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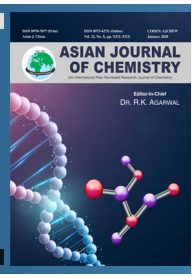

Isoxazoles-A Biocompatible Radical Scavenging Agents: Citrus Juice Mediated Environmentally Benign Synthesis and Characterization

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This study demonstrates the efficient eco-friendly synthesis of a series of isoxazole derivatives **5a-h** through (3+2) annulation of chalcones **3a-h** and hydroxylamine (**4**) in citrus juice medium. The synthesized compounds were characterized by spectroscopic and CHN analysis, and assessed *in vitro* for their antioxidant susceptibilities by DPPH and hydroxyl radical scavenging assays. The result shows that compounds **5a**, **5b**, **5d** and **5h** have excellent DPPH and hydroxyl radical scavenging activity in both assays and therefore these molecule could serve as potent antioxidant agents.

Keywords: Isoxazoles, Citrus juice, Hydroxylamine, Annulation, Antioxidant, Chalcone, Cyclocondensation.

INTRODUCTION

Design and discovery of small molecules with antioxidant effects is the pivotal area of research in recent years. Chalcones are bioactive molecules that show broad spectrum of biological properties such as anti-diabetic, antiviral, antimicrobial, anti-oxidant, cytotoxic [1,2], *etc*. and are useful scaffolds for the construction of biologically potent heterocycles like pyrazoles [3,4], isoxazoles [5,6], benzothiazepines [7,8], *etc*.

Five membered heterocyclic compounds like isoxazole derivatives are the building blocks in the synthesis of bioactive molecules. These class of compounds were reported to synthesize through various methods, a few to mention off the available protocols for the synthesis of isoxazoles being; The use of either *tert*-butyl nitrite or isoamyl nitrite enables an efficient one-pot synthesis of 3,5-disubstituted isoxazoles from substituted aldoximes and alkynes under conventional heating conditions [9]. Regioselective synthesis that involves an acid catalyzed cyclization of 3-(hydroxyimino)alkanenitrile produces isoxazoles [10], and chemoselective synthesis involving the treatment of α-haloketoximes with phosphine, acyl chloride and a base [11]. Discovery of 1,3-dipolar cycloaddition reactions by Huisgen' open the gate for easier route for the synthesis of five membered heterocycles [12]. For instance, the cycloadditions reactions *in situ* generated nitrile oxide by the catalytic dehydrogenation of aldoximes with chloramine-T as oxidizing agent to acetyl acetone [13], to an alkene [14] and chalcones [15] produces isoxazoles. The [3+2] additions of copper(I) acetylides to nitrile oxides forms isoxazoles with high regeoselectivity [16].

Recent reports on isoxazoles reveals that gold catalyzed oxyboration reaction with activated substrates form borylated isoxazoles [17]. The enol-form of 3-sulfonyloxyimino-2-methyl-1-phenyl-1-butanones undergoes an intramolecular cyclisation under neutral reaction conditions form isoxazoles [18]. Iron (III) mediated self-coupling and cross-coupling reaction of two alkynes in the presence of an additive KI form isoxazoles with good chemo selectivity [19]. The primary alcohols were smoothly transformed into 3-substitued isoxazoles in one pot by successive treatment with $PhI(OAc)_2$, NH_2OH, NCS in the presence of TEMPO, followed by reaction with alkynes in the presence of Et_3N [20]. Regioselective synthesis of fluoro-alkylated isoxazoles from amines and alkynes was developed, the method is scalable, operationally simple, mild, and tolerant of a broad range of functional groups. Mechanistic investigations reveal that the transformation involves an unprecedented Cu-catalyzed cascade sequence involving $RCHN_2$ [21].

