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REGULAR ARTICLE

Synthesis, antioxidant and α-amylase inhibition activity of naphthalene-containing 2,4,5-trisubstituted imidazole derivatives

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Abstract. A series of naphthalene ring containing 2,4,5-trisubstituted imidazole derivatives (**2a**–**2l**) were synthesized using one-pot multicomponent reaction. The reactions were carried out using naphthaldehyde and substituted benzil in the presence of ammonium acetate in acetic acid media. All newly synthesized imidazole derivatives were characterized by FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectral analysis. Newly synthesized imidazole derivatives were screened for their *in-vitro* antioxidant activity by DPPH free radical scavenging assay method and α-amylase inhibition activity by DNS method. All the compounds showed excellent α-amylase activity at 10, 50 and 100 μg/mL and compounds **2d**, **2g**, **2k** exhibited good antioxidant activity.

Keywords. 2,4,5-trisubstituted imidazole; one-pot multicomponent reaction; antioxidant activity; α-amylase activity.

1. Introduction

In the recent years, imidazole derivatives received significant attention due to their biological and pharmacological importance. Many imidazole derivatives are occurring in natural compounds extracted from herbs. The substituted imidazole derivatives have a wide range of applications in pharmaceutical industries as an antioxidant,[1] anticancer,[2] anti-inflammatory,[3] antimicrobial,[4,5] antihypertension activity.[6] On the other hand, the trisubstituted imidazole moieties are promising candidates for α-amylase inhibition,[7] C17, 20-lyase inhibition,[8] glucosidase inhibition[9,10] and kinase inhibition.[11]

The antioxidant property of the compound is very important to protect damage against free radicals that are produced in our body as a result of a biochemical reaction. Free radicals are generated due to internal factors such as inflammation and external factors such as environmental pollution, and UV exposure. These free radicals are dangers to the human body and which causes oxidative stress. Oxidative stress leads to cancer,[12–14] heart diseases,[15] osteoarthritis,[16,17] stroke,[18] respiratory diseases,[19] immune deficiency,[20] Parkinson's disease,[21] emphysema[22] and other inflammatory or ischemic conditions. Therefore, there is an urgent need to design and develop a highly active antioxidant compounds.

α-Amylase inhibitors are the targets for the many researchers in drug-design for the development of a new class of compounds for the treatment of hyperlipaemia, diabetes and obesity. Enzyme inhibitors are the potential target in many diseases which control many important biochemical reactions. α-Amylase inhibitors are the substances which control carbohydrate digestion and monosaccharide absorption. In this aspect, α-amylase inhibitors are particularly important in maintaining a constant glucose level in the blood by delaying the breakdown of starch. Many available α-amylase inhibitors are the microbial origin and their usage

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has been limited due to their side effects. Various α-amylase inhibitors are synthesized[23,24] and screened for their inhibitory activity which include iminosugars, thiosugars, disaccharides, carbosugars and non-sugar derivatives. The α-amylase inhibitors with a high degree of potency and specificity are still needed for the exploration of a new class of inhibitors. In this respect, several naphthalene incorporated heterocyclic compounds were synthesized and tested for their biological activities such as anticonvulsant,[25,26] antimicrobial,[27–29] antioxidant[30] and anticancer activity.[31,32] In view of the above observation, in our study we have synthesized naphthalene incorporated 2,4,5-trisubstituted imidazole derivatives and have screened for their antioxidant and α-amylase inhibition activity.

