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Efficient and Facile Synthesis of Benzimidazole Induced Schiff Bases and their Potent Antibacterial Activity and Computational Study

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Synthesized benzimidazole induced Schiff base analogues were characterized by mass, ^{13}C NMR, ^{1}H NMR and UV-visible spectroscopy. To get more information about binding mechanism, molecular docking studies were carried out and the obtained results concluded that the compounds could effectively bind with receptor. *in vitro* Antibacterial screening was carried out against four strains (*S. aureus, B. subtilis, P. aeruginosa* and *E. coli*) and exhibited good antibacterial activity. The gastrointestinal absorption (HIA) and brain penetration (BBB) was evaluated by The BOILED-Egg model, which showed that two compounds anticipated being effectively effluated by the P-glycoprotein from central nervous system after penetration and can accounts for brain access and passive gastrointestinal absorption. Computational screening showed 0.55 bioavailability score for all synthesized compounds.

Keywords: Benzimidazole, Schiff base, Antibacterial activity, Gastrointestinal absorption, Brain penetration, Molecular docking.

INTRODUCTION

Benzimidazole is a privileged bicyclic ring system and its moieties are important class of heterocyclic compounds which are creating a interest among the researchers because of their wide scope of pharmacological activities [1-5]. The class of these molecules ends up being vital as they have various pharmacological properties including antibacterial [6,7], antifungal [8], analgesic [9], antioxidant [10,11], anti-inflammatory [12], anti-allergic [13] and antitumoral agent [14]. Various benzimidazole analogues have been found to possess biological activity as phosphodiester inhibitor [15], neuropeptide Y receptor and Y5-receptor antagonist [16]. On the other hand, the Schiff base and its derivatives possess broad spectrum of biological activities because of their structural likenesses with natural biological compounds [17]. Synthesis of Schiff base has received a lot of consideration attributable to differed biological activities displayed by number of its derivatives [18-22]. Attributable to the incredible biological and synthetic importance of this heterocyclic core, synthesis of benzimidazole and Schiff base derivatives has long been a region of intense development. In order to get more insight, the computational investigations of synthesized molecules such as ADME [23,24], target prediction [25], *in silico* drug-likeness, pharmacokinetics, molecular docking [26-28] and *in silico* based virtual screening tools [29,30] has become helpful and important for the additional investigation to improve activity.

With this consideration, it was decided to study benzimidazole induced Schiff bases, which are not yet investigated for their relative computational analysis. In the present work, benzimidazole induced Schiff bases were synthesized by efficient, facile route and characterized by spectroscopic techniques. The synthesized compounds were screened for ADME, target prediction, pharmacokinetics and *in silico* drug-likeness. *in vitro* Antibacterial activities were also evaluated by disc diffusion method. In order to explore binding interaction and activity, molecular docking has been carried out with target proteins of various bacterial strains.

EXPERIMENTAL

Evaluation of brain penetration (BBB) and gastrointestinal absorption (HIA): Two necessary pharmacokinetic researches to evaluate at various periods of the drug discovery

measures are brain access and gastrointestinal absorption. Since, aside from toxicity and viability, many drug development dissatisfactions are mindful to helpless bioavailability and pharmacokinetics. BOILED-Egg method works by processing the polarity and lipophilicity of orchestrated molecules, which is proposed as an exact prescient model. The BOILED-Egg is valuable model in order to get fast, instinctive, effectively reproducible yet measurably uncommon way to anticipate the brain access and passive gastrointestinal absorption of molecules, valuable for drug revelation and improvement. The HIA and BBB evaluations were obtained by The BOILED-Egg model utilizing the well known online gizmo called Swiss ADME [30].

Synthesis of 2-(3-Nitrophenyl)-1*H*-benzo[*d*]imidazole: To a stirred mixture of equivalent *o*-phenylenediamine (**1**) and *m*-nitrobenzaldehyde (**2**) in ethanol added 30 mol% of NH_4Cl and heated at 90 ºC for 4 h. With the help of TLC (Pet ether: ethyl acetate) reaction was monitored. The precipitated product as pale yellow solid after poured into ice-cold water was recrystallized from hot ethanol.

