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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NOVEL IMIDAZOLE BEARING ISOXAZOLE DERIVATIVES

HITENDRA K. MAHETA[a], ANIL S. PATEL and YOGESH T. NALIAPARA[*]

Department of Chemistry, Saurashtra University, RAJKOT – 360005 (Guj.) INDIA
[a]Department of Chemistry, Singhania University, JHUNJHUNU – 333515 (Raj.) INDIA

ABSTRACT

A series of 1-(4-methoxybenzyl)-2-butyl-4-chloro-5-(3-arylisoxazol-5-yl)-1*H*-imidazoles **(4a-l)** were prepared by condensing 3-(1-(4-methoxybenzyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)-1-aryl-2-en-1-one **(3a-l)** with hydroxylamine hydrochloride in presence of 40% sodium hydroxide in methanol. Some of these compounds showed potential antimicrobial activity.

Key words: Chalcones, Imidazole, Isoxazoles, Antimicrobial activity.

INTRODUCTION

In recent years, attention has increasingly been given to the synthesis of isoxazole derivatives as a source of new antibacterial agents. The synthesis of novel isoxazole derivatives remains a main focus of medicinal research. Isoxazole derivatives have been reported to possess antioxidant[1], antiinflammatory[2], antibacterial[3], antimicrobial[4-6], antiulcer[7], anthelmintics[8], anticancer[9,10], antiviral[11], antitubercular[12] and anti-HIV[13] properties. Isoxazole are potent, selective agonists at human cloned dopamine D4 receptors[14] and exhibit GABAA antagonist[15], analgesic[16], antifungal,[17] COX-2 inhibitory[18,19] and antinociceptive[20] properties.

Many synthetic methods have been employed in the synthesis of isoxazoles[21], including reactions of hydroxylamine with 1,3-dicarbonyl compounds[22], *α,β*-unsaturated carbonyl compounds[23], and *α,β*-unsaturated nitriles[24]. The reaction of an oxime-derived dianion and an ester[25] or amide[26,27] also provides isoxazoles[28,29].

[*]Author for correspondence; E-mail: naliaparachem@yahoo.co.in, hmaheta03@yahoo.com;
Fax: 91-281-2576802

Encouraged by the diverse biological activities of imidazole bearing isoxazole compounds, it was decided to prepare a new series of imidazole containing isoxazoles. The classical synthesis of the title compound involves the base-catalyzed condensation of substituted aromatic aldehydes and substituted ketones to give α,β-unsaturated ketones (chalcones), which on cyclisation with hydroxylamine hydrochloride in alkaline medium give corresponding isoxazole derivatives.

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. Thin layer chromatography using silica gel G (E. Merck) plates was used to access the reactions and purity of the synthesized compounds. All the products have been characterized by elemental analysis, IR, ^{1}H NMR and mass spectral study. IR spectra were recorded on Shimadzu FTIR-8400 spectrophotometer in KBr disc and noteworthy absorption levels (cm^{-1}) are listed. ^{1}H NMR spectra were recorded on Bruker spectrometer (400 MHz) using TMS as an internal standard, chemical shift in δ ppm. Mass spectra were determined using direct inlet probe on a GCMS-QP2010 mass spectrometer, Elemental analysis was performed on a Carlo Erba EA 1108 elemental analyzer.

General synthetic procedure for (3a-l)

1-(4-Methoxybenzyl)-2-butyl-4-chloro-1*H*-imidazole-5-carbaldehyde **(1)** (0.01 mol) was dissolved in methanol (50 mL). To this, aryl acetophenone **(2)** (0.01 mol was added. The content was stirred at room temperature for 24 hr in presence of catalytical amount of 40% NaOH. The progress of reaction was monitored on TLC and resulting solution was poured on to crushed ice; thus, the solid seprated was filtered and crystallized from methanol/ethanol.

