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SYNTHESIS, CHARACTERIZATION AND EVALUATION OF BENZYLIDENE ANALOGUES AS A NEW CLASS OF POTENTIAL ANTIOXIDANT AGENTS

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Abstract: Seventeen analogues of benzylidene were synthesized and evaluated for *in vitro* hydrogen peroxide scavenging activity. The structure of the newly synthesized compounds were confirmed by elemental and spectral (IR, ^{1}H-NMR, ^{13}C-NMR) studies. The antioxidant activity of the titled compounds was evaluated. Compounds: **4h** – N'-[2-amino-3-(morpholinomethyl)benzylidene]isonicotinohydrazide**, 4p** 7-(4-{2-amino-3-[(2-isonicotinoylhydrazono)methyl]benzyl}piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and **4q** 7-(4-{2-amino-3-[(2 isonicotinoylhydrazono)methyl]benzyl}piperazin-1-yl)-1-ethyl-6,8-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid were the most active compounds with significant hydrogen peroxide scavenging activity.

Keywords: 2-aminobenzaldehyde, isoniazid, Mannich bases and antioxidant activity

The normal metabolic functioning of aerobic cells is related to the free radical formation. The oxygen utilized in the cell growth gives rise to a number of oxygen free radicals. Further, these oxygen free radicals interact with lipidic molecules to produce hydroxyperoxides and various other peroxides also, radicals like superoxide, hydroxyls and lipoid peroxides, which lead to cytotoxicity due to their interaction with biological systems (1, 2). The uncontrolled generation of free radicals may lead to various diseases and disorders like prostate cancer, coronary heart disease and also ageing (3). In demand to minimize the damage caused by free radicals, various synthetic antioxidants like butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), propyl gallate (PG) and tertiary-butylhydroxyquinine (TBHQ) are utilized. But ironically, two of them i.e., BHA and BHT are suspected to cause liver damage and carcinogenesis (4). So, in order to make a balance, it is very essential to develop such antioxidants which protect the body from effect of free radicals and also do not cause much harm to human body. Nowadays, the multicomponent organic synthesis has various advantages like lower reaction time, higher reaction rate, higher yields and enhanced reproducibility. Even the diversity, efficiency and easy approach to various organic molecules whether small or highly functionalized have made this approach of keen interest and value in making of various combinatorial libraries and optimization process in the drug discovery (5, 6). Mannich reaction is a three component condensation reaction involving active hydrogen containing compound, formaldehyde and a secondary amine (7). The aminoalkylation of aromatic substrates by Mannich reaction is of considerable importance for the synthesis and modification of biologically active compounds (8). Mannich bases have been reported as potential biological agents. They find application as antioxidant (9), antimicrobial (10), antitubercular (11), antimalarial (12) anticancer (13), analgesic (14) and vasorelaxing (15). Keeping all this in background, we tried to develop and explore this particular class as potential antioxidants without any side effects. The antioxidant properties of the Mannich bases obtained were evaluated by their hydrogen peroxide scavenging activity.

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MATERIALS AND METHODS

Melting points of the synthesized compounds were determined in open-glass capillaries on Stuart SMP10 melting point apparatus and were uncorrected. The purity of the compounds was checked by thin layer chromatography (TLC). Silica gel plates (Kieselgel 0.25 mm, 60G F_{254}) were obtained from Merck (Darmstadt, Germany) and used for TLC and the spots were visualized by iodine vapors and UV light as visualizing agents. The IR spectra (ν, cm^{-1}) were obtained on Perkin-Elmer 1600 FTIR spectrometer in KBr pellets. ^{1}H-NMR spectra (δ, ppm) were recorded in DMSO-d_6 solutions on a Varian-Mercury 300 MHz spectrometer using tetramethylsilane as the internal standard. ^{13}C-NMR spectra were recorded in DMSO-d_6 solutions on Bruker Avance II 400 spectrometer at 400 MHz using tetramethylsilane as the internal standard. Elemental analyses were performed on an ECS 4010 Elemental Combustion System. The necessary chemicals were purchased from Loba Chemie and Sigma-Aldrich companies.

