e	89.34
1f	79.65
1g	76.34
1h	84.21
1i	80.29
1j	79.13
1k	66.23
1l	93.24
1m	88.42
Ascorbic acid	96.78

[##]Assay conditions for the radical scavenging activity of the compounds are given in the supporting information, ref. SI [2]

Cytotoxic study. The assessment of cytotoxicity determines negative impacts of the compound in the *in vitro* study of cell lines. In order to ascertain the cytotoxicity of synthesized compounds **1a-m** against both plant and animal cell lines, the synthesized compounds were tested against mouse fibroblast cell line (animal cell line) and *Vigna radiata* (plant seed germination cell line) (Table 4). In cytotoxicity assessment, DMSO was taken as reference compound. These compounds **1a-m** were found safer towards both the examined cell lines.

Table 4. Percentage cell viability values of the compounds **1a-m**[†]

Compound	Mouse fibroblast cell line	Plant seed germination cell line
1a	97.23	100
1b	90.42	100
1c	89.18	99
1d	94.22	100
1e	95.10	95
1f	93.43	97
1g	84.32	99
1h	94.97	100
1i	94.23	96
1j	94	100
1k	90.34	100
1l	90.55	95
1m	91.87	97
DMSO control	23.12	70

[†]Assay conditions for the cytotoxic study of the compounds are given in the supporting information, ref. SI [3]

Conclusions

The present study demonstrates a successful extension of hypervalent iodine-mediated metal-free approach to access a series of 2-[(3-aryl-isoxazol-5-yl)methoxy]benzaldehydes (**1**). The targeted compounds have been synthesized in good to moderate yields with easy workup and purification. Further, the properties associated with the synthesized compounds indicated the utilization of these targets in synthetic as well as in medicinal chemistry. Some of the compounds showed excellent MIC values comparable to that of well-known marketed broad-spectrum drugs, amoxycillin and fluconazole. Besides, antioxidant profile of these compounds further enhances their potential from the pharmacological point of view.

Experimental Section

General. All the chemicals used in the synthesis were of analytical grade and procured from Sigma Aldrich and CDH and were used without further purification. Progress of each reaction was checked by thin layer chromatography (TLC), using (Merck) silica plates. A mixture of petroleum ether and ethyl acetate was used as eluent. Crude compounds were purified by recrystallisation using chloroform as solvent. Melting points were recorded with open glass capillaries in melting point apparatus. IR spectra were recorded using Perkin Elmer Spectrophotometer, Central Instrumentation Lab, J. C. Bose University of Science and Technology, YMCA,

Faridabad. ^{1}H and ^{13}C NMR were recorded on BrukerAvance Neo 500 MHz spectrometer taking TMS as internal standard at SAIF, Panjab University, Chandigarh. HRMS data was reported on Synapt XS HD Mass spectrometer at SAIF, Panjab University, Chandigarh.

Synthesis of 2-(2-Propynyloxy)benzaldehyde (3).[44] To a stirred solution of salicylaldehyde (0.600 g, 4.92 mmol), were added propargyl bromide (0.700 g, 5.90 mmol) and potassium carbonate (1.4g, 9.84 mmol) in *N,N'*-dimethylformamide (DMF, 20 ml). The resulting mixture was refluxed for 4h. The reaction mixture was cooled down to room temperature and was diluted with 10 ml of 5% aqueous sodium chloride solution. The resulting mixture was then extracted with diethyl ether (15mL×3). The organic layer was washed with 5% aqueous sodium chloride solution (15 mL). The organic layer on evaporation yielded pale yellow solid **3**; yield: 72%, M.pt. 67-68 ˚C (Lit. M.pt. 69-70 ˚C).

General procedure for the synthesis of 2-[(3-aryl-isoxazol-5-yl)methoxy]benzaldehydes (**1a-m**). To a solution of aldoxime (**2**, 1mmol) in 6mL methanol, 2-(2-propynyloxy)benzaldehyde (**3**, 0.120g, 0.75mmol) was added at room temperature. This reaction mixture was kept on stirring at room temperature. Thereafter, a solution of (diacetoxy)iodobenzene (DIB, 0.386g, 1.2mmol) and 2-3 drops trifluoroacetic acid (TFA) in 4mL methanol were added portionwise in 30 minutes. The reaction mixture was kept on stirring at room temperature till the completion of the reaction (6-8 h) as checked by TLC. Solvent was evaporated to get crude product which was recrystallized in chloroform to get pure 2-[(3-aryl-isoxazol-5-yl)methoxy]benzaldehydes (**1a-m)**.