(3a) (E)-3-(2-Butyl-4-chloro-1-(4-methoxybenzyl)-1H-imidazol-5-yl)-1-phenylprop-2-en-1-one, Yellow solid; yield: 87%; mp 178-180°C; R_f 0.78; Anal. Calcd. for $C_{24}H_{25}ClN_2O_2$: C, 70.49; H, 6.16; N, 6.85; Found: C, 70.50; H, 6.12; N, 6.78; IR,(KBr, cm^{-1}): 1680 (C=O), 1500 (C=C), 3065 (Aromatic ring), 1637 (C=N); ^{1}H NMR ($CDCl_3$) δ *ppm* : 0.88 (3H, t, CH_3 of butyl), 1.34 (2H, m, CH_2 of butyl), 1.66 (2H, m, CH_2 of butyl), 2.64 (2H, t, CH_2 of butyl), 3.87 (3H, s, -OCH_3), 5.17 (2H, s, Ar-CH_2), 6.86 (6H, d, Ar-H), 7.54 (1H, dd, CH=CH), 7.71 (1H, dd, CH=CH) and 7.91 (3H, d, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ /ppm): 20.02, 35.55, 42.94, 54.92, 114.11, 120.33, 130.61, 146.88, 157.60, 178.32: MS: m/z 408 (M^+).

(3b) (E)-3-(2-Butyl-4-chloro-1-(4-methoxybenzyl)-1H-imidazol-5-yl)-1-(p-tolyl) prop-2-en-1-one, Yellow solid; yield: 79%; mp 153-155°C; R_f 0.88; Anal. Calcd. for $C_{25}H_{27}ClN_2O_2$: C, 70.99; H, 6.43; N, 6.62; Found: C, 70.90; H, 6.42; N, 6.72; IR,

(KBr, cm^{-1}): 1650 (C=O), 1573 (C=C), 2954 (CH_3), 2837 (Aromatic ring), 1589 (C=N); ^1H NMR($CDCl_3$) δ *ppm* : 0.78 (3H, t, CH_3 of butyl), 1.25 (2H, m, CH_2 of butyl), 1.57 (2H, m, CH_2 of butyl), 2.39 (3H, s, CH_3 of phenyl), 2.55 (2H, t, CH_2 of butyl), 3.67 (3H, s, OCH_3), 5.08 (2H, s, Ar-CH_2), 6.77 (4H, d, Ar-H), 7.33 (2H, d. Ar-H), 7.43 (1H, dd, CH=CH), 7.45 (1H, dd, CH=CH), 7.60 (2H, d, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ / ppm): 24.44, 30.90, 33.99, 46.90, 57.21, 110.90, 134.25, 148.09, 151.26, 160.10, 192.90. MS: m/z 423 (M^+).

(3c) (E)-3-(2-Butyl-4-chloro-1-(4-methoxybenzyl)-1H-imidazol-5-yl)-1-(4-methoxy phenyl) prop-2-en-1-one, Yellow solid; yield: 83%; mp 138-143°C; R_f 0.84; Anal. Calcd. for $C_{25}H_{27}ClN_2O_3$: C, 68.41; H, 6.20; N, 6.38; Found: C, 68.30; H, 6.22; N, 6.32; IR,(KBr, cm^{-1}): 1666 (C=O), 1614 (C=C), 2999 (CH_3), 2729 (Aromatic ring), 1487 (C=N); ^1H NMR($CDCl_3$) δ *ppm* : 0.88 (3H, t, CH_3 of butyl), 1.34 (2H, m, CH_2 of butyl), 1.66 (2H, m, CH_2 of butyl), 2.64 (2H, t, CH_2 of butyl), 3.78 and 3.87 (6H, s, OCH_3), 4.97 (2H, s, Ar-CH_2), 6.88 (6H, d, Ar-H), 7.54 (2H, d. CH=CH), 7.71 (2H, d, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ / ppm): 14.44, 30.33, 36.01, 55.90, 112.15, 123.00, 128.90, 136.21, 144.60, 164.88, 189.77, MS: m/z 439 (M^+).

General synthesis procedure for (4a-l)

In a solution of 3-(1-(4-methoxybenzyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl)-1-aryl-2-en-1-one (0.01 mol) in methanol (50 mL), hydroxylamine hydrochloride (0.01 mol) was added. The reaction mixture was refluxed on oil bath for 8 hrs. in the presence of 40 % NaOH. The reaction was monitored by TLC. The excess solvent was distilled out; there after, reaction mixture was cooled and poured on to crushed ice. The product was isolated and crystallized from ethanol/methanol/isopropyl alcohol.

