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Synthesis, Antioxidant, and Antibacterial Activities of Two Novel Series of 3,5-Disubstituted Isoxazole Ether-Linked Isoxazolines and 3,5-Disubstituted Pyrazole Ether-Linked Isoxazolines Mediated by Chloramine-T

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Abstract—Two short novel series of five membered heterocyclic 3,5-disubstituted–Isoxazole ether-linked Isoxazoline derivatives (**Xa–f**) and 3,5-disubstituted-Pyrazole ether-linked Isoxazoline derivatives (**XIa–f**) were synthesized via 1,3-dipolar cycloaddition reaction of Isoxazole ether-linked allyloxymethyl (**VI**) and pyrazole ether-linked allyloxymethyl (**VII**) with aromatic aldoximes (**VIIIa–f**) which undergo oxidative dehydrogenation with chloramine-T (**IX**) to give 3,5-disubstituted isoxazole ether-linked isoxazoline derivatives (**Xa–f**) and 3,5-disubstituted pyrazole ether-linked Isoxazoline derivatives (**XIa–f**) in good yield. The newly synthesized compounds were screened for anti-oxidant and anti-microbial activities. 3,5-Disubstituted isoxazole ether-linked isoxazoline derivatives (**Xc–d**) and 3,5-disubstituted Pyrazole ether-linked isoxazoline derivatives (**XIc–d**) exhibited antioxidant activity at 10 μg/mL, as well as antimicrobial activity at 100 μg/mL compared with standard vitamin C and ciprofloxacin, respectively. Structures of newly synthesized compounds were established on the basis of their elemental analysis and spectral IR, ^{1}H NMR, and ^{13}C NMR.

Keywords: isoxazoles, pyrazoles, isoxazolines, ether-linked, chloramine-T, antioxidant, antibacterial

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INTRODUCTION

Unconventional heterocyclic rings have constantly aroused considerable interest in chemistry and biology. Isoxazoles, pyrazoles, and isoxazolines are principal class of five membered ring system, exhibiting a wide variety of biological and medicinal importance [1–6]. Isoxazoles have been largely studied as core components of many natural products such as muscimol [7, 8], ibotenic acid [9] and drugs like leflunomide [10], valdecoxib [11]. The significant biological activities observed for pyrazoles due to their widespread inherent medicinal properties such as antimicrobial [12, 13], antipyretic [14], antitumour [3, 15], antiviral [16], anti-tubulin [17, 18], antidepressant [3], insecticides [19–21] and fungicides [22, 23]. Isoxazolines have also been reported to possess antibacterial [3] diuretic [24], analgesic [25], antidiabetic [26], and hypolipaemic [27]. These class of compounds along with their derivatives have attracted the attention of medicinal chemists due to their efficacy in synthetic chemistry and in pharmacology including antioxidant [3, 7, 13, 29, 30], neurotoxic [31], tuberculostatic [32],

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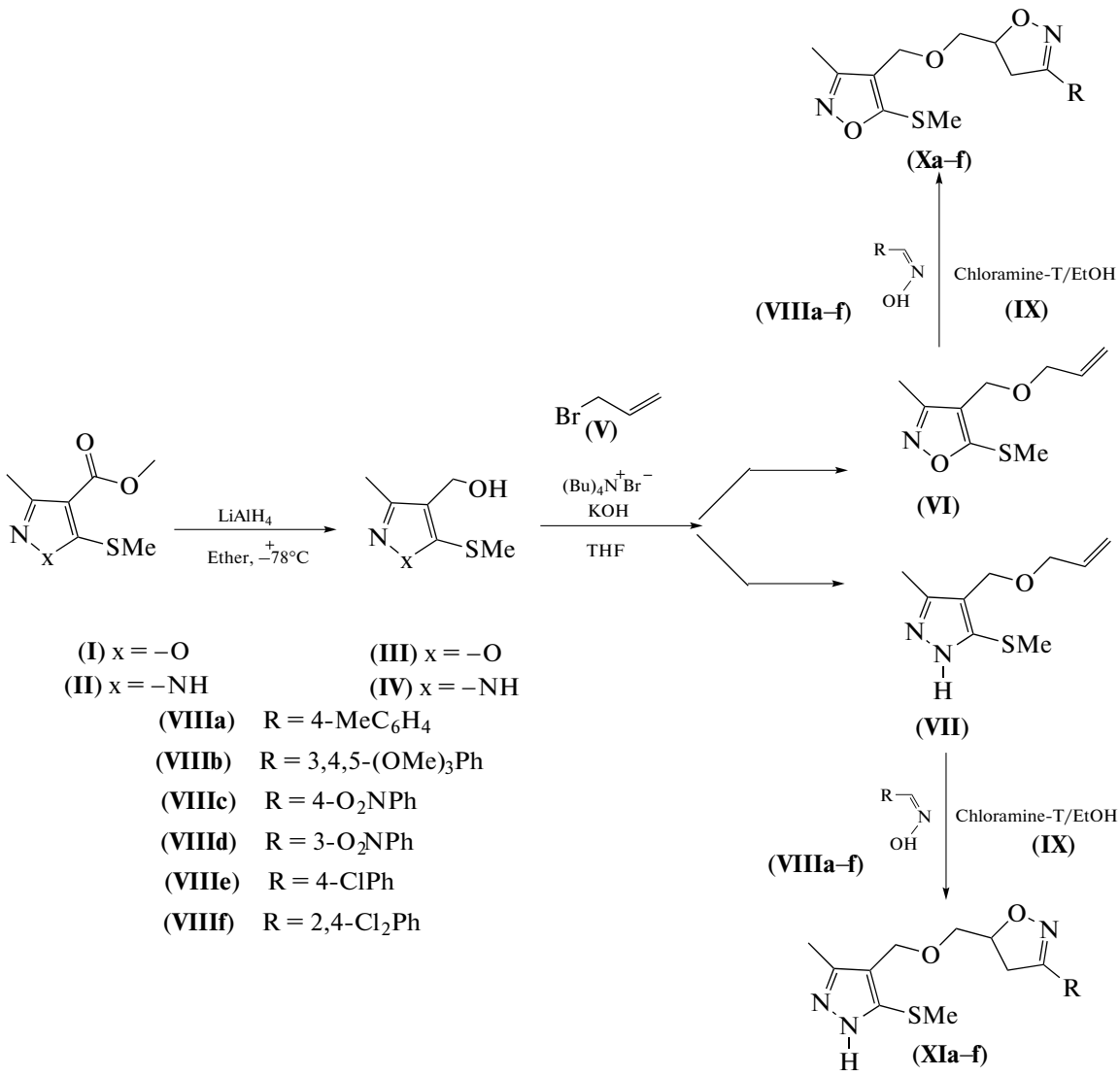
antiviral [7, 33, 34], antidepressant [35, 36] and anti-inflammatory [7–37] activities. Among the various nitrogenic heterocycles, synthesis of linked Isoxazole, Pyrazole or Isoxazoline to each other or to another heterocyclic moieties attract more attention for further study on the synthesis and biological activity of these compounds. Literature survey revealed so far, few methods exist for synthesis of linked Isoxazole, Pyrazole and Isoxazoline derivatives [38–40]. As a part of our strategy to develop a simple, stepwise, and high yield procedure to prepare novel sought-after linked heterocycles compounds, we would like to report herein a convenient synthesis of novel isoxazoline linked analogues *via* 1,3-dipolar cycloaddition of aromatic oxime to desired allyl in the presence of Chloramine-T and the evaluation of their antioxidant and antibacterial activities.