2-[(3-Phenylisoxazol-5-yl)methoxy)]benzaldehyde (1a).[45] White solid; 52% yield, M.pt.146 ˚C, IR (KBr) (ν, cm^{-1}) 2735 (C-H), 1715 (C=O), 1620 (C=N), 1666 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ (ppm): 10.53 (d, J= 0.5Hz, 1H), 7.87-7.89 (dd, J_1 = 6.0 Hz, J_2=1.5Hz, 1H), 7.79-7.82 (m, 2H), 7.56-7.59 (m, 1H), 7.44-7.47 (m, 3H), 7.06-7.13 (m, 2H), 6.69 (s, 1H), 5.34 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ (ppm): 189.1, 167.4, 162.7,159.8, 135.9, 130.2, 129.1, 128.3, 126.8, 125.3, 122.1, 112.5, 101.7, 61.8; HRMS (ESI) *m/z* calcd for $C_{17}H_{13}O_3N$ $[M+H]^+$280.0974, found 280.1019.

2-[(3-(4-Chlorophenylisoxazol-5-yl)methoxy)]benzaldehyde (1b). White solid, 61% yield, M.pt. 168-170 ˚C, IR (KBr) (ν, cm^{-1}) 2735 (C-H), 1720 (C=O), 1625 (C=N), 1664 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ(ppm) 10.55 (d, J= 0.5Hz, 1H), 7.90-7.92 (dd, J_1 = 6.0 Hz, J_2 = 1.5Hz, 1H), 7.76-7.79 (m, 2H), 7.59-7.63 (m, 1H), 7.45-7.47 (m, 2H), 7.09-7.17 (m, 2H), 6.69 (s, 1H), 5.37 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ (ppm): 189.3, 167.4, 161.1, 159.6, 136.6, 135.8, 131.0, 129.8, 127.2, 126.8, 125.3, 122.4, 112.3, 100.8, 61.8; HRMS(ESI) *m/z* calcd for $C_{17}H_{12}O_3NCl$ $[M+H]^+$ 314.0584, found 314.0585.

2-[(3-(4-Bromophenylisoxazol-5-yl)methoxy)]benzaldehyde (1c). White solid, 59% yield, M.pt. 164 ˚C, IR (KBr) (ν, cm^{-1}) 2745 (C-H), 1716 (C=O), 1620 (C=N), 1664 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ (ppm) 10.52 (d, J= 0.5Hz, 1H), 7.88-7.89 (dd, J_1 = 6Hz, J_2 = 1.5Hz, 1H), 7.67-7.70 (m, 2H), 7.56-7.61 (m, 3H), 7.06-7.14 (m, 2H), 6.67 (s, 1H), 5.34 (s, 2H), ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ (ppm), 189.0, 167.9, 161.8, 159.8, 135.9, 132.2, 129.1, 128.2, 127.4, 125.4, 124.6, 122.1, 112.6, 101.5, 61.7. HRMS (ESI) *m/z* calcd for $C_{17}H_{12}O_3NBr[M+H]^+$ 358.0079, $[M+H+2]^+$ 360.0058, found 358.0055, 360.0099.

2-[(3-(4-Methylphenylisoxazol-5-yl)methoxy)]benzaldehyde (1d). White solid, 53% yield, M.pt 140-143˚C, IR (KBr) (ν, cm^{-1}) 2740 (C=H), 1710 (C=O), 1620 (C-N), 1666 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ(ppm): 10.53 (d, J= 0.5Hz, 1H), 7.87-7.89 (dd, J_1 = 6.0, J_2=1.5 Hz, 1H), 7.68-7.71 (m, 2H), 7.56-7.59 (m,1H), 7.26 (s, 1H), 7.06-7.13 (m, 2H), 6.66 (s, 1H), 5.33 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ (ppm) 189.2, 167.2, 162.6, 159.9, 140.5, 135.9, 129.6, 128.9, 126.5, 125.6, 125.4, 122.0, 112.7, 101.6, 61.8, 21.4; HRMS (ESI) *m/z* calcd for $C_{18}H_{15}O_3N$ $[M+H]^+$294.1130, found 294.1124.

2-[(3-(4-Methoxyphenylisoxazol-5-yl)methoxy)benzaldehyde (1e).[45] White solid; 55% yield, M.pt. 126-130 ˚C , IR (KBr) (ν, cm^{-1}) 2765 (C-H), 1714 (C=O), 1615 (C=N), 1667 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ (ppm);

10.46 (d, J= 0.5Hz, 1H), 7.80-7.82 (dd, J_1 = 6.0, J_2 = 1.5 Hz, 1H), 7.66-7.69 (m, 2H), 7.48-7.52 (m, 1H), 6.99-7.06 (m, 2H), 6.89-6.91 (m, 2H), 6.56 (s, 1H), 5.25 (s, 2H), 3.78 (s, 3H);^{13}C NMR (125 MHz $CDCl_3$,TMS) δ (ppm); 189.2, 167.0, 162.3, 161.1, 159.8, 135.9, 128.9, 128.2, 125.4, 122.0, 121.0, 114.3, 112.7, 101.4, 61.8, 55.3; HRMS(ESI) *m/z* calcd for $C_{18}H_{15}O_4N$ $[M+H]^+$ 310.1079, found 310.1098.

