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Design And In Silico Study Of N-Substituted-1H-Benzimidazol- 2-Yl) Methyl)-2-(Pyridin-3-Yl)-3H-Benzimidazol-5-Amine Derivatives

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Abstract

A series of bis-benzimidazole clubbed with pyridine were design (1-12) and reported their ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity) prediction studies. Bioactivity prediction, physicochemical properties, and toxicity profiles for designed benzimidazole derivatives studied by using Molinspiration, admetSAR, and Osiris property explorer online software's. To predict drug like properties and bioactivity score of design molecules, used Molinspiration web server. 'Lipinski's rule of five' is followed by all designed derivatives and can be considered as good oral drug. Prediction of Toxicity, drug relevant properties were calculated using Osiris property explorer software. Bioactivity prediction also shows good enzyme inhibition activity of designed compounds. Among designed compounds, some compounds show good predicted ADMET properties in terms of Gastrointestinal absorption.

Key words

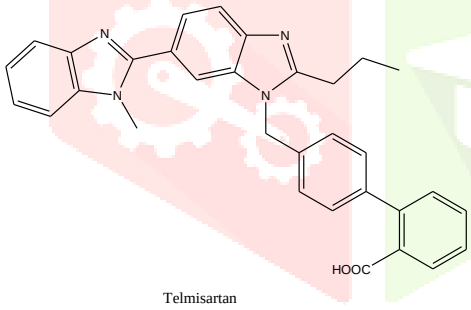
Benzimidazole; ADMET; Osiris, Molinspiration, Bioactivity

Introduction

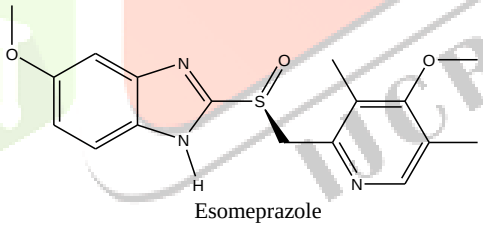
Benzimidazole consists of fused benzene ring with heterocyclic ring of imidazole. It is a heterocyclic aromatic compound contains two nitrogen as heteroatoms. It has useful medicinal properties. Nowadays, globally several peoples are affected by different microbial diseases which shows resistance to many available antimicrobial agents like antibiotics (such as cephalosporins, penicillins, fluoroquinolones, etc.) So, there is an urgent need to develop such a chemotherapeutic agent which overcomes the resistance and also reduce the duration of therapy [1].

The benzimidazole molecule has proved its importance in the drug discovery process. Several different drugs have been used therapeutically in medicinal field containing benzimidazole moiety. In the field of medicinal chemistry, benzimidazole has been an important pharmacophore. The well-known drug likes proton pump inhibitors (omeprazole, lansoprazole), antihypertensives (candesartan, telmisartan), anthelmintics (flubendazole, albendazole, mebendazole), antihistamines (astemizole), contains benzimidazole ring [2-4]. Due to medicinal values benzimidazole, its derivatives have received much consideration of research community.

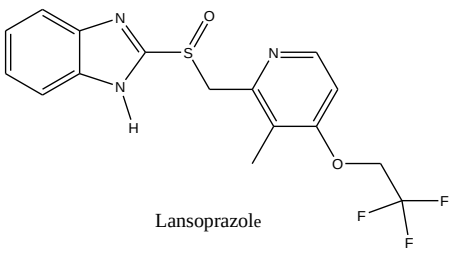
During literature survey, we found that benzimidazole derivatives containing two benzimidazole rings shows good biological activities. The well-known drugs Telmisartan (Antihypertensive) and many other benzimidazole derivative containing two benzimidazole nucleus has been shown good biological activities. It is also found that, in many natural products pyridine nucleus is present and is highly significant in chemistry of biological systems. Pyridine is found in several enzymes of living organisms; it involved in different oxidation–reduction processes in the form of NADP. Pyridine shows potent activity in biological systems as it presents in important vitamins such as pyridoxine and niacin. The pyridine derivatives are used in manufacture of pharmaceuticals (particularly anti-histamines and piroxicam) as an intermediate. Also, drugs like Esomeprazole and lansoprazole contains substituted heterocyclic rings of benzimidazole and pyridine **(Figure-1)**. Esomeprazole and Lansoprazole are widely used in the treatment of acid related gastric diseases as they act as gastric parietal cell proton inhibitors (PPIs) and shows ability to inhibit acid secretion. Pyridine containing some derivatives reported as anticancer drugs (streptonigrin, streptonigrone, and lavendamycin) and as HMG-CoA enzyme inhibitor (cerivastatin) [5-7].



