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Imidazole-pyrazole hybrids: Synthesis, characterization and *in-vitro* bioevaluation against *α*-glucosidase enzyme with molecular docking studies

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ABSTRACT

Herein, substituted imidazole-pyrazole hybrids (**2a-2n**) were prepared *via* a multi component reaction employing pyrazole-4-carbaldehydes (**1a-1d**), ammonium acetate, benzil and arylamines as reactants. All the new compounds were characterized through their spectral and elemental analyses. Further these compounds were tested against *α*-glucosidase enzyme. The compounds **2k**, **2l** and **2n** possessed good inhibition potencies, however, compounds **2f** (IC_{50} value: 25.19 ± 0.004 μM) and **2m** (IC_{50} value: 33.62 ± 0.03 μM) were the most effective compounds of the series. Furthermore, molecular docking helped to understand the binding interactions of **2f** and **2m** with the understudy yeast's *α*-glucosidase enzyme.

1. Introduction

Imidazole, a fundamental class of heterocycles, is a unique template of multifaceted applications. This nitrogen containing molecule is not only a natural motif (element of DNA base, histidine, alkaloids, biotin, vitamin B12, etc.) but also documented as plant growth regulators and pesticides in agriculture [1–3]. They are widely used in catalysis, analytical and organometallic chemistry, as dyes and fluorescent molecules in optical industries, in solar cells and organic light emitting diodes and also employed for various other purposes [4–6]. Different imidazole based clinical drugs have also broadened the therapeutic scope of this scaffold. Therefore, medicinal candidature of imidazole as various enzymes inhibitors [7–10], antimicrobial [11–13], antiviral [14], antitubercular [15,16], antitumor [17], anticancer [18], anti-inflammatory [19], antiepileptic [20] and antiplatelet [21] drugs, etc. is an exceptional one (Fig. 1).

Various studies have shown that diabetes mellitus is an emerging threat to human health which might lead to death. Recent evidences have supported the existence of relationship between *α*-glucosidase enzyme and type 2 diabetes mellitus. To deal with this disease, inhibition of *α*-glucosidase enzyme's functioning can help in controlling blood sugar [22–24]. Literature reveals that imidazole-pyrazole hybrids containing molecules could also function as potent inhibitors of targeted enzyme [25]. These observations have encouraged us to continue our previous research, where diazoles linked with other heterocycles proved as effective inhibiting agents [26–28]. Herein, we would like to share some new discoveries. The purpose of present study was to evaluate synthesized compounds against *α*-glucosidase enzyme to examine whether these compounds have better targeting potentials or not. To the best of our knowledge, such tetrasubstituted imidazoles (**2a-2n**) were not yet tested against *α*-glucosidase (Fig. 2).

2. Results and discussion

2.1. Chemistry

To synthesize designed imidazolylpyrazole scaffolds, synthetic route of Scheme 1 was employed. Initially, different substituted pyrazole-4-carbaldehydes were prepared [29]. A versatile MCR Debus-Radziszewski reaction was utilized to construct an imidazole nucleus over a pyrazole moiety. This reaction has involved microwave irradiation of a mixture of four components: a pyrazole-4-carbaldehyde, substituted aniline, benzil and ammonium acetate. The acetic acid was used as a solvent. The present reaction is fairly compatible with various aldehydes having different electron donating/withdrawing groups (**1a-1d**). In this way, some functionally diversified compounds (**2a-2n**) were prepared.

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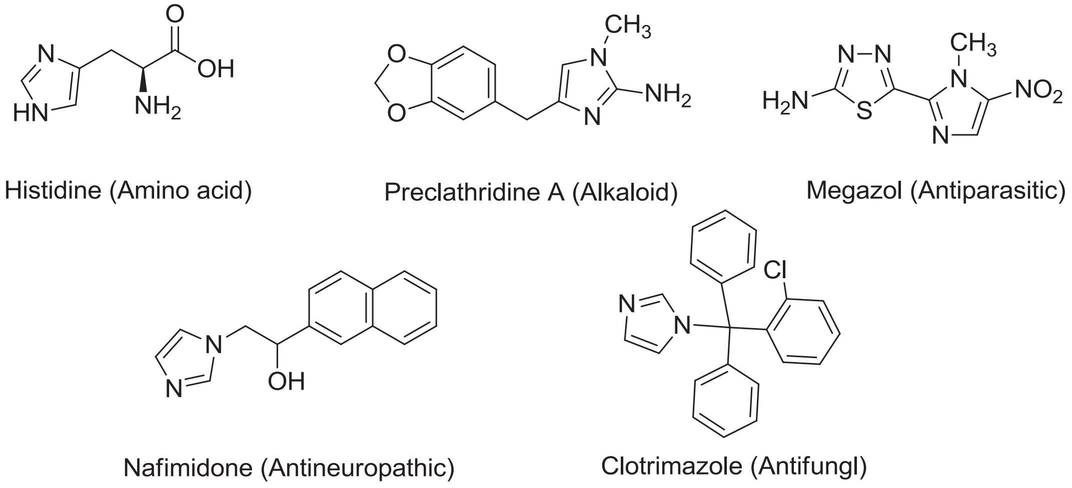


Fig. 1. Biologically important imidazole-based compounds.

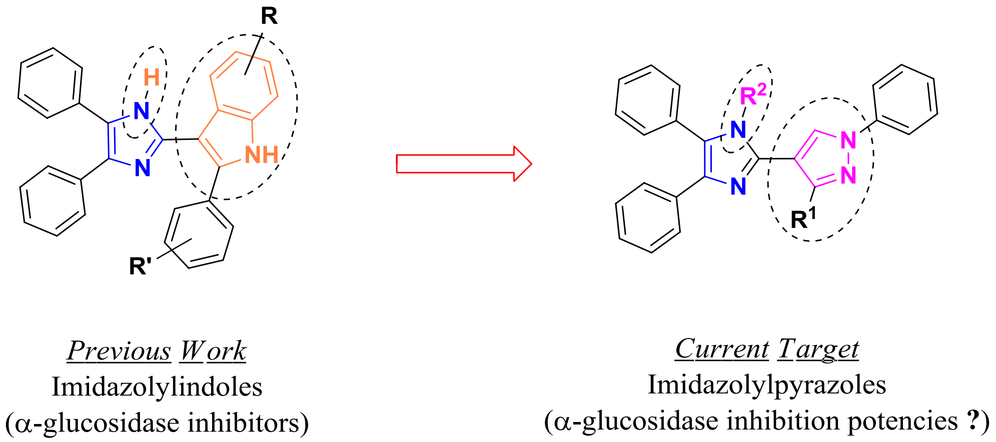


Fig. 2. Designing of potent imidazole-pyrazole hybrids.

The elemental composition and structural identification of novel derivatives (**2a-2n**) were carried out by different spectroscopic means. As expected, the ^{1}H NMR spectra of highly arylated imidazolylpyrazoles showed a complex pattern of signals in aromatic region. Somewhere beautiful splitting pattern of aromatic protons with appropriate *J* values were also detected. In all compounds, H-5 of pyrazole was easily distinguished in the region of 8.10–8.45 ppm as a singlet and supported the proposed structure. The characteristic signals of linking carbons: C-4 of pyrazole and C-2 of imidazole were found around 112.00 ppm and 140.00 ppm respectively in ^{13}C NMR spectra which has confirmed the development of new C—C bond between two hetaryl rings. All mass spectra have distinct molecular ion peaks due to the stability of compounds. The IR data and elemental analyses were also in support of suggested structural patterns.