Reduction of 2-(3-nitrophenyl)-1*H*-benzo[*d*]imidazole: To a hot solution of 2-(3-nitrophenyl)-1*H*-benzo[*d*]imidazole in water, added 30% sodium polysulphide solution with vigorous stirring, boiled for 1 h and then it was poured into cold water. The obtained solid was dissolved in conc. HCl and filtrate was treated with NH_4OH. The precipitated product as yellow solid was recrystallized from hot distilled water.

Synthesis of Schiff bases: To a stirred mixture of equivalent moles of substituted benzaldehyde (**4**) and 3-(1*H*-benzo[*d*]imidazol-2-yl)aniline (**3**) in ethanol, 0.5 mL of acetic acid was added and stirred for 9 h at room temperature. The precipitated solid was filtered, washed and recrystallized from hot ethanol to obtain pure solid (**5a-g**) (**Scheme-I**).

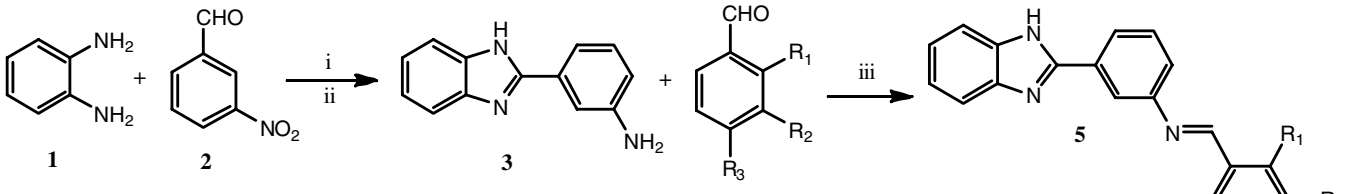
3-(1*H*-benzo[*d*]imidazol-2-yl)-*N*-(3-nitrobenzylidene)-aniline (5a): Yield: 82%; m.p.: 238-240 ºC. ^{1}H NMR (DMSO-d_6) δ (ppm): 12.97 (s, 1H, NH), 8.94 (s, 1H, CH=N), 8.53 (s, ArH, 1H), 8.24 (m, ArH, 1H), 8.22-8.13 (d, ArH, 2H), 8.09 (d, ArH, 1H), 7.66-7.55 (m, ArH, 2H), 7.54-7.50 (m, ArH,1H), 7.45-7.40 (d, ArH, 1H), 7.20 (m, ArH, 2H), 7.10 (d, ArH, 1H). ^{13}C NMR (DMSO-d_6), δ (ppm): 160.25, 157.40, 152.06, 141.12, 137.79, 135.30, 135.20, 128.72, 128.50, 127.05, 126.23, 126.00, 125.60, 123.10, 122.48, 121.30, 120.06, 119.15, 118.71, 117.99. MS: *m/z* ($C_{20}H_{14}N_4O_2$), M^+ = 341.20.

3-(1*H*-Benzo[*d*]imidazol-2-yl)-*N*-(3-bromobenzylidene)aniline (5b): Yield: 86%; m.p.: 210-212 ºC. ^{1}H NMR (DMSO-d_6) δ (ppm): 13.08 (s, 1H, NH), 9.02 (s, 1H, CH=N), 8.26 (s, ArH, 1H), 8.13-8.29 (d, ArH, 2H), 8.06 (d, ArH, 1H), 7.88 (s, ArH, 1H), 7.52 (m, ArH, 3H), 7.46–7.41(m, ArH, 2H), 7.15 (d, ArH, 1H), 6.93 (d, ArH, 1H). ^{13}C NMR (DMSO-d_6), δ (ppm): 160.80, 156.48, 154.02, 140.22, 136.98, 135.20, 135.85, 128.67, 128.55, 126.92, 126.20, 126.15, 125.65, 123.32, 123.10, 121.20, 120.25, 119.51, 118.80, 111.33. MS: *m/z* ($C_{20}H_{14}N_3Br$), M^+ = 375.31.