Telmisartan



Esomeprazole



Lansoprazole

Figure-1: Structure of Telmisartan, Esomeprazole and Lansoprazole

In the synthetic chemistry field, consideration of Green chemistry principles becomes very important to minimise pollution. In the synthesis of any molecule consideration of green chemistry starts with design, use of reagent, the type of product and method of its manufacturing and uses. In Silico study, predicted bioactivity is also very important from green chemistry point of view. By using computer aided drug design

and by knowing predicted bioactivity of molecule before its synthesis, own can decide about synthesis of new molecule. It help to save time, energy, chemicals and help in minimising pollution. [8-10]

By considering the above facts, we focused toward the design and prediction of bioactivity of new bis-benzimidazole derivatives which contains two benzimidazole rings and pyridine nucleus . In order to increase the bioactivity of benzimidazole derivatives, in designed compound we substitute the hydrogen atoms of position 2 and 5 by different groups. Thus, we designed derivatives of benzimidazole in which the pyridine group on the benzimidazole ring at 2-position is maintained while 5-position is substituted by substituted benzimidazole ring **(Table-1).** Further we studied the predicted bioactivity of designed compounds using Molinspiration, admetSAR, and Osiris property explorer. The general structure of the series designed compound is showed in **Figure-2.** The chemical structure and IUPAC name of designed compound are shown in **Table-2.**

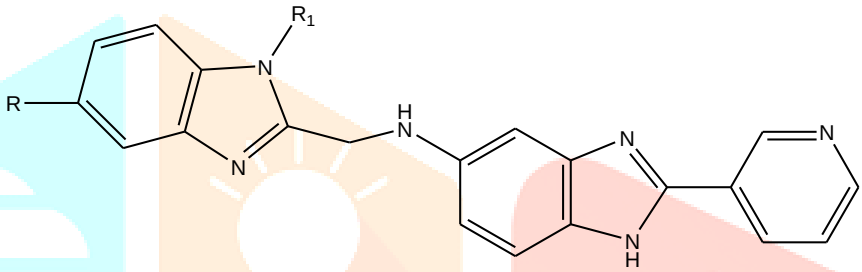
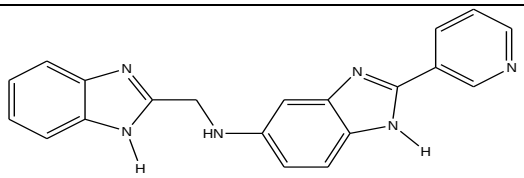
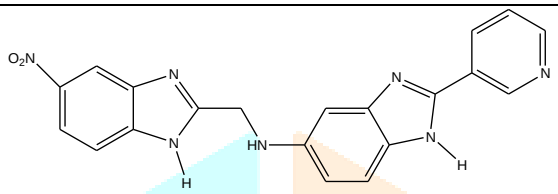
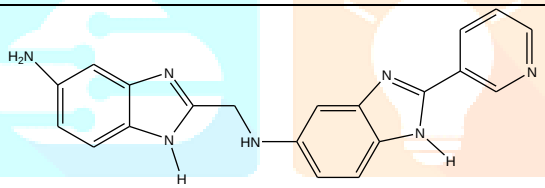
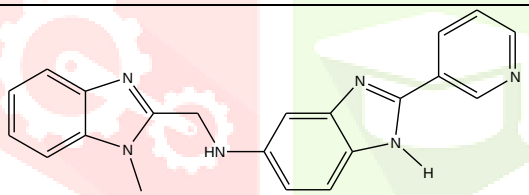
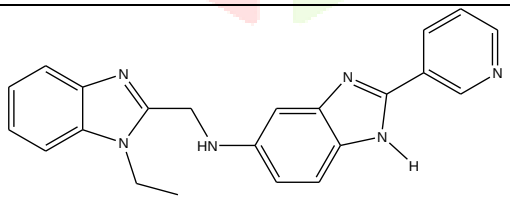
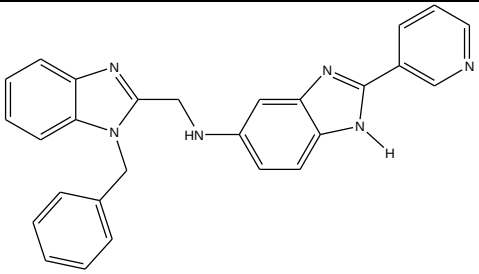