A Cu(I)-free cyclization of nitrile oxides with terminal ynamides form isoxazoles, which can undergo another cycli-

zation with internal ynamides in the presence of Au(I) catalyst to give pyrroles [22]. A mild, palladium-catalyzed cascade annulation of alkynyl oxime ethers with allyl halides forms functionalized isoxazoles with good functional group compatibility and convenient operation [23]. A metal-free C-sp^3-H bond functionalization of ketones with *t*-butyl nitrite followed by a 1,3-dipolar cycloaddition to alkynes or alkenes provides isoxazoline with diverse functionalities [24]. A catalytic intramolecular cyclization of 2-alkynone *O*-methyl oximes and subsequent fluorination proceeds smoothly at room temperature in the presence of (IPr)AuCl, AgOTs, Selectfluor, and $NaHCO_3$ in an efficient one-pot cascade route to fluoroisoxazoles [25]. A cascade reaction sequence of α-azido acrylates and aromatic oximes is an efficient, straightforward and metal-free route for 3,4,5-trisubstituted isoxazoles [26], an enamine-triggered metal-free [3+2] cycloaddition reactions of aldehydes and *N*-hydroximidoyl chlorides in the presence of triethylamine [27], 1,3-dipolar cycloaddition of nitrile oxide to furfural acetone [28] and the reaction of terminal alkynes with *n*-BuLi, subsequent treatment with aldehydes, and molecular iodine [29].

Literature reveals that isoxazole derivatives can serve as useful molecules with potent bioactivities. These classes of compounds were known to exhibit antihypertensive [30], analgesic [31], antifungal [32], antioxidant [33], antitumor [34], anticancer [35], anti-inflammatory [36], anti-tuberculosis [37], antibacterial [38] activities. This study demonstrates the efficient use of citrus juice as eco-friendly medium for the [3+2] annulation reactions of chalcones and hydroxylamine for the synthesis of isoxazoles, and results of their *in vitro* DPPH and hydroxyl radical scavenging assays.