4-(((3-(1*H*-Benzo[*d*]imidazol-2-yl)phenyl)imino)-methyl)-*N*,*N*-dimethylaniline (5c): Yield: 84%; m.p.: 196 ºC. ^{1}H NMR (DMSO-d_6) δ (ppm): δ 12.99 (s, 1H, NH), 8.71 (s, 1H, CH=N), 8.16 (d, ArH, 1H), 8.28-8.11 (d, ArH, 2H), 8.10(d, ArH, 1H), 7.56-7.52 (m, ArH, 2H), 7.46(d, ArH, 1H), 7.32 (m, ArH, 1H), 7.10 (d, ArH, 1H), 6.78 (d, ArH, 1H), 3.41 (t, 6H, NCH_3). ^{13}C NMR (DMSO-d_6), δ (ppm): 160.75, 154.69, 152.06, 151.76, 141.12, 135.13, 134.39, 128.30, 126.02, 125.49, 125.30, 122.68, 122.40, 120.39, 119.43, 118.28, 109.02, 104.15, 45.15. MS: *m/z* ($C_{22}H_{20}N_4$), M^+ = 341.04.

4-(((3-(1*H*-Benzo[*d*]imidazol-2-yl)phenyl)imino)-methyl)-2-methoxyphenol (5d): Yield: 79%; m.p.: 190-191 ºC. ^{1}H NMR (DMSO-d_6) δ (ppm): 13.10 (s, 1H, NH), 8.86 (s, 1H, CH=N), 8.23 (d, ArH, 1H), 8.18 (d, ArH, 1H), 7.59 (d, ArH, 2H), 7.51 (m, ArH, 2H), 7.48 (m, ArH, 1H), 7.42 (s, ArH, 1H), 7.41– 7.37 (d, ArH, 1H), 7.22 (m, ArH, 1H), 7.02-6.98 (d, 1H), 6.40 (s, 1H, OH), 3.95 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6), δ (ppm): 160.38, 152.92, 152.13, 147.40, 141.73, 131.30, 130.18, 129.21, 127.50, 126.10, 123.11, 123.06, 122.31, 121.22, 120.45, 119.98, 118.98, 115.28, 114.75, 109.31, 56.11 MS: *m/z* ($C_{21}H_{17}N_3O_2$), M^+ = 343.48.

2-(((3-(1*H*-Benzo[*d*]imidazol-2-yl)phenyl)imino)-methyl)phenol (5e): Yield: 88%; m.p.: 232 ºC. ^{1}H NMR (DMSO-d_6) δ (ppm): 13.05 (s, 1H, NH), 11.61 (s, 1H, OH), 8.97 (s, 1H, CH=N), 8.28 (d, ArH, 1H), 8.22 (s, ArH, 1H), 8.12 (d, ArH, 1H), 7.65 (d, ArH, 1H), 7.53 (m, ArH, 2H), 7.48-7.43 (m, ArH, 1H), 7.42-7.37 (m, ArH, 1H), 7.26 (m, ArH, 2H), 7.02-6.98 (d, ArH, 2H). ^{13}C NMR (DMSO-d_6), δ (ppm): 162.12, 160.68, 153.81, 151.93, 141.44, 135.20, 133.38, 132.40, 126.83,



1 **2** **3** **4**

Compound	R_1	R_2	R_3
5a	-H	$-NO_2$	-H
5b	-H	-Br	-H
5c	-H	-H	$-N(Me)_2$
5d	-H	$-OCH_3$	-OH
5e	-OH	-H	-H
5f	-H	-H	-OH
5g	-H	-Cl	-H

Reagent and condition:
i) NH_4Cl, 90 °C
ii) Sodium polysulphide, heat
iii) Ethanol, acetic acid, RT

Scheme-I

126.00, 125.95, 125.51, 123.70, 122.46, 121.32, 119.88, 119.64, 119.45, 118.38, 115.20. MS: *m/z* ($C_{20}H_{15}N_3O$), M^+ = 312.29.