(4a) 1-(4-Methoxybenzyl)-2-butyl-4-chloro-5-(3-phenylisoxazol-5-yl)-1H-midazole. Yellow solid; yield: 71%; mp 180-183°C; R_f 0.62; Anal. Calcd. for $C_{24}H_{24}ClN_3O_2$: C, 68.32; H, 5.73; N, 9.96; Found: C, 68.30; H, 5.72; N, 9.92; IR (KBr, cm^{-1}): 2860 (Aromatic ring), 1799 (C-O stretching), 1579 (C-N stretching), 1460 (Aromaic C=C stretching), 761 (C-Cl stretching); ^1H NMR (400 MHz $CDCl_3$ +DMSO-d6, δ/ppm): 0.78-0.82 (t, 3H, CH_3 of butyl), 1.25-1.30 (m, 2H, CH_2 of butyl), 1.57–1.63 (m, 2H, CH_2 of butyl), 2.55-2.59 (t, 2H, CH_2 of butyl), 3.67 (s, 3H, OCH_3), 5.08 (s, 2H, phenyl-CH_2), 6.77-6.87 (d, 4H, phenyl-H), 7.18 (s, 1H, Isoxazole), 7.33-7.64 (m, 5H, phenyl-H); ^{13}C NMR (100 MHz, $CDCl_3$, δ/ppm): 16.21, 23.95, 32.92, 53.45, 117.09, 120.55, 129.46, 133.01, 148.88. 153.50, 160.10: MS: m/z 422 (M^+).

(4b) 1-(4-Methoxybenzyl)-2-butyl-4-chloro-5-(3-4-methylphenylisoxazol-5-yl)-1H-imidazole. Off white solid; yield: 65%; mp 174-176°C; R_f 0.61; Anal. Calcd. for

$C_{25}H_{26}ClN_3O_2$: C, 68.88; H, 6.01; N, 9.64; Found: C, 68.85; H, 5.88; N, 9.60; IR (KBr, cm^{-1}): 3316, 2852 (Aromatic ring), 1655 (C-O stretching), 1598 (C-N stretching), 1543, 1506 (Aromatic C=C stretching), 731 (C-Cl stretching); ^{1}H NMR (400 MHz $CDCl_3$ + DMSO-d6, δ/ppm): 0.77-0.81 (t, 3H, CH_3 of butyl), 1.23–1.28 (m, 2H, CH_2 of butyl), 1.56-1.61 (m, 2H, CH_2 of butyl), 2.39 (s, 3H, phenyl-CH_3), 2.54-2.58 (m, 2H, CH_2 of butyl), 3.67 (s, 3H, phenyl-OCH_3), 4.80 (s, 2H, phenyl-CH_2), 6.64-6.66 (m, 4H, phenyl-H), 6.85 (s, 1H, Isoxazole), 7.43-7.44 (m, 4H, phenyl-H); ^{13}C NMR (100 MHz, $CDCl_3$, δ/ppm): 15.11, 25.48, 30.22, 55.90, 122.11, 126.92, 133.92, 140.54, 152.02, 156.09, 162.72. MS: m/z 436 (M^+).

(4c) 1-(4-Methoxybenzyl)-2-butyl-4-chloro-5-(3-(4-methoxyphenyl)isoxazol-5-yl]-1H-imidazole. Pale yellow solid; yield 68%; mp 186-172°C; R_f 0.68; Anal. Calcd. for $C_{25}H_{26}ClN_3O_3$: C, 66.44; H, 5,80; N, 9.30; Found: C, 66.42; H, 5,78; N, 9.28; IR (KBr, cm^{-1}): 2954, 2837 (Aromatic ring), 1649 (C-O stretching), 1589 (Aromatic C=C stretching), 1573 (C-N stretching), 777 (C-Cl stretching); ^{1}H NMR (400 MHz $CDCl_3$ + DMSO-d6, δ/ppm): 0.87-0.92 (t, 3H, CH_3 of butyl), 1.33–1.40 (m, 2H, CH_2 of butyl), 1.65–1.74 (m, 2H, CH_2 of butyl), 2.56-2.61 (t, 2H, CH_2 of butyl), 3.72 and 3.83 (s, 6H, phenyl-OCH_3), 5.12 (s, 2H, phenyl-CH_2), 6.71-6.73 (d, 2H, phenyl-H), 6.83–6.89 (d, 4H, phenyl-H), 7.26 (s, 1H, Isoxazole), 7.42-7.44 (d, 2H, phenyl-H); ^{13}C NMR (100 MHz, $CDCl_3$, δ/ppm): 17.04, 22.81, 36.66, 52.43, 119.94, 122.73, 131.00, 144.06, 149.34, 150.11, 166.22. MS: m/z 452 (M^+).