RESULTS AND DISCUSSION

Chemistry

Based on the above information, we planned to prepare 3,5-disubstituted isoxazole linked to 4,5-dihydroisoxazol-5-yl derivatives (**Xa–f**) and (**XIa–f**) to study the biological activities of these prosperous heterocyclic compounds. To accomplish this mission it was necessary to first synthesize the 4-((allyloxy)methyl)-3-methyl-5-(methylthio)isoxazole (**VI**) and 4-((allyloxy)methyl)-3-methyl-5-(methylthio)-1*H*-pyrazole (**VII**). The initial starting materials (I), (II), (III) and (IV) were prepared according to procedures in references [41, 42]. Generally, the stirring of compounds (3-methyl-5-(methylthio)isoxazol-4-yl)methanol (**III**) and (3-methyl-5-(methylthio)-1*H*-pyrazol-4-yl)methanol (**IV**) with excess of allyl bromide (**V**), in the presence of tetrabutylammonium bromide (used as phase transfer catalyst) and potassium hydroxide [39], 4-((allyloxy)methyl)-3-methyl-5-(methylthio)isoxazole (**VI**) and 4-((allyloxy)methyl)-3-methyl-5-(methylthio)-1*H*-pyrazole (**VII**) were prepared as white crystalline solid and yellow crystalline solid respectively. The IR spectrum of compounds (**VI**) and (**VII**) showed characteristic bands at 3310, 3121–3111, 2936–2761, 1342–1339, 1141–1102 and 1230–1211 cm^{-1} due to presence –NH, $-CH_3$, –C=CH, C=N, –C–O–C–, –C–O–N functional groups respectively. Compound (**VI**) exhibits two multiplets at δ 5.28–5.32 ppm and at δ 5.65–5.72 ppm, and compound (**VII**) exhibits at δ 5.23–5.31 ppm and at δ 5.54–5.68 ppm corresponding to the vinylic CH_2 and CH groups, respectively. Two multiplets at δ 4.43–4.51 ppm, δ 4.68–4.92 ppm and at δ 4.16–4.28 ppm, and at δ 4.58–4.88 correspond to the CH_2O and allylic CH_2O groups, respectively. The olefinic groups in compounds (**VI**) and (**VII**) were used to form another isoxazoline ring. Refluxing of (**VI**) and (**VII**) with compound (**VIIIa–f**) in the presence of chloramine-T for 4 h gave the respective isoxazolines derivatives (**Xa–f**) 48–71% yields and pyrazolines derivatives (**XIa–f**) in good to very good yields as shown in Scheme 1. The structures of the 12 novel compounds were established on elemental analysis and from spectral data. The IR spectrum of compounds (**Xa–f**) and (**XIa–f**) showed general vibrational frequencies of the parent molecule in the IR study were 3220–3120 cm^{-1}, 3082–3010 cm^{-1}, 2978–2805 cm^{-1}, 1655–1560 cm^{-1}, 1150–1048 cm^{-1} and 1361–1210 cm^{-1} due to –NH, $-CH_3$, –C=CH, C=N, –C–O–C–, –C–O–N stretching frequencies, respectively. Also, the IR spectra of these products revealed the aromatic C=C and other substituent absorption at the expected regions that confirms the formation of the products. The elemental data analysis further confirms the structures of the desired products. In the ^1H NMR spectra of the generalized parent molecule a two singlets appear in the range of δ 2.03–2.38 ppm assigned to methyl groups and in the range of δ 2.40–2.92 ppm assigned to methylthio groups on isoxazole and pyrazole rings respectively, three multiplets within the range of δ 3.10–3.50 ppm, δ 4.11–4.41 ppm and δ 5.09–5.51 ppm correspond to the protons of $-CH_2$-, $-OCH_2$-, and –CH-groups respectively, a singlet at δ 4.45–5.61 ppm assigned to the protons of $-OCH_2$-group attached to isoxazole or pyrazole ringe, a two doublets within the ranges δ 7.30–8.42 ppm assigned to aromatic protons, a multiple at range of δ 7.42–8.35 ppm assigned to aromatic protons at ortho positions for the compounds (**Xd**) and (**XId**), existence a singlet at δ 7.23 and 7.52 ppm attributed to aromatic protons in compounds (**Xb**) and (**XIb**) respectively. Compounds had shown their characteristic peaks according to the substituents like a singlet signals in the ranges at δ 10.12 to 11.86 ppm for –NH group in compounds (**XIa–f**). The ^{13}C NMR spectra at these products are also in accordance with proposed structures, for example the ^{13}C NMR spectra of these compounds exhibits the signals of C_4, C_5 δ 74.18–79.52 ppm and signals near δ 151.20–163.46 ppm assignable to the –C=N group of isoxazoline and pyrazole rings, respectively. Therefore, all the chemical shifts of ^1H NMR and ^{13}C NMR spectra confirm proposed structures of the products (**Xa–f**) and (**XIa–f**) as shown in Scheme 1.