4-(((3-(1*H*-Benzo[*d*]imidazol-2-yl)phenyl)imino)-methyl)phenol (5f): Yield: 85%; m.p.: 246-248 ºC. ^{1}H NMR (DMSO-d_6) δ (ppm): 13.08 (s, 1H, NH), 10.91 (s, 1H, OH), 8.88 (s, 1H, CH=N), 8.34 (d, ArH, 1H), 8.14 (d, ArH, 1H), 7.70 (d, ArH, 1H), 7.50 (m, ArH, 2H), 7.47-7.40 (m, ArH, 1H), 7.39-7.37(m, ArH, 1H), 7.30 (m, ArH, 2H), 6.98 (d, ArH, 1H). ^{13}C NMR (DMSO-d_6), δ (ppm): 161.10, 160.73, 153.20, 151.02, 141.40, 134.10, 131.38, 129.83, 126.10, 125.72, 125.11, 123.62, 122.43, 119.76, 119.53, 118.20, 118.18, 115.24. MS: *m/z* ($C_{20}H_{15}N_3O$), M^+ = 313.30

3-(1*H*-Benzo[*d*]imidazol-2-yl)-*N*-(3-chlorobenzylidene)-aniline (5g): Yield: 93%; m.p.: 203 ºC. ^{1}H NMR (DMSO-d_6) δ (ppm): 12.75 (s, 1H, NH), 8.71 (s, 1H, CH=N), 8.39 (s, ArH, 1H), 8.25 (d, ArH, 1H), 8.13 (d, ArH, 2H), 8.07-8.05 (d, ArH, 1H), 7.95(s, ArH, 1H), 7.54-7.52 (m, ArH, 3H), 7.44-7.42 (m, ArH, 1H), 7.16(d, ArH, 1H), 6.91-6.89 (d, ArH, 1H). ^{13}C NMR (DMSO-d_6), δ (ppm): 160.05, 157.30, 152.03, 151.79, 140.12, 137.09, 132.66, 132.47, 129.43, 128.62, 128.37, 127.55, 127.12, 126.32, 125.48, 121.28, 120.09, 119.34, 118.62, 115.22. MS: *m/z* ($C_{20}H_{14}N_3Cl$), M^+ = 330.81.

RESULTS AND DISCUSSION

The synthesized benzimidazole induced Schiff base analogues were characterized by MS, ^{1}H & ^{13}C NMR spectral analsysis. In ^{1}H NMR, the δ values in the range of 6.0-9.0 ppm indicated presence of aromatic protons and prominent singlet for imine was found in the range of δ 8.6-9.4 ppm. The computational techniques like ADME, target prediction, molecular docking and BOILED-Egg (Brain or IntestinaL EstimateD permeation method) were utilized to get more knowledge into exploratory discoveries.

UV-visible studies: The spectra were recorded at room temperature in ethanol. Compounds **5a-g** showed λ_{max} in the range of 330-390 nm (Fig. 1). Compound **5a** showed a hypsochromic shift (blue shift) as compared to compounds **5c** and **5d**, due to absence of auxochrome whereas compound **5d** showed bathochromic shift (red shift) as compared to compound **5a**, due to auxochrome-chromophore interaction.

