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Data Article

Phenylboronic acid catalyzed synthesis of polysubstituted 1,4-dihydropyridine derivatives as promising antioxidant agents correlated with molecular docking

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ABSTRACT

A series of polysubstituted 1,4-dihydropyridines (**4a-i**) were designed and developed using Ph-B $(OH)_2$ catalyst. Further, compounds were confirmed by various spectroscopic techniques. After that all compounds were studied for molecular docking against the human peroxidase enzyme (1PRX). Results of docking revealed that many compounds exhibited low binding score. To get a reference from the docking study, all synthesized molecules were evaluated for in vitro antioxidant assay using DPPH, H_2O_2 and NO methods. Most of the tested compounds exhibited good to moderate inhibition. Amongst, these compounds **4a** (0.150, 0.141, 0.154 μM) and **4b** (0.146, 0.134, 0.149 μM) possessed more significant activity than positive control ascorbic acid.

1. Rationale

More than ten decades ago, the synthesis of 1,4-dihydropyridines (DHPs) was reported by Hantzsch [1]. DHPs are an important class of heterocyclic chemistry due to their pharmacological and biological activities such as anti-anginal [2], antihypertensive [3] and calcium channel antagonists [4] for cardiovascular disease. Subsequently, numerous clinically significant drugs appeared on the market with various functional groups in their main skeleton, such as Nifedipine, Nimodipine, Nicardipine, Isradipine, Felodipine and Amlodipine [5–8] (Fig. 1).

Currently, numerous efforts have been taken up to improve the Hantzsch reaction by utilizing various alternate processes [9–13]. Good variety in multicomponent reactions (MCRs), established using several ionic liquids as various Lowry-Bronsted acids, with several advantages has been reported [14–16]. In past years, several attempts has carried out to construct 1,4-DHPs by using diverse catalyst which showed comparative less yield Herewith we reported new derivatives by utilizing $PhB(OH)_2$ catalyst with yield increment.

On other hand, pyridine-containing heterocycles showed antioxidant activity [17,18]. Oxidative stress (OS) is extremely important for molecular pathogenesis, especially influencing the redox regulation of cellular signaling pathways [19]. Oxidative stress intently connects with the presence of nitrogen and oxygen free radicals, known as reactive nitrogen species and reactive oxygen species (RNS & ROS). Antioxidants (AOs) are characterized as substances that, when present in low fixations contrasted with those of an oxidizable substrate, inhibit or significantly delay the oxidation cycle [20]. Due to its synthetic applications and medicinal significance urge to

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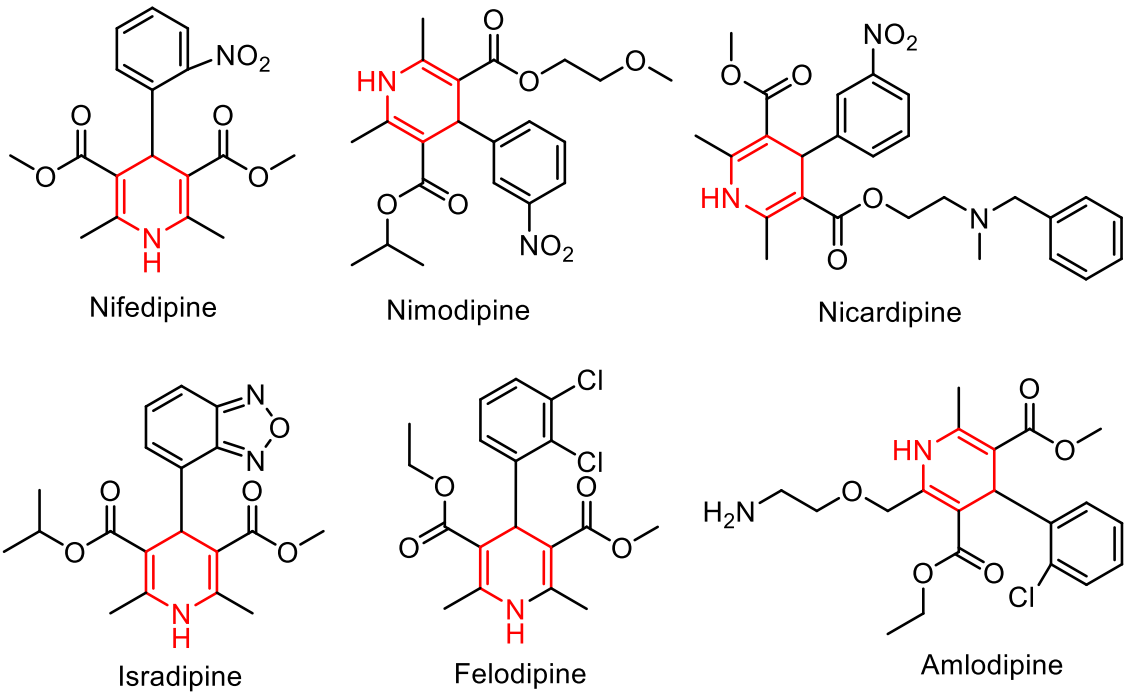