Scheme 1.

Antioxidant Activity

The 2,2-diphenyl-1-picryl-hydrazyl (DPPH·) radical scavenging activity (RSA) evaluation is a standard assay in antioxidant activity studies and offers a rapid technique for screening the RSA of specific compounds or extracts [41–44]. The interaction of synthesized compounds (**Xa–f**) and (**XIa–f**) with stable DPPH free radical indicates their free radical scavenging ability. Majority of the tested compounds in these series showed moderate to high interaction with the DPPH radical at 10 μg/mL concentration. Maximum DPPH RSA was observed in compounds (**Xa–f**) derivatives particularly compounds (**Xc**) and (**XIc**) ($p < 0.05$), which has a substituent on the phenyl ring (Table 1).

Structure activity relationship results for the synthesized compounds showed that the Isoxazoles ether-linked Izoxazolines derivatives (**Xa–f**) have free radical scavenging ability more than Pyrazoles ether-linked Isoxazolines. Compounds (**Xc–e**) and (**XIc–e**) which has electron-withdrawing nitro and chloro functional groups at para/meta position of phenyl rings attached to C-3 carbon of Isoxazoline moiety delivered excellent activities. The presence of electron-donating groups on the phenyl ring at positions might not favor for the activity. Compounds (**Xa–b**), (**XIa–b**), which contain –Me and –OMe, groups on the phenyl ring showed lowest radical scavenging activity. The maximum anti-oxidant activity was observed in compounds in the following order (**XIc**) < (**Xe**) < (**Xf**) < (**Xd**) < (**Xc**), which is comparable to that of standard vitamin C at similar concentration. The presence of electron-withdrawing groups on the phe-

Table 1. Anti-oxidant activity of synthesized novel series of Isoxazole ether-linked Isoxazoline derivatives (**Xa**–**f**) and Pyrazole ether-linked Isoxazoline derivatives (**XIa**–**f**)

Compound	DPPH radical scavenging activity, % at 10 μg/mL	Anti-lipidperoxidation, % at 40 μg/mL
(Xa)	38.09 ± 2.11	33.12 ± 1.12
(Xb)	35.06 ± 1.13	30.08 ± 0.35
(Xc)	78.14 ± 1.42	63.02 ± 0.09
(Xd)	75.01 ± 1.80	56.05 ± 0.30
(Xe)	71.11 ± 1.04	55.16 ± 0.86
(Xf)	74.02 ± 1.41	54.05 ± 0.54
(XIa)	43.18 ± 0.10	31.11 ± 0.77
(XIb)	46.24 ± 0.68	29.06 ± 1.16
(XIc)	68.13 ± 0.14	58.13 ± 1.22
(XId)	63.02 ± 1.16	46.07 ± 0.41
(XIe)	63.04 ± 1.12	42.09 ± 0.63
(XIf)	65.15 ± 0.42	47.20 ± 1.04
Vitamin C	93.20 ± 0.55	ND
Vitamin E	ND	70.06 ± 1.80

Anti-oxidant and anti-lipid peroxidation activities were expressed in percentage compared with standard vitamin C and E, respectively. ND = Not determined. The data representmean value (SEM) of 3 duplicates.

nyl ring of isoxazoles derivatives (**Xa**–**f**) is mostly effective particularly with a strong electron-withdrawing group such as NO_2. Antioxidant activity of these compounds is related to their electron or hydrogen radical donating ability to DPPH radical so that they become stable diamagnetic molecules. This might be the reason for the higher antioxidant activity of the first series of compounds (**Xa**–**f**). Moreover, aromatized heterocyclic compounds having isoxazole unit displayed slightly higher activity than pyrazole unit. This may be due to the presence of electron withdrawing oxygen atom. It was also noticed that compounds having electron withdrawing fluoro substituent on aromatic ring enhanced the activity when compared with the unsubstituted ones. Besides, the compounds having a greater number of electron withdrawing groups showed increased antioxidant activity.

Evaluation of anti-lipid peroxidation activity of new compounds was performed by the formation of thiobarbituric acid reactive species (TBARS) using egg yolk homogenate as lipid-rich media. The result showed that all newly synthesized compounds inhibited the ferric chloride-induced lipid peroxidation at 40 μg/mL concentration with a varying degree when compared with standard biological anti-oxidant vitamin E (Table 1). The maximum anti-lipid peroxidation inhibition was observed in izoxazoles derivatives (**Xa**–**f**) particularly isoxazoles (**Xc**), (**Xd**), and (**Xf**) ($p < 0.05$), which has a strong electron-withdrawing group such as NO_2 and Cl on the phenyl ring (Table 1). However, number of isoxazole ether-linked isoxazoline (**Xa**–**b**) and pyrazole ether-linked Isoxazoline derivatives (**Xa**–**b**) showed moderate anti-lipid peroxidation inhibition comparable to that of standard vitamin E at similar concentration. The presence of electron-donating groups such as –OMe and –Me on the phenyl ring at 3 or 4 position of Phenyl ring for either Isoxazoles or pyrazoles derivatives might not favor the activity. Pyrazole ether-linked isoxazoline (**XIb**), which has methoxy group as the electron-donating substituent on phenyl ring at position 3,4,5 exhibited the lowest inhibition. In general, it appears that the presence of electron with drawing groups on the phenyl ring favors the activity. This might be the reason for the enhancement of activity of the other compounds, which showed high to moderate activities in the order **(Xc)** > **(XIc)** > **(Xd)** > **(Xe)** > **(Xf)**.

Antibacterial Activity

The synthesized compounds were evaluated for in vitro anti-microbial activity using the agar disc diffusion method against various bacterial strains namely: *Staphylococcus aureus*, *Bacillus substilis*, *Escherichia coli*, and *Pseudomonas aeruginosa*. The results are presented in (Table 2).