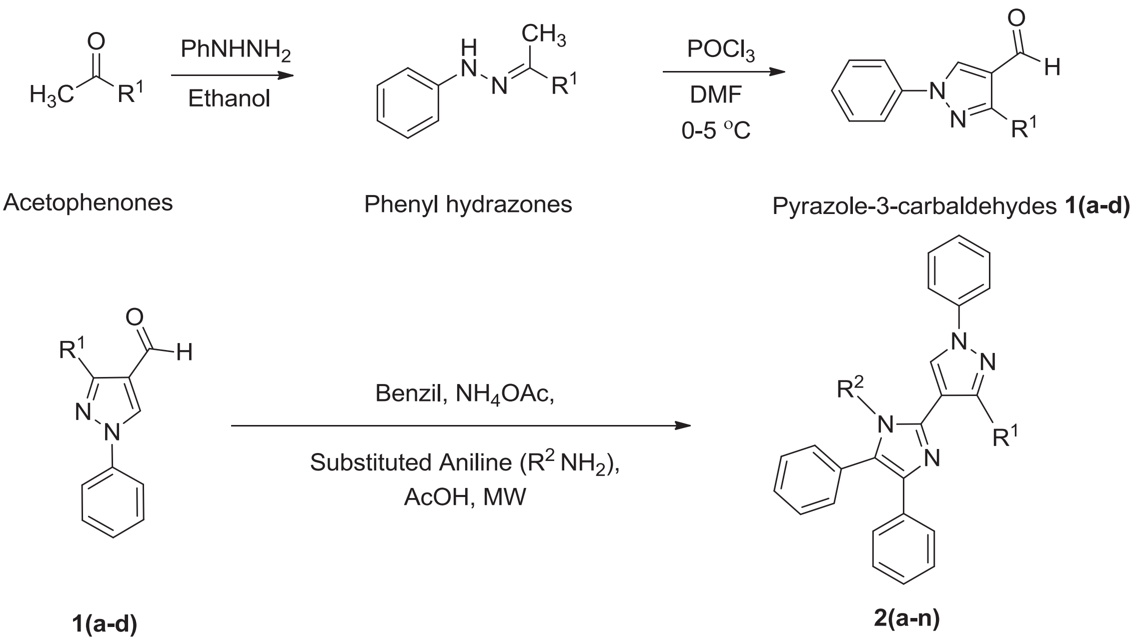
2.2. α-Glucosidase enzyme inhibition

These newly prepared imidazolylpyrazoles (**2a-2n**) were evaluated for their *in vitro* α-glucosidase inhibition using acarbose as standard reference (Table 1). In terms of percentage inhibition, all compounds have shown good results. There were visible influences of R^1 and R^2 substitutions on inhibition potencies of prepared compounds.

As evident from literature [25–28], here also, the introduction of electron donating substitutions due to electron withdrawing substitutions resulted in significant decrease in inhibition strength. The *p*-$OCH_3C_6H_4$ group containing derivatives **2a** (IC_{50} (μM): 178.82 ± 0.28), **2b** (IC_{50} (μM): 162.93 ± 0.32) and **2c** (IC_{50} (μM): 182.17 ± 0.37) have weak to moderate binding capabilities but the replacement of this methoxy group with other functionalities helped in recovering the inhibition potentials. The *p*-ClC_6H_4 substituted compounds **2d** (IC_{50} (μM): 168.92 ± 0.27), **2e** (IC_{50} (μM): 85.71 ± 0.09) and **2g** (IC_{50} (μM): 132.81 ± 0.29) have improved inhibitory effects. However, the product **2f** was proved to be the most significant agent (Inhibition (%): 96.21 ± 0.11, IC_{50} (μM): 25.19 ± 0.004). Probably, the synergistic effects of chloro and bromo substituents in one molecule augment the active nature of compound which can also be observed in case of compound **2i** (IC_{50} (μM): 84.61 ± 0.01). The compounds **2h** and **2j**, where only *p*-BrC_6H_4 functionality was present as R^1, have executed moderate inhibitory effects. The electron withdrawing group containing molecules have shown excellent results and served as potent scaffolds. Therefore, switching to the *m*-$NO_2C_6H_4$ group (as R^1 in compounds **2k**-**2n**) has contributed in regaining the enhanced binding affinities of molecules with enzyme's active sites. Out of these examples, compound **2m** has displayed even better activity than that of positive control acarbose with inhibition (%): 97.52 ± 0.26, IC_{50} (μM): 33.62 ± 0.03.

2.3. Molecular docking studies

The docking studies were carried out for analyzing the probable inhibitory action of the leading α-glucosidase inhibitors **2f** and **2m** of the series. The crystal structure α-glucosidase from *Saccharomyces cerevisiae* is not yet available from the Protein Data Bank (PDB), therefore in order to carry out molecular docking studies its homology model was



1a. R^1 = p-OCH$_3$C$_6$H$_4$
1b. R^1 = p-ClC$_6$H$_4$
1c. R^1 = p-BrC$_6$H$_4$
1d. R^1 = m-NO$_2$C$_6$H$_4$

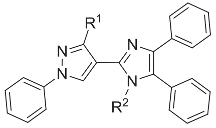
2a. R^1 = p-OCH$_3$C$_6$H$_4$, R^2 = p-OCH$_3$C$_6$H$_4$
2b. R^1 = p-OCH$_3$C$_6$H$_4$, R^2 = p-BrC$_6$H$_4$
2c. R^1 = p-OCH$_3$C$_6$H$_4$, R^2 = 3,5-(CH$_3$)$_2$C$_6$H$_3$
2d. R^1 = p-ClC$_6$H$_4$, R^2 = p-OCH$_3$C$_6$H$_4$
2e. R^1 = p-ClC$_6$H$_4$, R^2 = p-ClC$_6$H$_4$
2f. R^1 = p-ClC$_6$H$_4$, R^2 = p-BrC$_6$H$_4$
2g. R^1 = p-ClC$_6$H$_4$, R^2 = 3,5-(CH$_3$)$_2$C$_6$H$_3$
2h. R^1 = p-BrC$_6$H$_4$, R^2 = p-OCH$_3$C$_6$H$_4$
2i. R^1 = p-BrC$_6$H$_4$, R^2 = p-ClC$_6$H$_4$
2j. R^1 = p-BrC$_6$H$_4$, R^2 = 3,5-(CH$_3$)$_2$C$_6$H$_3$
2k. R^1 = m-NO$_2$C$_6$H$_4$, R^2 = p-ClC$_6$H$_4$
2l. R^1 = m-NO$_2$C$_6$H$_4$, R^2 = p-OCH$_3$C$_6$H$_4$
2m. R^1 = m-NO$_2$C$_6$H$_4$, R^2 = p-BrC$_6$H$_4$
2n. R^1 = m-NO$_2$C$_6$H$_4$, R^2 = 3,5-(CH$_3$)$_2$C$_6$H$_3$

Scheme 1. General scheme of the synthesis of compounds **2a-2n**.

built and validated.

Fig. 3 shows 3D and 2D interactions of most probable docked conformation of compound **2f**. The inhibitor **2f** was found to have a snug fit inside the binding cavity. A hydrogen bonded interaction (1.74 Å) was observed between the unsubstituted nitrogen atom of pyrazole ring and amino acid Asn241. The binding energy was calculated to be −21 kJ/mol. Molecular docking studies of second most active inhibitor **2m** were also carried out, the results are presented in Fig. 4. The compound **2m** was found to have a similar binding mode as that of **2f**, the unsubstituted nitrogen atom of the pyrazole ring was making a hydrogen

Table 1
α-Glucosidase inhibition results of imidazolylpyrazoles (**2a-2n**).



(2a-2n)

Sr. No.	Compd. No.	Substitutions		Substitutions	
		R^1	R^1	Percentage Inhibition (%) at 0.5 mM	IC$_{50}$ (μM)
1	**2a**	p-OCH$_3$C$_6$H$_4$	p-OCH$_3$C$_6$H$_4$	99.56 ± 0.77	178.82 ± 0.28
2	**2b**	p-OCH$_3$C$_6$H$_4$	p-BrC$_6$H$_4$	91.12 ± 0.84	162.93 ± 0.32
3	**2c**	p-OCH$_3$C$_6$H$_4$	3,5-(CH$_3$)$_2$C$_6$H$_3$	96.13 ± 0.89	182.17 ± 0.37
4	**2d**	p-ClC$_6$H$_4$	p-OCH$_3$C$_6$H$_4$	98.65 ± 0.79	168.92 ± 0.27
5	**2e**	p-ClC$_6$H$_4$	p-ClC$_6$H$_4$	93.19 ± 0.52	85.71 ± 0.09
6	**2f**	p-ClC$_6$H$_4$	p-BrC$_6$H$_4$	96.21 ± 0.11	25.19 ± 0.004
7	**2g**	p-ClC$_6$H$_4$	3,5-(CH$_3$)$_2$C$_6$H$_3$	89.54 ± 0.86	132.81 ± 0.29
8	**2h**	p-BrC$_6$H$_4$	p-OCH$_3$C$_6$H$_4$	89.76 ± 0.19	104.75 ± 0.06
9	**2i**	p-BrC$_6$H$_4$	p-ClC$_6$H$_4$	87.25 ± 0.21	84.61 ± 0.01
10	**2j**	p-BrC$_6$H$_4$	3,5-(CH$_3$)$_2$C$_6$H$_3$	75.23 ± 1.74	412.42 ± 1.15
11	**2k**	m-NO$_2$C$_6$H$_4$	p-ClC$_6$H$_4$	96.76 ± 0.38	42.23 ± 0.07
12	**2l**	m-NO$_2$C$_6$H$_4$	p-OCH$_3$C$_6$H$_4$	95.79 ± 0.32	43.14 ± 0.05
13	**2m**	m-NO$_2$C$_6$H$_4$	p-BrC$_6$H$_4$	97.52 ± 0.26	33.62 ± 0.03
14	**2n**	m-NO$_2$C$_6$H$_4$	3,5-(CH$_3$)$_2$C$_6$H$_3$	91.25 ± 0.54	58.73 ± 0.13
Acarbose				92.23 ± 0.14	38.25 ± 0.12