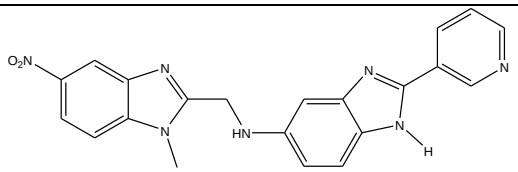
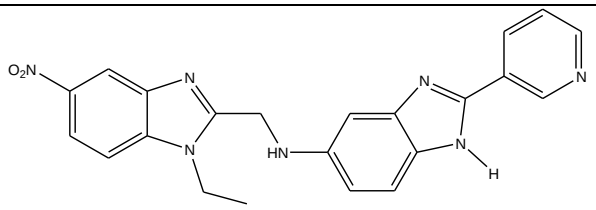
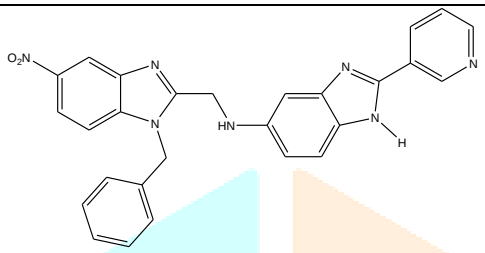
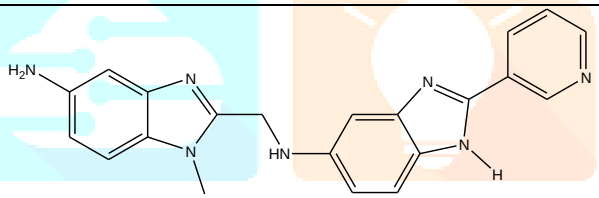
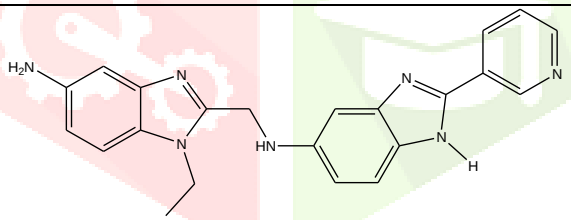
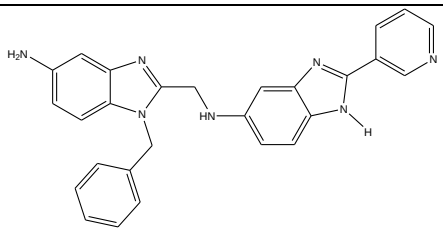
Figure-2: General structure of designed molecule

Table-1: Substituents attached to general molecule

Compound code	R	R_1	Compound code	R	R_1
1	-H	-H	**7**	$-NO_2$	$-CH_3$
2	$-NO_2$	-H	**8**	$-NO_2$	$-C_2H_5$
3	$-NH_2$	-H	**9**	$-NO_2$	$-CH_2$-Ph
4	-H	$-CH_3$	**10**	$-NH_2$	$-CH_3$
5	-H	$-C_2H_5$	**11**	$-NH_2$	$-C_2H_5$
6	-H	$-CH_2$-Ph	**12**	$-NH_2$	$-CH_2$-Ph

Table- 2: Chemical Structure and IUPAC name of designed benzimidazole derivatives (1-12)