The result showed that Isoxazole ether-linked isoxazoline derivatives (**Xc**–**d**) and pyrazoles ether-linked isoxazoline derivatives (**XIc**–**d**) exhibited maximum anti-bacterial activity against all the tested microorganisms at a concentration of 100 μg/mL similar to that of standard antibiotic *Ciprofloxacin*. The activity

Table 2. Anti-bacterial activity synthesized novel series of isoxazole ether-linked isoxazoline derivatives (**Xa**–**f**) and pyrazole ether-linked isoxazoline derivatives (**XIa**–**f**)

Compound	*S. aureus*	*B. subtilis*	*E. coli*	*P. aeruginosa*
(Xa)	14 ± 0.14	10 ± 0.32	13 ± 0.17	NA
(Xb)	NA	NA	NA	NA
(Xc)	25 ± 0.62	14 ± 1.11	22 ± 1.33	14 ± 0.15
(Xd)	21 ± 0.13	10 ± 0.13	19 ± 0.24	8 ± 0.23
(Xe)	16 ± 0.23	9 ± 0.42	NA	11 ± 0.68
(Xf)	13 ± 0.55	8 ± 0.25	17 ± 0.41	12 ± 0.52
(XIa)	11 ± 0.87	9 ± 0.95	11 ± 0.63	NA
(XIb)	16 ± 1.03	7 ± 1.12	13 ± 0.45	10 ± 0.83
(XIc)	22 ± 0.90	12 ± 0.21	17 ± 0.52	15 ± 1.50
(XId)	21 ± 0.64	12 ± 0.39	14 ± 0.20	13 ± 0.33
(XIe)	15 ± 0.12	10 ± 0.48	NA	9 ±0.46
(XIf)	15 ± 0.53	8 ± 0.60	12 ± 0.36	7 ±0.90
Ciprofloxacin	29 ± 1.40	18 ± 0.89	26 ± 0.18	18 ± 0.77

Zone of inhibition, mm. Gram-positive bacterial strains: *S. aureus*, *Staphylococcus aureus*; *B. subtillis*, *Bacillus subtillis*. Gram-negative bacterial strains: *E. coli*, *Escherichia coli*; *P. aeruginosa*, *Pseudomonas aeruginosa*. The concentration of test compounds was 100 μg/mL. Solvent used, DMSO. NA = Not active. The data represent mean value (SEM).

is considerably affected by substituents present at para position of phenyl ring. The results clearly indicated that the functional groups on phenyl ring of Izoxazoline moiety have a considerable influence on the antibacterial activity.

EXPERIMENTAL

Chemistry

Melting points (°C, uncorrected) were determined using the Thomas Hoover melting point apparatus. IR spectra was recorded (KBr) on Shimadzu 8300 spectrometer, in range 400–4000 cm^{-1}. An elemental analysis was carried out on an Elementor vairo-EL instrument. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra was measured on $CDCl_3$ for the products (**Xa**–**f**) and (**XIa**–**f**) and TMS was used as an internal reference. Microbial stains were obtained from NCL Pune, Maharastra, India (*Escherichia coli* NCIM 2065; *Staphylococcus aureus* NCIM 2079; *Bacillus subtilis* NCIM 2063; *Pseudomonas aeruginosa* NCIM 5029).

Typical procedure for synthesis 4-((allyloxy)-methyl)-3-methyl-5-(methylthio)isoxazole (VI). A mixture of methyl 3-methyl-5-(methylthio)isoxazole-4-carboxylate, (**II**) (0.94 g, 5 mmol) and allyl bromide (**V**) (0.65 g, 5 mmol) tetrabutylammonium bromide (0.17 g, 0.53 mmol) and potassium hydroxide (0.29 g, 5.18 mmol) was stirred overnight in THF (15 mL). After completion of the reaction (monitored by TLC), the solvent was evaporated under vacuum, the residue was extracted with ethyl acetate (2 × 15 mL), washed with water (2 × 10 mL) and dried (Na_2SO_4). The solvent was evaporated, and the residue was subjected to the column chromatography using chloroform/acetone (9 : 1) as eluent to give the product (**VI**) as white crystalline solid in 56% (0.56 g) yield. mp 72–73°C; IR (KBr) (ν_{max}, cm^{-1}): 3121, 3069, 2936; ^1H NMR (400 MHz, $CDCl_3$): δ 2.18 (s, 3H, $-CH_3$), 2.47 (s, 3H, $-SCH_3$), 4.43–4.51 (m, 2H, $-OCH_2-$), 4.68–4.92 (m, 2H, $-OCH_2-$), 5.28–5.32 (m, 1H, $=CH_2$), 5.65–5.72 (m, 1H, =CH–). ^{13}C NMR (100 MHz $CDCl_3$): δ 11.34, 14.47, 62.16, 78.43, 104.04, 116.97, 139.23, 156.45, 162.55; Anal. calcd. for $C_9H_{13}NO_2S$: C, 54.25; H, 6.58; N; 7.03. Found: C, 53.64; H, 6.02; N, 7.55.

4-((Allyloxy)methyl)-3-methyl-5-(methylthio)-1*H*-pyrazole (VII). From (**III**) (0.93 g, 5 mmol) and allyl bromide (**V**) (0.65 g, 5 mmol) tetrabutylammonium bromide (0.17 g, 0.53 mmol) and potassium hydroxide (0.29 g, 5.18): as yellow crystalline solid in 61% (0.6 g) yield. mp 61–63°C; IR (KBr) (ν_{max}, cm^{-1}): 3310, 3111, 3047, 2761; ^1H NMR (400 MHz, $CDCl_3$): δ 2.26 (s, 3H, $-CH_3$), 2.51 (s, 3H, $-SCH_3$), 4.40–4.48 (m, 2H, $-OCH_2-$), 4.58–4.88 (m, 2H, $-OCH_2-$), 5.23–5.31 (m, 1H, $=CH_2$), 5.54–5.68 (m, 1H, =CH–), 10.10 (br, 1H, –NH). ^{13}C NMR (100 MHz $CDCl_3$): δ 11.55, 13.68, 62.20, 77.23, 114.34, 116.47, 135.12, 136.48, 154.86; Anal. calcd. for $C_9H_{14}N_2OS$: C, 54.52; H, 7.12; N; 14.13. Found: C, 53.78; H, 6.34; N, 14.96.