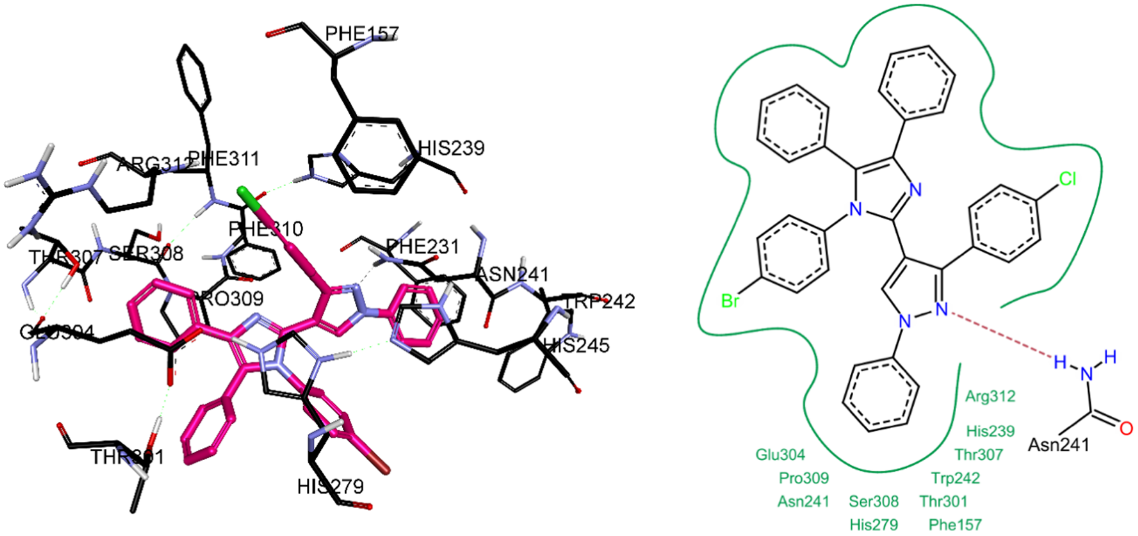


Fig. 3. Most probable docked conformation of most potent inhibitor **2f**.

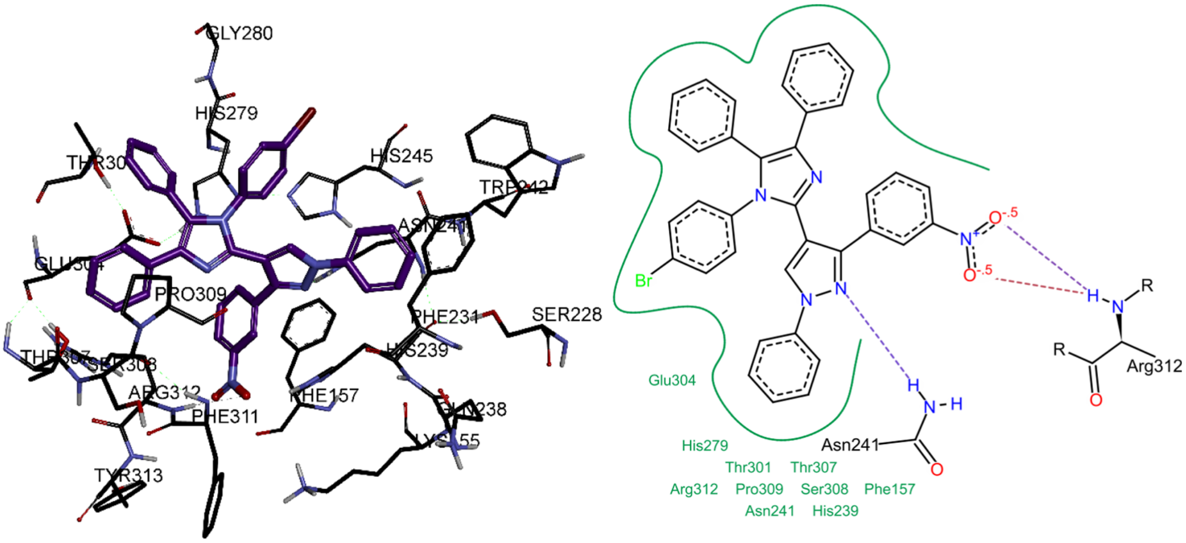


Fig. 4. Possible docked conformation of inhibitor **2m**.

bond with Asn241 (1.36 Å). Moreover, the oxygen atoms of the nitro group were acting as hydrogen bond acceptor towards amino acid Arg312. The calculated binding energy was −19 kJ/mol.

To further gain insight into the structural elements, responsible for the observed inhibitory effect against the enzyme, the most active inhibitor **2f** bound to protein was subjected to binding affinity evaluation using Hyde utility of LeadIT Software. Hyde allows visual approximation of favorable and unfavorable contributions due to the structure/bound conformation of inhibitor with the surrounding amino acids. The structural elements (atoms and torsions) that are contributing favorably to the overall binding energy are visually coloured in green, similarly the structural elements that are not contributing favorably are coloured in red, and neutral elements are in white.

As can be seen from Fig. 5, overall the aromatic phenyl rings substituted on pyrazole and imidazole rings are contributing favorably to the binding energy. The only unfavorable structural element was the un-substituted nitrogen atom of the imidazole ring, this lead to the speculation that if this nitrogen atom is replaced by some other atoms such as carbon or other heteroatom, it may lead to even better binding affinity and therefore inhibition against α-glucosidase.

3. Conclusion

The present research is about initial efforts to synthesize novel tetrasubstituted imidazolylpyrazoles in good yields which could also be valuable as α-glucosidase inhibitors. Therefore, these compounds were first evaluated for their inhibitory potentials against yeast's α-glucosidase enzyme. Most of these molecules have displayed moderate to excellent results. However, on the basis of SAR studies and molecular docking, **2f** (IC_{50} value: 25.19 ± 0.004 μM) and **2m** (IC_{50} value: 33.62 ± 0.03 μM) were identified to be promising α-glucosidase inhibitors.

4. Experimental

4.1. General methods

The chemicals were used as purchased from the manufacturers (Merck, Sigma-Aldrich and Acros). The melting points (uncorrected) were taken on Gallen Kamp. The Agilent Technologies Cary 630 FTIR was employed for FTIR spectra. The ^{1}H (^{13}C) NMR spectra, in $CDCl_3$/DMSO-d_6, were recorded on Bruker DPX Instruments of 500 (126) or

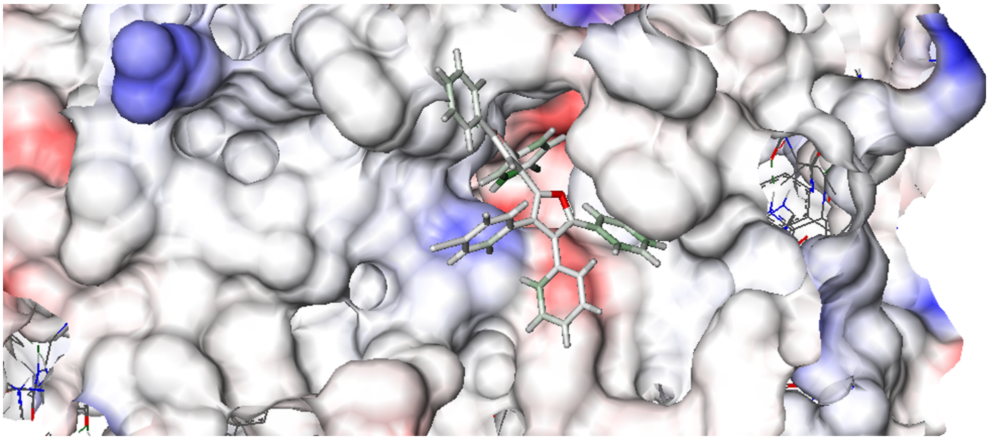


Fig. 5. Hyde affinity analysis of most active inhibitor **2f**.