(4d) 1-(4-Methoxybenzyl)-2-butyl-4-chloro-5-(3-(2-hydroxyphenyl)isoxazol-5-yl)-1H-imidazole. Yellow solid; yield: 59%; mp 165-170°C; R_f 0.52; Anal. Calcd for $C_{24}H_{24}ClN_3O_3$: C, 65.82; H, 5.52; N, 9.60; Found: C, 65.80; H, 5.50; N, 9.58; IR (KBr, cm^{-1}): 2944 (OH stretching), 2830 (Aromatic ring), 1630 (C-O stretching), 1580 (Aromatic C=C stretching), 1563 (C-N stretching), 777 (C-Cl stretching); ^{1}H NMR (400 MHz $CDCl_3$ + DMSO-d6, δ/ppm): 0.78-0.83 (t, 3H, CH_3 of butyl), 1.36–1.44 (m, 2H, CH_2 of butyl), 1.44–1.57 (m, 2H, CH_2 of butyl), 2.36-2.41 (t, 2H, CH_2 of butyl), 3.78 (s, 3H, phenyl-OCH_3), 5.09 (s, 2H, phenyl-CH_2), 6.64-6.70 (d, 2H, phenyl-H), 6.78–6.82 (d, 4H, phenyl-H), 7.12 (s, 1H, Isoxazole), 7.44-7.48 (d, 2H, phenyl-H); 8.90 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$, δ/ppm): 14.12, 26.10, 33.43, 55.21, 114.72, 125.88, 137.95, 147.30, 154.21, 165.01. MS: m/z 438 (M^+).

(4e) 1-(4-Methoxybenzyl)-2-butyl-4-chloro-5-(3-(4-hydroxyphenyl)isoxazol-5-yl)-1H-imidazole. Yellow solid; yield: 59%; mp 160-165°C; R_f 0.66; Anal. Calcd for $C_{24}H_{24}ClN_3O_3$: C, 65.82; H, 5.52; N, 9.60; Found: C, 65.79; H, 5.49; N, 9.57; IR (KBr,cm^{-1}): 2947 (OH stretching), 2835 (Aromatic ring), 1640 (C-O stretching), 1554 (C-N stretching), 1523 (Aromatic C=C stretching), 797 (C-Cl stretching); ^{1}H NMR (400 MHz $CDCl_3$ +

DMSO-d6, δ/ppm): 0.76-0.85 (t, 3H, CH_3 of butyl), 1.33–1.40 (m, 2H, CH_2 of butyl), 1.40–1.51 (m, 2H, CH_2 of butyl), 2.40-2.44 (t, 2H, CH_2 of butyl), 3.88 (s, 3H, phenyl-OCH_3), 4.98 (s, 2H, phenyl-CH_2), 6.66-6.74 (d, 2H, phenyl-H), 6.80–6.85 (d, 4H, phenyl-H), 7.22 (s, 1H, Isoxazole), 7.50-7.58 (d, 2H, phenyl-H); 8.98 (s, 1H, phenyl-OH); ^{13}C NMR (100 MHz, $CDCl_3$, δ/ppm): 12.98, 22.94, 34.90, 52.87, 111.93, 120.76, 135.70, 144.44, 151.75. 162.97. MS: m/z 438 (M^+).

(4f) 1-(4-Methoxybenzyl)-2-butyl-4-chloro-5-(3-(4-chlorophenyl)isoxazol-5-yl)-1H-imidazole. Off white solid; yield: 42%; mp:192-194°C; R_f 0.56; Anal. Calcd for $C_{24}H_{23}Cl_2N_3O_2$: C, 63.16; H, 5.08; N, 9.21; Found: C, 63.13; H, 5.06; N, 9.19; IR (KBr, cm^{-1}): 2967, 2735 (Aromatic ring), 1697 (C-O stretching), 1534 (C-N stretching), 1512 (Aromatic C=C stretching), 789 (C-Cl stretching); ^{1}H NMR (400 MHz $CDCl_3$+DMSO-d6, δ/ppm): 0.81-0.88 (t, 3H, CH_3 of butyl), 1.40–1.46 (m, 2H, CH_2 of butyl), 1.48–1.57 (m, 2H, CH_2 of butyl), 2.56-2.62 (t, 2H, CH_2 of butyl), 3.65 (s, 3H, phenyl-OCH_3), 5.17 (s, 2H, phenyl-CH_2), 6.24-6.66 (m, 6H, phenyl-H), 7.37 (s, 1H, Isoxazole), 7.44-7.51 (d, 2H, phenyl-H); ^{13}C NMR (100 MHz, $CDCl_3$, δ/ppm): 15.76, 27.03, 30.99, 58.21, 117.33, 128.92, 138.56, 149.02, 157.53. 165.03. MS: m/z 456 (M+).