Com-pound Code	Structure	IUPAC Name and Smiles
1		N-((1H-benzimidazol-2-yl)methyl)-2-(pyridin-3-yl)-1H-benzimidazol-5-amine Smiles:c5ccc4[nH]c(CNc3ccc2nc(c1cccnc1)[nH]c2c3)nc4c5
2		N-((5-nitro-1H-benzimidazol-2-yl)methyl)-2-(pyridin-3-yl)-1H-benzimidazol-5-amine Smiles:O=N(=O)c5ccc4nc(CNc3ccc2nc(c1cccnc1)[nH]c2c3)[nH]c4c5
3		2-((2-(pyridin-3-yl)-1H-benzimidazol-5-ylamino)methyl)-1H-benzimidazol-5-amine Smiles:Nc5ccc4nc(CNc3ccc2nc(c1cccnc1)[nH]c2c3)[nH]c4c5
4		N-((1-methyl-1H-benzimidazol-2-yl)methyl)-2-(pyridin-3-yl)-1H-benzimidazol-5-amine Smiles:Cn5c(CNc3ccc2nc(c1cccnc1)[nH]c2c3)nc4ccccc45
5		N-((1-ethyl-1H-benzimidazol-2-yl)methyl)-2-(pyridin-3-yl)-1H-benzimidazol-5-amine Smiles:CCn5c(CNc3ccc2nc(c1cccnc1)[nH]c2c3)nc4ccccc45
6		N-((1-benzyl-1H-benzo[d]imidazol-2-yl)methyl)-2-(pyridin-3-yl)-1H-benzo[d]imidazol-5-amine Smiles:c6ccc(Cn5c(CNc3ccc2nc(c1cccnc1)[nH]c2c3)nc4ccccc45)cc6

7		N-((1-methyl-5-nitro-1H-benzimidazol-2-yl)methyl)-2-(pyridin-3-yl)-1H-benzoimidazol-5-amine Smile:Cn5c(CNc3ccc2nc(c1cccnc1)[nH]c2c3)nc4ccc(N(=O)=O)cc45
8		N-((1-ethyl-5-nitro-1H-benzimidazol-2-yl)methyl)-2-(pyridin-3-yl)-1H-benzimidazol-5-amine Smiles: CCn5c(CNc3ccc2nc(c1cccnc1)[nH]c2c3)nc4ccc(N(=O)=O)cc45
9		N-((1-benzyl-5-nitro-1H-benzimidazol-2-yl)methyl)-2-(pyridin-3-yl)-1H-benzimidazol-5-amine Smiles:O=N(=O)c6ccc5nc(CNc3ccc2nc(c1cccnc1)[nH]c2c3)n(Cc4ccccc4)c5c6
10		2-((2-(pyridin-3-yl)-1H-benzimidazol-5-ylamino)methyl)-1-methyl-1H-benzimidazol-5-amine Smiles:Cn5c(CNc3ccc2nc(c1cccnc1)[nH]c2c3)nc4ccc(N)cc45
11		2-((2-(pyridin-3-yl)-1H-benzimidazol-5-ylamino)methyl)-1-ethyl-1H-benzimidazol-5-amine Smiles:CCn5c(CNc3ccc2nc(c1cccnc1)[nH]c2c3)nc4ccc(N)cc45
12		2-((2-(pyridin-3-yl)-1H-benzimidazol-5-ylamino)methyl)-1-benzyl-1H-benzimidazol-5-amine Smiles:Nc6ccc5nc(CNc3ccc2nc(c1cccnc1)[nH]c2c3)n(Cc4ccccc4)c5c6

Druglikeness, bioactivity prediction and ADMET Studies

Once drug entered in body, initially it gets absorb by cells, then it distributes in various parts of body, it metabolises and finally eliminated from the body. Hence, absorption, distribution, metabolism and excretion (ADME) properties play a significant role to determine bioactivity of molecules in drug development. During study of ADME properties, consideration of toxicity is also important.

The molecular properties of designed molecules were calculated on the basis 'Lipinski's rule of 5' as a molecular descriptor. Lipinski's rule of 5 is useful to determine predicted bioavailability of the orally administered compound. The five properties considered in Lipinski's rule of 5 are of log P, hydrogen bond acceptors molecular weight, hydrogen bond donor and Total polar surface area. According to the rule, calculated logP ≤5, hydrogen bond acceptors ≤10, molecular weight ≤500, a molecule bearing hydrogen bond donors ≤5 and molecule should have a great potential for oral bioavailability [11]. If molecules cross more than one value of above rules have difficulties with bioavailability. The druglikeness score was calculated by using Molsoft web serve. Also, all the designed molecules followed Veber's rule as they have TPSA less than 140^{o} and rotatable bonds less than10. It indicates designed compounds may show good oral absorption. Online software admetSAR gives predicted values of Human intestinal absorption (HIB), Caco-2 permeability, Blood Brain Barrier permeability (BBB), and Human Oral Bioavailability. Water solubility of compounds indicated by Log S values. Lesser value of the log S indicates the greater water solubility [12]. The parameters such as water solubility (Log S), topographical polar surface areas (TPSA), Caco-2 permeability, human intestinal absorption (HIA), and blood–brain barrier (BBB) penetration gives the measure of absorption [13]. The results were shown in **Table- 2** and **Table-3.**

Percentage absorption is indicated by %ABS. The values of %ABS ranges in between 64.80–84.35% indicates good absorption in the intestine.