Fig. 1. Marketed drug having 1,4-dihydropyridine motif.

design for the improvement of the biologically active novel pyridine compounds using MCR approach. Besides, the drive of our work was to improve the reactivity with appropriate substitution in reactants to diminish the time of reaction, minimizing the side products and use of catalyst. In continuation of our past work on the synthesis of heterocyclic scaffolds with medicinal interest [21–29], herein we wish to report polysubstituted 1,4-dihydropyridine derivatives.

2. Procedure

2.1. Materials and methods

All melting points are uncorrected. Commercial chemicals, reagents, and solvents were used without further purification. The purity of the reaction products was monitored by TLC on Merck Silica Gel G60 F254 plates with spot visualization with UV light (254 and 365 nm), iodine vapour, and aqueous $KMnO_4$. The ^1H and ^{13}CNMR spectra were recorded on a Bruker Advanced 400 MHz spectrometer at 400 (^1H) and 101 MHz (^{13}C) in DMSO-d_6. The ^1H NMR chemical shifts were measured in ppm relative to internal TMS. Mass spectra were recorded on a Shimadzu GC-MSQP-2010 mass spectrometer in EI (70 eV) model using the direct inlet probe technique and m/z is reported in atomic units per elementary charge.

2.2. Chemistry

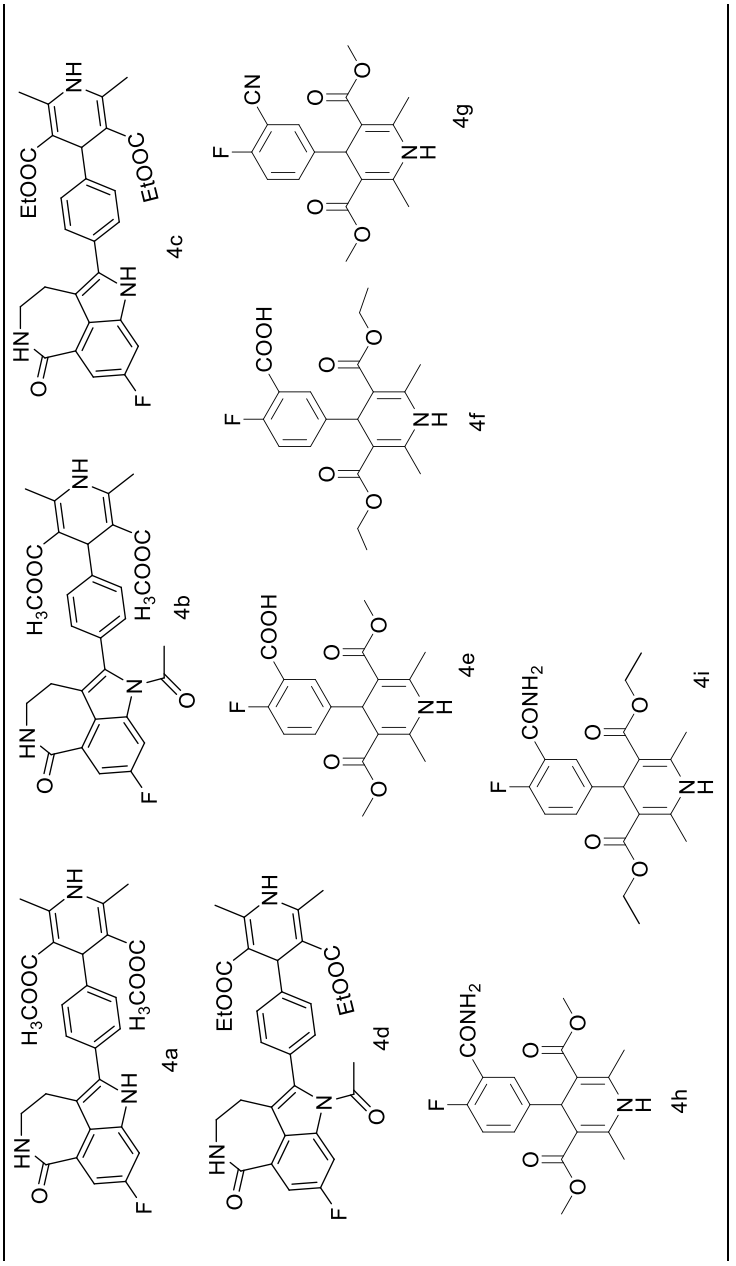
2.2.1. General procedure for the synthesis of azepino indole substituted 1,4-dihydropyridines (4a-d)