(4g) 1-(4-Methoxybenzyl)-2-butyl-4-chloro-5-(3-(4-bromophenyl)isoxazol-5-yl)-1H-imidazole. Light brown solid; yield: 60%; mp: 185-188°C; R_f 0.48; Anal. Calcd for $C_{24}H_{23}BrClN_3O_2$: C, 57.56; H, 4.63; N, 8.39; Found: C, 57.54; H, 4.61; N, 8.36; IR (KBr, cm^{-1}): 2767, 2335 (Aromatic ring), 1607 (C-O stretching), 1521 (C-N stretching), 1478, 1460 (Aromatic C=C stretching), 680 (C-Br stretching), 787 (C-Cl stretching); ^{1}H NMR (400 MHz $CDCl_3$ + DMSO-d6, δ/ppm): 0.88-0.92 (t, 3H, CH_3 of butyl), 1.36–1.44 (m, 2H, CH_2 of butyl), 1.51–1.66 (m, 2H, CH_2 of butyl), 2.66-2.71 (t, 2H, CH_2 of butyl), 3.88 (s, 3H, phenyl-OCH_3), 5.02 (s, 2H, phenyl-CH_2), 6.68-6.77 (m, 6H, phenyl-H), 7.26 (s, 1H, Isoxazole), 7.56-7.58 (d, 2H, phenyl-H); ^{13}C NMR (100 MHz, $CDCl_3$, δ/ppm): 13.61, 24.78, 31.28, 55.90, 110.94, 124.79, 135.41, 151.97, 155.92. 160.73. MS: m/z 501 (M^+).

(4h) 1-(4-Methoxybenzyl)-2-butyl-4-chloro-5-(3-(4-fluorophenyl)isoxazol-5-yl)-1H-imidazole. Pale yellow solid; yield: 55%; mp: 180-183°C; R_f 0.45; Anal. Calcd for $C_{24}H_{23}FClN_3O_2$: C, 65.53; H, 5.27; N, 9.55; Found: C, 65.50; H, 5.25; N, 9.52; IR (KBr, cm^{-1}): 2834 (Aroomatic ring), 1690 (C-O stretching), 1543 (C-N stretching), 1484, 1434 (Aromatic C=C stretching), 776 (C-F stretching), 878 (C-Cl stretching); ^{1}H NMR (400 MHz $CDCl_3$ + DMSO-d6, δ/ppm): 0.68-0.77 (t, 3H, CH_3 of butyl), 1.27-1.38 (m, 2H, CH_2 of butyl), 1.55-1.59 (m, 2H, CH_2 of butyl), 2.60-2.65 (t, 2H, CH_2 of butyl), 3.60 (s, 3H, phenyl-OCH_3), 4.87 (s, 2H, phenyl-CH_2), 6.25-6.46 (d, 4H, phenyl-H), 7.33 (s, 1H, Isoxazole),

7.51-7.54 (d, 4H, phenyl-H); ^{13}C NMR (100 MHz, $CDCl_3$, δ/ppm): 16.76, 22.48, 34.80, 57.21, 119.42, 128.71, 132.56, 153.77, 157.03. 164.08. MS: m/z 440 (M^+).