3-Methyl-5-(methylthio)-4-(((3-(*p*-tolyl)-4,5-dihydroisoxazol-5-yl)methoxy)methyl)isoxazole (Xa). *Typical procedure:* A mixture of 4-((allyloxy)methyl)-3-methyl-5-(methylthio)isoxazole (**VIa**) (1 g, 5 mmol), oxime (**VIIa**) (0.68 g, 5 mmol) and Chloramine-T.$3H_2O$ (1.42 g, 5 mmol) in ethanol (30 mL) were refluxed under stirring for 4 h. TLC monitored the

progress of the reaction. After completion the reactions the solvent was then concentrated under reduced pressure. The residual mass was extracted into ether (25 mL), washed successively with water (2 × 20 mL) and 10% NaOH solution (10 mL), brine solution (2 × 15 mL) and dried over anhydrous sodium sulphate. Ether was evaporated and the crude product was purified by column chromatography using chloroform/acetone (9 : 1) as eluent to give the product (**VIa**) as colorless crystalline solid in 66% (1.1 g) yield. mp 82–83°C; IR (KBr) (ν_{max}, cm^{-1}): 3075, 2805, 1715, 1618; ^1H NMR (400 MHz, $CDCl_3$): δ 2.24 (s, 3H, $-CH_3$), 2.40 (s, 3H, $-CH_3$), 2.80 (s, 3H, $-SCH_3$), 3.10–3.43 (m, 2H, $-CH_2-$), 4.15–4.40 (m, 2H, $-OCH_2-$), 4.55 (s, 2H, $-OCH_2-$), 5.20–5.32 (m, 1H, –CH–), 7.30 (d, 8.2 Hz, 2H, Ar), 7.78 (d, 8.2 Hz, 2H, Ar). ^{13}C NMR (100 MHz $CDCl_3$): δ 12.15, 13.65, 23.54, 36.12, 65.10, 74.18, 75.42, 98.88, 126.35, 126.80, 128.50, 144.34, 153.16, 160.12, 163.20; Anal. calcd. for $C_{17}H_{20}N_2O_3S$: C, 61.42; H, 6.06; N; 8.43. Found: C, 60.33; H, 5.52; N, 7.91.

3-Methyl-5-(methylthio)-4-(((3-(3,4,5-trimethoxyphenyl)-4,5-dihydroisoxazol-5-yl)methoxy)methyl)-isoxazole (Xb). Obtained from (**VI**) (0.98 g, 5 mmol), oxime (**VIIIb**) (1.1 g, 5 mmol) and Chloramine-T·$3H_2O$ (1.42 g, 5 mmol) as white crystalline solid in 69% (1.4 g) yield. mp 95–97°C; IR (KBr) (ν_{max}, cm^{-1}): 3082, 2816, 1608; ^1H NMR (400 MHz, $CDCl_3$): δ 2.30 (s, 3H, $-CH_3$), 2.92 (s, 3H, $-SCH_3$), 3.32–3.46 (m, 2H, $-CH_2-$), 3.89 (s, 9H, $-OCH_3$), 4.20–4.39 (m, 2H, $-OCH_2-$), 4.51 (s, 2H, $-OCH_2-$), 5.18–5.36 (m, 1H, –CH–), 7.23 (s, 2H, Ar), ^{13}C NMR (100 MHz $CDCl_3$): δ 11.10, 13.46, 37.21, 53.13, 54.10, 62.28, 64,30, 75.42, 77.34, 96.70, 110.28, 112.35, 127.05, 144.60, 154.20, 155.20, 158.18, 158.33, 160.02; Anal. calcd. for $C_{19}H_{24}N_2O_3S$: C, 55.87; H, 5.92; N; 6.86. Found: C, 55.36; H, 5.12; N, 6.04.

3-Methyl-5-(methylthio)-4-(((3-(4-nitrophenyl)-4,5-dihydroisoxazol-5-yl)methoxy)methyl)isoxazole (Xc). Obtained from (**VI**) (0.98 g, 5 mmol), oxime (**VIIIc**) (0.83 g, 5 mmol) and Chloramine-T·$3H_2O$ (1.42 g, 5 mmol) as yellow crystalline solid in 77% (1.4 g) yield. mp 71–73°C; IR (KBr) (ν_{max}, cm^{-1}): 3060, 2903, 1627; ^1H NMR (400 MHz, $CDCl_3$): δ 2.26 (s, 3H, $-CH_3$), 2.65 (s, 3H, $-SCH_3$), 3.23–3.41 (m, 2H, $-CH_2-$), 4.12–4.28 (m, 2H, $-OCH_2-$), 4.45 (s, 2H, $-OCH_2-$), 5.34–5.49 (m, 1H, –CH–), 7.42 (d, 6.08 Hz, 2H, Ar), 7.71 (d, 6.08 Hz, 2H, Ar). ^{13}C NMR (100 MHz $CDCl_3$): δ 11.08, 15.23, 35.32, 62.56, 75.62, 76.90, 99.35, 126.40, 127.56, 127.60, 127.98, 134.11, 151.26, 157.18, 160.24, 163.46; Anal. calcd. for $C_{16}H_{17}N_3O_5S$: C, 52.88; H, 4.72; N; 11.56. Found: C, 52.01; H, 5.12; N, 12.07.

3-Methyl-5-(methylthio)-4-(((3-(3-nitrophenyl)-4,5-dihydroisoxazol-5-yl)methoxy)methyl)isoxazole (Xd). Obtained from (**VI**) (0.98 g, 5 mmol), oxime (**VIIId**) (0.83 g, 5 mmol) and Chloramine-T·$3H_2O$ (1.42 g, 5 mmol) as yellow crystalline solid in 88% (1.6 g) yield. mp 80–83°C; IR (KBr) (ν_{max}, cm^{-1}): 3010, 2978, 1560; ^1H NMR (400 MHz, $CDCl_3$): δ 2.30 (s, 3H, $-CH_3$), 2.54 (s, 3H, $-SCH_3$), 3.33–3.50 (m, 2H, $-CH_2-$), 4.22–4.36 (m, 2H, $-OCH_2-$), 4.50 (s, 2H, $-OCH_2-$), 5.27–5.50 (m, 1H, –CH–), 7.42–8.35 (m, 4H, Ar). ^{13}C NMR (100 MHz $CDCl_3$): δ 12.13, 14.16, 38.20, 64.43, 75.10, 75.40, 100.23, 121.36, 124.32, 126.45, 132.20, 133.06, 146.48, 158.62, 158.94, 160.33; Anal. calcd. for $C_{16}H_{17}N_3O_5S$: C, 52.88; H, 4.72; N; 11.56. Found: C, 51.90; H, 4.08; N, 10.98.