700 (175) MHz. TMS was used as standard and *J*-values are calculated in Hz. The MS were recorded on GC MS DFS-Thermo. The elemental percentages (CHN) were determined on Perkin Elmer 2400 Series II CHN/S Analyzer.

*4.2. General protocol for the synthesis of imidazolylpyrazoles (**2a-2n**)*

An equimolar mixture of pyrazole-4-carbaldehyde (**1a-1d**), benzil, ammonium acetate and substituted aniline in acetic acid was irradiated under microwave. The reaction completion was observed by TLC. The mixture was poured over crushed ice, crude product was separated and further recrystallized with ethanol to get pure product (**2a-2n**).

In this way, following compounds (**2a-2n**) were synthesized:

*4.2.1. 3-(4-Methoxyphenyl)-4-(1-(4-methoxyphenyl)-4,5-diphenyl-1H-imidazol-2-yl)-1-phenyl-1H-pyrazole (**2a**)*

From *p*-anisidine (0.27 g) and **1a** (0.56 g), **2a** was obtained as a white solid; m.p. 180 °C; Yield: 0.77 g; 75%; IR (ν_{max}-cm^{-1}; neat): 3102–2839 (C—H), 1602 (C═N), 1594 (C═C), 1252 & 1022 (Ar-O-CH$_3$); ^{1}H NMR (CDCl$_3$, 500 MHz), δ: 3.66 (s, 3H; —OCH$_3$), 3.80 (s, 3H; —OCH$_3$), 6.44 (d, 2H, *J* = 9.0 Hz; Ar^3-2H), 6.50 (d, 2H, *J* = 9.0 Hz; Ar^3-2H), 6.80 (d, 2H, *J* = 8.8 Hz; Ar^2-2H), 7.13 (dd, 2H, *J* = 7.5, 1.9 Hz; Ar^4-2H), 7.20–7.24 (m, 4H; Ar^4-3H & Ar^5-1H), 7.26–7.30 (m, 3H; Ar^1-1H & Ar^5-2H), 7.37 (d, 2H, *J* = 8.8 Hz; Ar^2-2H), 7.45 (t, 2H, *J* = 8.0 Hz; Ar^1-2H), 7.65 (d, 2H, *J* = 7.3 Hz; Ar^5-2H), 7.72 (d, 2H, *J* = 8.0 Hz; Ar^1-2H), 8.19 (s, 1H; H-5 Pyrazole); ^{13}C NMR (CDCl$_3$, 126 MHz), δ: 55.37 (—OCH$_3$), 55.42 (—OCH$_3$), 111.94 (C-4 Pyrazole), 113.52, 113.73, 119.00, 125.73, 126.65, 126.73, 127.38, 128.04, 128.30, 128.50, 128.85, 128.86, 129.07, 129.38 (CH-5 Pyrazole), 129.56, 130.58 (C-4 Im), 130.76, 131.06, 134.47, 137.85 (C-5 Im), 139.82, 140.94 (C-2 Im), 152.02 (C-3 Pyrazole), 158.64 ($\underline{C}$-OCH$_3$), 159.70 ($\underline{C}$-OCH$_3$); MS (EI+): *m/z* (%) 574.6 (M$^+$, 100); Anal. Calcd. For $C_{38}H_{30}N_4O_2$: C, 79.42; H, 5.26; N, 9.75%. Found: C, 79.35; H, 5.19; N, 9.55%.

*4.2.2. 4-(1-(4-Bromophenyl)-4,5-diphenyl-1H-imidazol-2-yl)-3-(4-methoxyphenyl)-1-phenyl-1H-pyrazole (**2b**)*

From *p*-bromoaniline (0.38 g) and **1a** (0.56 g), **2b** was obtained as a white solid; m.p. 178 °C; Yield: 0.79 g; 70%; IR (ν_{max}-cm^{-1}; neat): 3127–2943 (C—H), 1600 (C═N), 1591 (C═C), 1249 & 1016 (Ar^2-O-CH$_3$); ^{1}H NMR (CDCl$_3$, 500 MHz), δ: 3.81 (s, 3H; —OCH$_3$), 6.39 (d, 2H, *J* = 8.6 Hz; Ar^2-2H), 6.79 (d, 2H, *J* = 8.7 Hz; Ar^3-2H), 7.02 (d, 2H, *J* = 8.6 Hz; Ar^2-2H), 7.11 (d, 2H, *J* = 6.5 Hz; Ar^4-2H), 7.21–7.34 (m, 9H; Ar^1-1H, Ar^3-2H, Ar^4-3H & Ar^5-3H), 7.48 (t, 2H, *J* = 7.7 Hz; Ar^1-2H), 7.65 (d, 2H, *J* = 7.2 Hz; Ar^5-2H), 7.77 (d, 2H, *J* = 7.7 Hz; Ar^1-2H), 8.36 (s, 1H; H-5 Pyrazole); ^{13}C NMR (CDCl$_3$, 126 MHz), δ: 55.43 (—OCH$_3$), 111.64 (C-4 Pyrazole), 113.75, 118.99, 121.62 (C-Br), 125.50, 126.80, 126.94, 127.41, 128.32, 128.35, 128.69, 129.01, 129.16, 129.47, 129.59 (CH-5 Pyrazole), 129.99, 130.24 (C-4 Im), 130.98, 131.37, 134.08, 134.94, 138.30 (C-5 Im), 139.69, 140.63 (C-2 Im), 151.86 (C-3 Pyrazole), 159.77 ($\underline{C}$-OCH$_3$); MS (EI+): *m/z* (%) 622.4 (M$^+$, 88.0), 624.5 ([M + 2]$^+$, 90.1); Anal. Calcd. For $C_{37}H_{27}BrN_4O$: C, 71.27; H, 4.36; N, 8.99%. Found: C, 71.39; H, 4.46; N, 9.03%.

*4.2.3. 4-(1-(3,5-Dimethylphenyl)-4,5-diphenyl-1H-imidazol-2-yl)-3-(4-methoxyphenyl)-1-phenyl-1H-pyrazole (**2c**)*

From 3,5-dimethylaniline (0.27 g/0.27 mL) and **1a** (0.56 g), **2c** was obtained as a white solid; m.p. 172 °C; Yield: 0.83 g; 81%; IR (ν_{max}-cm^{-1}; neat): 3054–2837 (C—H), 1613 (C═N), 1596 (C═C), 1249 & 1025 (Ar^2-O-CH$_3$); ^{1}H NMR (CDCl$_3$, 500 MHz), δ: 2.02 (s, 6H; 2 × CH$_3$), 3.85 (s, 3H; —OCH$_3$), 6.21 (s, 2H; Ar^3-2H), 6.70 (s, 1H; Ar^3-1H), 6.85 (d, 2H; *J* = 7.1 Hz; Ar^2-2H), 7.05–7.10 (m, 2H; Ar^4-1H & Ar^5-1H), 7.20–7.28 (m, 4H; Ar^4-4H), 7.30–7.35 (m, 3H; Ar^1-2H & Ar^2-2H), 7.38–7.43 (m, 2H; Ar^5-2H), 7.48–7.55 (m, 2H; Ar^1-2H), 7.67–7.71 (m, 2H; Ar^5-2H), 7.75–7.82 (m, 2H; Ar^1-2H), 8.24 (s, 1H; H-5 Py); ^{13}C NMR (CDCl$_3$, 125 MHz), δ: 21.04 (2 × CH$_3$), 55.34 (—OCH$_3$), 112.32 (C-4 Py), 113.73, 119.06, 125.65, 125.79, 126.63, 126.64, 127.39, 127.96, 128.28, 128.37, 129.22, 129.33, 129.36, 129.57, 130.47 (CH-5 Py), 130.88 (C-4 Im), 131.03, 134.69, 135.86, 137.84 (2 × C-CH$_3$), 137.96 (C-5 Im), 139.93, 140.73 (C-2 Im), 152.21 (C-3 Py), 159.62 (C-OCH$_3$); MS (EI+): *m/z* (%) 572.6 (M$^+$, 100); Anal. Calcd. For $C_{39}H_{32}N_4O$: C, 81.79; H, 5.63; N, 9.78%. Found: C, 81.91; H, 5.76; N, 9.92%.

