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Synthesis, Anti-inflammatory Activity, Molecular Docking and ADMET Study of Pyrazolo-phthalazine Derivatives

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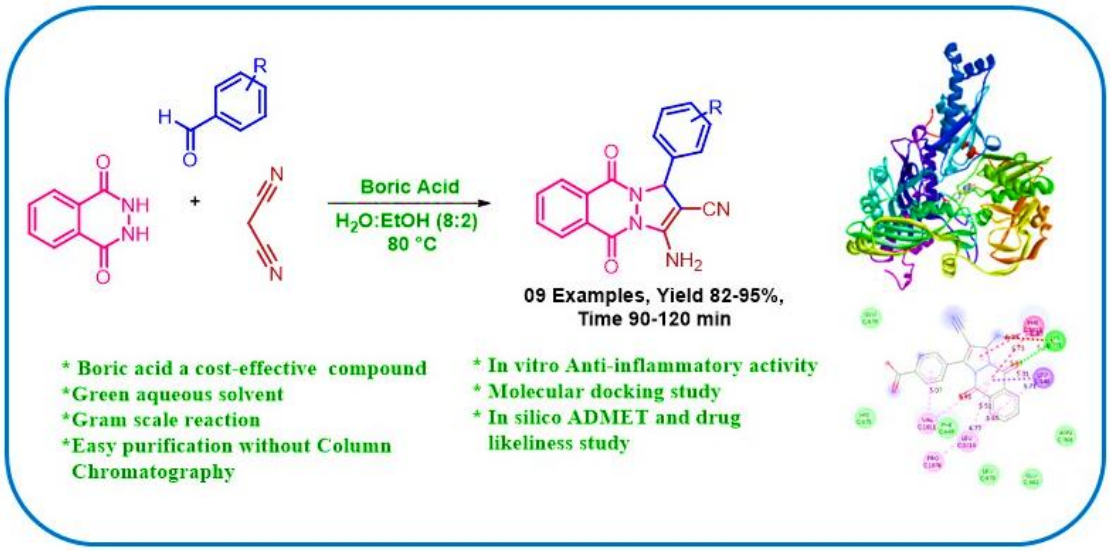
Abstract

We herein disclose a simple, efficient, and straightforward one-pot multicomponent approach for the synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives through the reaction of substituted aldehydes, malononitrile, and phthalhydrazide in H_2O-EtOH (8:2) at 80 °C, using boric acid as an inexpensive and environmentally benign promoter. The highlights of the present method include a non-toxic, easily available and cost-effective compound. The desired products were obtained in a shorter reaction time with good to excellent yields, simple purification without chromatography and an environmentally benign aqueous solvent system. All synthesized compounds were evaluated for anti-inflammatory activity using the protein denaturation method. Compounds **5a**, **5d**, **5e** and **5i** showed excellent anti-inflammatory activities. The *in vitro* anti-inflammatory results were further validated by computational approaches, including in silico ADMET profiling, drug-likeness prediction, and molecular docking studies. *In silico* analysis demonstrated that all compounds met Veber's Rule and Lipinski's Rule of Five criteria and exhibited high binding affinities for bovine xanthine oxidase (**PDB ID: 3NVY**), highest for **5d** (-8.0 Kcal/mol) and lowest for **5g** (-7.1

Kcal/mol). Collectively, these findings underscore the efficacy and robustness of the methodology employed.

Keywords: 1H-Pyrazolo[1,2-*b*]phthalazine-5,10-diones, Cost-effective, Molecular docking, ADMET, One-pot reaction and Anti-inflammatory activity.

Graphical Abstract:



Introduction

In 1991, the term “green chemistry” was first coined by Paul T. Anastas, and the Environmental Protection Agency defined green chemistry or sustainable chemistry as “the design of chemical processes and products that eliminate or reduce the generation or use of hazardous substances”. Therefore, the development of environmentally favourable protocols is one of the great challenges for organic chemists [1-3]. On the other hand, heterocycles containing phthalazine moiety are of attract more attention of researcher, because they show great pharmacological and biological activities [4-6].

1H-Pyrazolo[1,2-*b*]phthalazine-5,10-dione moieties, constitute one of the privileged heterocyclic frameworks known to exhibit important biological activities such as anticonvulsant [7], cardiotonic [8], vasorelaxant [9], cytotoxic [10, 11], antimicrobial [12], antifungal [13], anticancer [14], antituberculosis and antioxidant activity [15]. Moreover, the titled compounds, pyrazolo[1,2-b]phthalazine-diones, were also found to have analgesic,

antihypoxic, and anti-pyretic activities [16]. Some of the marketed drug molecules containing the phthalazine moiety are Vatalanib, Zopolrestate, Azelastine and Hydralazine also reported (**Figure 1**).

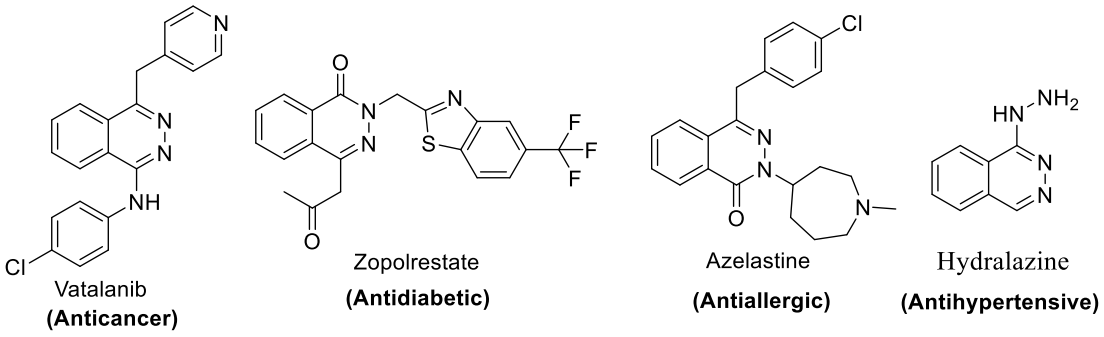


Figure 1. Phthalazine moiety containing drug molecules.

In view of the importance of these heterocycles, number of methods has been reported for the synthesis of 1H-pyrazolo[1,2-*b*]phthalazine-5,10-diones derivatives. Very recently, Zahra Moghadasi and et. al. developed a green, efficient synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones using a novel magnetic copper nanoparticle catalyst, Cu@β-CD@$AlFe_2O_4$. The catalyst, prepared by anchoring copper onto *β*-cyclodextrin-modified $AlFe_2O_4$, reactions with malononitrile, aromatic aldehydes, and phthalhydrazide were carried out under solvent-free microwave conditions at room temperature [17], Izarul Islam and co-worker reported an organocatalyst 3-picolinic acid mediated synthesis of some phthalazine derivatives in EtOH at 80 °C [18], Mamaghani et. al. reported a Tetramethylguanidine-functionalized nano catalyst for the synthesis of pyrazolo phthalazine-diones in EtOH at 80 °C [19], Gore et. al. employed Ammonium Acetate as a catalyst for the same synthesis in aqueous ethanol [20], Farzaneh Mohamadpour reported synthesis of 1H-pyrazolo[1,2-*b*]phthalazine-5,10-dione in presence of Polyfluorinated alcohol as a reusable green reaction medium at reflux condition [21], Zeba N. Siddiqui et al. developed a tandem multicomponent approach for the synthesis of 1H-pyrazolo[1,2-*b*]phthalazine-5,10-dione by employed the mesoporous MPC@TMG, a basic heterogeneous organocatalyst in water at the room temperature [22]. Some other approaches for synthesis of 1H-pyrazolo[1,2-*b*] phthalazine-5,10-diones has been also reported in the literature includes; Imidazole (20 mol%) in H_2O:EtOH (1:1) at 80 °C [23], 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) at 50 °C [24] , WEPBA in ethanol under microwave irradiation [25], visible light irradiation in aqueous ethyl lactate [26], Fe_3O_4@SiO_2-imine/ phenoxy-Cu(II) [27], CMC in solvent free condition at 80 °C [28], Fe_3O_4@GOQDs-N-(β-alanine) in H_2O at rt [29], Cu-II Anchored onto the Magnetic Talc ((γFe_2O_3/talc /Cu-II NPs)