2. Experimental

2.1 *Materials and methods*

Chemicals used in the present work were purchased from Sigma-Aldrich (India), Merck (Germany) and S. D. Fine Chemicals (India). All the laboratory grade solvents used were distilled before use. Melting points were determined by an open capillary method and were uncorrected. The IR spectra of the compounds (KBr pellet method) were recorded on a JASCO FT/IR-4600 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded by using JEOL (500 MHz) NMR spectrometer and Agilent (400 MHz) NMR spectrometer respectively. The compounds were dissolved in either DMSO$-d_6$ or $CDCl_3$ for recording the spectra in the presence of TMS as an internal standard. Chemical shift values were presented in δ (ppm) scale. The mass spectra were recorded on a Agilent mass spectrometer instrument. The completion of the reactions was checked by thin layer chromatography (TLC) on silica gel coated aluminum sheets (silica gel 60 F254). The compounds name was given as per chem draw software. Antioxidant activity was carried out by DPPH free radical scavenging assay method. α-Amylase inhibition activity by DNS method. The chemicals used for antioxidant and α-amylase inhibition study was purchased from Hi-Media (Mumbai)-India. Absorbance was recorded using Systronics-169 Visible Spectrophotometer.

2.2 *General procedure for the synthesis naphthalene incorporated 2,4,5-trisubstituted imidazoles (2a-2l)*

A mixture of naphthaldehyde (10 mmol), substituted benzil (10 mmol) and ammonium acetate (50 mmol) were dissolved in acetic acid in two necked 100 mL round bottom flask. The reaction mixture was refluxed for 12–14 h. The completion of reaction was monitored by TLC using petroleum ether and ethyl acetate (3:1) as eluent. After completion of the reaction, the mixture was poured into ice cold water. The solid compound precipitated was filtered and dried. All the crude products were purified by column chromatography except **2a**, **2b**, **2c**, **2d** and **2h**, which purified by recrystallization using ethanol.

2.2a *4,5-bis(3-methoxylphenyl)-2-(naphthalen-2-yl)-1H-imidazole (2a)*: Pale yellow solid; M.p. 184 – 186 °C; FT-IR (KBr, cm^{-1}) ν_{max}: 3410.19 (N-H), 3051.80 (Ar-H) 1607.38 (C=C), 1585.20 (C=N); ^{1}H NMR (500 MHz, DMSO $- d_6$) δ (ppm): 3.70 (s, 3H, -OCH_3), 3.77 (s, 3H, -OCH_3), 6.83 (m, 1H, ArH), 6.98 (dd, J = 8.3 Hz, 1H, ArH), 7.12 (m, 2H, ArH), 7.19 (d, J = 7.6 Hz, 2H, ArH), 7.25 (t, J = 7.9 Hz, 1H, ArH), 7.38 (t, J = 7.9 Hz, 1H, ArH), 7.55 (dd, J = 15.6 Hz, 6.5 Hz, 2H, ArH), 7.96 (q, J = 7.6 Hz, 2H, ArH), 8.02 (d, J = 8.3 Hz, 1H, ArH), 8.26 (dd, J = 9.0 Hz, 1.4 Hz, 1H, ArH), 8.61 (s, 1H, ArH), 12.85 (s, 1H, NH), ^{13}C NMR (400 MHz, DMSO $- d_6$) δ (ppm): 49.9, 50.2, 107.3, 107.7, 108.4, 109.0, 114.7, 115.9, 18.6, 118.8, 121.4, 121.7, 122.8, 122.9, 123.1, 123.3, 123.6, 124.2, 124.8, 127.3, 127.8, 128.0, 131.5, 132.4, 140.4, 154.1, 154.3; MS (m/z): Calcd.406.16, found 407.17 [M+1].