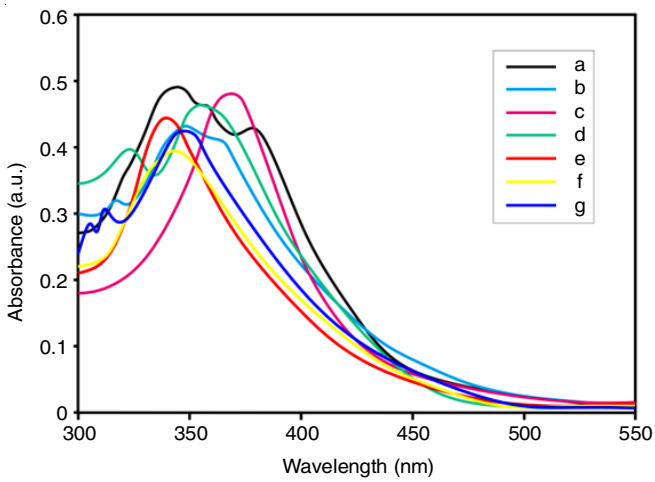


Fig. 1. UV-visible spectra

Antibacterial activities: Compounds **5a-g** were screened against four pathogenic strains *viz.*, *S. aureus*, *B. subtilis*, *P. aeruginosa* and *E. coli* following disc diffusion method. The antibacterial activity of Schiff bases containing benzimidazole was correlated with the zone of inhibition of ciprofloxacin as a standard control (Table-1). The bacterial test results exhibited good to moderate activity. Compounds **5d** and **5g** exhibited maximum activity against *Staphylococcus aureus* while other compounds displayed moderate activity. For *B. subtilis* most of compounds exhibited excellent activity and for *P. aeruginosa* and *E. coli,* compounds **5e** and **5g** exhibited maximum activity, while the remaining compounds displayed good to moderate activity. As all analogues demonstrated good antibacterial action against the microorganisms tested, it shows that this essential moiety can be a possible framework for antibacterial medications.

TABLE-1
ANTIBACTERIAL ACTIVITY DATA OF THE SYNTHESIZED BENZIMIDAZOLE INDUCED SCHIFF BASES (**5a-g**)

Compd.	Zone of inhibition (mm)			
	Gram-positive		Gram-negative	
	S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*
5a	18	22	17	19
5b	20	20	21	19
5c	18	22	20	18
5d	22	23	18	20
5e	17	20	23	21
5f	18	18	19	19
5g	21	20	22	20
Ciprofloxacin	23	24	22	20

Computational study

Molecular docking study: Molecular docking of all the synthesized compounds was carried out using the tool called DockThor (http://www.dockthor.Incc.br). The molecular docking was performed against different targets with PDB IDs: 3OSV, 1KZN, 1BAG, 1D7U and 1M17 (anticancer target). The compared results of docking against the standard drugs ciprofloxacin and erlotinib are shown in Table-2. The 3D interaction sites of compound **5g** with 3OSV and 1KZN is shown in Fig. 2. The results revealed that compounds **5a-g** have good docking score against selected targets and docking score (most dock) values were -9.421, -9.416, -8.584, -8.679 kcal mol^{-1} for compounds **5b**, **5c**, **5d** and **5f** respectively, which showed effective interaction with receptors.

Pharmacokinetics, ADME, drug-likeness and Swiss target prediction study: The pharmacokinetic study demonstrated that benzimidazole induced Schiff base analogues are the inhibitors of CYP1A2 and CYP2C19 and showed high GI absorption (Table-3). The results of drug-likeness studies showed no violation for Lipinski′s rule of five, yet some analogues are violating others. The polar surface area (TPSA) values are allied with the percent oral absorption and were found within range of 41.04-86.86 (Table-4). The quite good 0.55 oral bioavailability score was acquired. All synthesized compounds were screened against various targets to investigate further utilizing the tool called Swiss target prediction and it is found that

TABLE-2
MOLECULAR DOCKING SCORES OF THE SYNTHESIZED BENZIMIDAZOLE INDUCED SCHIFF BASES (**5a-g**)

Compounds	Docking score (kcal/mol)				
	3OSV	1KZN	1BAG	1D7U	1M17
	P. aeruginosa	*E. coli*	*B. subtilis*	Bacterial target (common)	Anticancer target (Epidermal_growth factor receptor tyrosine_kinase)
5a	-8.159	-8.928	-5.562	-8.466	-8.281
5b	-8.262	-8.813	-9.421 (most dock)	-8.993 (most dock)	-8.393
5c	-8.299	-9.416 (most dock)	-8.627	-8.747	-8.361
5d	-8.584 (most dock)	-7.711	-9.072	-8.851	-8.545
5e	-7.866	-8.669	-7.988	-7.099	-7.794
5f	-8.292	-8.780	-8.663	-6.986	-8.679 (most dock)
5g	-8.526	-8.732	-9.366	-8.959	-8.030
Ciprofloxacin	-7.554	-7.054	-8.136	-7.582	-
Erlotinib	-	-	-	-	-9.158