(4i) 1-(4-Methoxybenzyl)-2-butyl-4-chloro-5-(3-(3-aminophenyl)isoxazol-5-yl)-1H-imidazole. Yellow solid; yield: 54%; mp: 156-158^{o}C; R_f 0.59; Anal. Calcd for $C_{24}H_{25}ClN_4O_2$: C, 65.97; H, 5.77; N, 12.82; Found: C, 65.95; H, 5.74; N, 12.80; IR (KBr, cm^{-1}): 3440 (-NH stretching of primary amine), 2934, 2785 (Aromatic ring), 1643 (C-O stretching), 1584 (C-N stretching), 1434 (Aromatic C=C stretching), 987 (C-Cl stretching); ^{1}H NMR (400 MHz $CDCl_3$+DMSO-d6, δ/ppm): 0.81-0.90 (t, 3H, CH_3 of butyl), 1.36–1.44 (m, 2H, CH_2 of butyl), 1.48–1.52 (m, 2H, CH_2 of butyl), 2.66-2.73 (t, 2H, CH_2 of butyl), 3.76 (s, 3H, phenyl-OCH_3), 4.90 (s, 2H, phenyl-CH_2), 6.42-6.57 (d, 4H, phenyl-H), 7.44 (s, 1H, Isoxazole), 7.55-7.65 (d, 4H, phenyl-H), 9.88 (s, 2H, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$, δ/ppm): 14.95, 19.98, 37.01, 50.90, 124.78, 131.90, 136.24, 148.51, 162.12. MS: m/z 437 (M^+).

(4j) 1-(4-Methoxybenzyl)-2-butyl-4-chloro-5-(3-(4-aminophenyl)isoxazol-5-yl)-1H-imidazole. Yellow solid; yield: 60%; mp: 182-185^{o}C; R_f 0.59; Anal. Calcd for $C_{24}H_{25}ClN_4O_2$: C, 65.97; H, 5.77; N, 12.82; Found: C, 65.94; H, 5.75; N, 12.79; IR (KBr, cm^{-1}): 3437 (-NH stretching of primary amine), 2930, 2775 (Aromatic ring), 1653 (C-O stretching), 1594 (C-N stretching), 1464 (Aromatic C=C stretching), 977 (C-Cl stretching); ^{1}H NMR (400 MHz $CDCl_3$+DMSO-d6, δ/ppm): 0.88-0.92 (t, 3H, CH_3 of butyl), 1.30–1.36 (m, 2H, CH_2 of butyl), 1.44–1.48 (m, 2H, CH_2 of butyl), 2.60-2.66 (t, 2H, CH_2 of butyl), 3.87 (s, 3H, phenyl-OCH_3), 4.86 (s, 2H, phenyl-CH_2), 6.40-6.46 (d, 4H, phenyl-H), 7.40 (s, 1H, Isoxazole), 7.48-7.52 (d, 4H, phenyl-H), 9.90 (s, 2H, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$, δ/ppm): 14.09, 18.99, 36.90, 50.54, 123.99, 131.78, 134.20, 145.15, 161.90. MS: m/z 437 (M^+).

(4k) 1-(4-Methoxybenzyl)-2-butyl-4-chloro-5-(3-(3-nitrophenyl)isoxazol-5-yl)-1H-imidazole. Light yellow solid; yield: 51%; mp: 195-197^{o}C; R_f 0.73; Anal. Calcd for $C_{24}H_{23}ClN_4O_4$: C, 61.74; H, 4.97; N, 12.00; Found: C, 61.72; H, 4.94; N, 11.98; IR (KBr, cm^{-1}): 2964, 2865, 2490 (Aromatic ring), 1689 (C-O stretching), 1575 (C-N stretching), 1478 (Aromatic C=C stretching), 890 (C-Cl stretching); ^{1}H NMR(400 MHz $CDCl_3$+DMSO-d6, δ/ppm): 0.76-0.81 (t, 3H, CH_3 of butyl), 1.26–1.32 (m, 2H, CH_2 of butyl), 1.66–1.68 (m, 2H, CH_2 of butyl), 2.44-2.48 (t, 2H, CH_2 of butyl), 3.60 (s, 3H, phenyl-OCH_3), 4.90 (s, 2H, phenyl-CH_2), 6.44-6.52 (d, 6H, phenyl-H), 7.26 (s, 1H, Isoxazole), 7.50-7.55 (d, 2H, phenyl-H); ^{13}C NMR (100 MHz, $CDCl_3$, δ/ppm): 12.92, 15.72, 33.99, 53.81, 120.94, 135.75, 137.98, 144.05, 156.92. MS: m/z 467 (M^+).