Chemistry

The synthesis of target compounds were carried as outlined in synthetic scheme. Compounds **4a**–**4q** are readily prepared in good yields and purity. Equimolar quantity of isoniazid (**1a**) and 2-aminobenzaldehyde (**2a**) in 15 mL of absolute ethanol was refluxed for 7 h to form acid hydrazone. The completion of reaction was confirmed by TLC. Then, 2-aminobenzylidene isonicotinohydrazide **(3a)** along with formaldehyde and substituted secondary amines were refluxed for 25–37 h in the presence of 50 mL of absolute ethanol and the pH was adjusted to 4 with hydrochloric acid to form titled compounds **4a-4q**. The types of substituted secondary amines are specified in Table 1. The synthesized new Mannich bases were characterized on the basis of the spectral and analytical studies.

Synthesis of 2-aminobenzylidene isonicotinohydrazide.

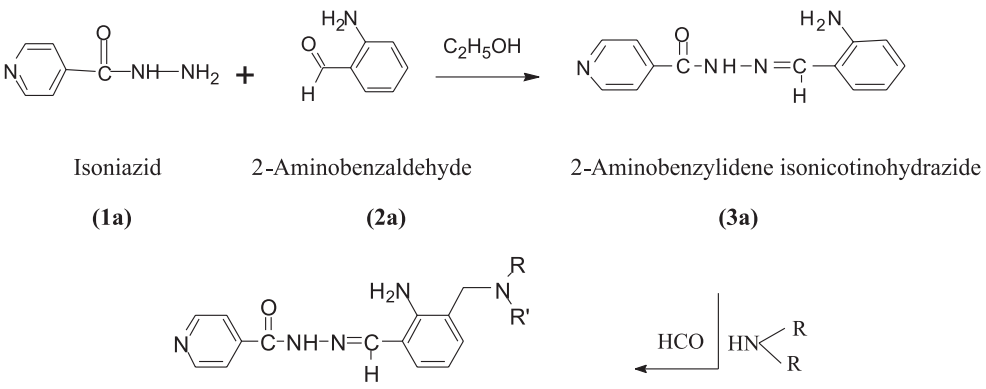
A mixture of 2-aminobenzaldehyde (1.21 g, 0.01mol) and isoniazid (1.37 g, 0.01 mol) in 15 mL of absolute ethanol was refluxed for 7 h. The completion of reaction was confirmed by TLC. The reaction mixture was then poured in ice cold water and the precipitate obtained was filtered and dried in an oven at low temperature. The product was recrystallized from methanol.

N'-(2-Aminobenzylidine)isonicotinohydrazide (3a)

Yield 58%; m.p. 205–208°C; IR (KBr; cm^{-1}): 3465, 3275, 3181, 2985, 2857, 2849, 1674, 1648, 1557, 1085. ^{1}H-NMR (300 MHz, DMSO-d_6 δ, ppm): 11.95 (s, 1H, -NH-N=), 8.65 (d, 2H, pyridine, *J* = 4.1 Hz), 8.37 (s, 1H, -N=C-H), 7.94 (d, 2H, pyridine, *J* = 3.7 Hz), 7.69 (d, 2H, benzylidene, *J* = 8.2 Hz), 7.37 (d, 2H, benzylidene, *J* = 7.8), 5.42 (s, 2H, NH_2, D_2O exchangeable); ^{13}C-NMR (400 MHz, DMSO d_6, δ, ppm): 163.54, 161.18, 149.83, 143.37, 139.85, 132.68, 130.15, 122.85, 121.23, 118.59, 115.84. Analysis: calcd. for $C_{13}H_{11}N_3O_2$: C 64.72, H 4.60, N 17.42%; found: C 64.78, H 4.62, N 17.34%.

Synthesis of substituted Mannich bases (4a–4q)

The synthesis of 17 Mannich bases **4a**–**4q** have been carried out. Among them, compounds **4a**–**4j** have been reported with their antimicrobial activity elsewhere (10), while compounds **4k**–**4q** were unpub-

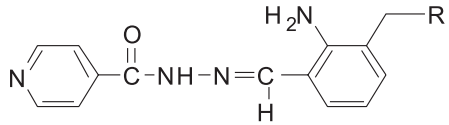


Isoniazid (**1a**) — 2-Aminobenzaldehyde (**2a**) — 2-Aminobenzylidene isonicotinohydrazide (**3a**)

Substituted Mannich bases (**4a**–**4q**)

Scheme 1. Synthetic pathway for the formation of title compounds

Table 1. Physical data of synthesized Mannich bases.