4-(((3-(4-Chlorophenyl)-4,5-dihydroisoxazol-5-yl)-methoxy)methyl)-3-methyl-5-(methylthio)isoxazole (Xe). Obtained from (**VI**) (0.98 g, 5 mmol), oxime (**VIIIe**) (0.78 g, 5 mmol) and Chloramine-T·$3H_2O$ (1.42 g, 5 mmol) as white crystalline solid in 61% (1.07 g) yield. mp 98–100°C; IR (KBr) (ν_{max}, cm^{-1}): 3074, 2819, 1590; ^1H NMR (400 MHz, $CDCl_3$): δ 2.38 (s, 3H, $-CH_3$), 2.53 (s, 3H, $-SCH_3$), 3.26–3.43 (m, 2H, $-CH_2-$), 4.11–4.26 (m, 2H, $-OCH_2-$), 4.52 (s, 2H, $-OCH_2-$), 5.31–5.45 (m, 1H, –CH–), 7.65 (d, 6.08 Hz, 2H, Ar), 7.82 (d, 6.08 Hz, 2H, Ar). ^{13}C NMR (100 MHz $CDCl_3$): δ 12.53, 14.35, 38.02, 64.40, 78.47, 79.22, 100.11, 126.23, 126.87, 127.38, 127.91, 129.38, 139.20, 154.52, 159.14, 162.11; Anal. calcd. for $C_{16}H_{17}ClN_2O_3S$: C, 54.46; H, 4.86; N; 7.94. Found: C, 53.66; H, 5.32; N, 8.58.

4-(((3-(2,4-Dichlorophenyl)-4,5-dihydroisoxazol-5-yl)methoxy)methyl)-3-methyl-5-(methylthio)isoxazole (Xf). Obtained from (**VI**) (0.98 g, 5 mmol), oxime (**VIIIf**) (0.95 g, 5 mmol) and Chloramine-T·$3H_2O$ (1.42 g, 5 mmol) as colorless crystalline solid in 67% (1.3 g) yield. mp 112–113°C; IR (KBr) (ν_{max}, cm^{-1}): 3081, 2962, 1655; ^1H NMR (400 MHz, $CDCl_3$): δ 2.27 (s, 3H, $-CH_3$), 2.50 (s, 3H, $-SCH_3$), 3.17–3.44 (m, 2H, $-CH_2-$), 4.19–4.36 (m, 2H, $-OCH_2-$), 4.48 (s, 2H, $-OCH_2-$), 5.30–5.41 (m, 1H, –CH–), 7.92 (d, 6.08 Hz, 1H, Ar), 8.42 (d, 6.08 Hz, 1H, Ar), 8.76 (s, 1H, Ar). ^{13}C NMR (100 MHz $CDCl_3$): δ 12.40, 13.15, 37.83, 65.13, 77.38, 79.52, 99.61, 127.14, 127.65, 128.16, 131.80, 134.20, 137.30, 155.06, 157.50, 160.27; Anal. calcd. for $C_{16}H_{16}Cl_2N_2O_3S$: C, 49.62; H, 4.16; N; 7.23. Found: C, 50.29; H, 5.06; N, 7.34.

5-(((3-Methyl-5-(methylthio)-1*H*-pyrazol-4-yl)-methoxy)methyl)-3-(*p*-tolyl)-4,5-dihydroisoxazole (XIa). A mixture of 4-((allyloxy)methyl)-3-methyl-5-(methylthio)-1*H*-pyrazole (**VII**) (0.99 g, 5 mmol), oxime (**VIIIa**) (0.68 g, 5 mmol) and Chloramine-T·$3H_2O$ (1.42 g, 5 mmol) in ethanol (30 mL) were refluxed under stirring for 4 h. TLC monitored the progress of the reaction. After completion the reactions the solvent was then concentrated under reduced pressure. The residual mass was extracted into ether (25 mL), washed successively with water (2 × 20 mL) and 10%

NaOH solution (10 mL), brine solution (2 × 15 mL) and dried over anhydrous sodium sulphate. Ether was evaporated and the crude product was purified by column chromatography using chloroform/acetone (9 : 1) as eluent to give the product (**XIa**) as white crystalline solid in 72% (1.2 g) yield. mp 63–65°C; IR (KBr) (ν_{max}, cm^{-1}): 3218, 3088, 2849, 1602; ^1H NMR (400 MHz, $CDCl_3$): δ 2.00 (s, 3H, $-CH_3$), 2.18 (s, 3H, $-CH_3$), 2.64 (s, 3H, $-SCH_3$), 3.13–3.28 (m, 2H, $-CH_2-$), 4.22–4.46 (m, 2H, $-OCH_2-$), 4.55 (s, 2H, $-OCH_2-$), 5.19–5.28 (m, 1H, –CH–), 7.34 (d, 8.2 Hz, 2H, Ar), 7.56 (d, 8.2 Hz, 2H, Ar), 11.24 (br, 1H, –NH). ^{13}C NMR (100 MHz $CDCl_3$): δ 12.17, 12.81, 21.66, 38.42, 64.30, 75.23, 75.80, 111.32, 128.32, 128.50, 128.77, 129.31, 131.12, 140.23, 142.14, 153.12, 155.67; Anal. calcd. for $C_{17}H_{21}N_3O_2S$: C, 61.61; H, 6.39; N; 12.68. Found: C, 60.20; H, 6.51; N, 12.02.