2.2b *4,5-bis(3-methoxylphenyl)-2-(naphthalen-1-yl)-1H-imidazole (2b)*: Off white solid; M.p.: 185−186 °C; FT-IR (KBr, cm^{-1}) ν_{max}: 3418.18 (N-H), 3049.80 (Ar-H), 1606.41 (C=C), 1579.41 (C=N); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.77 (s, 6H, -OCH_3), 6.83 (dd, J = 8.3 Hz, 2.1 Hz,2H, ArH), 6.90 (dd, J = 8.3 Hz, 2.1 Hz, 1H, ArH), 7.06(s, 1H,ArH), 7.11 (d, J = 7.6 Hz, 1H, ArH), 7.23 (d, J = 8.3 Hz, 1H, ArH), 7.34 (q, J = 8.7 Hz, 3H, ArH), 7.56 (m, 2H, ArH), 7.78 (dd, J = 6.9 Hz, 1.4 Hz, 1H, ArH), 7.92 (m, 2H, ArH), 8.82 (d, J = 8.3 Hz, 1H, ArH), 9.33 (s, 1H, NH); ^{13}C NMR (400 MHz, DMSO$-d_6$), δ (ppm): 49.9, 50.1, 107.1, 107.9, 108.5, 108.8, 114.8, 115.7, 120.3, 121.2, 121.6, 121.7, 121.8, 122.5, 122.9, 123.3, 124.0, 124.3, 124.7, 125.4, 127.2, 128.7, 131.7, 132.1, 140.5, 154.2, 154.3; MS (m/z): Calcd.406.16, found 407.03 [M+1].

2.2c *4,5-bis(4-methylphenyl)-2-(naphthalen-1-yl)-1H-imidazole (2c)*: Off white solid; M.p.: 280−284 °C; FT-IR (KBr, cm^{-1}) ν_{max}: 3391.21 (N-H), 3063.37 (Ar-H), 1614.13 (C=C), 1590.02 (C=N); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 2.36 (s, 3H, $-CH_3$), 2.40 (S,3H, $-CH_3$), 7.15 (d, J = 8.3 Hz, 2H, ArH), 7.22 (d, J = 7.6 Hz, 2H, ArH), 7.42 (d, J = 7.6 Hz, 2H,ArH), 7.56 (m, 3H, ArH), 7.66 (d, J = 8.3 Hz, 2H, ArH), 7.77 (m, 1H, ArH), 7.91 (m, 2H, ArH), 8.84 (d, J = 8.3 Hz, 1H,ArH), 9.22 (s, 1H, NH); ^{13}C NMR (400 MHz, DMSO $- d_6$), δ (ppm): 21.2, 125.6, 126.5, 127.0, 127.5, 128.0, 128.5, 128.6, 129.6, 130.7, 133.0, 134.0, 135.9, 137.3, 145.6; MS (m/z): Calcd.374.17, found 373.17 [M-1].

2.2d *4,5-bis(4-methylphenyl)-2-(naphthalen-2-yl)-1H-imidazole (2d)*: Off white solid; M.p. 246−248 °C; FT-IR (KBr, cm^{-1}) ν_{max}: 3418.21 (N-H), 3051.80 (Ar-H), 1614.13 (C = C), 1589.06 (C = C); ^{1}H NMR (500 MHz, DMSO $- d_6$) δ (ppm): 2.30 (s,3H, $-CH_3$), 2.36 (s, 3H,

$-CH_3$), 7.13 (d, J = 7.6 Hz, 2H, ArH), 7.26 (d, J = 8.3 Hz, 2H, ArH), 7.45 (dd, J = 27.2, 7.9 Hz, 4H, ArH), 7.55 (m, 2H, ArH), 7.95 (dd, J = 13.4 Hz, 7.9 Hz, 2H, ArH), 8.00 (d, J = 8.3 Hz, 1H, ArH), 8.24 (dd, J = 8.6 Hz,1.7 Hz, 1H, ArH), 8.60 (s, 1H, ArH), 12.74 (s, 1H, NH); ^{13}C NMR (400 MHz, DMSO$-d_6$), δ (ppm): 15.9, 118.5, 118.6, 121.3, 121.7, 122.7, 122.9, 123.1, 123.2, 124.0, 127.7, 128.0, 131.4, 141.2; MS (m/z): Calcd. 374.17, found 375.05 [M+1].