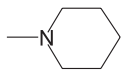
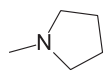
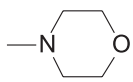
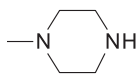
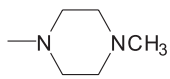
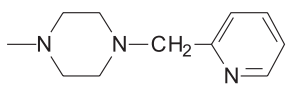
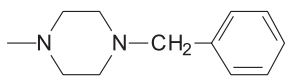
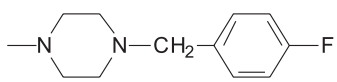
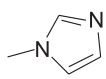
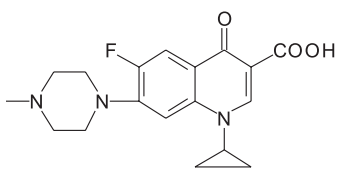
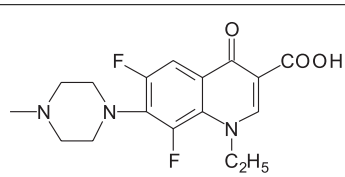
Compound	R	Molecular formula	Yield (%)	M.p. (°C)
4a	$-N(CH_3)_2$	$C_{16}H_{29}N_5O$	48	222–224
4b	$-N(C_2H_5)_2$	$C_{18}H_{23}N_5O$	52	215–217
4c	$-N(C_3H_7)_2$	$C_{20}H_{27}N_5O$	45	210–212
4d	$-N(C_4H_9)_2$	$C_{22}H_{31}N_5O$	48	208–210
4e	$-N(C_6H_5)_2$	$C_{26}H_{23}N_5O$	53	196–198
4f		$C_{19}H_{23}N_5O$	57	188–190
4g		$C_{18}H_{21}N_5O$	55	199–201
4h		$C_{18}H_{21}N_5O_2$	42	219–221
4i		$C_{18}H_{22}N_6O$	47	206–208
4j		$C_{19}H_{24}N_6O$	46	211–213
4k		$C_{23}H_{25}N_7O$	52	59–61
4l		$C_{25}H_{28}N_6O$	48	73–75
4m		$C_{24}H_{25}FN_6O$	44	65–67
4n	$-N(CH_2C_6H_5)_2$	$C_{28}H_{27}N_5O$	60	190–192
4o		$C_{17}H_{16}N_6O$	52	183–185
4p		$C_{31}H_{30}FN_7O_4$	67	247–249
4q		$C_{30}H_{29}F_2N_7O_4$	64	228–230

Table 2. Hydrogen peroxide scavenging activity of synthesized compounds.

Compound	Scavenging of hydrogen peroxide at different concentrations (%)		
	100 µg/mL	300 µg/mL	500 µg/mL
4a	41.52	39.68	39.68
4b	40.18	39.77	39.52
4c	38.72	41.15	40.72
4d	39.57	41.65	41.92
4e	42.88	38.75	39.26
4f	42.76	43.38	44.81
4g	45.82	43.32	43.87
4h	51.18	54.75	55.85
4i	35.44	36.29	38.53
4j	41.65	40.92	38.83
4k	39.37	40.26	41.19
4l	38.83	39.19	39.57
4m	39.15	40.27	41.12
4n	39.15	40.27	41.12
4o	36.85	37.19	39.57
4p	51.52	54.19	53.55
4q	49.32	53.19	54.33
BHA	63.27	66.19	68.25
Ascorbic acid	51.47	53.45	55.38

lished. The synthesis was performed with good yields from commercially available materials. The 2-aminobenzylidene isonicotinohydrazide (576 mg, 0.0024 mol) along with (0.1 mL, 0.0036 mol) of formaldehyde and (0.0024 mol) of substituted secondary amines were placed in 100 mL round bottom flask to which 50 mL of absolute ethanol was added and the pH was adjusted to 4 with hydrochloric acid and refluxed for 25–37 h to form titled compounds **4a**–**4q**. The completion of reaction was confirmed by TLC. The reaction mixture was concentrated on water bath, cooled and at room temp. diethyl ether was added. The reaction mixture was kept for 3–7 h in refrigerator and then filtered and washed with n-hexane. The products were recrystallized from absolute ethanol.