5-(((3-Methyl-5-(methylthio)-1*H*-pyrazol-4-yl)-methoxy)methyl)-3-(3,4,5-trimethoxyphenyl)-4,5-dihydroisoxazole (XIb). Obtained from (**VII**) (0.98 g, 5 mmol) oxime (**VIIIb**) (0.68 g, 5 mmol) and Chloramine-T·$3H_2O$ (1.42 g, 5 mmol) as colorless crystalline solid in 64% (1.3 g) yield. mp 67–68°C; IR (KBr) (ν_{max}, cm^{-1}): 3170, 3042, 2958, 1610; ^1H NMR (400 MHz, $CDCl_3$): δ 2.07 (s, 3H, $-CH_3$), 2.92 (s, 3H, $-SCH_3$), 3.20–3.34 (m, 2H, $-CH_2-$), 3.84 (s, 9H, $-OCH_3$), 4.23–4.40 (m, 2H, $-OCH_2-$), 4.53 (s, 2H, $-OCH_2-$), 5.09–5.33 (m, 1H, –CH–), 7.52 (s, 2H, Ar), 10.12 (br, 1H, –NH). ^{13}C NMR (100 MHz $CDCl_3$): δ 13.05, 14.31, 39.02, 54.31, 55.12, 55.82, 64.14, 74.60, 77.23, 104.33, 104.60, 115.11, 127.16, 138.44, 143.25, 151.20, 153.41, 154.22, 158; Anal. calcd. for $C_{19}H_{25}N_3O_5S$: C, 56.00; H, 6.18; N; 10.31. Found: C, 56.81; H, 5.62; N, 9.75.

5-(((3-Methyl-5-(methylthio)-1*H*-pyrazol-4-yl)-methoxy)methyl)-3-(4-nitrophenyl)-4,5-dihydroisoxazole (XIc). Obtained from (**VII**) (0.98 g, 5 mmol), oxime (**VIIIc**) (0.68 g, 5 mmol) and Chloramine-T·$3H_2O$ (1.42 g, 5 mmol) as colorless crystalline solid in 46% (0.83 g) yield. mp 83–84°C; IR (KBr) (ν_{max}, cm^{-1}): 3120, 3076, 2930, 1644; ^1H NMR (400 MHz, $CDCl_3$): δ 2.03 (s, 3H, $-CH_3$), 2.40 (s, 3H, $-SCH_3$), 3.28–3.39 (m, 2H, $-CH_2-$), 4.18–4.31 (m, 2H, $-OCH_2-$), 4.49 (s, 2H, $-OCH_2-$), 5.27–5.36 (m, 1H, –CH–), 7.68 (d, 8.08 Hz, 2H, Ar), 7.92 (d, 8.08 Hz, 2H, Ar), 11.86 (br, 1H, –NH). ^{13}C NMR (100 MHz $CDCl_3$): δ 13.03, 14.35, 36.11, 60.12, 76.80, 77.74, 112.66, 127.42, 127.63, 127.82, 127.93, 135.24, 137.13, 151.44, 153.14, 160.08; Anal. calcd. for $C_{16}H_{18}N_4O_4S$: C, 53.03; H, 5.01; N; 15.46. Found: C, 53.90; H, 4.80; N, 15.89.

5-(((3-Methyl-5-(methylthio)-1*H*-pyrazol-4-yl)-methoxy)methyl)-3-(3-nitrophenyl)-4,5-dihydroisoxazole (XId). Obtained from (**VII**) (0.98 g, 5 mmol), oxime (**VIIId**) (0.68 g, 5 mmol) and Chloramine-T·$3H_2O$ (1.42 g, 5 mmol) as colorless crystalline solid in 51% (0.92 g) yield. mp 70–72°C; IR (KBr) (ν_{max}, cm^{-1}): 3202, 3070, 2816, 1590; ^1H NMR (400 MHz, $CDCl_3$): δ 2.16 (s, 3H, $-CH_3$), 2.60 (s, 3H, $-SCH_3$), 3.24–3.36 (m, 2H, $-CH_2-$), 4.16–4.32 (m, 2H, $-OCH_2-$), 4.45 (s, 2H, $-OCH_2-$), 5.21–5.46 (m, 1H, –CH–), 7.63–8.30 (m, 4H, Ar), 11.24 (br, 1H, –NH). ^{13}C NMR (100 MHz $CDCl_3$): δ 12.09, 13.44, 37.21, 63.55, 74.31, 75.33, 115.51, 121.40, 125.17, 126.62, 132.47, 134.13, 140.18, 146.15, 154.03, 159.21; Anal. calcd. for $C_{16}H_{18}N_4O_4S$: C, 53.03; H, 5.01; N; 15.46. Found: C, 53.64; H, 5.52; N, 14.93.

3-(4-Chlorophenyl)-5-(((3-methyl-5-(methylthio)-1*H*-pyrazol-4-yl)methoxy)methyl)-4,5-dihydroisoxazole (XIe). Obtained from (**VII**) (0.98 g, 5 mmol), oxime (**VIIIe**) (0.68 g, 5 mmol) and Chloramine-T·$3H_2O$ (1.42 g, 5 mmol) as colorless crystalline solid in 59% (1.03 g) yield. mp 92–93°C; IR (KBr) (ν_{max}, cm^{-1}): 3183, 3035, 2910, 1571; ^1H NMR (400 MHz, $CDCl_3$): δ 2.20 (s, 3H, $-CH_3$), 2.45 (s, 3H, $-SCH_3$), 3.30–3.47 (m, 2H, $-CH_2-$), 4.23–4.39 (m, 2H, $-OCH_2-$), 4.61 (s, 2H, $-OCH_2-$), 5.28–5.41 (m, 1H, –CH–), 7.80 (d, 8.08 Hz, 2H, Ar), 7.96 (d, 8.08 Hz, 2H, Ar), 11.08 (br, 1H, –NH). ^{13}C NMR (100 MHz $CDCl_3$): δ 12.42, 13.74, 37.46, 62.33, 77.11, 76.98, 115.11, 126.31, 126.90, 127.04, 127.34, 134.10, 139.23, 153.63, 159.81; Anal. calcd. for $C_{16}H_{18}ClN_3O_2S$: C, 54.62; H, 5.16; N; 11.94. Found: C, 53.91; H, 5.23; N, 10.86.