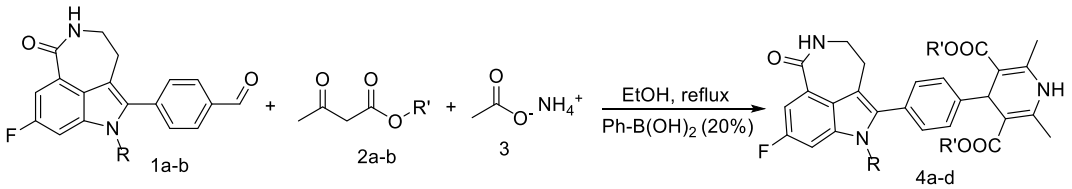
Starting material 1a-b were synthesized by using the reported method [35]. To a stir solution of compound **1a** or **1b** (1.0 mmol) and Ethanol (20 mL) at RT has added ammonium acetate (**3**) (1.0 mmol), methyl acetoacetate (**2b**) or ethyl acetoacetate (**2a**) (2.0 mmol), phenylboronic acid (20 mole %) was stirred for 6 hours at 60-65°C. Progress of the reaction was monitored by TLC. After completion of the reaction pour the reaction mass into the water. The solid precipitate was filtered and washed with water. Dry the solid under vacuum at 60°C to get compounds (**4a-b**) and (**4c-d**) respectively.

2.2.2. General procedure for the synthesis of aryl halide substituted 1,4-dihydropyridines (4e-i)

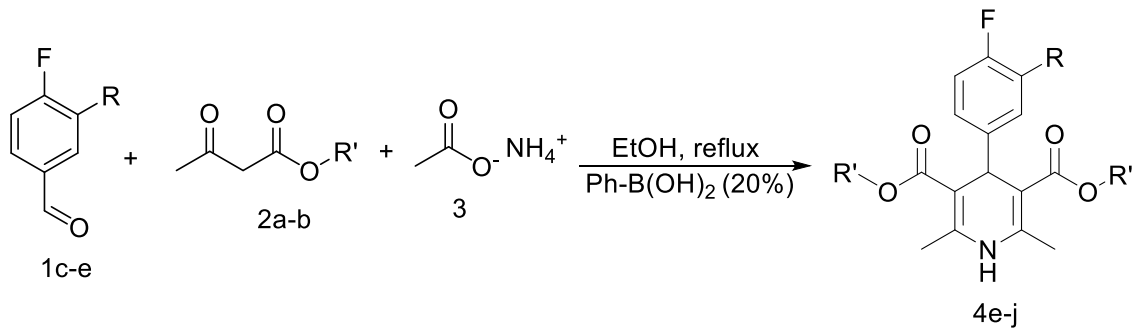
To a stir solution of aryl halide substituted aldehydes 1c-e (1 mmol) in ethanol (20 mL) was added ammonium acetate (**3**) (1.0 mmol), phenylboronic acid (20 mole %), methyl acetoacetate (**2a**) or ethyl acetoacetate (**2b**) (2.0 mmol) was stirred for 6-7 hours at 60-65°C. Progress of the reaction was monitored by TLC. After completion of the reaction cool the reaction mass for RT and precipitate solid was filtered out and washed with ethanol. Dry the solid under vacuum at 60°C to get compounds (**4e-j**).

2.2.3. Synthesized compounds


4a
4b
4c
4d
4e
4f
4g
4h
4i



Scheme 1. Ph-B(OH)$_2$ catalyzed synthesis of 1,4-DHPs having azepine fused indole motif.



Scheme 2. Ph-B(OH)$_2$ catalyzed synthesis of aryl halide substituted 1,4-DHPs.

2.3. Biological evaluation

2.3.1. Antioxidant assay

The synthesized compounds **4a-j** were evaluated for their free radical scavenging capacity. The antioxidant activity was carried out by 2,2-diphenyl-1-picrylhydrazyl (DPPH), hydrogen peroxide (H_2O_2), and nitric oxide (NO) methods [30–34]. All obtained results were compared with the reference drug ascorbic acid.