N'-(2-amino-3-{[4-(pyridin-2-yl)piperazin-1-yl]methyl}benzylidene)isonicotinohydrazide (4k)

IR (KBr; cm^{-1}): 3395, 3284, 3159, 2992, 2865, 2838, 1675, 1648, 1559, 1077. ^{1}H-NMR (300 MHz, DMSO-d_6, δ, ppm): 11.88 (s, 1H, -NH-N=), 8.92 (d, 2H, pyridine, J = 4.2 Hz), 8.79 (s, 1H,-N=C-H), 8.72 (d, 2H, pyridine, J = 3.9 Hz), 8.19 (d, 2H, pyridine, J = 3.5 Hz), 7.74 (d, 2H, pyridine, J = 3.1 Hz), 7.35 (d, 2H, benzylidene, J = 2.7 Hz), 7.17 (t, 1H, benzylidene), 4.55 (s, 2H, NH_2 D_2O exchangeable), 3.59 (s, 2H, Ar-CH_2-N), 2.69-2.57 (m, 8H, 4CH_2, piperazine). ^{13}C-NMR (400 MHz, DMSO-d_6, δ ppm): 163.54, 154.29, 149.38, 147.94, 143.18, 139.26, 137.83, 132.37, 127.81, 122.75, 117.36, 115.33, 113.14, 108.85, 54.37, 52.47, 51.13. Analysis: calcd. for $C_{23}H_{25}N_7O$ (415.49): C 66.49, H 6.06, N 23.60%; found: C 66.72, H 5.85, N 23.58.

N'-(2-amino-3-{[(4-benzylpiperazin-1-yl)methyl]benzylidene}isonicotinohydrazide (4l)

IR (KBr; cm^{-1}): 3355, 3275, 3173, 2986, 2865, 2843, 1677, 1645, 1539, 1086. ^{1}H-NMR (300 MHz, DMSO-d_6, δ, ppm): 11.92 (s, 1H, -NH-N=), 8.95 (d, 2H, pyridine, J = 4.3 Hz), 8.83 (s, 1H,-N=C-H), 8.73 (d, 2H, pyridine, J = 3.7 Hz), 7.69–7.53 (m, 5H, phenyl), 7.08 (d, 2H, benzylidene, J = 3.3 Hz), 6.94 (t, 1H, benzylidene), 4.59 (s, 2H, NH_2, D_2O exchangeable), 3.55 (s, 2H, Ar-CH_2-N), 3.42 (s, 2H, Ar-CH_2-Ar), 2.55-2.43 (m, 8H, 4CH_2, piperazine). ^{13}C-NMR (400 MHz, DMSO-d_6, δ, ppm): 163.25, 149.27, 147.92, 143.25, 139.47, 136.55, 131.83, 127.59, 126.85, 125.12, 122.18, 117.29, 113.72,

60.63, 53.75, 52.19. Analysis: calcd. for $C_{25}H_{28}N_6O$ (428.53): C 70.07, H 6.59, N 19.61%; found: C 70.28, H 6.43, N 19.56%.

N'-(2-amino-3-{[4-(4-fluorophenyl)piperazin-1-yl]methyl}benzylidene)isonicotinohydrazide (4m)

IR (KBr; cm^{-1}): 3369, 3288, 3167, 2985, 2860, 2847, 1685, 1643, 1567, 1077. ^{1}H-NMR (300 MHz, DMSO-d_6, δ, ppm): 11.83 (s, 1H, -NH-N=), 8.89 (d, 2H, pyridine, *J* = 4.2 Hz), 8.79 (s, 1H,-N=C-H), 8.55 (d, 2H, pyridine, *J* = 3.9 Hz), 7.89–7.77 (m, 4H, phenyl), 7.54 (d, 2H, benzylidene, *J* = 3.2 Hz), 6.95 (t, 1H, benzylidene), 4.49 (s, 2H, NH_2 D_2O exchangeable), 3.53 (s, 2H, Ar-CH_2-N), 2.64–2.59 (m, 8H, 4CH_2, piperazine). ^{13}C-NMR (400 MHz, DMSO-d_6, δ, ppm): 163.65, 152.19, 149.37, 147.29, 144.37, 144.26, 143.27, 131.34, 127.15, 122.15, 117.65, 114.95, 113.88, 52.24, 51.75, 49.74. Analysis: calcd. for $C_{24}H_{25}FN_6O$ (432.49): C 66.65, H 5.83, N 19.43%; found: C 66.57, H 5.79, N 19.55.%

N'-(2-amino-3-{[(dibenzylamino)methyl]benzylidene}isonicotinohydrazide (4n)