[30], SiO_2–H_2SO_4 Nanoparticles [31], DBU-based ionic liquids [32], 2-aminopyridine [33], Glycerol in MW [34], CuO NPs (10 mol%) in solvent free condition at 100 °C [35], Proline (10 mol%) in EtOH: H_2O (2:1) at 80 °C [36], $[Bu_3NH][HSO_4]$ in solvent free condition at 80 °C [37], [DBUH][OAc] at 60-65 °C [38], C@TiO_2-SO_3H-IL in H_2O at 100 °C [39], $H_5BW_{12}O_{40}$-IL MNPs solvent free condition at 80 °C [40], ZrO_2 NPs Solvent-free, 100°C [41], NMIL (0.5 mol%) in solvent free condition at 110 °C [42], β-Cyclodextrin (20 mol%) in H_2O:EtOH (4:1) as a solvent at 100 °C [43], PbO NPs solvent free condition at 80 °C [44], Fe_3O_4@SiO_2-imid-PMA in solvent free condition at 80 °C or ultrasound in room temp.[45], $NaHCO_3$ in solvent free condition at 120 °C [46], $Ni_{0.5}Zn_{0.5}Fe_2O_4$@hydroxyapatite (NZF@HAP-Cs) solvent free at 110 °C [47], $Cu(OAc)_2.H_2O$(15mol%) solvent free at 80 °C [48], TBBDA/PBBS (0.05 g) in solvent-free condition at 100 °C [49], Electrocatalysis in PrOH [50], CAN (5 mol%) in PEG 400 [51], SBA-15 (SBA-Pr-SO_3H) in solvent free condition at 80 °C [52], CuI NPs (10 mol%) at 70 °C, SF [53], $InCl_3$ (20 mol%) in solvent free condition at 100 °C [54], ZnO NPs 20 mol%, 80-100 °C [55], Al-KIT-6 (300 mg) in EtOH at reflux condition [56], $NiCl_2{\cdot}6H_2O$ (15 mol%) in EtOH at reflux condition [57], (DBU[CH_3COO] solvent free, room temp.[58], Et_3N (20 mol%) in EtOH at 50 °C U.S. [59]. All these reported methodologies it is having their own beauty and benefits. But most of them suffers from drawbacks such as longer reaction time, metal and toxic catalyst, hazardous organic solvents, expensive reagents, harsh reaction conditions, tedious workup procedure and unsatisfactory yields. The use of expensive catalyst or reagents and environmentally hazard methods which leads to restrict the use of these derivatives in practical application. However, the development of greener, efficient and simpler procedures to eliminate the use and generation of hazardous substances is the foremost goal of green chemistry. Therefore, research on 1H-pyrazolo[1,2-*b*]phthalazine-5,10-diones, finding a novel boric acid and alternative greener approach would be highly desirable.

In recent years Boric acid use as a catalyst in organic synthesis has attracted great interest because of its cheap, easily and commercially available, environmentally friendly, nontoxic, excellent solubility in water and easy to handle [60-62]. Because of such behavior Boric acid plays an important role as a catalyst in various organic transformations such as Chan-Lam amination reaction [63],esterification, Aza-Michael addition [64], Chemo selective reduction of quinolines [65], Friedel-Crafts reactions [66], and Tischenko reaction [67] etc. Some other important organic transformations are also carried out by using Boric acid as a non-toxic and eco-friendly catalyst [68-76]. To the best of our knowledge, the use of Boric acid

mediated synthesis of 1H-pyrazolo[1,2-*b*]phthalazine-5,10-diones in aqueous medium has not been reported.

Materials and methods

General information

Chemicals were purchased from Spectrochem, Sigma Aldrich and used without further purification. ^{1}H-NMR and ^{13}C-NMR was recorded on a Bruker Avance-II spectrophotometer operating at 500 MHz and 125 MHz, respectively. The mass spectra were recorded under ESI mode with Waters Corporation, U.K, (model Alliance 2795, Q-TOF MICROMASS).

Experimental

General Procedure for the Synthesis of 1H-Pyrazolo[1,2-*b*]phthalazine-5,10-diones:

In 25 mL round bottom flask take mixture of carbonyl compound aldehyde (2 mmol), malononitrile (2 mmol) and phthalahydrazide (2 mmol) were added in Boric acid (1 equiv.) solvent containing H_2O-EtOH (8:2). The reaction mixture was stirred at 80 °C. After completion of the reaction (monitored by TLC), the reaction mixture was poured in cold water. Filtered the product and washed with hot water. The crude product was recrystallized by aqueous ethanol to afford the desired product.

Gram Scale Reaction

The feasibility of the present method was also examined for the gram scale experiment with p-chlorobenzaldehyde (1.40 gm, 10 mmol), Malononitrile (0.66 gm, 10 mmol), Phthalhydrazide (1.62 gm, 10 mmol) and Boric acid (0.69 gm, 1 equiv.) in solvent H_2O-EtOH (8:2, 50 mL). The reaction mixture was stirred at 80 ºC. The reaction was found to proceed smoothly affording the desired product 3-amino-1-(4-chlorophenyl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile 3.29 gm (94.27%) yield. This experiment proves the potency of boric acid for large scale production also well.

Biological activities

In vitro anti-inflammatory activity

The reaction mixture consisted of 450 µl of protein solution (1% Bovine Serum Albumin-prepared by using 100 mg of Bovine Serum Albumin dissolve in 10 ml of Phosphate Buffered Saline and the resulting mixture mixed gently until fully dissolved) and 50 µl of different concentration of test compounds (200, 100, 50, 25 and 12.5 µg/ mL). Then the reaction mixture was incubated at 37 °C in the incubator for 20 min and then heated at 70 °C for 5 min. After cooling, their absorbance was measured at 660 nm by using a spectrophotometer. Diclofenac sodium at different concentrations (10, 20, 50 and 100 µg/ mL) was used as a

reference drug and treated similarly to determine absorbance. The percentage inhibition of protein denaturation was calculated using the formula: % Inhibition = C-T/C were T= absorbance of the test sample and C = absorbance of control [77,78].

Ligand library preparation

The chemical structures of the synthesized pyrazolo-phthalazine derivatives **(5a-5i)** were created and illustrated using ACD/ChemSketch software [79]. Hydrogen atoms were added to these designed structures with BIOVIA Discovery Studio [80] Energy minimization (EM) of the protonated ligands was carried out using the MMFF94 force field and the steepest descent algorithm. The optimized ligand structures obtained were then converted into pdbqt files compatible with AutoDock Vina by employing the OpenBabel plugin within PyRx 0.8 [81,82] This prepared ligand library, containing the designed compounds, was utilized for subsequent in silico studies.

Theoretical drug-likeness and ADME(T) prediction

The drug-likeness and predicted pharmacokinetic characteristics of the synthesized pyrazolo-phthalazine derivatives (5a-5i) were evaluated using the SwissADME and pkCSM online tools [83,84].

Molecular docking study

Protein preparation

A previously reported 3D crystal structure of bovine xanthine oxidase protein (**PDB ID: 3NVY**) with a resolution of 2.00 Å was chosen from the literature and obtained from the RCSB Protein Data Bank [85]. The retrieved protein structure was then prepared by removing water molecules and heteroatoms to clean the structure [79]. The ionization and tautomeric states of the amino acids in the cleaned protein structure were adjusted by adding polar hydrogen atoms. The protein preparation process was carried out using BIOVIA Discovery Studio software [80].

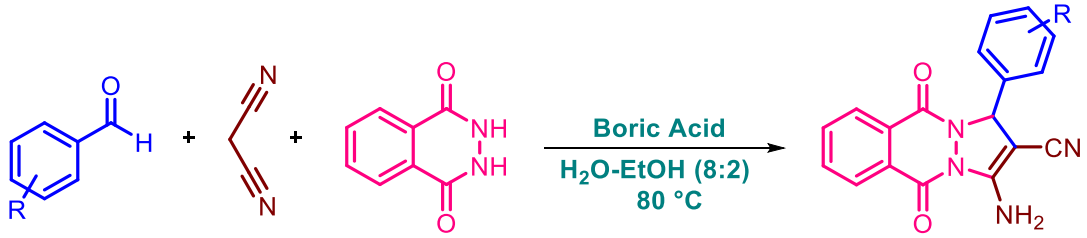
Docking

The docking study was conducted using the AutoDock Vina feature within PyRx 0.8 [86,87]. First, the prepared structure of bovine xanthine oxidase protein (PDB ID: 3NVY) was imported and underwent energy minimization, then converted into an AutoDock macromolecule. The energy-minimized protein and ligand structures were selected in the AutoDock Vina module to carry out the docking process [88]. A maximized grid box was set in the Vina workspace to encompass the entire protein structure, with the exhaustiveness parameter set to eight [89,90]. To determine the best ligand conformation, the pose exhibiting

the most negative binding affinity was selected and saved for further evaluation. Finally, the binding interactions of this selected pose were visualized using BIOVIA Discovery Studio [80].

Results and Discussion

In continuation of our work on development of newer and greener methodologies [91-94], we open up a novel path for the synthesis of 1H-pyrazolo[1,2-*b*]phthalazine-5,10-diones derivatives **(5a-5i)** as one-pot synthesis involving three component reaction of substituted aldehydes **(1)**, malononitrile **(2)** and phthalhydrazide **(3)** reaction in presence of commercially available, non-toxic boric acid in aqueous medium H_2O-EtOH (8:2) at 80 °C **(Scheme 1)**.



Scheme 1 General scheme for the synthesis of 1H-pyrazolo[1,2-*b*]phthalazine5,10-diones

To test catalytic efficiency of our boric acid for the synthesis of 1H-pyrazolo[1,2-*b*]phthalazine-5,10-diones, we compared present reaction conditions with some previously reported methodologies and results are summarized in **Table 1**. From comparison the **Table 1** its clearly shows that Boric acid has playing a very crucial role for 1H-pyrazolo[1,2-*b*]phthalazine-5,10-diones synthesis. Some benefits of our methods include non-toxic, cheap, commercially available boric acid, green aqueous solvent, shorter reaction time (1.5-2.0 hr) with good to excellent yields (82-95%). This feature makes the method more prominent and effective for synthesis of 1H-pyrazolo[1,2-*b*]phthalazine-5,10-diones derivatives.

Table 1 Comparative study with a reported method against the present work for synthesizing 1H-pyrazolo[1,2-*b*]phthalazine-5,10-diones derivatives.