2.4. Molecular docking

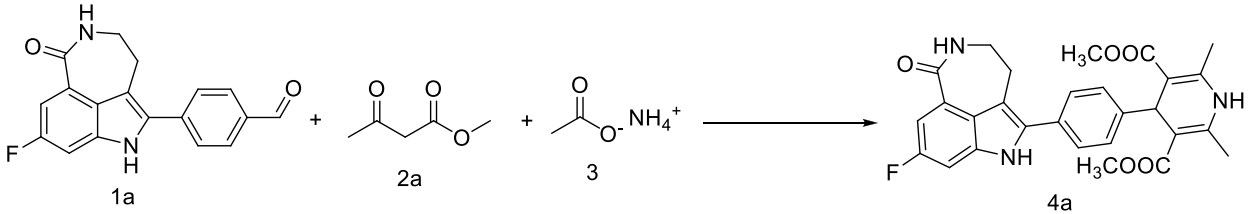
Molecular docking was utilized to explain the binding mode of the ligand to deliver easy information for optimization in structure. Molecular docking is a most important tool to establish the possible drug-receptor interaction which might be responsible for the biological response. Ascorbic acid is known to bind with the active sites of DPPH. The crystal structure of HORF6 (PDB ID: 1PRX) was selected for the docking study [36]. The 2D structures of ligands were drawn in Chem Bio Draw Ultra 14.0 and 3D structures were created by using ChemBio3D Ultra 14.0. For the final preparation of ligand preparations, translated using the "Open babel" Translator Molecular Mechanics (MM) method. The process of making protein receptors by eliminating the water molecule and addition of polar hydrogen followed by Kollman charge by using Auto dock vina software. The active site was defined from the coordinates in the original PDB file. Auto dock vina (http://vina.scripps.edu) [37] was used for molecular docking. The distance between donor and acceptor atoms that form a hydrogen bond was fixed as 1.0 Å. For further studies in auto dock vina, initially, the PDB structures were converted in PDBQT format, and a grid box with dimensions 48 × 42 × 60 Å was created around the protein receptor assigned with the assistance of Auto Dock Tools and spacing (Angstrom): 0.482 Å. The structure of the drug was downloaded from the protein data bank (http://www.rcsb.org). The protocol simplifies flexible compound docking for different compound conformers within the rigid receptor. The best conformation for each compound was chosen and the interaction was visualized in Discovery studio 4.1.0. Software.

2.5. Spectral data

Dimethyl-4-(4-(8-fluoro-1-oxo-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-5-yl)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**4a**): Yield: 85.1% as a yellow powder, Mp: 248-250°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.55 (s, 1H), 8.94 (s, 1H), 8.21 (s, 1H), 7.47 (m, 3H), 7.29 (t, *J*=6.8 Hz, 3H), 4.97 (s, 4H), 3.58 (t, *J*= 3.6 Hz, 6H), 3.38 (m, 2H), 3.02 (s, 2H), 2.29 (t, *J*=3.2 Hz, 6H), ^{13}C NMR (100 MHz, DMSO-d_6) δ: 168.41, 167.33, 159.47, 157.14, 147.36, 145.88, 136.33, 136.61, 135.48, 135.45, 129.46, 127.74, 127.34, 125.72, 125.64, 123.22, 111.45, 109.56, 109.31, 101.31, 100.63, 100.38, 56.01, 50.68, 41.89, 40.13, 28.70, 18.20. Mass m/z: 504.28, Elemental Analysis: $C_{28}H_{26}FN_3O_5$, calculated: C, 66.79; H, 5.20; F, 3.77; N, 8.35; O, 15.89, Found: C, 66.82; H,5.10; N,8.38.

Dimethyl-4-(4-(6-acetyl-8-fluoro-1-oxo-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-5-yl)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**4b**): Yield: 76.5% as a yellow powder, Mp: 258-260°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.84 (s, 1H), 8.95 (s,

Table 1
Reaction optimization of model reaction for compound **4a.**



Entry	Catalyst (mol %)	Reaction Condition[a]	Time (h)	Yield (%)[b]
1	-	Ethanol, Reflux	18	29
2	-	Methanol, Reflux	18	12
3	-	MeCN, Reflux	19	18
4	-	DMF, rt	17	5
5	Ph-B(OH)$_2$ (10%)	Ethanol, Reflux	8	78
6	**Ph-B(OH)$_2$ (20%)**	**Ethanol, Reflux**	**6**	**85**
7	Ph-B(OH)$_2$ (25%)	Ethanol, Reflux	6	82
8	TMS-Cl (20%)	DMF, rt	10	76
9	Con. HCl (20%)	Ethanol, Reflux	12	50
10	Con. HCl (20%)	Methanol, Reflux	20	45
11	Con. HCl (20%)	MeCN, Reflux	18	52
12	p-TSA (10%)	MeCN, Reflux	12	40
13	p-TSA (10%)	Ethanol, Reflux	15	58

[a] 4-(8-fluoro-1-oxo-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-5-yl)benzaldehyde (1 mmol, 1), Ethyl acetoactate OR Methyl acetoacetate (2.1 mmol, 2) and solvents with catalyst at different temperature.

[b] Isolated yield.

Bold value indicates final optimal condition.