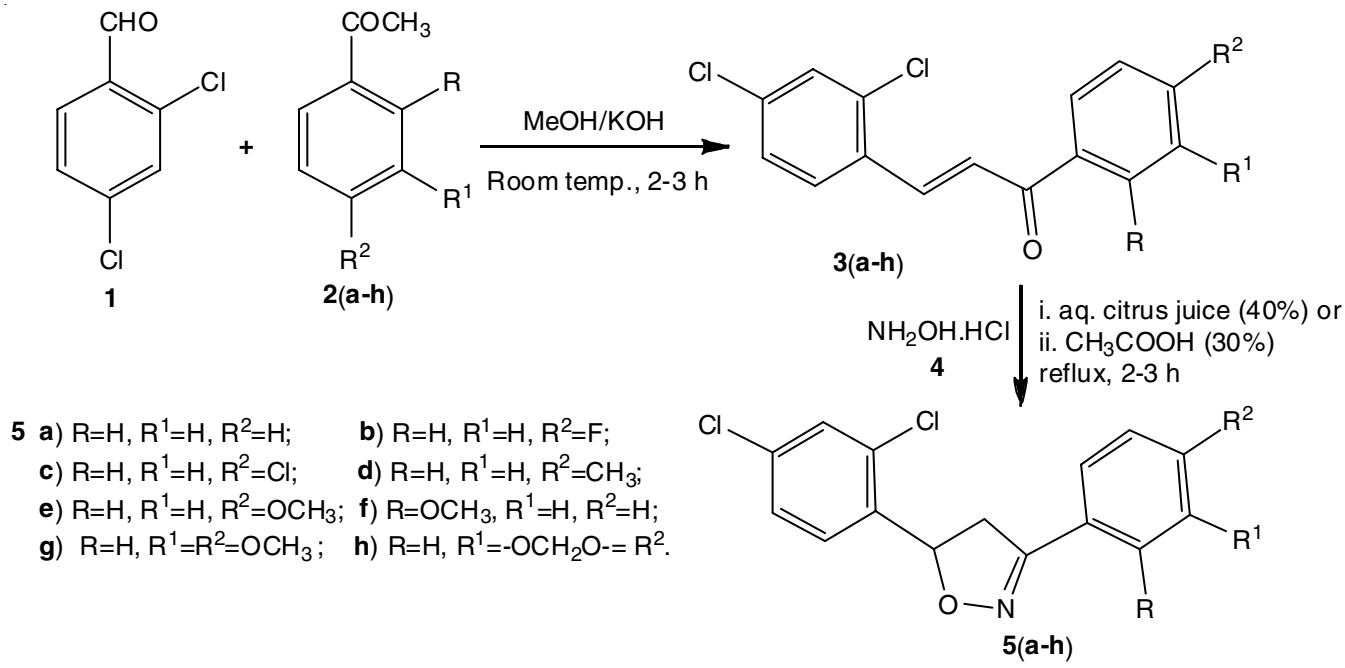
EXPERIMENTAL

Synthesis of 3,5-diaryl-4,5-dihydroisoxazoles (5a-h): To a solution mixture of chalcones (**3a-h**) (5 mmol) and hydroxylamine hydrochloride (**4**) (10 mmol) in freshly prepared citrus juice (30 mL, aq. 40%), tetrabutylammonium bromide (TBAB) (0.001 mmol) was added. Then the mixture refluxed on a water bath for 2-3 h. After the completion, the reaction mixture was filtered and the filtrate quenched into crushed ice. The separated solids were filtered, and washed successively with 5% $NaHCO_3$ and water; the crude solids crystallized from methyl alcohol to get target molecules **5a-h** in moderate yields.

Alternatively, a solution mixture of chalcones (**3a-h**) (5 mmol) and hydroxylamine hydrochloride (**4**) (10 mmol) in acetic acid (30%) was refluxed on a water bath for 2-3 h. After the completion, the mixture was filtered, and filtrate was quenched into crushed ice. The separated solids are filtered and washed with water. The crude products were crystallized from methyl alcohol to urge target products **5a-h** (**Scheme-I**).

5-(2,4-Dichlorophenyl)-3-phenyl-4,5-dihydroisoxazole (5a): Yield 66%, m.p. 98-100 ºC. ^{1}H NMR ($CDCl_3$, δ ppm): 3.591 (dd, 1H, *J* = 6.4, 16.5 Hz, C_4-H_a), 3.777 (dd, 1H, *J* = 7.4, 13.1 Hz, C_4-H_b), 5.818 (dd, 1H, *J* = 7.1, 12.8 Hz, C_5-H), 7.194-7.243 (m, 2H, Ar-H), 7.564-7.870 (m, 5H, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 42.1 (1C, C-4), 75.6 (1C, C-5), 126.2 (1C), 128.0 (2C), 128.6 (2C), 129.1 (1C), 129.7 (1C), 130.0 (1C), 130.4 (1C), 131.2 (1C), 133.2 (1C), 134.7 (1C), 156.9 (1C, C-3). MS (ES^+) *m/z*: 295.04 (M+4, 11), 293.02 (M+2, 62), 291.01 (M+, 100); Anal. calcd. (found) % for $C_{15}H_{11}NOCl_2$: C, 61.67 (61.56); H, 3.80 (3.82); N, 4.79 (4.76).

5-(2,4-Dichlorophenyl)-3-(4-fluorophenyl)-4,5-dihydroisoxazole (5b): Yield 68%, m.p. 121-123 ºC. ^{1}H NMR ($CDCl_3$, δ ppm): 3.560 (dd, 1H, *J* = 6.0, 16.2 Hz, C_4-H_a), 3.756 (dd, 1H, *J* = 6.4, 11.2 Hz, C_4-H_b), 5.763 (dd, 1H, *J* = 6.6, 12.1 Hz, C_5-H), 7.210-7.696 (m, 7H, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 39.8 (1C, C-4), 74.8 (1C, C-5), 116.2 (2C), 126.3 (1C), 127.2 (1C), 128.8 (2C), 129.7 (1C), 130.3 (1C), 133.6 (1C), 134.3 (1C), 135.8 (1C), 156.7 (1C, C-3), 165.6 (1C). MS (ES^+) *m/z*:



5 **a**) R=H, R^1=H, R^2=H; **b**) R=H, R^1=H, R^2=F;
c) R=H, R^1=H, R^2=Cl; **d**) R=H, R^1=H, R^2=CH_3;
e) R=H, R^1=H, R^2=OCH_3; **f**) R=OCH_3, R^1=H, R^2=H;
g) R=H, R^1=R^2=OCH_3; **h**) R=H, R^1=-OCH_2O-= R^2.