Entry	Catalyst	Reaction conditions	Time (hr/min)	Yield (%)	Ref.
1	3-Picolinic acid	10 mol %, in EtOH at 80 °C	8-10 hr	75-93	[18]
2	Catalyst free	Catalyst-free, TFE, reflux	3.5-5.5 hr	81-92	[21]
3	Imidazole	20 mol %, in H_2O: EtOH (1:1), at 80 °C	0.5-4 hr	85-94	[23]
4	HFIP	3 mL, at 50 °C	3-4.5 hr	81-93	[24]
5	Catalyst free	CFL (23 W), in EL/H_2O (2:1) at rt	2-5 hr	83-94	[26]
6	[Bn-DBU] [TFA]	28 mol%, solvent-free at 100 °C	8-25 min	76-93	[32]

7	ZrO_2 NPs	Solvent-free, 100 °C	35-45 min	87-96	[41]
8	NMIL	0.5 mol%, solvent free, 110 °C	40-80 min	75-92	[42]
9	β-Cyclodextrin	20 mol%, 100 °C in H_2O: EtOH (4:1)	2.5-5 hr	82-92	[43]
10	$NaHCO_3$	Solvent free, at 120 °C	15-50 min	85-98	[46]
11	NZF@HAP-Cs	Solvent free, at 110 °C	10-30 min	86-98	[47]
12	$Cu(OAc)_2{\cdot}H_2O$	15 mol%, 80 °C, solvent free	3-5 hr	73-89	[48]
13	Al-KIT-6	300 mg, reflux in EtOH	4 hr	84–93	[56]
14	$NiCl_2{\cdot}6H_2O$	15 mol%, refluxes in EtOH	2-6 hr	80–94	[57]
15	**Boric acid**	**1 eq. at 80 °C, in H_2O-EtOH (8:2)**	**1.5-2 hr**	**82-95**	**This work**

Bold indicates the best result of present works.

To optimize the reaction conditions, we commenced our studies by performing a series of trial by using benzaldehydes, malononitrile, and phthalhydrazide as our model reaction in presence boric acid using water, ethanol, and / or ethanol-water various mixture combinations as solvent from room temperature to 100 °C with different amount of the boric acid. The reaction goes ahead without boric is slower with less yields (25%) with longer reaction times. Under the optimized conditions, the reaction of 4-chlorobenzaldehyde with malononitrile and phthalhydrazide was then carried out, and it furnished the product 3-amino-1-(4-chlorophenyl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (5b) in 95% yield within 1.5 hr **(Table 5, entry 2)**. The results show that a boric acid plays a significant role in this reaction. Encouraged by the initial success, we applied the best protocol to a variety of aldehydes. Generally, all the reactions were performed using one equivalent boric acid as a promoter in H_2O-EtOH (8:2) at 80 °C and all the reaction done within 1.5-2 hr to give the desired products in admirable yields.

Table 2 Effect of temperature on reaction time and product yield[a]

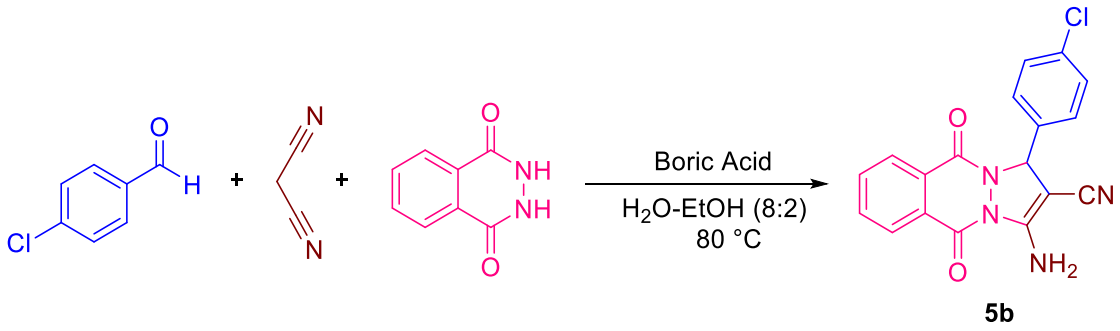
Entry	Temp. (°C)	Time (hr)	Yield[b] (%)
1	R.T.	12	No reaction
2	40	12	trace
3	60	12	60
4	**80**	**1.5**	**95**
5	100	1.5	94

Bold indicate the best result of present works.

[a] Reaction conditions: 4-Clorobenzaldehyde (2 mmol), malononitrile (2 mmol), phthalahydrazide (2 mmol), Boric acid (1 equiv.) and H_2O: EtOH (8:2), 10 mL at 80 °C. [b] Isolated yield.

Temperature plays a key role in the reaction; notably, at lower temperatures, only trace amounts of the product were formed, and significantly longer reaction times were needed. An increase in temperature from room temperature to 120 °C resulted in higher yields and shorter reaction times. We obtained the best results at 80 °C (**Table 2, entry 4** and hence all the reactions were accomplished at the temperature 80 °C. Further increase in temperature up to 100 °C had very negligible effect on yield and reaction time.

The effect of boric acid loading was investigated in the model reaction (**Scheme 2**) at 80 °C in H_2O–EtOH (8:2). Optimal conditions were achieved using one equivalent boric acid, **(Table 3, entry 6)** which afforded a 95% yield in 1.5 h. Further increases in boric acid loading did not influence the reaction rate or product yield **(Table 3, entries 6 and 7)**.



Scheme 2 Model reaction for synthesis of 3-amino-1-(4-chlorophenyl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile **(5b)**.

Table 3 Influence of boric acid amount on product yield at 80 °C in aqueous media.

Entry	Boric acid (mol %)	Time (hr)	Yield[a] (%)
1	Without Boric acid	12	25
2	Boric acid (0.2 equiv.)	10	35
3	Boric acid (0.4 equiv.)	6	60
4	Boric acid (0.6 equiv.)	4	72
5	Boric acid (0.8 equiv.)	1.5	80
6	**Boric acid (1 equiv.)**	**1.5**	**95**
7	Boric acid (1.5 equiv.)	1.5	93
8	Boric acid (2 equiv.)	1.5	94

Bold indicate the best result of present works.
[a] Reaction conditions: 4-Clorobenzaldehyde (2 mmol), malononitrile (2 mmol), phthalahydrazide (2 mmol), Boric acid (1 equiv.) and H_2O: EtOH (8:2) 10 mL, at 80 °C, [b] Isolated yield.

To test the noteworthy influence of solvents on the transformation, we investigated the reaction in a range of solvents to access the response of boric acid. The corresponding results are presented in **Table 4**. First trial for model reaction is conducted in solvent free condition; the desire product obtained in very trace amount. After that we employed the solvent H_2O, EtOH, different combinations of water-ethanol such as H_2O-EtOH (1:1), H_2O-EtOH (7:3) and H_2O-EtOH (8:2). Among all these combinations, H_2O-EtOH (8:2) was identified as the most effective solvent system, providing the highest yield **(Table 4, entry 6)**, and was therefore chosen for further studies.

Table 4 Optimization of solvent conditions for the synthesis of 1H-pyrazolo[1,2-*b*]phthalazine-5,10-diones.[a]

Entry	Solvent (mol %)	Time (h)	Yield[b] (%)
1	without solvent	12	trace
2	H_2O	12	60
3	EtOH	6	80
4	H_2O-EtOH (1:1)	3	84
5	H_2O-EtOH (7:3)	2	90
6	**H_2O-EtOH (8:2)**	**1.5**	**95**

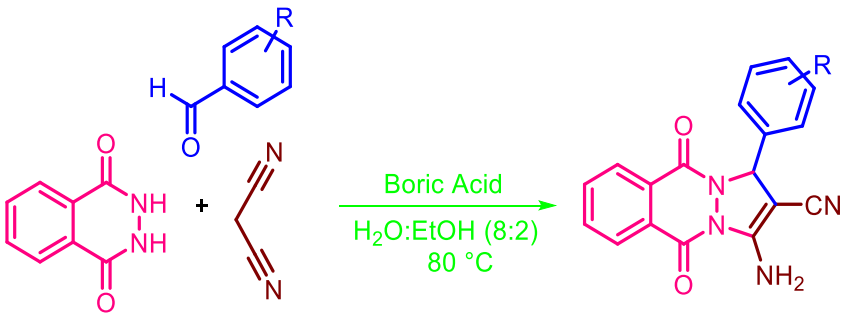
Bold indicate the best result of present works.
a Reaction conditions: 4-Clorobenzaldehyde (2 mmol), malononitrile (2 mmol), phthalahydrazide (2 mmol), Boric acid (l equiv.) and H_2O-EtOH (8:2, 10 mL), at 80 °C, *b* Isolated yield.