Formula to calculate of percentage absorption is shown as below-

$$\%ABS=109 - 0.345 \times TPSA$$

We used methotrexate (MTX) as standard reference which showed violation from Lipinski's rule of 5, it showed negative logP values. Methotrexate, also known as amethopterin, is an anticancer agent and also act as immune-system suppressant. It is used to treat cancer, ectopic pregnancies and autoimmune diseases. The bioactivity scores of the designed compounds as GPCR ligand, kinase inhibitor, protease inhibitor, ion channel modulator, nuclear receptor ligand and enzyme inhibitor were studied and reported in **Table-3.** If a molecule having a bioactivity score for enzyme inhibition less than −0.50, it is presumed to be inactive, values between −0.50 to 0.00 are expected to be moderately active and more than 0.00 is most likely expected considerable biological activity [14].

Pharmacokinetic parameters like toxicity potential, solubility and drug-likeness of designed benzimidazole derivatives were determined using cheminformatics tool Osiris property explorer. The results of solubility, drug-likeness and drug score screening is given by values and toxicity potential (mutagenicity, irritant effect, tumorigenicity and reproductive system) were represented by colour codes either green or red. Properties shown in red colour indicates high risks of undesired effects and green colour indicates drug like behaviour, compatibility and safety in-vivo.

Table-2: Drug-likeness properties of the designed compounds using the Molinspiration

Compound Code	MW	Log P	TPSA	N ON	N OHNH	N Rotb	N Violation	%ABS
1	340.39	3.30	82.28	6	3	4	0	80.61
2	385.39	3.24	128.11	9	3	5	0	64.80
3	355.40	2.35	108.31	7	5	4	0	71.74
4	354.42	3.37	71.43	6	2	4	0	84.35
5	368.44	3.75	71.43	6	2	5	0	84.35
6	430.51	4.97	71.43	6	2	6	0	84.35
7	399.41	3.31	117.25	9	2	5	0	68.51
8	413.44	3.68	117.25	9	2	6	0	68.51
9	475.51	4.90	117.25	9	2	7	0	68.51
10	369.43	2.42	97.45	7	4	4	0	75.37
11	383.46	2.80	97.45	7	4	5	0	75.37
12	445.53	4.02	97.45	7	4	6	0	75.37
MTX	454.45	-1.97	210.55	13	7	9	2	36.36

Table-3: Bioactivity scores of the series by using the Molinspiration software

Compound code-	1	2	3	4	5	6	7	8	9	10	11	12	MTX
GPCR ligand	0.21	0.06	0.25	0.14	0.1	0.18	-0.00	-0.03	0.06	0.18	0.14	0.21	0.51
Ion channel modulator	0.23	0.16	0.28	0.13	0.09	0.04	0.08	0.04	-0.03	0.18	0.14	0.08	0.23
Kinase inhibitor	0.55	0.36	0.62	0.44	0.37	0.28	0.26	0.20	0.14	0.51	0.43	0.34	0.38
Nuclear receptor ligand	-0.24	-0.36	-0.28	-0.34	-0.33	-0.18	-0.38	-0.38	-0.24	-0.37	-0.36	-0.22	-0.38
Protease inhibitor	0.02	-0.1	0.1	-0.05	-0.12	-0.02	-0.16	-0.22	-0.12	0.03	-0.04	0.04	0.27
Enzyme inhibitor	0.22	0.11	0.30	0.14	-0.02	0.14	0.04	0.01	0.06	0.22	0.18	0.21	0.72

Table- 4: Toxicity and drug-relevant properties of designed compounds using Osiris property explorer