2-[(3-(4-Nitrophenylisoxazol-5-yl)methoxy)benzaldehyde (1f). Yellow solid, 50% yield, M.pt. 170-172 ˚C, IR (KBr) (ν, cm^{-1}) 2736 (C-H), 1735 (C=O), 1623 (C=N), 1658(C=C); ^{1}H NMR (500 MHz, DMSO, TMS) δ (ppm); 10.47 (d, J= 0.5Hz, 1H), 8.36-8.39 (m, 2H), 8.20-8.23 (m, 2H), 7.70-7.77 (m, 2H), 7.41-7.43 (m, 1H), 7.48 (s, 1H), 7.16-7.19 (m, 1H), 5.60 (s, 2H); ^{13}C NMR (125 MHz, DMSO, TMS) δ (ppm) : 189.0, 169.0, 159.5, 136.2, 134.1, 127.9, 127.7, 124.5, 124.2, 121.7, 113.9, 102.4, 61.4; HRMS (ESI) *m/z* calcd for $C_{17}H_{12}O_5N_2$ $[M+H]^+$325.0824, found 325.1812.

2-[(3-(4-Fluorophenylisoxazol-5-yl)methoxy)benzaldehyde (1g and 1g'). White solid, 48% yield, M.pt.156 ˚C, IR (KBr) (ν, cm^{-1}) 2735 (C-H), 1726 (C=O), 1620 (C=N), 1636 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ (ppm) 10.45 (d, J= 1Hz, 1H CHO one isomer), 10.37 (s, 1H CHO second isomer), 7.80-7.82 (dd, J_1 = 6.0, J_2 = 1.5 Hz, 1H), 7.71-7.76 (m, 5H), 7.44-7.53 (m, 2H), 6.96-7.10 (m, 8H), 6.58 (s, 1H), 6.58 (s, 1H), 5.26 (s, 2H), 5.27 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 189.1, 187.7, 167.6, 167.0, 165.0, 164.9, 163.0, 162.9, 161.7, 161.7, 159.8, 158.2, 135.9, 135.4, 129.0, 128.8, 128.8, 128.6, 127.9, 126.3, 125.4, 124.7, 124.7, 124.6, 123.6, 122.1, 116.2, 116.2, 116.1, 116.0, 114.3, 112.6, 101.8, 101.5, 62.0, 61.8; HRMS (ESI) *m/z* calcd for $C_{17}H_{12}O_3NF$ $[M+H]^+$ 298.0879, found 298.0918.

2-[(3-(3-Nitrophenylisoxazol-5-yl)methoxy)benzaldehyde (1h). Yellow solid, 49% yield, M.pt.162-165 ˚C, IR (KBr)(ν, cm^{-1}) 2735 (C-H), 1722 (C=O), 1620 (C=N), 1656 (C=C); ^{1}H NMR (500 MHz, DMSO , TMS) δ (ppm); 10.48 (d, J= 0.5Hz, 1H), 8.68-8.69 (m, 1H), 8.36-8.39 (m, 2H), 7.83-7.86 (m, 1H), 7.70-7.77 (m, 2H), 7.41-7.43 (m, 1H), 7.16-7.19 (m, 1H), 5.59 (s, 2H); ^{13}C NMR (125 MHz, DMSO, TMS) δ (ppm); 189.0, 168.9, 160.4, 159.6, 148.2, 136.2, 132.8, 130.7, 129.6, 127.7, 124.8, 124.5, 121.6, 121.0, 113.9, 102.2, 61.4; HRMS (ESI) *m/z* calcd for $C_{17}H_{12}O_5N_2$ $[M+H]^+$ 325.0824, found 325.0844.

2-[(3-(3-Chlorophenylisoxazol-5-yl)methoxy)benzaldehyde (1i). White solid, 56% yield, M.pt.152 ˚C, IR (KBr) (υ,cm^{-1}) 2742 (C-H), 1715 (C=O), 1627 (C=N), 1662 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ (ppm) 10.52 (d, J= 0.5Hz, 1H), 7.87-7.89 (dd, J_1 = 6.0Hz, J_2 = 1.5 Hz, 1H), 7.80-7.81 (m, 1H), 7.68-7.70 (m, 1H), 7.56-7.60 (m, 1H), 7.38-7.44 (m, 2H), 7.06-7.14 (m, 2H), 6.68 (s, 1H), 5.34 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ(ppm) 189.2, 167.9, 161.5, 159.7, 135.9, 135.1, 130.3, 130.2, 129.0, 126.9, 125.5, 124.9, 122.1, 112.6, 101.7, 61.7; HRMS (ESI) *m/z* calcd for $C_{17}H_{12}O_3NCl$ $[M+H]^+$314.0584, found 314.0833.