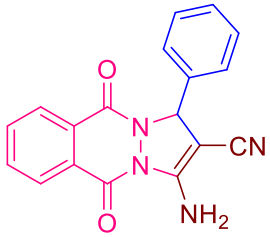
The study revealed that scope of the reactions by varying aldehydes, malononitrile, and phthalahydrazide, the reaction proceeds smoothly provide the desire 1-H-Pyrazolo[1,2-*b*] phthalazine-5,10-diones derivatives with an isolated yield (81-94%). All the results obtained are summarized in **Table 5** (**entries 5a-5i)**. Then, electron withdrawing substituents (4-CN, 4-Cl, 4-Br, 3-NO_2, 2-Cl-5-F, 4-CF_3, 4-COOH etc.) bearing aldehydes reacted with malononitrile and phthalhydrazide very smoothly, under standard conditions giving an isolated yield of the substituted 1-H-Pyrazolo[1,2-*b*] phthalazine-5,10-diones ranging from 82 to 95%, thereby concluding that electron withdrawing groups were uttered efficiently conferring a wide range of products. The afforded products exclusively as summarized in **Table 5**. The substituents on the aromatic ring had a noticeable impact on the conversion. In all cases, the conversion was completed within 1.5 to 2 hours, yielding good to excellent amounts of the desired products without by-products. The type of functional group on the aromatic ring of the aldehyde had a minor effect on the reaction time. Specifically, the reaction rate was slower for arylaldehydes

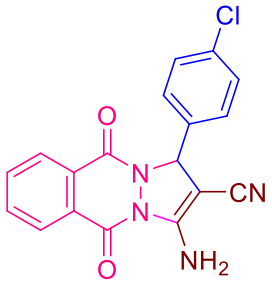
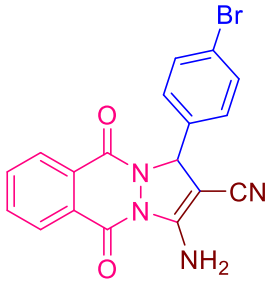
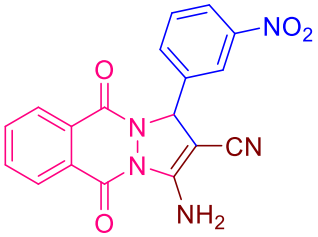
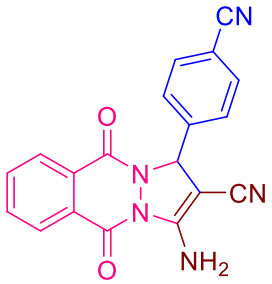
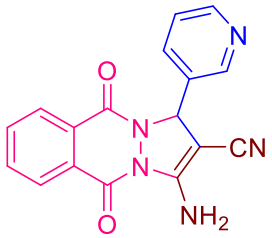
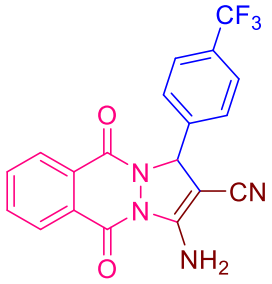
with electron-donating groups compared to the unsubstituted ones. In an analogous manner, heteroaromatic aldehyde like Pyridine-3-carboxaldehyde underwent efficient reactions, producing the corresponding 1H-pyrazolo[1,2-*b*]phthalazine-5,10-diones in good yield **(entry 5f, Table 5)**. Total nine derivatives were synthesized by using boric acid as promoter. Out of nine, two novel derivatives are reported here in first time **(Table 5, entry 5h and 5i)**.

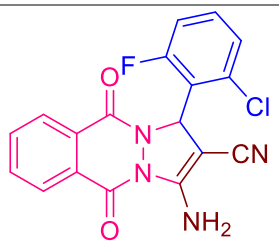
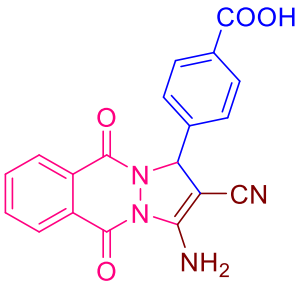
Most of the synthesized compounds were confirmed by spectral analysis such as ^{1}H-NMR, ^{13}C-NMR and Mass / HRMS spectra. In the ^{1}H-NMR spectra of compound **5b** deduced here shows one hydrogen singlet (1H-s) at δ 6.15 ppm is the pyrazol C-H. The two doublets (J= 8.5 Hz) at δ 7.46-7.42 & 7.53-7.52 ppm are due to the aromatic hydrogens of aldehyde benzene ring. The multiplets of two protons (2H, m) appear between at δ 7.98 ppm and 7.97 ppm is the aromatic hydrogens of phthalhydrazide ring. Again, the multiplets of one proton (1H, m) appears in between at δ 8.10 ppm & 8.08 ppm is due to another aromatic proton of phthalahydrazide ring. The two protons give singlet (2H, s) at δ 8.12 ppm is due to -NH_2. And the last peak of multiplets of one hydrogen (1H, m) appears between at δ 8.27 ppm & 8.26 ppm is due to another aromatic proton of phthalahydrazide ring. The appearance of peak in ^{13}C-NMR of **5b** at δ 61.3, 62.7, 116.4, 127.1, 127.7, 128.9, 129.0, 129.3, 133.3, 134.2, 135.1, 137.9, 151.2, 154.1 & 157.1 ppm., supports the formation of compound **5b.**

Table 5: Boric acid promoted synthesis of 1H-pyrazolo[1,2-*b*]phthalazine-5,10-diones in H_2O-EtOH (8:2) at 80°C.



Entry	Product	Time (h)	Yield (%)	M.P.(°C) [Lit.]
5a		1.5	90	276-278 [278-280][43]

5b		1.5	95	268-270 [270-272][43]
5c		1.5	88	274-276 [264-266][43]
5d		1.5	88	264-266 [256-258][43]
5e		1.5	91	282-284 [290-292][43]
5f		2.0	89	238-240 [232–234][43]
5g		1.5	89	280-282 [266-268][17]

5h		2.0	84	258-260
5i		1.5	82	290-292

Experimental conditions: aldehyde (2 mmol), phthalhydrazide (2 mmol), malononitrile (2 mmol) boric acid (1 equiv.), H_2O–EtOH (8:2, 10 mL) at 80°C.

Plausible mechanism:

The reaction starts with Knoevenagel condensation of aldehyde and malononitrile by activation of carbonyl group of aldehydes by electron deficient boric acid to form an ylidene malononitrile (I) as an intermediate. Then Michael addition takes place by the addition of phthalahydrazide on ylidene malononitrile (I) intermediate, after Michael addition cyclization of Michael adduct takes place to form the final product i.e., 1H-pyrazolo[1,2-*b*]phthalazine-5,10-diones (**Figure 2**).

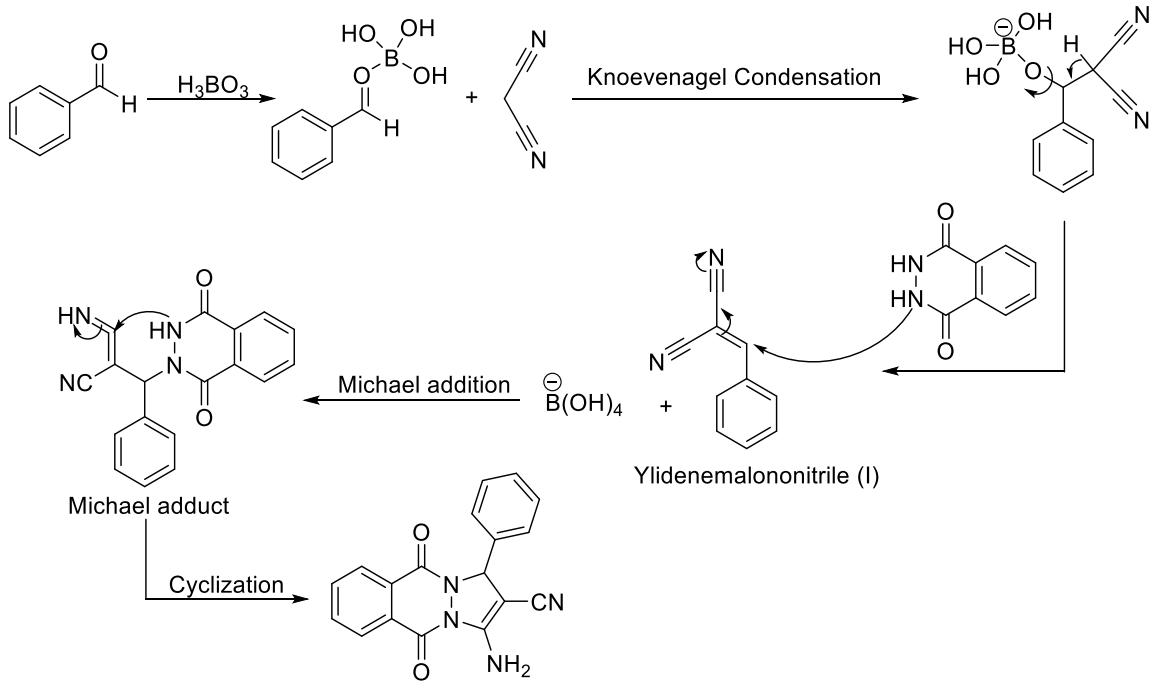


Figure 2 Plausible mechanism for boric acid catalysed synthesis of 1H-pyrazolo[1,2-*b*]phthalazine-5,10-diones.

Biological activities

In vitro anti-inflammatory activity

The anti-inflammatory activity of some synthesized compounds was studied against by the Protein denaturation method at the concentration of (12.5-200 µg/mL) with standard drug Diclofenac sodium (10-100 µg/mL). The results of anti-inflammatory activity of all the compounds (**5a-5i)** by using the Protein denaturation by Bovine Serum Albumin method are summarized in **Table 6**. The percentage inhibition of the samples (**5a-5i)** at the different concentration exhibited potent to moderate anti-inflammatory activity. Among these compounds **5a, 5d, 5e and 5i** shows potent inhibition of Protein denaturation are **61.17%**, **66.22%, 63.33%** and **68.79%** at 200 µg/mL concentration. Similarly, compounds **5a, 5d, 5e and 5i** shows potent inhibition of Protein denaturation **48.81%**, **58.59%**, **59.95%** and **60.24%** at concentration 100 µg/mL and that of standard drug Diclofenac sodium inhibition of Protein denaturation is **92.27%** at the concentration 100 µg/mL.

Table 6. In vitro anti-inflammatory activity of synthesized 1H-pyrazolo[1,2-*b*]phthalazine-5,10-diones derivatives in Protein denaturation method.