(4l) 1-(4-Methoxybenzyl)-2-butyl-4-chloro-5-(3-(4-nitrophenyl) isoxazol-5-yl)-1H-imidazole. Yellow solid; yield: 52%; mp: 190-194°C; R_f 0.73; Anal. Calcd for $C_{24}H_{23}ClN_4O_4$: C, 61.74; H, 4.97; N, 12.00; Found: C, 61.71; H, 4.95; N, 11.97; IR (KBr, cm^{-1}): 2956, 2845, 2460 (Aromatic ring), 1679 (C-O stretching), 1545(C-N stretching), 1454 (Aromatic C=C stretching), 879 (C-Cl stretching); ^{1}H NMR (400 MHz $CDCl_3$+DMSO-d6, δ/ppm): 0.78-0.82 (t, 3H, CH_3 of butyl), 1.28–1.34 (m, 2H, CH_2 of butyl), 1.62–1.66 (m, 2H, CH_2 of butyl), 2.40-2.46 (t, 2H, CH_2 of butyl), 3.67 (s, 3H, phenyl-OCH_3), 4.92 (s, 2H, phenyl-CH_2), 6.40-6.46 (d, 6H, phenyl-H), 7.22 (s, 1H, Isoxazole), 7.48-7.52 (d, 2H, phenyl-H); ^{13}C NMR (100 MHz, $CDCl_3$, δ/ppm): 11.90, 14.60, 32.77, 52.56, 119.66, 133.98, 136.81, 143.94, 155.85. MS: m/z 467 (M^+).

RESULTS AND DISCUSSION

Spectroscopy

The synthesis of the title compounds was achieved *via* chalcone formation **(3a-l)** which was generated by the condensation of 1-(4-mthoxybenzyl)-2-butyl-4-chloro-1*H*-imidazole-5-carbaldehyde (**1)** with different aromatic ketones (**2)** in presence of alkaline media in 18-24 hrs with good yields. The presence of chalcone moiety was confirmed by doublets of -CO-CH=CH-Ar at about δ 7.33-7.85 ppm, respectively and disappearance of a singlet at about δ 9.57-9.63 ppm of –CHO in the ^{1}H NMR spectra of compound (**3a-l)**. The structure was further confirmed by the presence of singlet around δ 125 and δ 140 in the ^{13}C NMR. Thus, obtained chalcones **(3a-l)** underwent cyclocondensation with hydroxylamine hydrochloride using NaOH as a basic catalyst to obtain the desired isooxazole derivatives (**4a-l**) in fair to good yields. Final compounds (**4a-l)** were characterized by the ^{1}H and ^{13}C NMR, mass and elemental analysis. The ^{1}H NMR spectrum of compounds (**4a-l)** showed the presence of typical singlet at about δ 6.8-7.5 ppm and disappearance of a doublet at about δ 7.33-7.85 ppm of chalcone.