2.2e *4,5-bis(4-bromophenyl)-2-(naphthalen-1-yl)-1H -imidazole (2e)*: Yellow solid; M.p.: 205 − 207 °C; FT-IR (KBr, cm^{-1}) ν_{max}: 3417.28 (N-H), 1600.63 (C=C), 1584.24 (C=N), 832; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.55 (m, 2H, ArH), 6.64 (d, J = 1.8 Hz, 2H, ArH), 7.56 (m, 4H, ArH), 7.64 (m, 2H, ArH), 7.6 (d, J = 3.4 Hz, 2H, ArH), 7.78 (d, J = 7.6 Hz, 2H, ArH), 8.7 (d,J = 8.3 Hz, 1H, ArH), 9.61 (s, 1H, NH); ^{13}C NMR (400 MHz, DMSO − d_6) δ (ppm): 121.2, 121.8, 121.9, 124.3, 125.3, 126.4, 126.7, 126.8, 127.6; MS (m/z): Calcd.501.96, found 500.98 [M-1].

2.2f *2-(naphthalen-1-yl)-4,5-diphenyl-1H-imidazole (2f)*: Pale yellow solid; M.p.: 262−263 °C; FT-IR (KBr, cm^{-1}) ν_{max}: 3417.24 (N-H), 3052.69 (Ar-H), 1600.63 (C=C), 1584.24 (C=N); ^{1}H NMR (500 MHz, DMSO$-d_6$) δ (ppm): 7.25 (t, J = 7.6 Hz, 1H, ArH), 7.36 (m, 3H, ArH), 7.45 (t, J = 7.6 Hz, 2H, ArH), 7.57 (m, 2H, AH), 7.62(m, 5H, AH), 7.97 (d, J = 8.3 Hz, 1H, ArH), 8.01 (d, J = 8.3 Hz, 2H, ArH), 9.18 (d, J = 9.0 Hz, 1H, ArH), 12.79 (s, 1H, NH); ^{13}C NMR (400 MHz, DMSO − d_6), δ (ppm): 120.3, 121.1, 121.7, 121.8, 122.2, 122.5, 122.7, 123.0, 123.3, 123.4, 123.7, 124.0, 125.4, 126.1, 128.7, 130.4, 132.2, 140.6; MS (m/z): Calcd.346.14, found 347.02 [M+1].

2.2g *2-(naphthalen-2-yl)-4,5-diphenyl-1H-imidazole (2g)*: Pale yellow solid; M.p.: 257−260 °C; FT-IR (KBr, cm^{-1}) ν_{max}: 3417.24 (N-H), 3054.69 (Ar-H), 1600.63 (C=C), 1584.01 (C=N); ^{1}H NMR (500 MHz, DMSO$-d_6$) δ (ppm): 7.25 (t, J = 7.6 Hz, 1H,ArH), 7.33 (t, J = 7.6 Hz, 2H,ArH), 7.40 (t, J = 7.2 Hz, 1H, ArH), 7.47 (t, J = 7.6 Hz, 2H, ArH), 7.55 (q, J = 7.6 Hz, 4H, ArH), 7.60 (d, J = 6.9 Hz, 2H, ArH), 7.96 (q, J = 7.1 Hz, 2H,ArH), 8.02 (d, J = 9.0 Hz, 1H,ArH), 8.26 (dd, J = 8.6 Hz, J = 1.7 Hz, 1H,ArH), 8.62 (s, 1H, ArH), 12.87 (s, 1H, NH); ^{13}C NMR (400 MHz, DMSO$-d_6$) δ(ppm):118.5, 118.7, 121.4, 121.6, 121.7, 122.2, 122.8, 122.9, 122.9, 123.1, 123.3, 123.5, 123.7, 126.1, 127.7, 128.0, 130.2, 132.4, 140.5; MS (m/z): Calcd.346.14, found 347.03 [M+1].