IR (KBr; cm^{-1}): 3363, 3278, 3161, 2975, 2863, 2855, 1687, 1651, 1572, 1075. ^{1}H-NMR (300 MHz, DMSO-d_6, δ, ppm): 11.87 (s, 1H, -NH-N=), 8.89 (d, 2H, pyridine, *J* = 4.1 Hz), 8.75 (s, 1H, -N=C-H), 8.29 (d, 2H, pyridine, *J* = 3.7 Hz), 7.84–7.69 (m, 10H, phenyl), 7.21 (d, 2H, benzylidene, *J* = 3.3 Hz), 6.94 (t, 1H, benzylidene), 4.55 (s, 2H, NH_2, D_2O exchangeable), 3.55 (s, 6H, Ar-CH_2-N). ^{13}C-NMR (400 MHz, DMSO-d_6, δ, ppm): 163.17, 149.28, 148.97, 143.19, 139.28, 137.25, 129.75, 128.57, 128.55, 127.13, 123.92, 120.75, 117.23, 112.84, 58.46. Analysis: calcd. for $C_{28}H_{27}N_5O$ (449.55): C 74.81, H 6.05, N 15.58%; found: C 74.84, H 6.14, N 15.46%.

N'-(3-[(1H-imidazol-1-yl)methyl)]-2-amonobenzylidene)isonicotinohydrazide (4o)

IR (KBr; cm^{-1}): 3329, 3278, 3164, 2957, 2858, 2841, 1678, 1655, 1565, 1078. ^{1}H-NMR (300 MHz, DMSO-d_6, δ, ppm): 11.83 (s, 1H, -NH-N=), 8.83 (d, 2H, pyridine, *J* = 4.3 Hz), 8.69 (s, 1H,-N=C-H), 7.84 (d, 2H, pyridine, *J* = 3.7 Hz), 7.64 (s, 1H, imidazole), 7.29 (d, 2H, benzylidene, *J* = 3.4 Hz), 7.11 (s, 1H, benzylidene), 6.92 (m, 2H, imidazole), 4.74 (s, 2H, NH_2, D_2O exchangeable), 3.79 (s, 2H, Ar-CH_2-N). ^{13}C-NMR (400 MHz, DMSO-d_6, δ, ppm): 163.29, 149.72, 148.77, 143.33, 139.72, 137.28, 131.18, 128.12, 123.29, 121.17, 118.19, 116.73, 113.14, 54.82. Analysis: calcd. for $C_{17}H_{16}N_6O$ (320.35): C 63.74, H 5.03, N 26.23%; found: C 63.77, H 5.11, N 26.12%.

7-(4-{[2-amino-3-(2-isonicotinoylhydrazono)methyl]benzyl}piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (4p)

IR (KBr; cm^{-1}): 3317, 3277, 3169, 2955, 2860, 2844, 1723, 1688, 1648, 1569, 1158, 1077. ^{1}H-NMR (300 MHz, DMSO-d_6, δ, ppm): 12.37 (s, 1H, COOH), 11.88 (s, 1H, -NH-N=), 8.75 (d, 2H, pyridine, *J* = 4.3 Hz), 8.67 (s, 1H, quinoline), 8.71 (s, 1H, -N=C-H), 8.19 (s, 1H, quinoline), 7.94 (d, 2H, pyridine, *J* = 3.8 Hz), 7.32 (d, 2H, benzylidene, *J* = 3.3 Hz), 6.74 (t, 1H, benzylidene), 6.45 (s, 1H, quinoline), 4.64 (s, 2H, NH_2, D_2O exchangeable), 4.18 (m, 1H, aziridine), 3.64 (s, 2H, Ar-CH_2-N), 2.92–2.77 (m, 8H, 4CH_2, piperazine), 1.32–1.23 (m, 4H, 2CH_2, aziridine). ^{13}C-NMR (400 MHz, DMSO-d_6, δ, ppm): 175.19, 165.29, 163.22, 152.49, 149.75, 147.94, 146.55, 145.92, 143.35, 139.88, 139.47, 133.48, 129.77, 122.84, 120.81, 117.89, 113.53, 112.52, 109.53, 108.88, 102.85, 54.89, 52.87, 49.82, 38.84, 11.83 Analysis: calcd. for $C_{31}H_{30}FN_7O_4$ (583.61): C 63.80, H 5.18, N 16.80%; found: C 63.85, H 5.11, N 16.82%.