Scheme-I: Synthetic route for the synthesis of isoxazoles (**5a-h**)

313.02 (M+4, 10), 311.01 (M+2, 63), 309.01 (M^+, 100); Anal. calcd. (found) (%) for $C_{15}H_{10}NOCl_2F$: C, 58.09 (57.96); H, 3.25 (3.23); N, 4.52 (4.50).

3-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-4,5-dihydroisoxazole (5c): Yield 75%, m.p. 133-135 ºC. ^{1}H NMR ($CDCl_3$, δ ppm): 3.623 (dd, 1H, *J* = 6.6, 16.9 Hz, C_4-H_a), 3.797 (dd, 1H, *J* = 7.0, 12.5 Hz, C_4-H_b), 5.855 (dd, 1H, *J* = 6.8, 12.9 Hz, C_5-H), 7.213-7.285 (m, 2H, Ar-H), 7.685-7.882 (m, 5H, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 40.9 (1C, C-4), 75.6 (1C, C-5), 127.2 (1C), 127.9 (1C), 128.2 (2C), 128.7 (2C), 129.8 (1C), 130.5 (1C), 133.6 (1C), 134.1 (1C), 136.9 (1C), 137.3 (1C), 156.7 (1C, C-3). Anal. calcd. (found) for $C_{15}H_{10}NOCl_3$ (%):C, 55.16 (55.10); H, 3.09 (3.07); N, 4.29 (4.26).

5-(2,4-Dichlorophenyl)-3-(*p*-tolyl)-4,5-dihydroisoxazole (5d): Yield 60%, m.p. 110-112 ºC. ^{1}H NMR ($CDCl_3$, δ ppm): 2.314 (s, 3H, CH_3), 3.632 (dd, 1H, *J* = 7.1, 17.5 Hz, C_4-H_a), 3.825 (dd, 1H, *J* = 7.4, 13.1 Hz, C_4-H_b), 5.848 (dd, 1H, *J* = 7.2, 13.0 Hz, C_5-H), 7.145-7.233 (m, 3H, Ar-H), 7.661-7.738 (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 42.1 (1C, C-4), 76.4 (1C, C-5), 126.7 (2C), 127.3 (1C), 127.6 (1C), 129.0 (2C), 129.8 (1C), 130.4 (1C), 133.3 (1C), 134.6 (1C), 135.8 (1C), 141.6 (1C), 159.9 (1C, C-3). MS (ES^+) *m/z*: 309.01 (M+4, 10), 307.03 (M+2, 64), 305.02 (M^+, 100); Anal. calcd. (found) % for $C_{16}H_{13}NOCl_2$: C, 62.76 (62.64); H, 4.28 (4.25); N, 4.57 (4.54).

5-(2,4-Dichlorophenyl)-3-(4-methoxyphenyl)-4,5-dihydroisoxazole (5e): Yield 70%, m.p. 114-116 ºC. ^{1}H NMR ($CDCl_3$, δ ppm): 3.575 (dd, 1H, *J* = 6.3, 16.7 Hz, C_4-H_a), 3.788 (dd, 1H, *J* = 6.9, 12.6 Hz, C_4-H_b), 3.856 (s, 3H, OCH_3), 5.798 (dd, 1H, *J* = 6.9, 12.7 Hz, C_5-H), 7.108-7.210 (m, 3H, Ar-H), 7.690-7.822 (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 40.6 (1C, C-4), 55.4 (1C, OCH_3), 75.3 (1C, C-5), 114.1 (2C), 122.6 (1C), 126.9 (1C), 128.1 (2C), 128.7 (1C), 130.0 (1C), 132.9 (1C), 133.8 (1C), 134.7 (1C), 157.4 (1C, C-3), 160.1 (1C). MS (ES^+) *m/z*: 325.03 (M+4, 12), 323.05 (M+2, 62), 321.02 (M^+, 100); Anal. calcd. (found) % for $C_{16}H_{13}NO_2Cl_2$ (%): C, 59.65 (59.52); H, 4.07 (4.05); N, 4.35 (4.32).