2.2h *4,5-bis(4-methoxylphenyl)-2-(naphthalen-1-yl)-1H-imidazole (2h)*: Off white solid; M.p.: 172−174 °C; FT-IR (KBr, cm^{-1}) ν_{max}: 3418.21 (N-H), 3046.98 (Ar-H), 1614.13 (C=C), 1574.59 (C=N); ^{1}H NMR (500 MHz, DMSO − d_6) δ (ppm): 3.71 (s,3H, $-CH_3$), 3.80 (s,3H, $-CH_3$), 6.71 (d, J = 6.9 Hz, 1H, ArH), 6.92 (m, 4H, ArH), 7.41 (t, J=8.6 Hz 1H, ArH),7.61 (m, 6H, ArH), 7.79 (d, J = 8.3 Hz, 1H, ArH), 7.99 (t, J = 6.9 Hz, 2H, ArH), 12.60 (s,1H, NH); MS (m/z):Calcd.406.16, found 407.14 [M+1].

2.2i *4-(4-chlorophenyl)-2-(napthalen-1-yl)-5-phenyl-1H-imidazole (2i)*: Off white solid; M.p. 255−257 °C; FT-IR (KBr, cm^{-1}) ν_{max}: 3418.21 (N-H), 3049.87 (Ar-H), 1599.66 (C=C), 1583.27 (C=N), 745.35 (C-Cl); ^{1}H NMR (500 MHz, DMSO − d_6) δ (ppm): 7.39 (t, J = 7.2 Hz, 1H, ArH), 7.41 (d, J = 7.6 Hz, 2H, ArH) ,7.49 (m,2H, ArH), 7.57 (d, J = 6.9 Hz, 2H, ArH),7.63 (m,5H, ArH), 7.96 (d, J = 7.6 Hz, 1H, ArH), 8.01 (d, J = 7.6 Hz, 2H, ArH), 9.14 (d, J= 8.3 Hz, 1H, ArH), 12.85 (s,1H,NH); ^{13}C NMR (400 MHz, DMSO − d_6) δ (ppm): 120.3, 121.2, 121.5, 121.8, 122.4, 123.0, 123.3, 123.4, 123.5, 123.5, 123.7, 123.8, 124.1, 125.0, 125.4, 125.8, 126.0, 127.2, 128.7, 129.2, 130.1, 130.9, 132.7, 140.8, 140.9; MS (m/z): Calcd.380.10, found 381.14 [M+1].

2.2j *4-(4-chlorophenyl)-2-(napthalen-2-yl)-5-phenyl-1H-imidazole (2j)*: Pale brown solid; M.p. 222−224 °C; FT-IR (KBr, cm^{-1}) ν_{max}: 3442.31 (N-H), 3056.62 (Ar-H), 1580.38 (C=N), 753.06 (C-Cl);^{1}H NMR (500 MHz, DMSO$-d_6$) δ (ppm): 7.40 (m, 4H, ArH), 7.53 (m, 7H, ArH), 7.96 (q, J = 7.6 Hz,2H, ArH), 8.02 (d, J = 9.0 Hz, 1H, ArH), 8,25 (dd, J = 8.6 Hz,1.7 Hz, 1H, ArH), 8.61 (s,1H, ArH), 12.92 (s, 1H, NH); ^{13}C NMR (400 MHz, DMSO − d_6) δ (ppm): 118.5, 118.8, 121.4, 121.8, 122.7, 122.8, 123.2, 123.3, 123.6, 127.8, 128.0, 140.8; MS (m/z):Calcd.380.10, found 380.98 [M+1].

2.2k *4,5-di(furan-2-yl)-2-(naphthalen-2-yl)-1H-imidazole (2k)*: Brown solid; M.p. 248−251 °C; FT-IR (KBr, cm^{-1}) ν_{max}: 3417.24 (N-H), 3057.58 (Ar-H), 1601.59 (C=C), 1555.31 (C=N); ^{1}H NMR (500 MHz, DMSO$-d_6$) δ (ppm): 6.61 (d,J = 42.7 Hz, 2H, ArH), 6.80 (dd,J = 100.0 Hz, J = 2.8 Hz, 2H,ArH), 7.57 (m,2H, ArH), 7.81 (d,J = 57.2 Hz, 2H, ArH), 7.96 (d,J = 7.6 Hz, 1H,ArH), 8.01 (t,J = 10.0 Hz, 2H, ArH), 8.25 (d, J = 9.0 Hz, 1H, ArH), 8.67 (s, 1H, ArH), 13.05 (s, 1H, NH); ^{13}C NMR (400 MHz, DMSO − d_6), δ (ppm): 102.0, 103.5, 106.4, 107.0, 114.7, 118.6, 119.4, 121.6, 121.8, 122.2, 122.7, 123.2, 123.3, 124.8, 127.9, 136.9, 137.7, 139.5, 141.3, 144.3; MS (m/z): Calcd.326.10, found 327.11 [M+1].