Entry	R	% Inhibition of Bovine Serum Albumin in 200 µg/mL	% Inhibition of Bovine Serum Albumin in 100 µg/mL
5a	H	**61.17**	**48.81**
5b	4-Cl	46.92	39.85
5c	4-Br	49.85	46.25
5d	3-NO_2	**66.22**	**58.59**
5e	4-CN	**63.33**	**56.95**
5f	3-pyridine	39.44	34.29
5g	4-CF_3	53.83	50.77
5h	2-Cl, 6-F	46.96	38.31
5i	4-COOH	**68.79**	**60.24**
Diclofenac sodium	-	-	**92.27**

Computational study

Molecular docking study

The molecular docking study was performed to investigate the binding behavior and possible protein-ligand interactions of the synthesized pyrazolo-phthalazine derivatives (5a-5i) against bovine xanthine oxidase (PDB ID: 3NVY). **Figure 3** represents the 3D structure of prepared bovine xanthine oxidase protein with the active site while **Figure 4** represents the 3D and 2D poses of the docked compounds within the binding pocket of the protein. The resulting binding affinity and interactions of the docked compounds with bovine xanthine oxidase (PDB ID: 3NVY) obtained via docking study are summarized in **Table 7 & 8**. The calculated binding energies ranged from -7.1 to -8.0 kcal mol^{-1} showing favorable interactions of all investigated derivatives with the selected binding site of the protein. Among the compounds, 5d exhibited the most favorable predicted binding energy (-8.0 kcal mol^{-1}) followed by 5h (-7.8 kcal mol^{-1}) and 5c (-7.4 kcal mol^{-1}). Compounds 5a, 5b and 5i showed comparable binding energies of -7.3 kcal mol^{-1} whereas 5e and 5f displayed -7.2 kcal mol^{-1} and 5g showed -7.1 kcal mol^{-1}.

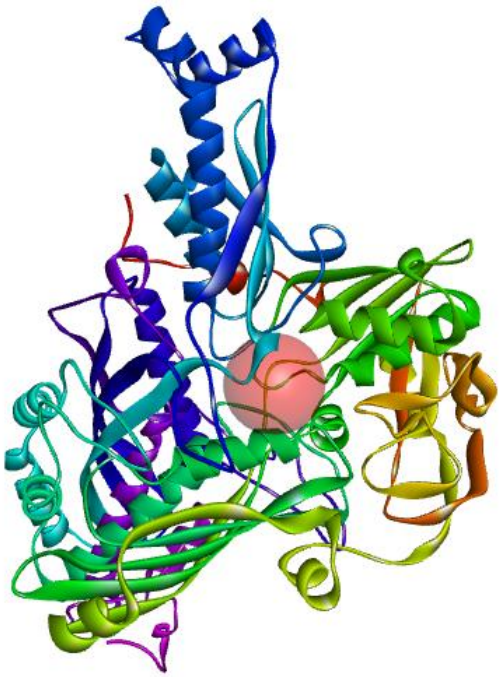


Figure 3. 3D structure of the prepared bovine xanthine oxidase protein highlighting the active site (PDB ID: 3NVY)

The docking results further revealed that the derivatives stabilized within the xanthine oxidase binding pocket through a combination of hydrogen bonding and hydrophobic interactions. Compound 5d which showed the lowest binding energy, formed a conventional hydrogen bond with Ser876 (3.93 Å) and an additional interaction with Lys771 (6.20 Å). It also exhibited C-H interaction with Pro1076 (4.85 Å) and extensive hydrophobic contacts

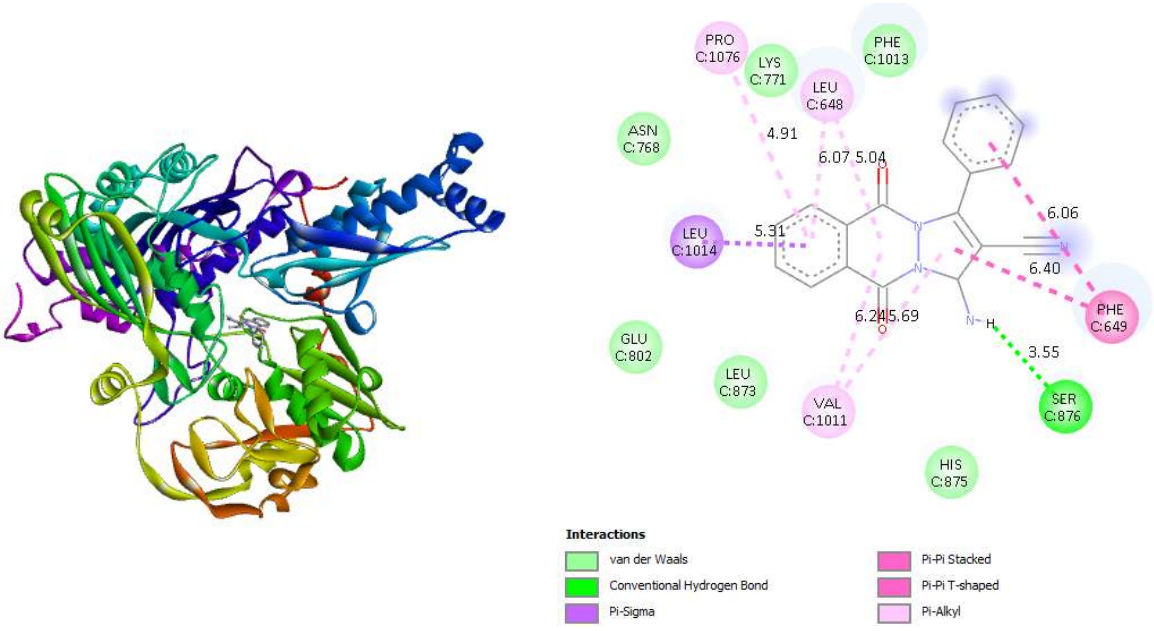
involving Val1011, Pro1076, Leu1014, Phe1013, Leu648 and Phe649. The comparatively extensive interaction network observed for 5d may contribute to its stronger predicted binding within the protein cavity.

Compounds **5a, 5c, 5e** and **5f** also formed conventional hydrogen bonds with Ser876 with interaction distances of 3.55, 3.63, 3.75 and 3.54 respectively. These compounds were additionally surrounded by hydrophobic residues particularly Phe649, Leu648, Val1011, Leu1014 and Pro1076 suggesting that non-polar contacts contribute substantially to ligand stabilization. In contrast, compounds **5h** and **5i** established conventional hydrogen bond interactions with Lys771 at 3.86 and hydrogen bond interactions with Lys771 at 3.86 and 5.15 Å respectively together with multiple hydrophobic contacts involving Phe1013, Val1011, Leu648, Leu1014 and Pro1076. Compound **5g** displayed a somewhat different interactions pattern. It formed conventional hydrogen binding interactions with Lys771 (5.28 Å), along with C-H and halogen interactions involving His875 and Glu879. Hydrophobic contacts with Phe1013, Leu1014, Pro1076 and Val1011 further contributed to its binding. However, an unfavourable interaction involving Lys771 (6.58 Å) was also observed, which may partly account for its comparatively weaker docking score of -7.1 kcal mol^{-1}. Similarly, compound **5i** showed an unfavourable interaction involving Lys771 (6.43 Å) despite maintaining several hydrophobic contacts. These preliminary docking investigations revealed that these compounds exhibit excellent interactions and further modifications will be needed to enhance the interactions.

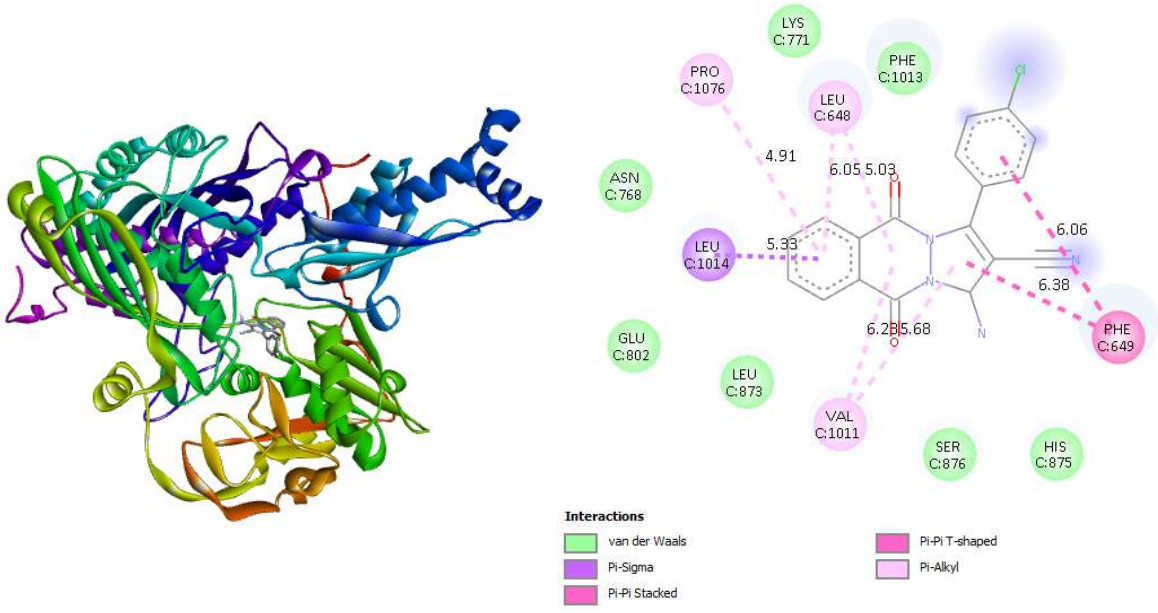
Table 7 Binding energies of the compounds with bovine xanthine oxidase protein (**PDB ID: 3NVY**)