5-(2,4-Dichlorophenyl)-3-(2-methoxyphenyl)-4,5-dihydroisoxazole (5f): Yield: 61% , gummy mass. ^{1}H NMR ($CDCl_3$, δ ppm): 3.645 (dd, 1H, *J* = 7.3, 17.8 Hz, C_4-H_a), 3.842 (dd, 1H, *J* = 7.8, 13.4 Hz, C_4-H_b), 3.860 (s, 3H, OCH_3), 5.875 (dd, 1H, *J* = 7.4, 13.2 Hz, C_5-H), 7.042-7.226 (m, 4H, Ar-H), 7.762-7.814 (m, 3H, Ar-H). Anal. calcd. (found) % for $C_{16}H_{13}NO_2Cl_2$ (%): C, 59.65 (59.56); H, 4.07 (4.04); N, 4.35 (4.33).

5-(2,4-Dichlorophenyl)-3-(3,4-dimethoxyphenyl)-4,5-dihydroisoxazole (5g): Yield: 69%, m.p. 136-138 ºC. ^{1}H NMR ($CDCl_3$, δ ppm): 3.574 (dd, 1H, *J* = 6.6, 17.3 Hz, C_4-H_a), 3.799 (dd, 1H, *J* = 6.7, 11.9 Hz, C_4-H_b), 3.850 (s, 6H, OCH_3), 5.844 (dd, 1H, *J* = 6.7, 12.7 Hz, C_5-H), 7.030-7.112 (m, 2H, Ar-H), 7.555-7.704 (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 41.2 (1C, C-4), 55.3 (2C, OCH_3), 75.9 (1C, C-5), 112.8 (1C), 115.1 (1C), 121.6 (1C), 127.3 (1C), 127.6 (1C), 129.5 (1C), 130.4 (1C), 131.7 (1C), 133.3 (1C), 136.2 (1C), 151.5 (1C), 157.7 (1C, C-3). MS (ES^+) *m/z*: 355.05 (M+4, 11), 353.04 (M+2, 65), 351.06 (M^+, 100); Anal. calcd. (found) % for $C_{17}H_{15}NO_3Cl_2$ (%): C, 57.97 (7.88); H, 4.29 (4.28); N, 3.98 (3.96) .

3-(Benzo[*d*][1,3]dioxol-5-yl)-5-(2,4-dichlorophenyl)-4,5-dihydroisoxazole (5h): Yield: 65% yield, gummy mass. ^{1}H NMR ($CDCl_3$, δ ppm): 3.589 (dd, 1H, *J* = 6.4, 16.5 Hz, C_4-H_a), 3.777 (dd, 1H, *J* = 6.9, 12.7 Hz, C_4-H_b), 5.861 (dd, 1H, *J* = 6.8, 12.9 Hz, C_5-H),6.034 (s, 2H, OCH_2O), 7.105-7.682 (m, 6H, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 42.2 (1C, C-4), 76.4 (1C, C-5), 103.2 (1C, OCH_2O), 112.5 (1C), 113.7 (1C), 120.9 (1C), 126.5 (1C), 127.2 (1C), 129.8 (1C), 130.8 (1C), 133.5 (1C), 135.7 (1C), 147.3 (1C), 150.7 (1C), 158.1 (1C, C-3). MS (ES^+) *m/z*: 339.05 (M+4, 9), 337.07 (M+2, 64), 335.03 (M^+, 100); Anal. calcd. (found) % for $C_{16}H_{11}NO_3Cl_2$ (%): C, 57.17 (57.05); H, 3.30 (3.26); N, 4.17 (4.14).

DPPH radical scavenging activity: The DPPH radical scavenging activity of the synthesized compounds **5a-h** was performed according to reported procedure [39]. A DPPH solution (1 mL, 0.1 mM) was mixed with different aliquots of test compounds (25, 50, 75 and 100 µg/mL) in methanol. Then the solution was allowed to stand for 20 min at room temperature. The absorbance was read against blank at 517 nm in an Elico SL 159 UV visible spectrophotometer. The free radical scavenging potential was calculated as a percentage (I %) of DPPH decoloration using the following equation:

$$\text{I (\%) of scavenging} = \frac{A_0 - A_1}{A_0} \times 100$$

where A_o is the absorbance of the control reaction mixture excluding the test compounds, and A_1 is the absorbance of the test compounds. Experiments were carried out in triplicate and the results are expressed as I% ± standard deviations.