2.2l *4-(3,4-dimethoxyphenyl)-5-(2-chlorophenyl)-2-(naphthalen-1-yl)-1H-imidazole (2l)*: Off white solid; M.p.: 185−187 °C; FT-IR (KBr, cm^{-1}) ν_{max}: 3417.24 (N-H), 3050.83 (Ar-H), 1612.20 (C=C), 1586.16 (C=N), 786 (C-Cl); ^{1}H NMR (500 MHz, DMSO − d_6) δ (ppm): 3.31 (s, 3H, -OCH_3), 3.35 (s, 3H,-OCH_3), 7.14 (d, J = 8.3 Hz, 2H, ArH), 7.25 (d, J = 7.6 Hz, 2H,ArH), 7.44 (d, J = 8.3 Hz, 2H, ArH), 7.50 (d, J = 7.6 Hz, 2H,ArH), 7.62 (t, J = 7.6 Hz, 2H, ArH), 7.94 (d, J = 7.6 Hz, 1H,ArH), 8.00 (d, J = 7.6 Hz,2H,ArH), 9.16 (d, J = 9.0 Hz,1H, ArH), 12.67 (s, 1H, NH); ^{13}C NMR (400 MHz, DMSO − d_6) δ

(ppm): 40.7, 50.0, 108.7, 109.1, 117.2, 118.0, 120.0, 120.3, 120.7, 121.1, 121.5, 121.7, 122.3, 122.6, 123.2, 123.5, 123.8, 124.1, 125.6, 126.9, 127.7, 127.9, 128.3, 131.9, 140.5, 152.9, 154.4; MS (m/z): Calcd.440.12, found 440.99 [M+1].

2.3 *Biological activity*

2.3a α-*Amylase inhibition assay*: The α-amylase inhibition assay was performed using the chromogenic DNS method reported by G. L. Miller.[33] The total assay mixture composed of 1400 μL of 0.05 M sodium phosphate buffer (pH=6.9), 50 μL of α-amylase and samples at concentration 10, 50 and 100 μg/mL were incubated at 37 °C for 10 min. The reaction was terminated with 1 mL of DNS reagent, placed in boiling water bath for 5 min, cooled to room temperature and the absorbance measured at 540 nm. The control α-amylase represented 100% enzyme activity and did not contain any samples of analysis. To eliminate the absorbance produced by sample appropriate extract controls with the extract in the reaction mixture in which the enzyme was added after adding DNS. The liberated sugar was determined by the help of standard maltose curve and activities were calculated according to the following formula.

$$\%\text{inhibition/induction} = \frac{\text{Activity in presence of compound}}{\text{Control activity}} \text{ X } 100$$

One unit of enzyme activity is defined as the amount of enzyme required to release one micromole of maltose from starch per minute under the assay conditions. The inhibitory/induction property shown by the sample was compared with that of control and expressed as percent induction/inhibition. This was calculated according to the following formula.

$$\text{Activity} = \frac{\text{Conc.of Maltose liberated X mL of enzyme used}}{\text{Mol.wt.of Maltose X incubation time (min.)}} \text{ X dilution factor}$$

Acarbose was used as a standard inhibitor and it was assayed at above mentioned test sample concentrations. The assay method was similar to the above-mentioned procedure, instead of test samples, acarbose was added. The experiments were conducted in triplicate and results were compared to that of test samples.