Compound	**Binding Energy (Kcal/mol)**
5a	-7.3
5b	-7.3
5c	-7.4
5d	-8.0
5e	-7.2
5f	-7.2
5g	-7.1
5h	-7.8

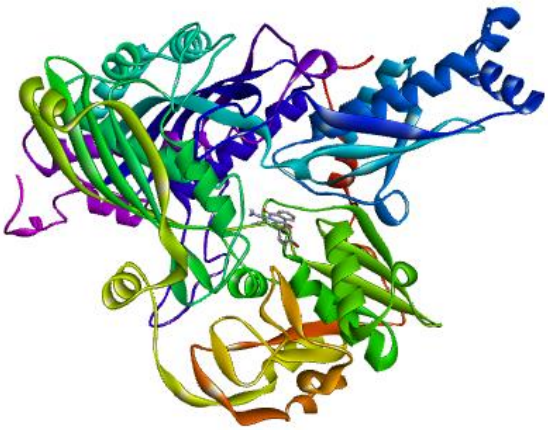
5i	-7.3

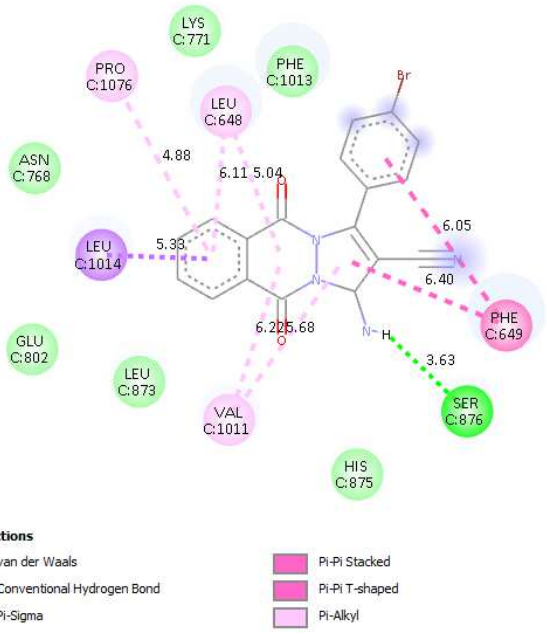

PRO C:1076
LYS C:771
PHE C:1013
LEU C:648
ASN C:768
4.91
6.07 5.04
6.06
LEU C:1014
5.31
6.40
PHE C:649
6.24 5.69
GLU C:802
3.55
LEU C:873
VAL C:1011
SER C:876
HIS C:875
Interactions
van der Waals
Conventional Hydrogen Bond
Pi-Sigma
Pi-Pi Stacked
Pi-Pi T-shaped
Pi-Alkyl

(5a)

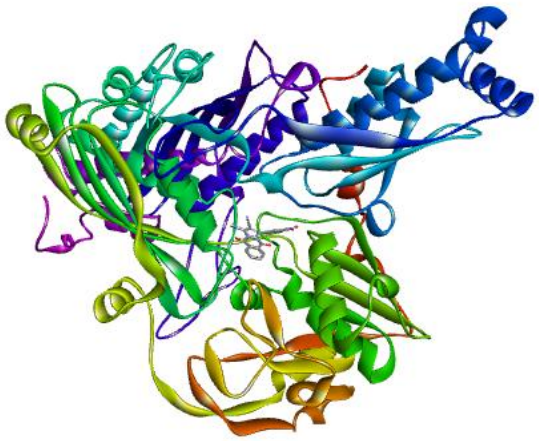

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PHE C:1013
LEU C:648
4.91
6.05 5.03
ASN C:768
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LEU C:1014
5.33
6.38
PHE C:649
6.23 5.68
GLU C:802
LEU C:873
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Interactions
van der Waals
Pi-Sigma
Pi-Pi Stacked
Pi-Pi T-shaped
Pi-Alkyl

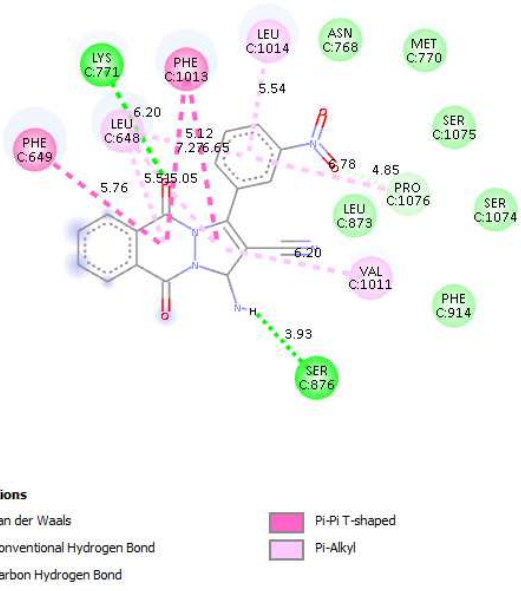
(5b)



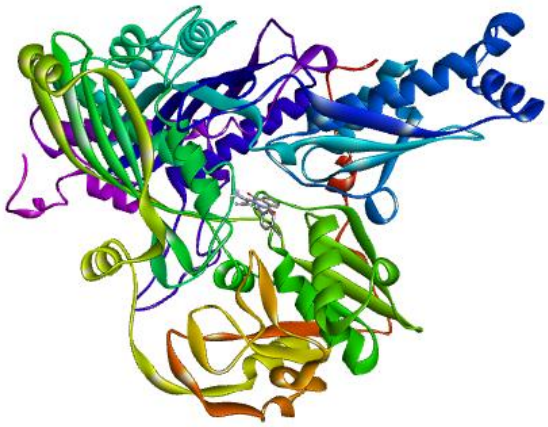

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PRO C:1076
PHE C:1013
LEU C:648
ASN C:768
LEU C:1014
GLU C:802
LEU C:873
VAL C:1011
HIS C:875
SER C:876
PHE C:649
Br
4.88
6.11
5.04
5.38
6.05
6.40
6.22
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Interactions
van der Waals
Conventional Hydrogen Bond
Pi-Sigma
Pi-Pi Stacked
Pi-Pi T-shaped
Pi-Alkyl

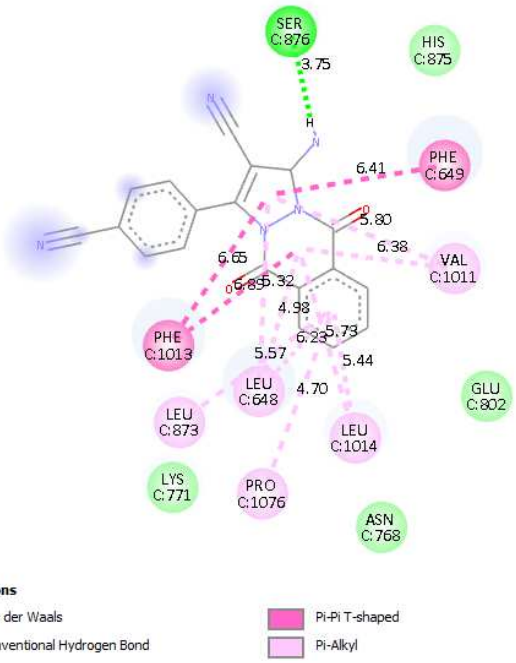
(5c)



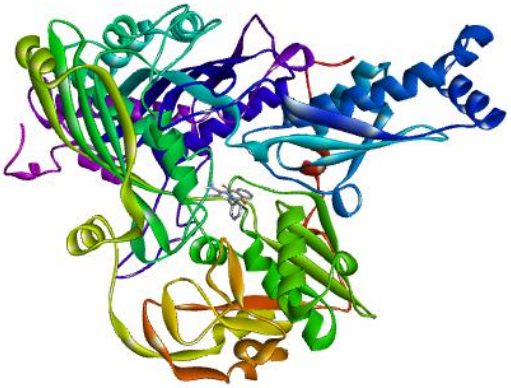

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ASN C:768
MET C:770
LYS C:771
PHE C:1013
SER C:1075
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PRO C:1076
SER C:1074
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7.27
6.65
6.78
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5.76
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6.20
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Interactions
van der Waals
Conventional Hydrogen Bond
Carbon Hydrogen Bond
Pi-Pi T-shaped
Pi-Alkyl