Table 2
In vitro antioxidant assay for synthesized compounds **4a-i.**

Entry	Compound	50 μM DPPH	H_2O_2	NO
1	**4a**	0.150	0.141	0.154
2	**4b**	0.146	0.134	0.149
3	**4c**	0.130	0.120	0.127
4	**4d**	0.117	0.108	0.112
5	**4e**	0.139	0.122	0.142
6	**4f**	0.089	0.073	0.094
7	**4g**	0.112	0.093	0.108
8	**4h**	0.129	0.113	0.128
9	**4i**	0.145	0.123	0.141
10	Ascorbic acid	0.116	0.109	0.120

Table 3
Docking score of screened compounds and Ascorbic acid against 1PRX receptor.

Sr No	Compound	Docking score(ΔG kcal/mol)
1	**4a**	-7.9
2	**4b**	-8.6
3	**4c**	-7.4
4	**4d**	-7.3
5	**4e**	-6.1
6	**4f**	-5.6
7	**4g**	-5.5
8	**4h**	-5.8
9	**4i**	-6.6
10	Ascorbic acid	-5.1

1H), 7.68 (d, *J*=10.8 Hz, 1H), 7.52 (q, *J*=18.6 Hz, 3H), 7.30 (d, *J*=7.6 Hz, 2H), 4.97 (s, 1H), 3.59 (s, 6H), 3.31 (s, 2H), 3.02 (s, 2H), 2.43 (s, 3H), 2.30 (s, 6H), ^{13}C NMR (100 MHz, DMSO-d_6) δ: 171.54, 169.76, 167.30, 159.15, 156.81, 147.74, 145.91, 137.22, 137.15, 137.12, 129.06, 127.54, 127.46, 123.81, 123.72, 123.64, 111.27, 111.01, 110.67, 103.32, 103.06, 101.25, 50.68, 41.89, 40.15, 27.38, 25.64, 18.20. Mass m/z: 546.28, Elemental Analysis: $C_{30}H_{28}FN_3O_6$, calculated: C, 66.05; H, 5.17; F, 3.48; N, 7.70; O, 17.60, Found: C, 66.1; H, 5.20; N, 7.80.

Diethyl-4-(4-(8-fluoro-1-oxo-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-5-yl)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**4c**): Yield: 70.5% as a light yellow powder, Mp: 262-264°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.55 (s, 1H), 8.85 (s, 1H), 8.21 (s, 1H), 7.49 (d. *J*=6.8 Hz, 2H), 7.43 (d, *J*=10.4 Hz, 1H), 7.30 (d, *J*=7.6 3H), 4.94 (s, 1H), 4.03 (s, 4H), 3.31 (s, 2H), 3.02 (s, 2H), 2.30 (s, 6H), 1.18 (s, 6H), ^{13}C NMR (100 MHz, DMSO-d_6) δ: 168.45, 166.90, 159.48, 157.15, 147.72, 145.55, 136.74, 136.63, 135.52, 129.37, 127.70, 127.55, 125.71, 125.62, 123.24, 111.41, 109.57, 109.32, 101.62, 100.64, 100.38, 59.06, 41.90, 40.12, 28.72, 18.24, 14.18. Mass m/z: 532.25, Elemental Analysis: $C_{30}H_{30}FN_3O_5$, calculated: C, 67.78; H, 5.69; F, 3.57; N, 7.90; O, 15.05, Found: C, 67.72; H, 5.70; N, 7.93.

Diethyl-4-(4-(6-acetyl-8-fluoro-1-oxo-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-5-yl)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**4d**): Yield: 72.3% as a light yellow powder, Mp: 271-273°C, ^{1}H NMR (400 MHz, DMSO-$_{d6}$) δ: 11.83 (s, 1H), 8.87 (s, 1H), 7.68 (d, *J*=10.8 Hz, 1H), 7.52 (q, *J*=18.4 Hz, 2H), 7.33-7.18 (m, 3H), 4.94 (s, 1H), 4.05-4.02 (m, 4H), 3.02 (s, 2H), 2.48 (s, 3H), 2.43 (s, 2H), 2.30 (s, 6H), 1.19-1.17 (m, 6H), ^{13}C NMR (100 MHz, DMSO-$_{d6}$) δ: 171.54, 169.79, 166.86, 159.14, 156.80, 148.10, 145.57, 137.30, 137.19, 137.10, 128.95, 128.85, 128.15, 127.81, 127.32, 125.26, 123.77, 123.69, 123.65, 111.26, 111.00, 110.61, 103.31, 103.06, 101.54, 59.05, 41.89, 27.38, 25.63, 20.98, 18.22, 14.16. Mass m/z: 574.31, Elemental Analysis: $C_{32}H_{32}FN_3O_6$, calculated: C, 67.00; H, 5.62; F, 3.31; N, 7.33; O, 16.73, Found: C, 67.12; H, 5.61; N, 7.34.