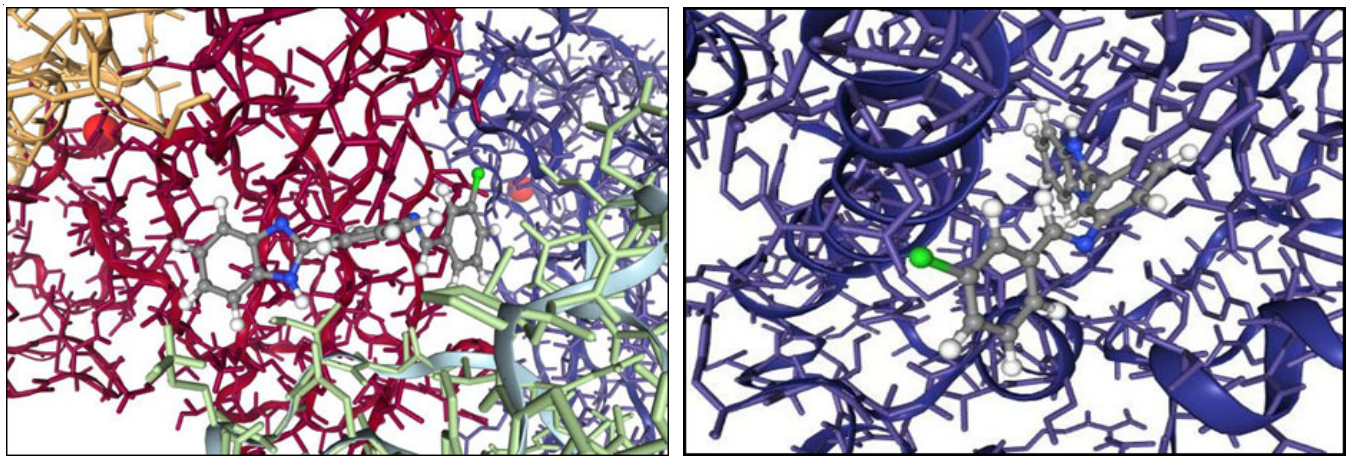


Fig. 2. 3D interactions of ligand-**5g** with target protein: 3SOV and 1KZN

TABLE-3
PHARMACOKINETIC PROFILE OF THE SYNTHESIZED BENZIMIDAZOLE INDUCED SCHIFF BASES (**5a-g**)

Compound	BBB permeant	GI absorption	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor
5a	No	High	Yes	Yes	Yes	Yes	No
5b	Yes	High	Yes	Yes	No	No	Yes
5c	Yes	High	Yes	Yes	Yes	Yes	Yes
5d	Yes	High	Yes	Yes	Yes	Yes	Yes
5e	Yes	High	Yes	Yes	No	Yes	Yes
5f	Yes	High	Yes	Yes	No	Yes	Yes
5g	Yes	High	Yes	Yes	No	No	Yes

TABLE-4
LIPOPHILICITY AND PHYSICO-CHEMICAL PROPERTY PROFILES OF THE SYNTHESIZED BENZIMIDAZOLE INDUCED SCHIFF BASES (**5a-g**)

Compound	**5a**	**5b**	**5c**	**5d**	**5e**	**5f**	**5g**
WLOGP	5.41	5.74	5.83	4.69	4.69	4.69	5.63
TPSA (Å)	86.86	41.04	44.28	70.5	61.27	61.27	41.04

compound **5f** (Fig. 3) and **5d** would prone to follow up on kinases having excellent percentage prediction of 60% and 80% respectively. All the synthesized compounds showed interaction with kinases with percentage of prediction in the range 13.3-80% and may be considered as promising candidates as anticancer agents.

Brain penetration (BBB) and gastrointestinal absorption (HIA) study: The BBB and HIA evaluations were obtained by The BOILED-Egg model and the obtained results are showed in Fig. 4. Blue dots (PGP+) address particles to be effluated whereas red dots (PGP–) address molecules anticipated not to be effluated by the P-glycoprotein from central