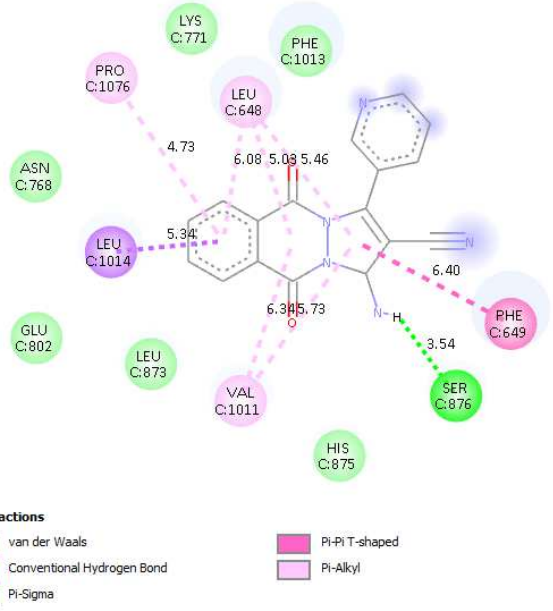
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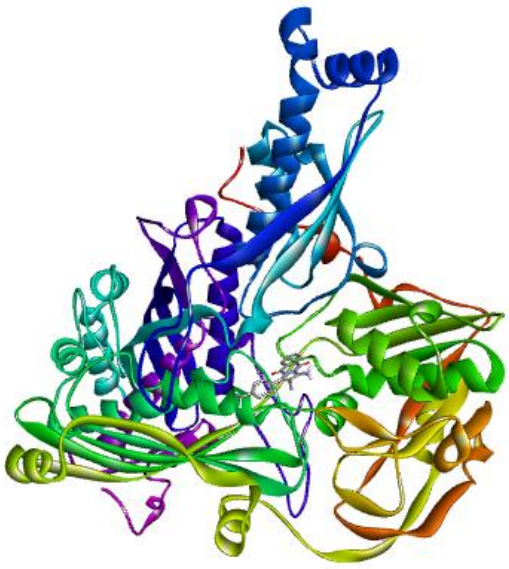

SER C:876
3.75
HIS C:875
PHE C:649
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5.80
6.38
VAL C:1011
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6.85
5.32
4.98
6.23
5.73
PHE C:1013
5.57
5.44
LEU C:648
4.70
GLU C:802
LEU C:873
LEU C:1014
LYS C:771
PRO C:1076
ASN C:768
Interactions
van der Waals
Conventional Hydrogen Bond
Pi-Pi T-shaped
Pi-Alkyl

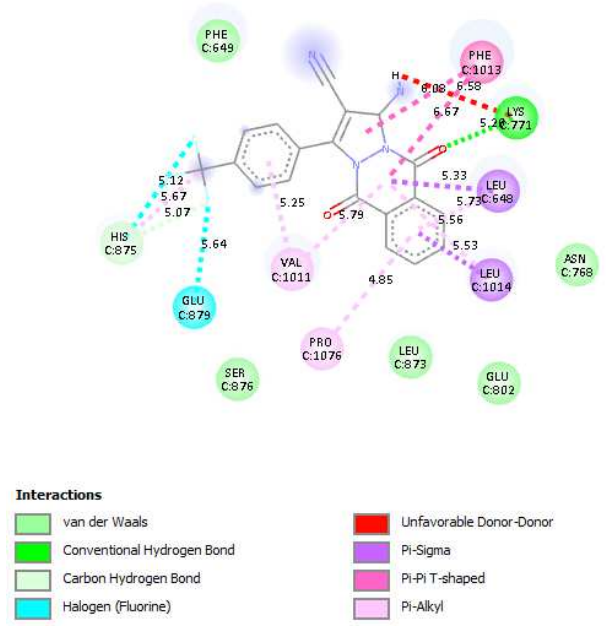
(5e)



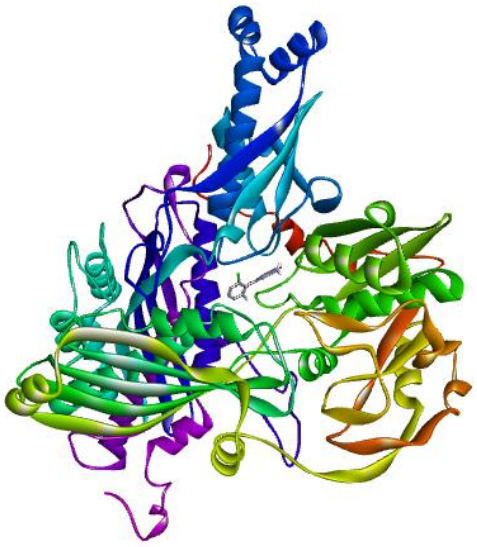

LYS C:771
PHE C:1013
PRO C:1076
LEU C:648
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6.08
5.03
5.46
ASN C:768
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LEU C:1014
6.40
6.34
5.73
PHE C:649
GLU C:802
3.54
LEU C:873
SER C:876
VAL C:1011
HIS C:875
Interactions
van der Waals
Conventional Hydrogen Bond
Pi-Sigma
Pi-Pi T-shaped
Pi-Alkyl

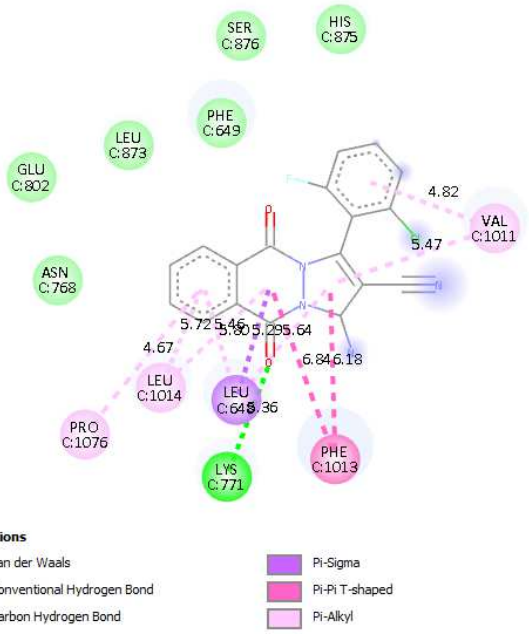
(5f)



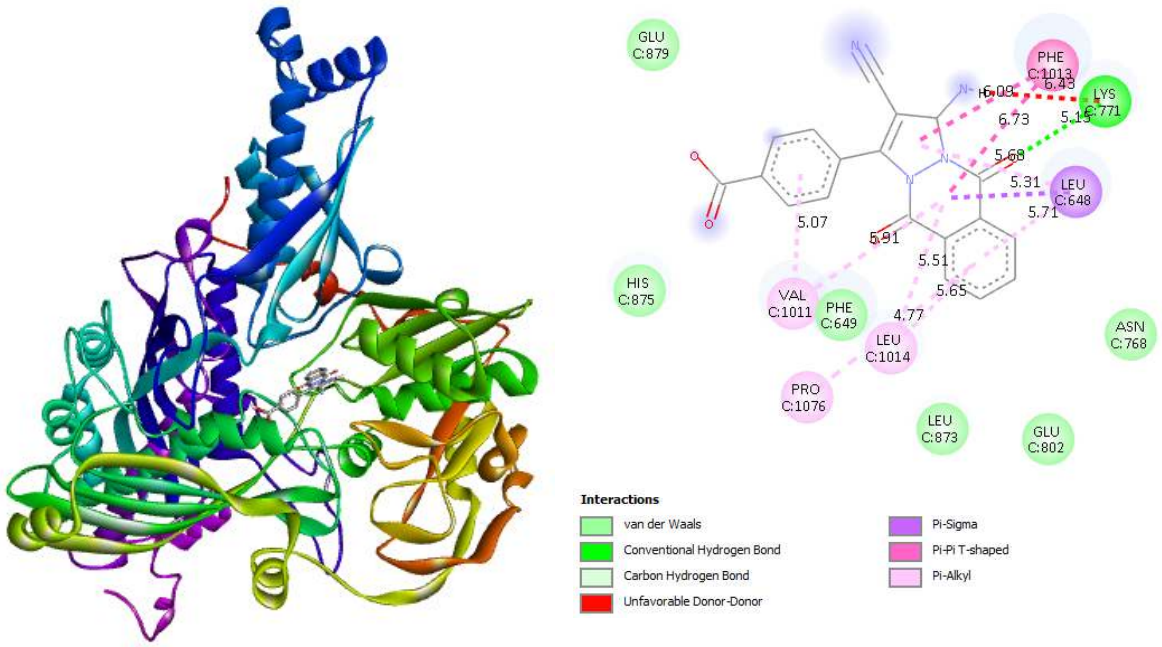

PHE C:649
PHE C:1013
LYS C:771
LEU C:648
HIS C:875
VAL C:1011
LEU C:1014
ASN C:768
GLU C:879
PRO C:1076
LEU C:873
SER C:876
GLU C:802
Interactions
van der Waals
Conventional Hydrogen Bond
Carbon Hydrogen Bond
Halogen (Fluorine)
Unfavorable Donor-Donor
Pi-Sigma
Pi-Pi T-shaped
Pi-Alkyl

(5g)




SER C:876
HIS C:875
PHE C:649
LEU C:873
GLU C:802
VAL C:1011
ASN C:768
LEU C:1014
LEU C:648
PRO C:1076
LYS C:771
PHE C:1013
Interactions
van der Waals
Conventional Hydrogen Bond
Carbon Hydrogen Bond
Pi-Sigma
Pi-Pi T-shaped
Pi-Alkyl

(5h)



(**5i**)

Figure 4. Docked poses (3D & 2D) of the synthesized compounds in the binding pocket of bovine xanthine oxidase protein (**PDB ID: 3NVY**)

Table 8 Binding affinity and interactions for pyrazolo-phthalazine derivatives (**5a-5i**) docked against bovine xanthine oxidase protein (**PDB ID: 3NVY**).