5-(3,5-bis(methoxycarbonyl)-2,6-dimethyl-1,4-dihydropyridin-4-yl)-2-fluorobenzoic acid (**4e**): Yield: 82.3% as a light yellow powder, Mp: 180-182°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.12 (s, 1H), 8.95 (s, 1H), 7.65 (q, *J*=7.0 Hz, 1H), 7.36 (m, 1H), 7.14 (t, *J*=8.0 Hz, 1H), 4.90 (s, 1H), 3.57 (d, *J*=6.4, 6H), 2.2 (s, 6H), ^{13}C NMR (100 MHz, DMSO-$_{d6}$) δ: 167.10, 166.25, 165.16, 160.84, 158.30, 156.24, 146.04, 143.93, 133.18, 133.09, 130.15, 129.38, 118.69, 118.59, 117.00, 116.78, 116.57, 116.35, 106.20, 101.84, 101.16, 51.90, 50.95, 50.71, 50.24, 20.09, 18.80, 18.20. Mass m/z: 362.29, Elemental Analysis: $C_{18}H_{18}FNO_6$, calculated: C, 59.50; H, 4.99; F, 5.23; N, 3.86; O, 26.42, Found: C, 59.52; H, 4.98; N, 3.87.

5-(3,5-bis(ethoxycarbonyl)-2,6-dimethyl-1,4-dihydropyridin-4-yl)-2-fluorobenzoic acid (**4f**): Yield: 79.3% as a light yellow powder, Mp: 185-187°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.09 (s, 1H), 8.87 (s, 1H), 7.69 (q, *J*=9.6 Hz, 1H), 7.35 (m, 1H), 7.14 (t, *J*=8.8 Hz, 1H), 4.87 (s, 1H), 4.06 (m, 4H), 2.27 (s, 6H), 1.13 (t, *J*=7.2 Hz, 6H), ^{13}C NMR (100 MHz, DMSO-$_{d6}$) δ: 166.63, 165.20, 165.17, 160.81, 158.27, 145.73, 144.36, 144.33, 133.49, 133.40, 130.73, 118.35, 118.25, 116.42, 116.19, 101.47, 59.05, 38.49, 18.15, 13.99, Mass m/z: 392.15, Elemental Analysis: $C_{20}H_{22}FNO_6$, calculated: C, 61.38; H, 5.67; F, 4.85; N, 3.58; O, 24.53, Found: C, 61.40; H, 5.69; N, 3.60.

Dimethyl 4-(3-cyano-4-fluorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**4g**): Yield: 67.2% as a light yellow