*4.2.4. 3-(4-Chlorophenyl)-4-(1-(4-methoxyphenyl)-4,5-diphenyl-1H-imidazol-2-yl)-1-phenyl-1H-pyrazole (**2d**)*

From *p*-anisidine (0.27 g) and **1b** (0.56 g), **2d** was obtained as a white solid; m.p. 202 °C; Yield: 0.80 g; 78%; IR (ν_{max}-cm^{-1}; neat): 3165–2840 (C—H), 1601 (C═N), 1578 (C═C), 1256 & 1073 (Ar^3-O-CH$_3$), 735 (C-Cl); ^{1}H NMR (CDCl$_3$, 500 MHz), δ: 3.70 (s, 1H; —OCH$_3$), 6.48 (d, 2H, *J* = 9.0 Hz; Ar^3-2H), 6.53 (d, 2H, *J* = 9.0 Hz; Ar^3-2H), 7.15 (dd, 2H, *J* = 7.6, 1.8 Hz; Ar^4-2H), 7.24–7.29 (m, 5H; Ar^1-1H, Ar^4-3H & Ar^5-1H), 7.30 (d, 2H, *J* = 8.5 Hz; Ar^2-2H), 7.32–7.35 (m, 2H; Ar^5-2H), 7.41 (d, 2H, *J* = 8.5 Hz; Ar^2-2H), 7.49 (t, 2H, *J* = 7.8 Hz; Ar^1-2H), 7.67 (dd, 2H, *J* = 7.2, 1.2 Hz; Ar^5-2H), 7.75 (d, 2H, *J* = 7.8 Hz; Ar^1-2H), 8.24 (s, 1H; H-5 Py); ^{13}C NMR (CDCl$_3$, 126 MHz), δ: 55.40 (—OCH$_3$), 112.36 (C-4 Py), 113.60, 119.10, 126.83, 126.98, 127.39, 128.13, 128.34, 128.40, 128.55, 128.66, 128.84, 129.18, 129.64, 129.67 (CH-5 Py), 130.58, 130.62 (C-4 Im), 131.05, 131.52, 134.03 (C-Cl), 134.32, 138.03 (C-5 Im), 139.66, 140.42 (C-2 Im), 150.92 (C-3 Py), 158.73 ($\underline{C}$-OCH$_3$); MS (EI+): *m/z* (%) 578.5 (M$^+$, 100), 580.5 ([M + 2]$^+$, 35.0); Anal. Calcd. For $C_{37}H_{27}ClN_4O$: C, 76.74; H, 4.70; N, 9.67%. Found: C, 76.61; H, 4.61; N, 9.74%.

*4.2.5. 3-(4-Chlorophenyl)-4-(1-(4-chlorophenyl)-4,5-diphenyl-1H-imidazol-2-yl)-1-phenyl-1H-pyrazole (**2e**)*

From *p*-chloroaniline (0.28 g) and **1b** (0.56 g), **2e** was obtained as a white solid; m.p. 235 °C (Lit [37] m.p. 232 °C); Yield: 0.71 g; 69%; IR (ν_{max}-cm^{-1}; neat): 3099–3055 (C—H), 1589 (C═N), 1561 (C═C), 756

(2 × C-Cl); ^{1}H NMR ($CDCl_3$, 500 MHz), δ: 6.44 (d, 2H, J = 8.2 Hz; Ar^3-2H), 6.87 (d, 2H, J = 8.2 Hz; Ar^3-2H), 7.08 (d, 2H, J = 6.5 Hz; Ar^4-2H), 7.18–7.26 (m, 10*H*; Ar^2-4H, Ar^4-3H & Ar^5-3H), 7.31 (t, 1H, J = 7.5 Hz; Ar^1-1H), 7.46 (t, 2H, J = 7.5 Hz; Ar^1-2H), 7.60 (d, 2H, J = 7.3 Hz; Ar^5-2H), 7.71 (d, 2H, J = 7.5 Hz; Ar^1-2H), 8.25 (s, 1H; H-5 Py); MS (EI+): m/z (%) 582.5 (M$^+$, 100), 584.5 ([M + 2]$^+$, 67.1), 586.4 ([M + 4]$^+$, 13.4); Anal. Calcd. For $C_{36}H_{24}Cl_2N_4$: C, 74.10; H, 4.15; N, 9.60%. Found: C, 73.92; H, 4.08; N, 9.50%.

*4.2.6. 4-(1-(4-Bromophenyl)-4,5-diphenyl-1H-imidazol-2-yl)-3-(4-chlorophenyl)-1-phenyl-1H-pyrazole **(2f)***

From *p*-bromoaniline (0.38 g) and **1b** (0.56 g), **2f** was obtained as a white solid; m.p. 220 °C; Yield: 0.81 g; 73%; IR (ν_{max}-cm^{-1}; neat): 3124–3059 (C—H), 1596 (C═N), 1561 (C═C), 763 (C-Cl); ^{1}H NMR ($CDCl_3$, 500 MHz), δ: 6.43 (d, 2H, J = 8.5 Hz; Ar^3-2H), 7.08 (d, 2H, J = 8.5 Hz; Ar^3-2H), 7.13 (d, 2H, J = 6.5 Hz; Ar^4-2H), 7.24–7.26 (m, 2H; Ar^4-2H), 7.28–7.33 (m, 8H; Ar^2-4H, Ar^4-1H & Ar^5-3H), 7.36 (t, 1H, J = 7.5 Hz; Ar^1-1H), 7.51 (t, 2H, J = 7.5 Hz; Ar^1-2H), 7.66 (d, 2H, J = 7.3 Hz; Ar^5-2H), 7.78 (d, 2H, J = 7.5 Hz; Ar^1-2H), 8.35 (s, 1H; H-5 Py); ^{13}C NMR ($CDCl_3$, 126 MHz), δ: 112.08 (C-4 Py), 119.11, 121.80 (C-Br), 127.04, 127.13, 127.42, 128.40, 128.42, 128.48, 128.77, 129.09, 129.17, 129.69, 130.10 (CH-5 Py), 130.77, 130.98, 131.34 (C-4 Im), 131.54, 134.03 (C-Cl), 134.22, 134.86, 138.54 (C-5 Im), 139.56, 140.14 (C-2 Im), 150.82 (C-3 Py); MS (EI+): m/z (%) 626.3 (M$^+$, 70.2), 628.4 ([M + 2]$^+$, 100), 630.5 ([M + 4]$^+$, 25.1); Anal. Calcd. For $C_{36}H_{24}ClBrN_4$: C, 68.86; H, 3.85; N, 8.92%. Found: C, 68.72; H, 3.73; N, 9.06%.

*4.2.7. 3-(4-Chlorophenyl)-4-(1-(3,5-dimethylphenyl)-4,5-diphenyl-1H-imidazol-2-yl)-1-phenyl-1H-pyrazole **(2g)***

From 3,5-dimethylaniline (0.27 g/0.27 mL) and **1b** (0.56 g), **2g** was obtained as a white solid; m.p. 170 °C; Yield: 0.86 g; 84%; IR (ν_{max}-cm^{-1}; neat): 3102–2840 (C—H), 1596 (C═N), 1561 (C═C), 744 (C-Cl); ^{1}H NMR ($CDCl_3$, 500 MHz), δ: 1.96 (s, 6H; 2 × CH_3), 6.11 (s, 2H; Ar^3-2H), 6.63 (s, 1H; Ar^3-1H), 7.09 (dd, 2H, J = 7.0, 1.5 Hz; Ar^4-2H), 7.18–7.20 (m, 6H; Ar^2-2H, Ar^4-3H & Ar^5-1H), 7.23–7.28 (m, 3H; Ar^1-1H & Ar^5-2H), 7.30 (d, 2H, J = 8.5 Hz; Ar^2-2H), 7.45 (t, 2H, J = 8.0 Hz; Ar^1-2H), 7.60 (d, 2H, J = 7.3 Hz; Ar^5-2H), 7.70 (d, 2H, J = 8.0 Hz; Ar^1-2H), 8.19 (s, 1H; H-5 Py); MS (EI+): m/z (%) 576.5 (M$^+$, 100), 578.5 ([M + 2]$^+$, 34.1); Anal. Calcd. For $C_{38}H_{29}ClN_4$: C, 79.08; H, 5.06; N, 9.71%. Found: C, 78.95; H, 4.86; N, 9.83%.