3-(2,4-Dichlorophenyl)-5-(((3-methyl-5-(methylthio)-1*H*-pyrazol-4-yl)methoxy)methyl)-4,5-dihydroisoxazole (XIf). Obtained from (**VII**) (0.98 g, 5 mmol), oxime (**VIIIf**) (0.68 g, 5 mmol) and Chloramine-T·$3H_2O$ (1.42 g, 5 mmol) as colorless crystalline solid in 73% (1.4 g) yield. mp 90–91°C; IR (KBr) (ν_{max}, cm^{-1}): 3134, 3060, 2893, 1647; ^1H NMR (400 MHz, $CDCl_3$): δ 2.05 (s, 3H, $-CH_3$), 2.41 (s, 3H, $-SCH_3$), 3.25–3.39 (m, 2H, $-CH_2-$), 4.26–4.41 (m, 2H, $-OCH_2-$), 4.92 (s, 2H, $-OCH_2-$), 5.13–5.32 (m, 1H, –CH–), 7.77 (d, 6.02 Hz, 1H, Ar), 7.78 (d, 6.02 Hz, 1H, Ar), 8.53 (s, 1H, Ar), 11.31 (br, 1H, –NH). ^{13}C NMR (100 MHz $CDCl_3$): δ 11.93, 12.23, 36.70, 64.25, 76.90, 78.21, 116.41, 127.25, 127.48, 128.20, 132.11, 133.53, 135.12, 143.09, 154.63, 159.31; Anal. calcd. for $C_{16}H_{17}Cl_2N_3O_2S$: C, 49.75; H, 4.44; N; 10.88. Found: C, 48.13; H, 4.78; N, 11.46.

Biological Activity. DPPH Radical Scavenging Activity

Antioxidant activity of compounds was determined using $DPPH^•$ as described by Blios [24]. All the synthetic compounds were taken at a concentration of 10 μg/mL and mixed with 5 mL of 0.1 mM methanolic solution of DPPH and incubated at 20°C for 20 min in darkness. The control was prepared as above without a compound, and methanol was used for the base line correction. Changes in the absorbance of the samples

were measured at 517 nm using UV–visible spectrophotometer (Shimadzu 160A). All the tests were performed in duplicates. RSA was expressed as percentage activity using the formula

$$\text{RSA } (\%) = \left[\left(A_0 - A_1/A_0 \times 100\right)\right],$$

where A_0 is the measurement of DPPH solution without compound and A_1 the measurement of DPPH solution with compound. The RSA of ascorbic acid was also measured and compared with all **s**ynthesized compounds.

Anti-Lipid Peroxidation

A modified TBARS assay was used to measure lipid peroxides formed using egg yolk homogenates as lipid-rich media [25]. Malonaldehyde, a secondary product of oxidation of polyunsaturated fatty acid reacts with two molecules of thiobarbutric acid (TBA) yielding a pinkish red chromogen with absorbance maxima at 540 nm. In this method, 0.5 mL of egg yolk homogenate, 10% distilled water and various concentrations of compound ranging 40μg/mL were mixed in the test tube and the volume was made upto 1mL using distilled water. Finally, 0.05 mL 0.07 M of $FeSO_4$ was added to the above mixture and incubated for 30 min to induce lipid peroxidation. Thereafter, 1.5 mL of 20% acetic acid (pH adjusted to 3.5 with NaOH) and 1.5 mL of 0.8% TBA and 0.05 mL of 20% TCA were added, vertexed and heated in a boiling water bath for 60 min. After cooling, 5mL of butanol was added to each tube and centrifuged at 3000 rpm for 10 min. The absorbance of the organic layer was measured at 530 nm. All the tests were performed in triplicates. Water is used in the place of synthesized compounds which served as control. Vitamin E was used as a positive control and compared. The percentage of inhibition was calculated using the formula

$$\text{Anti-lipid peroxidation } (\%) = \left(1 - E/C\right) \times 100,$$

where C is the absorbance of oxidized control, E the absorbance in the presence of compound.

Anti-Bacterial Activity

The in vitro anti-bacterial activity of synthesized compounds (**Xa–f**) and (**XIa–f**) was screened using the agar disc diffusion method.[26] Briefly, a suspension of the test microorganism (0.1 mL of 10^8 cells/mL) was spread on the solid media plates. Filter paper discs (6 mm in diameter) were impregnated with synthetic compounds at the concentration 100 μg/mL and placed on the inoculated plates and, after allowing at 4°C for 2 h, they were incubated at 37°C for 24 h. The diameters of the inhibition zones were measured in millimetres. *Ciprofloxacin* was used as the standard drug. The test microbial strains used are *E. coli* NCIM 2065, *S. aureus* NCIM 2079, *B. subtilis* NCIM 2063, *P. aeruginosa* NCIM 5029. To ensure that the solvent had no effect on bacterial growth, a control test was performed with test medium supplemented with ethanol and DMSO at the same dilution used in the experiments. The data represent mean value (SEM) of duplicate test.

CONCLUSIONS

The series of desired compounds, Isoxazole ether-linked Isoxazoline derivatives (**Xa–f**) and pyrazole ether-linked Isoxazoline derivatives (**XIa–f**) were synthesized. All the obtained compounds were effectively characterized by elemental analysis, IR, ^{1}H NMR, and ^{13}C NMR. These compounds were tested for their in vitro antibacterial and antioxidant activities. Isoxazole ether-linked Isoxazole derivatives (**Xc**) and (**Xd**), and Pyrazole ether-linked Izoxazoline derivatives (**XIc**) and (**XIc**) having Nitro groups on the phenyl ring at meta/para position demonstrated potent antioxidant, potent anti-lipid peroxidation and showed maximum anti-bacterial activity in comparison with their corresponding standard drug. This may be explained as the properties of the nitro group considerably depend on both its orientation with respect to the benzene ring as well as on the substituent in the para-position. The nitro group lies in the plane of the benzene ring for only a small number of molecules, whereas the mean value of the twist angle is 7.3 deg, mostly due to intermolecular interactions in the crystals. This distortion from planarity and the nature of para-substituent influences the aromaticity of the ring and properties of the nitro group due to electronic effects [45]. The results also revealed that the other compounds displayed good to moderate along with low or no inhibition. Further detailed studies are required to understand the mechanism of action of these compounds.

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COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any studies involving human participants performed by any of the authors and does not contain any studies involving animals performed by any of the authors.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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