7-(4-{2-amino-3-[(2-isonicotinoylhydrazono)methyl]benzyl}piperazin-1-yl)-1-ethyl-6,8-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (4q)

IR (KBr; cm^{-1}): 3329, 3269, 3165, 2988, 2862, 2840, 1727, 1680, 1645, 1564, 1155, 1082. ^{1}H-NMR (300 MHz, DMSO-d_6, δ, ppm): 12.25 (s, 1H, COOH), 11.74 (s, 1H, -NH-N=), 8.89 (d, 2H, pyridine, *J* = 3.9 Hz), 8.55 (s, 1H, quinoline), 8.27 (s, 1H, -N=C-H), 8.11 (s, 1H, quinoline), 7.85 (d, 2H, pyridine, *J* = 3.4 Hz), 7.69 (d, 2H, benzylidene, *J* = 2.9 Hz), 7.46 (t, 1H, benzylidene), 4.69 (s, 2H, NH_2, D_2O exchangeable), 4.33 (m, 2H, 2CH_2, quinoline), 3.64 (s, 2H, Ar-CH_2-N), 3.45–3.28 (m, 8H, piperazine), 1.37 (t, 3H, CH_3, piperazine). ^{13}C-NMR (400 MHz, DMSO-d_6, δ, ppm): 176.19, 166.18, 163.26, 152.18, 149.27, 148.91, 146.37, 143.19, 139.27, 134.17, 130.18, 129.71, 122.85, 121.58, 119.79, 117.87, 112.17, 108.51, 106.47, 55.85, 52.18, 48.42, 46.77, 17.85 Analysis.: calcd. for $C_{30}H_{29}F_2N_7O_4$ (589.59): C 61.11, H 4.96, N 16.63%; found: C 61.18, H 4.92, N 16.60%.

Hydrogen peroxide scavenging activity

A solution of hydrogen peroxide (40 mM) was prepared in phosphate buffer (pH 7.4). Different concentrations (100, 300, and 500 µg/mL) of all the

synthesized compounds were added to a hydrogen peroxide solution (0.6 mL, 40 mM). The absorbance of hydrogen peroxide at 230 nm was determined after 10 min against a blank solution containing phosphate buffer without hydrogen peroxide. The percentage scavenging of hydrogen peroxide by the synthesized compounds and the standard compounds were calculated using the following formula: Percentage scavenging $[H_2O_2] = [(A_0 - A_1)/A_0] \times 100$, where A_0 was the absorbance of the blank, and A_1 was the absorbance in the presence of the sample and standards (17). The percentage scavenging of hydrogen peroxide by the synthesized compounds at 100, 300 and 500 µg/mL concentration were absorbed and results are summarized in Table 2.

RESULTS AND DISCUSSION

In this study new Mannich bases have been synthesized and evaluated for antioxidant activity. In general, IR spectra of **4k**–**4q** showed absorption band at around 3395–3317, 3288–3269, 3169–2955, 2865–2838, 1688–1675, 1655–1645, 1567–1559, 1086–1075 cm^{-1} regions, confirming the presence of NH_2, NH, CH, CH_2, C=N, C=O, C=C, C-N, respectively. In ^{1}H-NMR spectra, the signals of the respective prepared derivatives were verified on the basis of their chemical shifts, multiplicities, and coupling constants. The spectra of most compounds showed the characteristic NH proton δ 11.92–11.74 ppm, 1 H proton of -N=C-H at δ 8.83–8.17 ppm, protons of pyridine were at around δ 8.95–7.74 ppm, characteristic protons of benzylidene at δ 7.69–6.74 ppm, 2 H protons of NH_2 at δ 5.74–4.49 ppm and 2 H protons of Ar-CH_2-N at δ 3.79-3.53 ppm. ^{13}C-NMR spectra of most compounds have characteristic C=O carbon atom signals which appeared at around δ 163.65–163.17 ppm, pyridine δ 154.29–108.85 ppm, benzylidene δ 148.97–112.84 ppm, -N=C-H δ 143.35–143.18 ppm, Ar-CH_2-N δ 58.46–51.75 ppm. The elemental analysis, and IR, ^{1}H-NMR and ^{13}C-NMR spectral data of synthesized compounds were found in agreement with the assigned molecular structures. The evaluation of antioxidant activities was carried out by the method of scavenging hydrogen peroxide. The results are presented in Table 2. From all the synthesized derivatives, compounds **4h** **4q** and **4p** showed the highest activity.

CONCLUSION

In conclusion, the present investigation has described the preparation of a series of Mannich bases and evaluation for their potent antioxidant activity. The synthesized compounds exhibit significant hydrogen peroxide scavenging activities *in vitro*. From all the synthesized derivatives, compounds: **4h** having morpholine moiety and **4p** and **4q** having fluoroquinoline and difluoroquinoline ring were the most active compounds with significant hydrogen peroxide scavenging activity. So, it was concluded that the presence of morpholine and quinoline was essential for high antioxidant activity.

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