2-[(3-(3-Methylphenylisoxazol-5-yl)methoxy)]benzaldehyde (1j). White solid, 54% yield, M.pt. 122 ˚C, IR (KBr) (ν, cm^{-1}) 2745 (C-H), 1710 (C=O), 1620 (C=N), 1668 (C=C); ^{1}H NMR (500 MHz,$CDCl_3$, TMS) δ (ppm); 10.53 (d, J= 1.5 Hz, 1H), 7.87-7.89 (dd, J_1 = 6.0, J_2 = 1.5 Hz, 1H), 7.63-7.64 (m, 1H), 7.55-7.60 (m, 2H), 7.33-7.76 (m, 1H), 7.25 (s, 1H), 7.06-7.13 (m, 2H), 6.67 (s, 1H), 5.33 (s, 2H), 2.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ (ppm); 189.2, 167.3, 162.7, 159.9, 138.7, 135.9, 131.0, 128.9, 128.8, 128.3, 127.4, 125.4, 123.9, 122.0, 112.7, 101.7, 61.8, 21.3; HRMS (ESI) *m/z* calcd for $C_{18}H_{15}O_3N$ $[M+H]^+$ 294.1130, found 294.1189.

2-[(3-(3-Methoxyphenylisoxazol-5-yl)methoxy)benzaldehyde (1k). White solid, 50% yield, M.pt. 126 ˚C , IR (KBr) (ν, cm^{-1}) 2760 (C-H), 1735 (C=O), 1628 (C=N), 1658 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ (ppm); 10.53 (d, J= 1Hz, 1H), 7.87-7.89 (dd, J_1 = 6.0, J_2 = 1.5Hz, 1H), 7.56-7.59 (m, 1H), 7.34-7.38 (m, 3H), 7.06-7.13 (m, 2H) 6.99-7.01 (m, 1H), 6.67 (s, 1H), 5.33 (s, 2H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ(ppm): 189.1, 167.4, 162.6, 160.0, 159.8, 135,9, 130.0, 129.7, 128.9, 125.4, 122.0, 119.3, 116.4, 112.7, 111.7, 101.8, 61.8, 55.4; HRMS (ESI) *m/z* calcd for $C_{18}H_{15}O_4N$ $[M+H]^+$ 310.1079, found 310.1124.

2-[(3-(3-Bromophenylisoxazol-5-yl)methoxy)benzaldehyde (1l). White solid, 56% yield, M.pt. 149 ˚C, IR (KBr) (ν, cm^{-1}) 2748 (C-H), 1740 (C=O), 1624 (C=N), 1658 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ (ppm) 10.53 (d, J=

1 Hz, 1H), 7.96-7.97 (m, 1H), 7.88-7.90 (dd, J_1 = 6, J_2 = 1.5 Hz, 1H), 7.73-7.75 (m, 1H), 7.57-7.60 (m, 2H), 7.32-7.35 (m, 1H), 7.11-7.14 (m, 1H), 7.06-7.07 (m, 1H), 6.68 (s, 1H), 5.35 (s, 2H);^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ(ppm) 189.1, 167.9, 161.4, 159.7, 135.9, 133.2, 130.5, 130.4, 129.8, 129.1, 125.4, 125.4, 123.0, 122.1, 112.6, 101.6, 61.7; HRMS (ESI) *m/z* calcd for $C_{17}H_{12}O_3NBr$ $[M+H]^+$ 358.0079, $[M+H+2]^+$ 360.0058 found 358.0101, 360.0099.

2-[(3-(3-Fluorophenylisoxazol-5-yl)methoxy)benzaldehyde (1m). White solid, 45% yield, M.pt. 148 ˚C, IR (KBr) (ν, cm^{-1}) 2752 (C-H), 1727(C=O), 1620 (C=N), 1664 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm) : 10.52 (s, 1H), 7.88-7.89 (dd, J_1= 6.0, J_2 = 1.5 Hz, 1H), 7.57-7.60 (m, 2H), 7.52-7.54 (m, 1H), 7.41-7.46 (m, 1H), 7.11-7.18 (m, 2H), 7.06-7.08 (m, 1H), 6.68 (s, 1H), 5.35 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ (ppm) : 189.1, 167.8, 164.0, 162.0, 161.7, 161.7, 159.7, 135.9, 129.0, 125.4, 122.6, 122.6, 122.1, 117.3, 117.1, 113.9, 113.7, 112.6, 101.7, 61.7; HRMS (ESI) *m/z* calcd for $C_{17}H_{12}O_3NF$ $[M+H]^+$ 298.0879 found 298.0911.

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Supplementary Material

^{1}H NMR, ^{13}C NMR, HRMS data and biological assay are provided in the Supplementary Information file.

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