2.3b *Antioxidant activity (Free radical scavenging activities by DPPH assay)*: Free radical scavenging activity was performed using the DPPH assay method reported by Sunil Kumar *et al.*[34] Different concentrations (10 μg, 50 μg and 100 μg) of the samples were dissolved in DMSO and reference Butylated hydroxy anisole (BHA) were taken in different test tubes. The volume was adjusted by adding 500 μL of methanol. Five mL of 0.1 mM methanolic solution of 1,1-diphenyl-2-picryl hydrazyl (DPPH) was added to the above test tubes and was shaken well for uniform concentration. A control without the test compounds, but with an equivalent amount of methanol was maintained. The test tubes were allowed to stand at room temperature for 20 min and absorbance of the samples was measured at 517 nm. Free radical scavenging activity was calculated by using the formula. The experiments were conducted in triplicate and mean values are reported here.

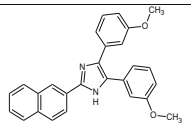
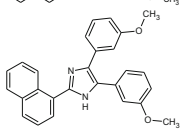
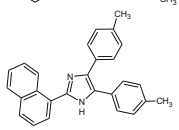
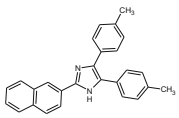
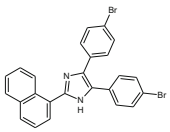
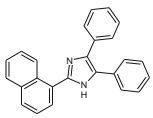
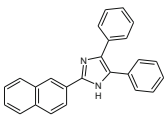
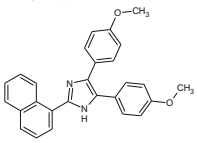
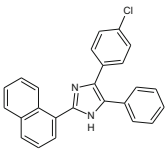
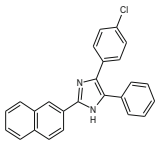
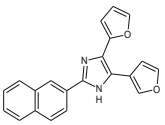
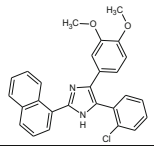
$$\%\text{free radical scavenging} = \frac{(\text{Control OD} - \text{Sample OD})}{\text{Sample OD}} \text{ X } 100$$

3. Results and Discussion

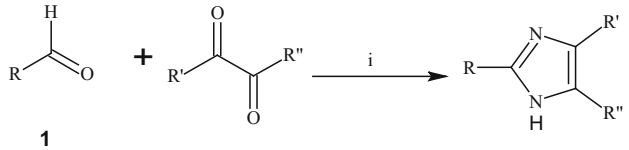
3.1 *Chemistry*

2,4,5-Trisubstituted imidazole derivatives (**2a**–**2l**) were synthesized by one-pot multicomponent reaction as shown in Scheme 1. The mechanism involves condensation followed by cyclization. In the cyclization process the water molecule is eliminated in acidic condition to reach the stable aromatic cyclic ring. The progress of the reaction was monitored by Thin Layer Chromatography (TLC) using petroleum ether and ethyl acetate (3:1) medium and yield of the isolated compounds were recorded after the purification by column chromatography or recrystallization. Newly synthesized imidazole derivatives were characterized by melting point, FT-IR, NMR, and mass spectral analyses. Analytical and spectral data of the synthesized compounds were in full agreement with the proposed structures. In the IR spectra of the compounds, the presence of NH group of imidazole ring, aromatic C-H, C=N and aromatic C=C bonds have been clearly identified from their respective stretching frequencies. The number of proton signals in ^{1}H NMR spectrum and carbon signals in ^{13}C NMR spectrum were very much correlated with the respective compounds. Further, the compounds molecular mass was obtained from the mass spectra of the compounds.

The complete characterization of the synthesized compounds has been given in the experimental section.

Product	Structure	Yield (%)[a]
2a		75
2b		69
2c		81
2d		86
2e		46
2f		89
2g		78
2h		46
2i		72
2j		78
2k		68
2l		65

[a]Isolated yield



1 **2a-2l**

i: Ammonium acetate, acetic acid, 120 °C, 12–14 h.