Hydroxyl radical scavenging activity: The hydroxyl radical scavenging assay of the synthesized compounds **5a-h** was performed by a known procedure [40]. A mixture of 0.1 mL of phosphate buffer; 0.2 mL of 2-deoxyribose, test compounds (25, 50, 75 and 100 µg/mL in methanol), 0.1 mL of H_2O_2 (10 mM), 0.1 mL of ascorbic acid (1 mM), 0.1 mL of EDTA and 0.01 mL of $FeCl_3$ (100 mM) was incubated at 37 ºC for 60 min. Thereafter, the reaction was terminated by adding 1 mL of cold 2.8% trichloroacetic acid and the reaction product was measured by adding 1 mL of 1% thiobarbituric acid (1g in 100 mL of 0.05 N NaOH) in boiling water for 15 min. Butylated hydroxy anisole (BHA) was used as a positive control. The experiments were conducted in triplicates with different concentrations of test samples in methanol; the absorbance was read against blank at 535 nm in an Elico SL 159 UV visible spectrophotometer. The results were expressed as I% ± standard deviations.

RESULTS AND DISCUSSION

In view of the broad spectrum of applications of isoxazoles, and in search of new potent antioxidant small molecules, herein we report for the first time, citrus juice mediated eco-friendly approach for the synthesis of 3,5-diaryl-4,5-dihydroisaxazoles, and the results of their *in vitro* screening of their antioxidant activities. The demonstrated synthesis opens the gate for future efforts at synthesizing isoxazoles. The required intermediate 3-(2,4-dichlorophenyl)-1-(aryl)prop-2-en-1-ones (**3a-h**) were synthesized by Claisen-Schmidt approach from 2,4-dichloro-

benzaldehyde (**1**) and substituted acetophenones (**2a-h**) according to our earlier reports [41,42]. The reaction of chalcones (**3a-h**) and hydroxylamine hydrochloride (**4**), in citrus extract medium in the presence of tetrabutylammonium bromide (TBAB) as phase transfer catalyst (PTC) under reflux conditions yielded 3,5-diaryl-4,5-dihydroisaxazoles (**5a-h**). Alternatively, the target compounds were synthesized by conventional heating in acetic acid (30%) medium.

The ^{1}H NMR spectra of synthesized series of compounds **5a-h** recorded on Agilent-NMR 400 MHz spectrometer shows that the C-4 carbon of isoxazole rings are of diastereotopic nature. Spectra shows a doublet of doublets in the region ä 3.560-3.645 (J = 6.0-7.3 Hz and J = 16.2-17.8 Hz) ppm for C_4-H_a; δ 3.756-3.842 (J = 6.4-7.8 Hz and J = 11.2-13.4 Hz) ppm for C_4-H_b and δ 5.763-5.875 (J = 6.6-7.4 Hz and J = 12.1-13.2 Hz) ppm for C_5-H protons, respectively. ^{13}C NMR spectra of compounds recorded on Agilent-NMR 100 MHz spectrometer shows the resonance signals in the region δ 39.8-42.2, 74.8-76.6 and 156.7-158.5 ppm for C-4, C-5 and C-3 carbons, respectively of the newly formed isoxazole ring. All compounds shows the aromatic and substituent protons and carbons in the corresponding region in their respective spectra. Mass spectra of the compounds recorded on ESI/APCI-Hybrid Quadrupole, Synapt G2 HDMS ACQUITY UPLC model spectrometer shows the base peaks comparable to their molecular masses, and peaks corresponding to M+2 and M+4 due to halogen isotopes. Further, CHN analysis data recorded on a Thermo Finnigan Flash EA 1112 CHN analyzer is in good agreement with the theoretically calculated values.