*4.2.8. 3-(4-Bromophenyl)-4-(1-(4-methoxyphenyl)-4,5-diphenyl-1H-imidazol-2-yl)-1-phenyl-1H-pyrazole **(2h)***

From *p*-anisidine (0.27 g) and **1c** (0.80 g), **2h** was obtained as a white solid; m.p. 200 °C; Yield: 0.78 g; 82%; IR (ν_{max}-cm^{-1}; neat): 3050–2839 (C—H), 1601 (C═N), 1578 (C═C), 1255 & 1013 (Ar^1-O-CH_3); ^{1}H NMR ($CDCl_3$, 500 MHz), δ: 3.63 (s, 3H; —OCH_3), 6.40 (d, 2H, J = 8.9 Hz; Ar^3-2H), 6.44 (d, 2H, J = 8.9 Hz; Ar^3-2H), 7.07 (dd, 2H, J = 7.7, 2.0 Hz; Ar^4-2H), 7.15–7.19 (m, 4H, Ar^4-3H & Ar^5-1H), 7.21–7.23 (m, 2H; Ar^5-2H), 7.23–7.28 (m, 3H; Ar^1-1H & Ar^2-2H), 7.32 (d, 2H, J = 8.4 Hz; Ar^2-2H), 7.41 (t, 2H, J = 7.8 Hz; Ar^1-2H), 7.57 (d, 2H, J = 7.4 Hz; Ar^5-2H), 7.67 (d, 2H, J = 7.9 Hz; Ar^1-2H), 8.15 (s, 1H; H-5 Py); ^{13}C NMR ($CDCl_3$, 126 MHz), δ: 55.42 (—OCH_3), 112.50 (C-4 Py), 113.62, 119.12, 122.29 (C-Br), 126.81, 127.00, 127.40, 128.11, 128.34, 128.56, 128.72, 128.87, 129.51, 129.65, 130.64 (CH-5 Py), 130.65 (C-4 Im), 131.06, 131.35, 132.01, 134.47, 138.19 (C-5 Im), 139.69, 140.44 (C-2 Im), 150.95 (C-3 Py), 158.74 ($\underline{C}$-OCH_3); MS (EI+): m/z (%) 622.5 (M$^+$, 97.1), 624.5 ([M + 2]$^+$, 100); Anal. Calcd. For $C_{37}H_{27}BrN_4O$: C, 71.27; H, 4.36; N, 8.99%. Found: C, 71.42; H, 4.48; N, 9.06%.

*4.2.9. 3-(4-Bromophenyl)-4-(1-(4-chlorophenyl)-4,5-diphenyl-1H-imidazol-2-yl)-1-phenyl-1H-pyrazole **(2i)***

From *p*-chloroaniline (0.28 g) and **1c** (0.80 g), **2i** was obtained as a white solid; m.p. 194 °C; (Lit [37] m.p. 198 °C);Yield: 0.68 g; 71%; IR (ν_{max}-cm^{-1}; neat): 3100–2929 (C—H), 1589 (C═N), 1554 (C═C), 756 (C-Cl); ^{1}H NMR ($CDCl_3$, 500 MHz), δ: 6.45 (d, 2H, J = 9.0 Hz; Ar^3-2H), 6.90 (d, 2H, J = 9.0 Hz; Ar^3-2H), 7.09 (dd, 2H, J = 7.9, 1.4 Hz; Ar^4-2H), 7.19 (d, 2H, J = 8.4 Hz; Ar^2-2H), 7.22–7.30 (m, 5H; Ar^4-2H & Ar^5-3H), 7.33 (t, 1H, J = 8.0 Hz; Ar^1-1H), 7.37 (d, 2H, J = 8.4 Hz; Ar^2-2H), 7.48 (t, 2H, J = 8.0 Hz; Ar^1-2H), 7.63 (dd, 2H, J = 8.5, 1.3 Hz; Ar^5-2H), 7.75 (d, 2H, J = 8.0 Hz; Ar^1-2H), 8.37 (s, 1H; H-5 Py); MS (EI+): m/z (%) 626.5 (M$^+$, 73.5), 628.4 ([M + 2]$^+$, 100), 630.5 ([M + 4]$^+$, 28.0); Anal. Calcd. For $C_{36}H_{24}ClBrN_4$: C, 68.86; H, 3.85; N, 8.92%. Found: C, 68.79; H, 3.78; N, 8.70%.

*4.2.10. 3-(4-Bromophenyl)-4-(1-(3,5-dimethylphenyl)-4,5-diphenyl-1H-imidazol-2-yl)-1-phenyl-1H-pyrazole **(2j)***

From 3,5-dimethylaniline (0.27 g/0.27 mL) and **1c** (0.80 g), **2j** was obtained as a white solid; m.p. 168 °C; Yield: 0.77 g; 81%; IR (ν_{max}-cm^{-1}; neat): 3143–2920 (C—H), 1596 (C═N), 1561 (C═C); ^{1}H NMR ($CDCl_3$, 500 MHz), δ: 2.02 (s, 6H; 2 × CH_3), 6.17 (s, 2H; Ar^3-2H), 6.69 (s, 1H; Ar^3-1H), 7.14–7.15 (m, 2H; Ar^4-2H), 7.25–7.36 (m, 9H; Ar^1-1H, Ar^2-2H, Ar^4-3H & Ar^5-3H), 7.40 (d, 2H, J = 8.2 Hz; Ar^2-2H), 7.50 (t, 2H, J = 7.5 Hz; Ar^1-2H), 7.66 (d, 2H, J = 7.4 Hz; Ar^5-2H), 7.76 (d, 2H, J = 7.5 Hz; Ar^1-2H), 8.30 (s, 1H; H-5 Py); ^{13}C NMR ($CDCl_3$, 125 MHz), δ: 21.11 (2 × CH_3), 112.57 (C-4 Py), 119.14, 122.20 (C-Br), 125.51, 126.79, 126.96, 127.41, 128.08, 128.33, 128.43, 129.32 (CH-5 Py), 129.54, 129.64, 130.48 (C-4 Im), 130.59, 130.99, 131.35, 131.97, 134.39, 134.40, 135.62 (C-5 Im), 138.07 (2 × C-CH_3), 139.73, 140.14 (C-2 Im), 151.09 (C-3 Py); MS (EI+): m/z (%) 620.5 (M$^+$, 96.0), 622.5 ([M + 2]$^+$, 100); Anal. Calcd. For $C_{38}H_{29}BrN_4$: C, 73.43; H, 4.70; N, 9.01%. Found: C, 73.59; H, 4.86; N, 8.94%.

*4.2.11. 4-(1-(4-Chlorophenyl)-4,5-diphenyl-1H-imidazol-2-yl)-3-(3-nitrophenyl)-1-phenyl 1H-pyrazole **(2k)***

From *p*-chloroaniline (0.28 g) and **1d** (0.58 g), **2k** was obtained as pale yellow solid; m.p. 184 °C; Yield: 0.78 g; 77%; IR (ν_{max}-cm^{-1}; neat): 3089–2840 (C—H), 1599 (C═N), 1578 (C═C), 1533 & 1346 (NO_2), 757 (C-Cl); ^{1}H NMR ($CDCl_3$, 500 MHz), δ: 6.56 (d, 2H, J = 8.7 Hz; Ar^3-2H), 6.90 (d, 2H, J = 8.7 Hz; Ar^3-2H), 7.12 (dd, 2H, J = 8.0, 1.5 Hz; Ar^4-2H), 7.19–7.23 (m, 3H; Ar^4-3H), 7.24–7.27 (m, 3H; Ar^5-3H), 7.34 (t, 1H, J = 9.0 Hz; Ar^1-1H), 7.42 (t, 1H; J = 8.0 Hz; Ar^2-1H), 7.48 (t, 2H, J = 9.0 Hz; Ar^1-2H), 7.59 (dd, 2H, J = 7.1, 1.4 Hz; Ar^5-2H), 7.72 (dd, 2H, J = 9.0, 1.1 Hz; Ar^1-2H), 7.85 (dt, 1H, J = 7.8, 1.3 Hz; Ar^2-1H), 8.08 (ddd, 1H, J = 8.2, 2.2, 1.0 Hz; Ar^2-1H), 8.19 (s, 1H; H-5 Py), 8.24 (d, 1H, J = 1.9 Hz; Ar^2-1H); MS (EI+): m/z (%) 593.5 (M$^+$, 100), 595.5 ([M + 2]$^+$, 37.1); Anal. Calcd. For $C_{36}H_{24}ClN_5O_2$: C, 72.78; H, 4.07; N, 11.79%. Found: C, 72.91; H, 4.14; N, 11.61%.