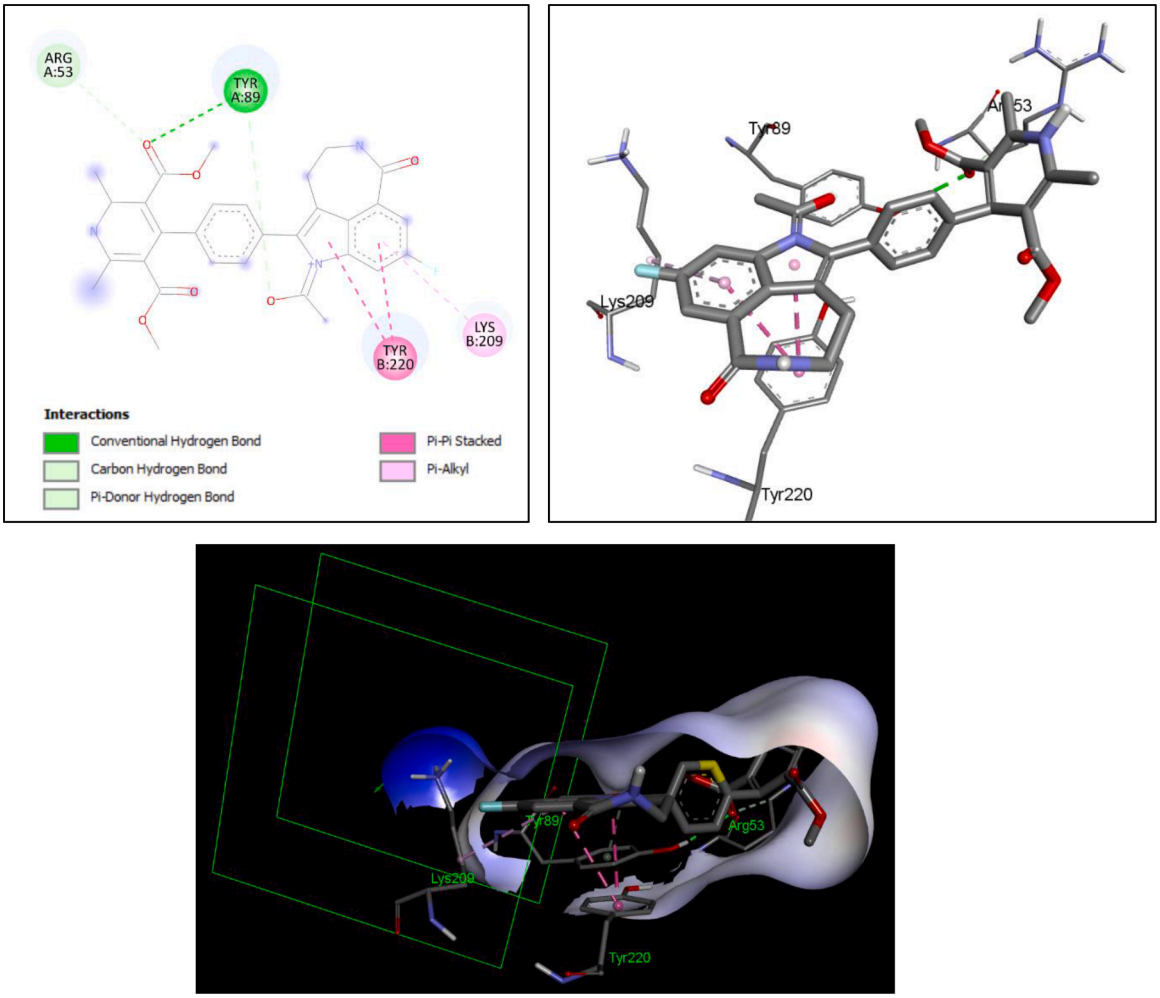


Fig. 2. 2D and 3D representation of ligand (**4b**) and protein interaction visualized by Discovery studio.

powder, Mp: 168-170°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.99 (s, 1H), 7.52 (q, *J*=5.6 Hz, 2H), 7.38 (t, *J*=8.8 Hz, 1H), 4.90 (s, 1H), 3.56 (s, 6H), 2.28 (s, 6H), ^{13}C NMR (100 MHz, DMSO-$_{d6}$) δ: 166.94, 162.16, 159.64, 146.55, 145.45, 145.42, 134.81, 134,73, 131.66, 116.32, 116.13, 114.18, 100.69, 99.62, 99.47, 50.73, 38.26, 18.21, Mass m/z: 345.24, Elemental Analysis: $C_{18}H_{17}FN_2O_4$, calculated: C, 62.79; H, 4.98; F, 5.52; N, 8.14; O, 18.58, Found: C, 62.79; H, 4.98; N, 8.14.

Dimethyl 4-(3-carbamoyl-4-fluorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**4h**): Yield: 80.2% as a light yellow powder, Mp: 158-160°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.96 (s, 1H), 7.60 (s, 2H), 7.42 (q, *J*=5.2 Hz, 1H), 7.25 (m, 1H), 7.10 (t, *J*=8.8 Hz, 1H), 4.89 (s, 1H), 3.55 (s, 6H), 2.27 (s, 6H), ^{13}C NMR (100 MHz, DMSO-$_{d6}$) δ: 167.16, 165.32, 158.93, 156.48, 145.97, 144.03, 144.0, 131,00, 130.92, 128.63, 123.30, 123.15, 115.51, 115.28, 56.01, 50.68, 38.04, 18.50, 18.20, Mass m/z: 361.26, Elemental Analysis: $C_{18}H_{19}FN_2O_5$, calculated: C, 59.66; H, 5.29; F, 5.24; N, 7.73; O, 22.08, Found: C, 59.64; H, 5.30; N, 7.75.

Diethyl 4-(3-carbamoyl-4-fluorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**4i**): Yield: 77.2% as a light yellow powder, Mp: 160-162°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.88 (s, 1H), 7.59 (s, 2H), 7.47 (q, *J*=4.8 Hz, 1H), 7.25 (m, 1H), 7.11 (q, *J*=8.4 Hz, 1H), 4.87 (s, 1H), 4.0 (m, 4H), 2.27 (s, 6H), 1.14 (t, *J*=7.2 Hz, 6H), ^{13}C NMR (100 MHz, DMSO-$_{d6}$) δ: 166.69, 165.26, 158.89, 156.44, 145.65, 144.41, 144.38, 131,37, 131.29, 129.16, 122.93, 122.79, 115.34, 115.11, 101.54, 59.06, 38.41, 18.20, 14.06, Mass m/z: 391.19, Elemental Analysis: $C_{20}H_{23}FN_2O_5$, calculated: C, 61.53; H, 5.94; F, 4.87; N, 7.18; O, 20.49, Found: C, 61.56; H, 5.98; N, 7.20.