DPPH radical scavenging activity: Preliminary assessment results indicated that amongst the synthesized compounds **5a-h**; compounds **5b** and **5h** have excellent DPPH radical scavenging abilities in the range of (27.36-52.12%) at the tested concentrations comparable to standard ascorbic acid, and therefore these molecule might serve as potent antioxidants. Compounds **5a** with radical scavenging ability of (16.16-24.88%); **5c** (17.92-26.20%) and **5d** (18.15-26.16%) show good activities. Compounds **5e** (11.95-16.35%), **5f** (8.75-15.98%) and **5g** (9.32-14.22%) show poorer or almost found inactive, this might be due to the presence of -OCH_3 substitutions (Table-1).

Hydroxyl radical scavenging activity: Amongst the synthesized compounds **5a-h**; compounds **5b** and **5h** have excellent hydroxyl radical scavenging susceptibilities in the range of 19.55-45.28% and 18.40-47.75%, respectively, which are comparable to standard BHA. Comparably good radical scavenging abilities exhibited by compounds **5a** (13.30-34.21 %); **5c** (14.01-36.44%) and **5d** (13.22-34.11%) show good activities. Compounds **5e** (10.77-19.04%), **5f** (5.32-14.34%), and **5g** (9.86-19.30%) found almost inactive. The greater activities of compounds **5a**, **5b**, **5d**, and **5h** might be attributed to the presence of no, fluoro, methyl and methylenedioxy substitutions, respectively (Table-1).

Conclusion

A series of new isoxazole analogues were synthesized efficiently through [3+2] annulation of chalcones and hydroxylamine in greener solvent citrus juice. The results of *in vitro* DPPH and hydroxyl radical scavenging activities revealed that some of the synthesized series of disubstituted isoxazoles could acts as potent antioxidants.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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TABLE-1
DPPH AND HYDROXYL RADICAL SCAVENGING ACTIVITIES OF COMPOUNDS **5a-h** AT DIFFERENT CONCENTRATIONS

Compound	% Radical Scavenging activity*							
	DPPH				Hydroxyl			
	25 µg/mL	50 µg/mL	75 µg/mL	100 µg/mL	25 µg/mL	50 µg/mL	75 µg/mL	100 µg/mL
5a	16.16 ± 0.66	18.54 ± 0.52	21.20 ± 0.55	24.88 ± 0.76	13.30 ± 0.65	18.67 ± 1.10	26.42 ± 0.54	34.21 ± 1.14
5b	27.36 ± 0.80	34.51 ± 1.05	44.52 ± 0.97	51.30 ± 1.10	19.55 ± 1.10	25.92 ± 1.00	34.74 ± 0.92	45.28 ± 1.50
5c	17.92 ± 1.50	19.33 ± 0.78	23.65 ± 0.57	26.20 ± 0.44	14.01 ± 0.60	18.86 ± 0.75	26.90 ± 1.25	36.44 ± 0.81
5d	18.50 ± 0.75	20.12 ± 0.84	23.32 ± 0.71	26.16 ± 1.10	13.22 ± 0.52	19.16 ± 0.65	27.88 ± 1.02	34.11 ± 0.98
5e	11.95 ± 0.50	12.34 ± 0.67	14.12 ± 0.86	16.35 ± 0.70	10.77 ± 0.50	13.22 ± 0.76	17.30 ± 0.55	19.04 ± 1.05
5f	8.75 ± 0.46	12.34 ± 0.66	14.42 ± 0.75	15.98 ± 0.84	5.32 ± 0.55	8.56 ± 0.45	12.78 ± 0.60	14.34 ± 0.50
5g	9.32 ± 0.56	12.88 ± 0.65	13.72 ± 1.05	14.22 ± 0.90	9.86 ± 0.48	13.76 ± 0.40	16.80 ± 0.83	19.30 ± 0.65
5h	27.95 ± 1.00	35.34 ± 1.20	46.22 ± 1.34	52.12 ± 1.12	18.40 ± 0.78	25.89 ± 1.12	36.26 ± 1.20	47.75 ± 1.24
AA	15.10 ± 0.84	17.85 ± 0.84	21.90 ± 0.55	24.50 ± 0.30	–	–	–	–
BHA	–	–	–	–	12.02 ± 0.05	17.95 ± 0.12	25.58 ± 0.20	32.03 ± 0.32

*Values are mean (I %) (n = 3) ± SD; AA = Ascorbic acid; BHA = Butylated hydroxy anisole.

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