*4.2.12. 4-(1-(4-Methoxyphenyl)-4,5-diphenyl-1H-imidazol-2-yl)-3-(3-nitrophenyl)-1-phenyl-1H-pyrazole **(2l)***

From *p*-anisidine (0.27 g) and **1d** (0.58 g), **2l** was obtained as a white solid; m.p. 214 °C; Yield: 0.85 g; 84%; IR (ν_{max}-cm^{-1}; neat): 3061–2969 (C—H), 1599 (C═N), 1582 (C═C), 1508 & 1348 (NO_2), 1254 & 1023 (Ar^1-O-CH_3); ^{1}H NMR ($CDCl_3$, 500 MHz), δ: 3.63 (s, 3H; —OCH_3), 6.45 (d, 2H, J = 8.8 Hz; Ar^3-2H), 6.57 (d, 2H, J = 8.8 Hz; Ar^3-2H), 7.14 (d, 2H, J = 6.8 Hz; Ar^4-2H), 7.19–7.27 (m, 6H; Ar^4-3H & Ar^5-3H), 7.33 (t, 1H, J = 7.8 Hz; Ar^1-1H), 7.42 (t, 1H, J = 8.0 Hz; Ar^2-1H), 7.47 (t, 2H, J = 7.8 Hz; Ar^1-2H), 7.61 (d, 2H, J = 7.3 Hz; Ar^5-2H), 7.72 (d, 2H, J = 7.8 Hz; Ar^1-2H), 7.90 (d, 1H, J = 7.7 Hz; Ar^2-1H), 8.09 (d, 1H, J = 8.8 Hz; Ar^2-1H), 8.17 (s, 1H; H-5 Py), 8.30 (s, 1H; Ar^2-1H); ^{13}C NMR ($CDCl_3$, 126 MHz), δ: 55.39 (—OCH_3), 112.78 (C-4 Py), 113.73, 119.21, 122.68, 122.86, 126.85, 127.31, 127.38, 128.20, 128.32, 128.58, 128.69, 128.78, 129.05, 129.71, 130.53 (CH-5 Py), 130.78 (C-4 Im), 131.10, 133.86, 134.32, 134.70, 138.41 (C-5 Im), 139.49, 139.80 (C-2 Im), 148.25 (C-3 Py), 149.56 (C-NO_2), 158.94 ($\underline{C}$-OCH_3); MS (EI+): m/z (%) 589.5 (M$^+$, 100); Anal. Calcd. For $C_{37}H_{27}N_5O_3$: C, 75.37; H, 4.62; N, 11.88%. Found: C, 75.54; H, 4.81; N, 11.97%.

*4.2.13. 4-(1-(4-Bromophenyl)-4,5-diphenyl-1H-imidazol-2-yl)-3-(3-nitrophenyl)-1-phenyl-1H-pyrazole **(2m)***

From *p*-bromoaniline (0.38 g) and **1d** (0.58 g), **2m** was obtained as a yellow solid; m.p. 190 °C; Yield: 0.88 g; 81%; IR (ν_{max}-cm^{-1}; neat): 3088–2940 (C—H), 1598 (C═N), 1577 (C═C), 1533 & 1346 (NO_2); ^{1}H NMR ($CDCl_3$, 500 MHz), δ: 6.50 (d, 2H, $J = 8.2$ Hz; Ar^3-2H), 7.06 (d, 2H, $J = 8.2$ Hz; Ar^3-2H), 7.13 (d, 2H, $J = 6.6$ Hz; Ar^4-2H), 7.25–7.27 (m, 6H; Ar^4-3H & Ar^5-3H), 7.35 (t, 1H, $J = 7.5$ Hz; Ar^1-H), 7.43 (t, 1H; $J = 7.9$ Hz; Ar^2-1H), 7.49 (t, 2H, $J = 7.5$ Hz; Ar^1-2H), 7.61 (d, 2H, $J = 7.3$ Hz; Ar^5-2H), 7.75 (d, 2H, $J = 7.5$ Hz; Ar^1-2H), 7.83 (d, 1H, $J = 7.4$ Hz; Ar^2-1H), 8.09 (d, 1H, $J = 7.8$ Hz; Ar^2-1H), 8.22 (s, 1H; H-5 Py), 8.31 (s, 1H; Ar^2-1H); ^{13}C NMR ($CDCl_3$, 126 MHz), δ: 112.08 (C-4 Py), 119.24, 122.08 (C-Br), 122.61, 122.78, 127.16, 127.17, 127.44, 128.40, 128.58, 128.84, 129.08, 129.22, 129.76, 129.92 (CH-5 Py), 130.03, 130.32 (C-4 Im), 131.04, 131.78, 133.59, 133.70, 134.41, 134.84, 138.70 (C-5 Im), 139.36, 139.43 (C-2 Im), 148.23 (C-3 Py), 149.31 (C-NO_2); MS (EI+): *m/z* (%) 637.5 (M^+, 98.0), 639.4 ($[M + 2]^+$, 100); Anal. Calcd. For $C_{36}H_{24}BrN_5O_2$: C, 67.72; H, 3.79; N, 10.97%. Found: C, 67.65; H, 3.70; N, 10.92%.

4.2.14. 4-(1-(3,5-Dimethylphenyl)-4,5-diphenyl-1H-imidazol-2-yl)-3-(3-nitrophenyl)-1-phenyl-1H-pyrazole (**2n**)

From 3,5-dimethylaniline (0.27 g/0.27 mL) and **1d** (0.58 g), **2n** was obtained as a light yellow solid; m.p. 158 °C; Yield: 0.88 g; 88%; IR (ν_{max}-cm^{-1}; neat): 3084–2944 (C—H), 1598 (C═N), 1576 (C═C), 1530 & 1344 (NO_2); ^{1}H NMR ($CDCl_3$, 500 MHz), δ: 1.95 (s, 6H; Ar^3-2 × CH_3), 6.20 (s, 2H; Ar^3-2H), 6.64 (s, 1H; Ar^3-1H), 7.10 (dd, 2H, $J = 7.3$, 1.5 Hz; Ar^4-2H), 7.17–7.26 (m, 6H; Ar^5-3H & Ar^4-3H), 7.33 (t, 1H, $J = 8.0$ Hz; Ar^1-H), 7.40 (t, 1H; $J = 8.0$ Hz; Ar^2-1H), 7.47 (t, 2H; $J = 8.5$, 7.5 Hz; Ar^1-2H), 7.58 (d, 2H, $J = 7.3$ Hz; Ar^5-2H), 7.70 (d, 2H, $J = 8.0$ Hz; Ar^1-2H), 7.84 (d, 1H, $J = 7.7$ Hz; Ar^2-1H), 8.08 (dd, 1H, $J = 8.2$, 1.2 Hz; Ar^2-1H), 8.15 (s, 1H; H-5 Py), 8.24 (s, 1H; Ar^2-1H); MS (EI+): *m/z* (%) 587.5 (M^+, 100); Anal. Calcd. For $C_{38}H_{29}N_5O_2$: C, 77.66; H, 4.97; N, 11.92%. Found: C, 77.53; H, 4.82; N, 11.74%.

4.3. α-Glucosidase inhibition assay

The present assay involved the slightly modified Pierre's protocol [30] where 10 µL (0.0234 units, Sigma Inc.) of *α*-glucosidases (Cat No. 5003-1KU Type I; isolated from *Saccharomyces cerevisiae*) in phosphate buffer of 6.8 pH and 10 µL (0.5 mM) of a test compound was taken and incubated the reaction mixture solution for 10 min at 37 °C. The initial spectrophotometric absorbance was taken at 400 nm. Later, 10 µL of 0.5 mM *p*-nitrophenyl-*α*-$_{D}$-glucopyranoside (code No. N1377 from Sigma Inc) was added and absorbance change after 20 min incubation at 37 °C was recorded at 400 nm. Acarbose was a positive control and assays were executed in triplicates. The IC_{50} values were calculated on EZ-Fit Enzyme Kinetics Software from Perrella Scientific Inc. Amherst, USA.