3. Data, value and validation

3.1. Chemistry

For the synthesis of targeted 1,4-dihydropyridine derivatives (**4a-i**) were accomplished by the Hantzsch synthesis of aldehydes, 1,3-dicarbonyl compounds, and ammonium acetate. This reaction was performed out in two different schemes with the variation of

aldehydes and substation of urea. Four molecules (**4a-d**) are shown in Scheme 1 which were synthesized using azepino indole-based aldehydes (**1a-b**), substituted ethyl acetoacetate (**2a-b**), and ammonium acetate whereas, compounds (**4e-i**) were synthesized using a same reaction of substituted benzaldehyde (**1c-e**), substituted ethyl acetoacetate (**2a-b**) and ammonium acetate (**3**) outlined in Scheme 2. For the synthesis of desire adducts (**4a-i**), optimized reaction conditions for compound **4a** under various conditions. Polar protic and polar aprotic solvents used for yield increments. By using ethanol solvent at reflux condition, the isolated yield was only 29% whereas using *p*-TSA as catalyst yield increment was observed up to 58%. By using TMS-Cl (20 mol%) catalyst, we found a good yield (76%). Eventually, we found the highest yield (85%) by using Ph-B$(OH)_2$ Therefore, we increased the amount of catalyst (25 mol %) but no more yield increment was observed. The final optimal condition was in ethanol solvent at reflux condition and using Ph-B $(OH)_2$ (20 mol%) as a catalyst (Table 1).

3.2. Antioxidant assay

All synthesized DHPs (**4a-i**) were evaluated for in vitro antioxidant assay using 2,2-diphenyl-1-picrylhydrazyl (DPPH), Hydrogen peroxide (H_2O_2) and Nitric oxide (NO) method. The assay was performed on fixed concentrations as 50 μg/mL. Result of antioxidant assay revealed that the compound **4b** showed the highest inhibition with inhibition 79.84 ± 0.23, 73.37 ± 0.51, 81.69 ± 0.32 (DPPH, H_2O_2, NO) in this series. Compound **4a** exhibited second highest inhibition. Compounds **4b** and **4b** showing good inhibition due to having azepino indole moiety. In contrast, compounds **4f** and **4g** exhibited lowest inhibition potential. All results of the assay were compared with the reference drug ascorbic acid. Result showed that molecules **4a** and **4b** showed more inhibition potential than positive control ascorbic acid. The results of all compounds are outlined in Table 2.

3.3. Molecular docking

The area of molecular docking has arisen during the last few decades and now is becoming an essential part of drug discovery and development. Binding energies are the most extensively used mode of measuring the binding affinity of the screened compounds carried out by Autodock vina in Table 3.

The virtual screening result revealed that all the inhibitors (**4a–i**) except a few shown strong affinities with almost similar docking score (Table 3). Additionally, **4a, 4b** & **4c** have remarkable activity with high specificity and selectivity to the receptor. Among all compounds, 4b have the lowest binding energy. Fig. 2 demonstrate the diagrammatical representation of molecular docking analysis of selected ligand (**4b**) with protein 1PRX by Autodock vina and visualization of docked protein using Discovery Studio. Molecular docking analysis of Ligand (**4b**) with protein 1PRX by Autodock vina showed interaction with amino acids TYR-89 with conventional hydrogen bond, ARG-53 with π-donor hydrogen bond, TYR-220 with π-π stacked, and LYS-209 with π-alkyl. Therefore, molecular docking study exhibited that many compounds have significant interactions within the active site residues of HORF6 1PRX receptor which might be the cause of remarkable free radical scavenging activity.

Conclusion

In conclusion, a new class of 1,4-dihydropyridine derivatives were designed and synthesized by using PhB$(OH)_2$ as a catalyst. Various catalyst and reaction condition was investigated for compound 4a but 20 mol% PhB$(OH)_2$ catalyst gave a significant yield with less reaction time. All derivatives were studied for molecular docking against the human peroxidase enzyme (1PRX) and found compound **4b** has the lowest binding energy. Furthermore, Synthesized molecules were screened for antioxidant assay by various methods such as DPPH, H_2O_2 and NO. The result of the antioxidant assay revealed that compounds **4a** and **4b** have significant inhibitory potential than reference standard acarbose. Rest all synthesized compounds exhibited good to moderate free radical scavenging capacity. Synthesized molecules can be potential candidate for next level clinical examinations and may resulted into futuristic drug.

Specifications Table

Subject area	Organic Chemistry, Biochemistry, Spectroscopy, Computational Chemistry
Compounds	1,4-dihydropyridine
Data category	Spectral, synthesized
Data acquisition format	NMR, Mass spectra, Elemental analysis
Data type	Analyzed
Procedure	Phenylboronic acid catalyzed synthesis of polysubstituted 1,4-dihydropyridine derivatives by Hantzsch synthesis
Data accessibility	Manuscript and supplementary data enclosed with this article

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Phenylboronic acid catalyzed synthesis of polysubstituted 1,4-dihydropyridine derivatives as promising antioxidant agents correlated with molecular docking (Original data) (Figshare).

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