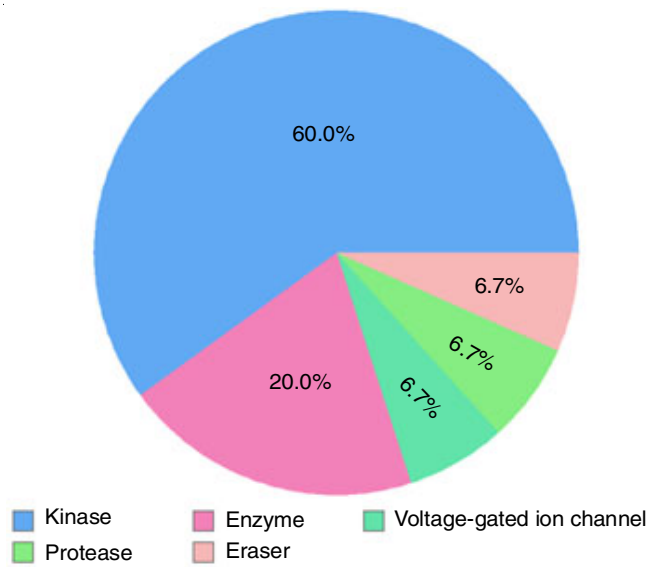


Fig. 3. Swiss target prediction graph of compound **5f**

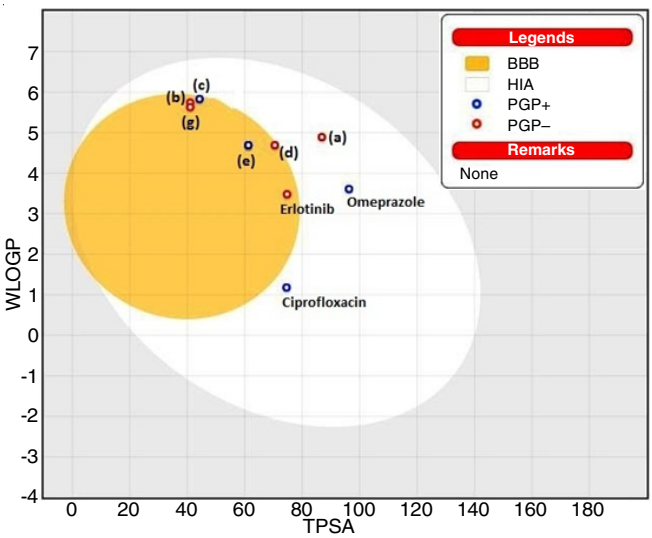


Fig. 4. Brain Or IntestinaL EstimateD permeation profile data (BOILED-Egg)

nervous system. The yellow (yolk) and white region indicates high likelihood of brain penetration and passive gastrointestinal absorption, respectively. The plot of WLOGP *versus* TPSA shows that compound **5a** and reference standards like omeprazole and ciprofloxacin are anticipated as very much ingested yet but not accessing the brain (in the white region). Compound **5a** is not effluated by P-gp (PGP-) (red dot) while omeprazole and ciprofloxacin, PGP+ (blue dots) are easily effluated after absorption. Compounds **5b, 5c, 5d, 5e, 5g** and standard erlotinib are anticipated as actively crossing the BBB (yolk region), but only **5c** and **5e** (PGP+) pumped-out from the brain (blue dots) and compounds **5b**, **5d**, **5g** (PGP–) and erlotinib are predicted as yolk penetrant (brain-penetrant) and not expose to dynamic efflux (red dots). Compound **5a** with a TPSA of 86.86 Å and a WLOGP of 5.41 (Table-4) is anticipated as HIA absorbed and yet not BBB permeant and not to be effluated by the P-glycoprotein from central nervous system (CNS).

Conclusion

All the synthesized benzimidazole induced Schiff base analogues were affirmed by mass, ^{13}C NMR, ^{1}H NMR and UV-visible spectroscopy. Results of molecular docking stated that the analogues could viably bind with receptor. The antibacterial screening against *S. aureus*, *B. subtilis*, *P. aeruginosa* and *E. coli*) exhibited good antibacterial activity against all the pathogens. The HIA and BBB evaluation obtained by The BOILED-Egg model showed that compounds **5c** and **5e** anticipated being effectively effluated by the P-glycoprotein from central nervous system after penetration and can accounts for brain access and passive gastrointestinal absorption. The computational screening showed 0.55 bioavailability score and most of compounds were proned to follow up on kinases having percentage target prediction of 30-80% and might be developed as promising analogues for future designing as anticancer agents.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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