Compound	Binding Energy (Kcal/mol)	Type of Interaction: Residue ID (Distance Å)
5a	-7.3	Conventional H-bond: Ser876 (3.55), Hydrophobic: Phe649 (6.40, 6.06), Val1011 (5.69, 6.40), Leu1014 (5.31), Pro1076 (4.91), Leu648 (5.04, 6.07)
5b	-7.3	Hydrophobic: Phe649 (6.38, 6.06), Val1011 (6.03, 5.68), Leu1014 (5.33), Pro1076 (4.91), Leu648 (5.03, 6.05)
5c	-7.4	Conventional H-bond: Ser876 (3.63), Hydrophobic: Phe649 (6.05, 6.40), Val1011 (6.22, 5.68), Leu1014 (5.33), Pro1076 (4.88), Leu648 (5.04, 6.11)
5d	-8.0	Conventional H-bond: Ser876 (3.93), Lys771 (6.20), C-H bond: Pro1076 (4.85), Hydrophobic: Val1011 (6.20), Pro1076 (6.78), Leu1014 (5.54), Phe1013 (6.65, 7.27), Leu648 (5.05, 5.12, 5.51), Phe649 (5.76).

5e	-7.2	Conventional H-bond: Ser876 (3.75), Hydrophobic: Phe649 (6.41), Val1011 (5.80, 6.38), Phe1013 (6.65, 6.85), Leu648 (4.98, 6.23, 6.32), Leu873 (5.57), Pro1076 (4.70), Leu1014 (5.44, 5.79)
5f	-7.2	Conventional H-bond: Ser876 (3.54), Hydrophobic: Phe649 (6.40), Leu648 (5.03, 5.46, 6.08), Pro1076 (4.73), Leu1014 (5.34), Val1011 (5.73, 6.34)
5g	-7.1	Conventional H-bond: Lys771 (5.28), C-H bond: His875 (5.07), Halogen: His875 (5.12), Glu879 (5.64), Hydrophobic: Phe1013 (6.08, 6.67), Leu1014 (5.53, 5.56), Pro1076 (4.85), Val1011 (5.25, 5.79), Unfavourable: Lys771 (6.58)
5h	-7.8	Conventional H-bond: Lys771 (3.86), Hydrophobic: Phe1013 (6.18, 6.84), Val1011 (4.82, 5.47), Leu648 (5.29, 5.64, 5.80), Leu1014 (5.46, 5.72), Pro1076 (4.67)
5i	-7.3	Conventional H-bond: Lys771 (5.15), Hydrophobic: Phe1013 (6.09, 6.73), Leu648 (5.31, 5.68, 5.71), Leu1014 (5.51, 5.65), Pro10776 (4.77), Val1011 (5.07, 5.91), Unfavourable: Lys771 (6.43)

Drug-likeliness and theoretical ADME prediction study

In the present study, the drug-likeness of synthesized pyrazolo-phthalazine derivatives (**5a-5i**) was evaluated through an analysis of their physicochemical properties alongside the application of Lipinski's Rule of Five (Ro5) and Veber's Rule. The computed physicochemical parameters and drug-likeness predictions are summarized in **Table 9**. Lipinski's Ro5, derived from empirical observations, posits that compounds with a molecular weight below 500 Daltons, logP values under 5, fewer than five hydrogen bond donors, and a total polar surface area (TPSA) less than 140 Å are more likely to exhibit oral bioavailability and serve as promising drug candidates [92-95]. Conversely, Veber's Rule specifies molecular flexibility by setting a limit of 10 rotatable bonds [96]. All compounds evaluated in this study followed

Veber's criteria, supporting the correlation between reduced molecular flexibility and improved pharmacokinetic properties and drug potential. Nevertheless, recent research has shown that many modern pharmaceuticals which do not conform to conventional Rule of Five criteria are nonetheless capable of showing advantageous pharmacokinetic profiles and effective therapeutic outcomes.

Table 9. Drug-likeness property prediction of synthesized pyrazolo-phthalazine derivatives (**5a-5i**).

Entry	MW (g/mol)	xLogP	HBA	HBD	MR	TPSA	nRot	Lipinski's Rule (Ro5)	Veber's Rule
5a	316.31	2.03	3	1	89.75	93.81	1	+	+
5b	350.76	2.65	3	1	94.76	93.81	1	+	+
5c	395.21	2.72	3	1	97.45	93.81	1	+	+
5d	361.31	1.85	5	1	98.58	139.63	2	+	+
5e	341.32	1.74	4	1	94.47	117.6	1	+	+
5f	317.3	0.96	4	1	87.55	106.7	1	+	+
5g	384.31	2.91	6	1	94.76	93.81	2	+	+
5h	368.75	2.75	4	1	94.72	93.81	1	+	+
5i	360.32	1.55	5	2	96.71	131.11	2	+	+

MW: molecular weight; mLogP: lipophilicity; HBA: hydrogen bond acceptor; HBD: hydrogen bond donor; MR: molar refractivity; TPSA: topological polar surface area; nRot: number of rotatable bonds.

The *in silico* ADMET analysis of pyrazolo-phthalazine derivatives **(5a-5i)** revealed key pharmacokinetic and safety characteristics. Pharmacokinetic properties were predicted using pkCSM [97]. Predicted properties are key to assessing their drug candidacy. The ADMET values are presented in **Table 10**. The evaluation of human intestinal absorption proved favourable outcomes, with absorption rates surpassing 90% for the majority of the synthesized derivatives, excluding compounds **5d** and **5f**. The human intestinal absorption was found least with a value of 66% in the compound **5i**. This prediction of human intestinal absorption suggests that these compounds may have oral bioavailability. The assessment of volume of distribution (VDss) revealed acceptable values with logVDss surpassing -0.15 for all compounds, excluding compounds **5f** and **5h**. These VDss results suggest a reasonable distribution of the compounds **5f** and **5h** throughout the body than other compounds. About blood-brain barrier (BBB) permeability, it is important to note that a logBB value greater than 0.3 indicates a compound's potential to readily cross the BBB, while a logBB value below -1 signifies limited BBB distribution. In this study, the predicted logBB values for the synthesized

compounds were below -1, indicating restricted penetration into the brain. Furthermore, predictions of CNS permeability (logPS) suggested that the synthesized compounds lack the capacity to penetrate the CNS. Metabolic profiling demonstrated satisfactory results with all compounds identified as substrates for CYP3A4 enzyme excluding **5f**. The excretion profiles of the synthesized compounds were within acceptable limits, supporting their potential as drug candidates. Notable, all compounds except **5a**, **5d**, **5f**, **5g**, and **5h** exhibited favourable in silico toxicity profiles, showing no evidence of AMES toxicity or mutagenic effects. This analysis enhances confidence in the safety profile of the prepared pyrazolo-phthalazine derivatives **(5a-5i)**. The results of the *in silico* ADMET and drug-likeness assessments offered a basis for the understanding of the pharmacokinetic characteristics, safety profiles, and potential for optimization of pyrazolo-phthalazine derivatives **(5a-5i)**. Results of this study encourage further investigations and refinement of these compounds.

Table 10. *In silico* ADMET property prediction of synthesized pyrazolo-phthalazine derivatives **(5a-5i)**.

Entry	Absorption		Distribution		Metabolism							Excretion	Toxicity
	Intestinal absorption (human)	VDss (human)	BBB permeability	CNS permeability	Substrate		Inhibitor					Total clearance	AMES toxicity
					CYP								
					2D6	3A4	1A2	2C19	2C9	2D6	3A4		
	Numeric (%absorbed)	Numeric (log L kg^{-1})	Numeric (log BB)	Numeric (log PS)	Categorical (yes/no)							Numeric (log mL min^{-1} kg^{-1})	Categorical (yes/no)
5a	93.405	-0.282	-0.230	-2.234	No	Yes	Yes	No	Yes	No	No	0.274	Yes
5b	94.564	-0.204	-0.421	-2.123	No	Yes	Yes	Yes	Yes	No	No	-0.253	No
5c	94.300	-0.186	-0.429	-2.100	No	Yes	Yes	Yes	Yes	No	No	-0.274	No
5d	88.245	-0.255	-0.786	-2.401	No	Yes	Yes	No	Yes	No	No	0.296	Yes
5e	91.054	-0.211	-0.434	-2.308	No	Yes	Yes	No	Yes	No	No	0.313	No
5f	88.342	0.006	-0.569	-2.952	No	No	Yes	No	No	No	No	0.421	Yes
5g	95.709	-0.284	-0.668	-2.077	No	Yes	Yes	Yes	Yes	No	Yes	0.054	Yes
5h	93.294	-0.076	-0.698	-2.171	No	Yes	Yes	Yes	Yes	No	Yes	-0.219	Yes
5i	66.068	-0.523	-0.710	-2.625	No	Yes	Yes	No	No	No	No	0.624	No

Conclusion

In conclusion, we have developed a greener and practically convenient transformation for easy access of 1H-pyrazolo[1,2-*b*]phthalazine-5,10-diones heterocycles in the presence of boric acid as a novel and ecofriendly promoter via one-pot tandem Knoevenagel-cyclocondensation of aldehydes, malononitrile, phthalhydrazide in aqueous ethanol at 80 ºC. The advantages of newly disclosed methods are boric acid is non-toxic compound, cheap, metal

free protocol, broad substrate scope, shorter reaction time, good to excellent yields of products, simple and clean workup of the desired product without column chromatography. Moreover, the synthetic utility of green solvent as a reaction media is a key advantage and approach towards the green chemistry. The compounds **5a, 5d**, **5e**, and **5i** exhibited potent inhibition of protein denaturation as compared to standard Diclofenac sodium drug. *In silico* screening confirmed the potential of the synthesized compounds, all of which met Lipinski's Rule of Five and showed strong binding affinities with bovine xanthine oxidase (PDB: 3NVY). These features underscore the compounds potential for sustainable and practical applications in bioactivity.

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