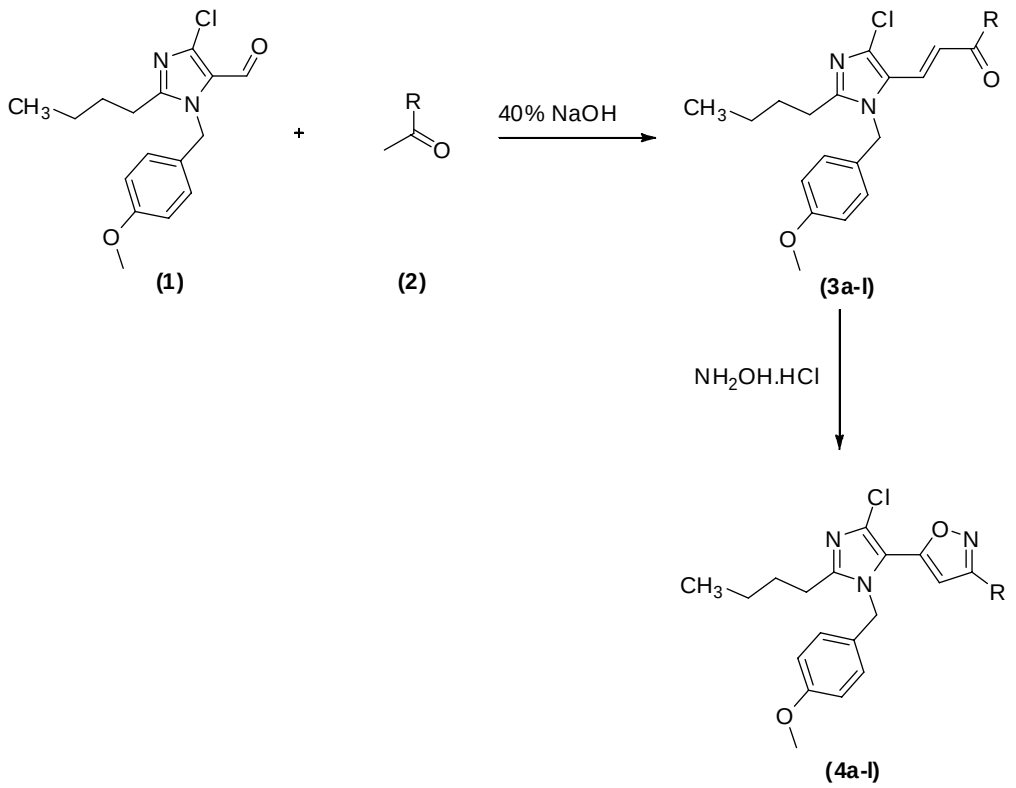
Antimicrobial activity

The antimicrobial activity was carried out by using the cup-plate agar diffusion method[10] by measuring the zone of inhibition in millimeter. All the compounds were screened *in vitro* for their antimicrobial activity against variety of bacterial strain such as *Salmonella typhimurium*, *Bacillus megaterium*, *Staphylo coccus aureus*, *Escherichiacoli* and Fungi *Aspergillus niger* using dimethyl formamide solvent at 50 μg/mL concentration. Standard drugs like ampicillin, chloramphanicol, norfloxacin and greseofulvin were used for comparison purpose.

The screening data indicated that several newly prepared isoxazoles derivatives exhibited significant antibacterial activity against the gram positive (*B.mega or S. typhi*) and gram negative compounds (*E. coli* or *S. aureus*) bacterial strains. Among these, compounds **(4a)** and **(4d)** showed comparable activity that of ampicillin or norfloxacin against *B.mega or S. typhi.* On the other hand, compounds **(4b)**, **(4c)** and **(4h)** showed potent activity against gram negative bacterial strains i.e. *E. coli* or *S.aureus* with the zone inhibition value comparable to positive standard **(4b)**, **(4c)**, **(4h)** vs ampicillin or norfloxacin). Interestingly, among the tested derivatives, **(4c**), **(4f)** and **(4g)** exhibited comparable antifungal activity against *A.niger* strains to that of greseofulvin.

Table 1: Inhibition zone (mean diameter of inhibition) as a criterion of the antibacterial activities of the newly synthesized compounds

Compd.	Zone of inhibition in m. m.				
	Antibacterial activity			Antifungal activity	
	B. mega	***S. aureus***	***S. typhi***	***E. coli***	***A. Niger***
4a	14	**22**	14	15	11
4b	12	10	**21**	10	13
4c	10	12	12	**23**	**20**
4d	**22**	**21**	10	14	13
4e	10	09	00	07	10
4f	12	12	09	10	**23**
4g	10	19	07	16	**20**
4h	08	11	**22**	**24**	07
4i	09	00	11	11	10
4j	11	10	09	13	12
4k	14	17	00	09	07
4l	00	12	04	16	13
Ampicillin	22	22	19	22	--
Chloramphenicol	22	25	23	25	--
Norfloxacin	22	23	22	23	--
Greseofulvin	--	--	--	--	22



Where R = (a) Phenyl, (b) 4-methyl phenyl, (c) 4-methoxy phenyl, (d) 2-hydroxy phenyl (e) 4-hydroxy phenyl, (f) 4-chloro phenyl, (g) 4-bromo phenyl, (h) 4-fluoro phenyl (i) 3-amino phenyl, (j) 4-amino phenyl, (k) 3-nitro phenyl, (l) 4-nitro phenyl

Scheme

CONCLUSION

In summary, a series of novel substituted isoxazole derivatives have been synthesized and evaluated for their antibacterial and antifungal activity. The synthesis of targeted compounds was achieved via chalcones followed by treatment with hydroxylamine hydrochloride and sodium hydroxide in methanol. The biological evaluation revealed that several derivatives **(4a)**, **(4b)**, **(4c)**, **(4d)**, **(4f)** and **(4g)** possessed significant antimicrobial activity against various grams positive and negative strains. From this study, we found that derivatives **(4h)** possessed significant activity against gram negative bacterial strains (*E. coli* or *S.aureus*) and warrant further investigations.

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