4.4. Molecular modeling studies

Homology model was built using oligo-1,6-glucosidase as a template protein. A search on BLAST database revealed oligo-1,6-glucosidase (PDB ID: 3A4A) from *Saccharomyces cerevisiae* among the top matched results and shares 72% identity and 85% similarity with *α*-glucosidase sequence [31]. Sequence alignment was carried out using Needleman-Wunsch global alignment algorithm embedded in Chimera. Structure was modelled using Modeller [32]. Ramachandran plot was constructed using Molprobity [33]. Before docking studies, the structures of compounds were optimized using semi empirical PM3 method in HyperChem [34]. Molecular docking studies were carried out using BioSolveIT's LeadIT software [35]. The docked conformations were visualized in Discovery Studio Visualizer 4.0 [36].

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References

[1] R.A. Field, A.H. Haines, E.J.T. Chrystal, M.C. Luszniak, Biochem. J. 274 (1991) 885–889.
[2] Z. Jin, Muscarine, Nat. Prod. Rep. 28 (2011) 1143–1191.
[3] J.-H. Choi, N. Abe, H. Tanaka, K. Fushimi, Y. Nishina, A. Morita, Y. Kiriiwa, R. Motohashi, D. Hashizume, H. Koshino, H. Kawagishi, J. Agric. Food Chem. 58 (2010) 9956–9959.
[4] C.A. Vock, C. Scolaro, A.D. Phillips, R. Scopelliti, G. Sava, P.J. Dyson, J. Med. Chem. 49 (2006) 5552–5561.
[5] D. Kumar, K.R.J. Thomas, C.-P. Lee, K.-C. Ho, J. Org. Chem. 79 (2014) 3159–3172.
[6] X. Chen, C. Jia, Z. Wan, X. Yao, Dyes. Pigments 104 (2014) 48–56.
[7] B. Narasimhan, D. Sharma, P. Kumar, Med. Chem. Res. 20 (2011) 1119–1140.
[8] D. Dimova, P. Iyer, M. Vogt, F. Totzke, M.H.G. Kubbutat, C. Schachtele, S. Laufer, J. Bajorath, J. Med. Chem. 55 (2012) 11067–11071.
[9] L. Zhang, X.M. Peng, G.L. Damu, R.X. Geng, C.H. Zhou, Med. Res. Rev. 34 (2014) 340–437.
[10] S. Kumar, M. Ceruso, T. Tuccinardi, C.T. Supuran, P.K. Sharma, Bioorg. Med. Chem. 24 (2016) 2907–2913.
[11] N. Rani, A. Sharma, R. Singh, Mini. Rev. Med. Chem. 13 (2013) 1812–1835.
[12] S.Q. Wen, P. Jeykkumar, S.R. Avula, L. Zhang, C.H. Zhou, Bioorg. Med. Chem. Lett. 26 (2016) 2768–2773.
[13] D. Zhao, S. Zhao, L. Zhao, X. Zhang, P. Wei, C. Liu, C. Hao, B. Sun, X. Su, M. Cheng, Bioorg. Med. Chem. 25 (2017) 750–758.
[14] T.G. Edwards, C. Fisher, Antiviral. Res. 152 (2018) 68–75.
[15] K. Gobis, H. Foks, K. Suchan, E.A. Kopec, A. Napiorkowska, K. Bojanowski, Bioorg. Med. Chem. 23 (2015) 2112–2120.
[16] M. Pieroni, B. Wan, V. Zuliani, S.G. Franzblau, G. Costantino, M. Rivara, Eur. J. Med. Chem. 100 (2015) 44–49.
[17] Z. Xiao, F. Lei, X. Chen, X. Wang, L. Cao, K. Ye, W. Zhu, S. Xu, Arch. Pharm. 351 (2018) 1–11.
[18] I. Ali, M.N. Lone, H.Y. Aboul-Enein, Med. Chem. Comm. 8 (2017) 1742–1773.
[19] A. Ravindernath, M.S. Reddy, Arab. J. Chem. 10 (2017) S1172–S1179.
[20] R. Mishra, S. Ganguly, Med. Chem. Res. 21 (2012) 3929–3939.
[21] A. Tanaka, K. Ito, S. Nishino, Y. Motoyama, H. Takasugi, Chem. Pharm. Bull. (Tokyo) 42 (1994) 560–569.
[22] (a) K. Wilson, J. Biol. Educ. 1 (1967) 337–348;
(b) H. Bischoff, Eur. J. Clin. Invest. 24 (1994) 3–10.
[23] (a) N.S. Moorthy, M.J. Ramos, P.A. Fernandes, Mini-Rev. Med. Chem. 12 (2012) 713–720;
(b) N. Kerru, A. Singh-Pillay, P. Awolade, P. Singh, Eur. J. Med. Chem. 152 (2018) 436–488.
[24] (a) M. Taha, N.H. Ismail, S. Imran, I. Ainaa, M. Selvaraj, M.S. Baharudin, M. Ali, K.M. Khan, N. Uddin, Med. Chem. Res. 26 (2017) 916–928;
(b) M. Taha, S.A.A. Shah, M. Afifi, S. Imran, S. Sultan, F. Rahim, K.M. Khan, Bioorg. Chem. 77 (2018) 586–592;
(c) M.T. Javid, F. Rahim, M. Taha, H.U. Rehman, M. Nawaz, A. Wadood, S. Imran, I. Uddin, A. Mosaddik, K.M. Khan, Bioorg. Chem. 78 (2018) 201–209.
[25] M. Ozil, M. Emirik, A. Belduz, S. Ulker, Bioorg. Med. Chem. 24 (2016) 5103–5114.
[26] (a) S. Naureen, F. Chaudhry, N. Asif, M.A. Munawar, M. Ashraf, F.H. Nasim, H. Arshad, M.A. Khan, Eur. J. Med. Chem. 102 (2015) 464–470;
(b) S. Naureen, S. Noreen, A. Nazeer, M. Ashraf, U. Alam, M.A. Munawar, M.A. Khan, Med. Chem. Res. 24 (4) (2015) 1586–1595;
(c) S. Naureen, F. Chaudhry, M.A. Munawar, M. Ashraf, S. Hamid, M.A. Khan, Bioorg. Chem. 76 (2018) 365–369.
[27] (a) F. Chaudhry, S. Choudhry, R. Huma, M. Ashraf, M. Al-Rashida, R. Munir, R. Sohail, B. Jahan, M.A. Munawar, M.A. Khan, Bioorg. Chem. 73 (2017) 1–9;
(b) F. Chaudhry, S. Naureen, R. Huma, A. Shaukat, M. Al-Rashida, N. Asif, M. Ashraf, M.A. Munawar, M.A. Khan, Bioorg. Chem. 71 (2017) 102–109.
[28] (a) F. Chaudhry, A.Q. Ather, M.J. Akhtar, A. Shaukat, M. Ashraf, M. Al-Rashida, M.A. Munawar, M.A. Khan, Bioorg. Chem. 71 (2017) 170–180;
(b) F. Chaudhry, S. Naureen, S. Choudhry, R. Huma, M. Ashraf, M. Al-Rashida, B. Jahan, M.H. Khan, F. Iqbal, M.A. Munawar, M.A. Khan, Bioorg. Chem. 77 (2018) 507–514.
[29] B.F. Abdel-Wahab, R.E. Khidre, A.A. Farahat, ARKIVOC I (2011) 196–245.
[30] C. Pierre, R.R. Tremblay, J.Y. Dube, J. Clin. Chem. 24 (2) (1978) 208–211.
[31] J.-H. Park, S. Ko, H. Park, Bull. Korean Chem. Soc. 29 (5) (2008) 921–927.
[32] A. Sali, T.L. Blundell, J. Mol. Biol. 234 (3) (1993) 779–815.
[33] V.B. Chen, W.B. Arendall, J.J. Headd, D.A. Keedy, R.M. Immormino, G.J. Kapral, L.W. Murray, J.S. Richardson, D.C. Richardson, Acta Crystallogr. D. Biol. Crystallogr. 66 (1) (2010) 12–21.
[34] HyperChem(TM) Professional 8.0, Hypercube, Inc., 1115 NW 4th Street, Gainesville, Florida 32601, USA.
[35] http://www.biosolveit.de/LeadIT/.
[36] Accelrys Software Inc., Discovery Studio Modeling Environment, Release 4.0, San Diego, CA: Accelrys Software Inc., 2013.
[37] G.D. Shirole, V.A. Kadnor, A.S. Tambe, S.N. Shelke, Res. Chem. Intermed. 43 (2017) 1089–1098.