Scheme 1. Synthesis of 2,4,5-trisubstituted imidazole derivatives (**2a**–**2l**).

3.2 *Biological results*

The α-amylase inhibition activity revealed that all newly synthesized imidazole derivatives showed good inhibition at concentrations 10, 50 and 100 µg/mL. Among the prepared imidazole compounds **2a**, **2b**, **2f** and **2g** showed a bit higher inhibition compared to other compounds at 10 µg/mL. The enhanced inhibition of 2,4,5-trisubstituted imidazole derivative compared with control enzyme might be due to the N-H of imidazole core moiety and bit enhanced variations of inhibition might be due to the effect of functional groups attached to imidazole. The α-amylases inhibition activity of the compounds (**2a-2l**) is shown in graphical representation (Figure 1).

Among the synthesized compounds, the compounds **2d**, **2g**, **2k** exhibit good antioxidant activity at 100 µg/mL and other compounds exhibit moderate antioxidant activity as compared to the reference BHA. The enhanced activity of **2d**, **2g**, **2k** imidazole derivatives may be due to 2-naphthyl substitution at second position and phenyl, 4-methyl-phenyl, furan substitution at 4,5 positions. The results of the antioxidant activity have been presented in Figure 2.

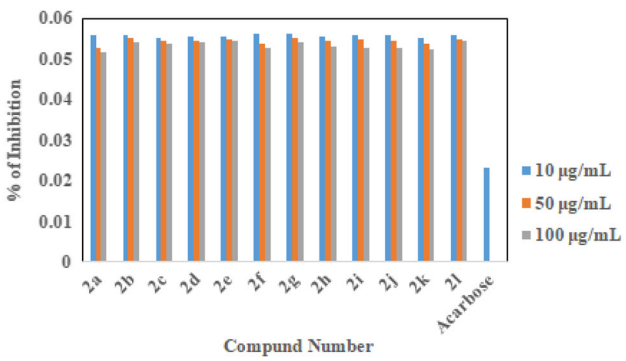


Figure 1. α- Amylase inhibition assay of 2,4,5-trisubstituted imidazole derivatives (**2a-2l**).

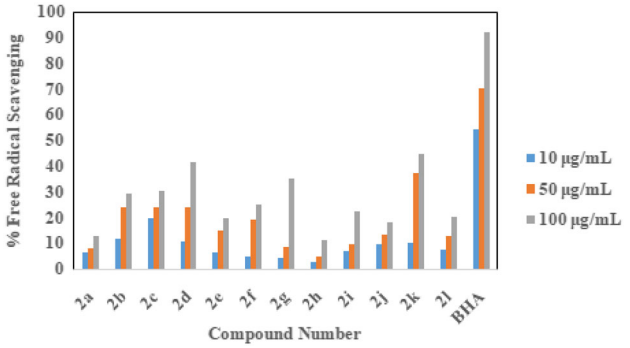


Figure 2. Antioxidant of 2,4,5-trisubstituted imidazole derivatives (**2a-2l**).

4. Conclusions

A series of naphthalene incorporated 2,4,5-trisubstituted imidazole derivatives (**2a-2l**) were synthesized by one-pot multicomponent reaction and characterized by FT-IR, NMR and mass spectral analysis. The purified final compounds were investigated for their α-amylase inhibition and antioxidant activities. All the compounds showed excellent α-amylase inhibition as compared with the control sample. Among the screened samples, **2d**, **2g**, **2k** exhibit good antioxidant activity compared to BHA standard. From this study, we conclude that the preparation of 2,4,5-trisubstituted imidazole using substituted benzil, naphthaldehyde, ammonium acetate and acetic acid media is the simplest method to construct imidazole ring. The biological study of the title compounds showed promising antioxidant and α-amylase inhibition activities. Hence, they are ideally suited for further notification to obtain more efficient antioxidant and α-amylase inhibition compounds.

Supplementary Information (SI)

^{1}H, ^{13}C NMR and Mass spectra of synthesized compounds are available at www.ias.ac.in/chemsci.

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