Compound Code-		1	2	3	4	5	6	7	8	9	10	11	12	MTX
Toxicity	Mutagenicity	G	G	R	G	G	G	G	G	G	R	R	R	G
	Tumorigenic	G	G	R	G	G	G	G	G	G	R	R	R	R
	Irritant effect	G	G	R	G	G	G	G	G	G	R	R	R	G
Drug-relevant properties	Solubility	-4.05	-4.51	-4.13	-3.72	-3.72	-4.51	-4.18	-4.18	-4.97	-3.79	-3.8	-4.59	-3.77
	Drug-likeness	1.01	-6.15	-0.71	2.51	2.35	2.68	-4.58	-4.71	-4.33	0.84	0.69	1.03	-7.09
	Drug Score	0.67	0.36	0.11	0.76	0.74	0.58	0.37	0.37	0.29	0.15	0.14	0.12	0.22

G=Green R=Red (Green colour means no risk or low risk, yellow colour means medium risk and red colour means more toxicity risk.)

Table-5: Absorption and distribution profile of designed compound by using admetSAR tool.

Compound Code	LogS	HIA	Caco-2 permeability	BBB	Human oral bioavailability
1	-2.502	0.9923	-0.7797	0.9765	0.5571
2	-2.945	0.9787	-0.8629	0.9786	0.6857
3	-2.405	0.9897	-0.8587	0.9672	0.5714
4	-2.971	0.9908	-0.5885	0.9907	0.5429
5	-3.121	0.9948	-0.6244	0.9828	-0.5143
6	-2.915	0.9908	-0.7786	0.9864	-0.5286
7	-3.135	0.9759	-0.7884	0.9829	0.6571
8	-3.322	0.9842	-0.8171	0.9806	0.6714
9	-3.119	0.9759	-0.8725	0.9829	0.6714
10	-2.85	0.9870	-0.7450	0.9907	0.5571
11	-3.00	0.9921	-0.7369	0.9828	0.5429
12	-2.788	0.9870	-0.8353	0.9864	0.5571
MTX	-3.065	0.9088	-0.8662	-0.9930	-0.08682

Result and discussion

All the designed compounds were subjected for the predicted bioactivity. The values of five properties considered in 'Lipinski's rule of 5' were calculated using online cheminformatics tool Molinspiration. All the designed molecules (**1–12**) showed no violation from Lipinski's rule of 5 **(Table-2).** Molinspiration web server is used to calculate the activity score for different target like GPCR (G-protein coupled receptor) ligand, ion channel modulator, kinase inhibitor, nuclear receptor ligand. Among the designed molecules, molecule 1, 3 and 12 showed good GPCR ligand affinity and molecule 1, 3, 10 and 12 showed better enzyme inhibition. Result indicates molecule 1, 3 and 10 has better kinase inhibitor activity **(Table-3**). Result obtained clearly shows change in kinase inhibiter activity as change in the substituent at position 5 and 3 of one of the benzimidazole ring. The molecules which having -NH_2 group as substituent at 5 position showed good kinase and also enzyme inhibition activity.

The results of drug score assessment and toxicity risks of designed benzimidazole derivatives were predicted by Osiris property explorer and result obtained are listed in **Table-4.** The results of toxicity showed that all compounds except 3, 10, 11 and 12 (which shows red colour for Mutagenicity, tumorigenicity and irritant effect) expected to show no toxicity regarding tumorigenicity, effect on reproductive system Mutagenicity and irritant effect and would be safe. From the above observations, it is found that the substituent present on the benzimidazole ring plays important role because each substituent shows different affinity towards receptor and also responsible to change ADMET properties. The molecule 4 and 5 in which nitrogen of benzimidazole ring having methyl and ethyl group as substituents showed higher drug score.

All the designed compounds were showed Human Intestinal Absorption (HIA) values more than 0.9, indicating good intestinal absorption. The designed molecules also showed excellent predicted BBB permeability. Except molecule 5 and 6, remaining molecule showed good Human Oral Bioavailability. All compounds expected to show good water solubility as their log S values are between −4.59 to −3.79. From the above observations, it is considered that, all the designed molecule would show good absorption, distribution and permeability through biological membranes **(Table-5).**

CONCLUSION

Synthesis of 5- substituted benzimidazole derivative is a part of our research. In present study new bis-benzimidazole derivatives were designed N-(substituted-1H-benzoimidazol-2-yl)methyl)-2-(pyridin-3-yl)-3H-benzimidazol-5-amine derivatives (1–12) by coupling benzimidazole and pyridine heterocycles and predicted there bioactivity. Among the designed compounds **1, 2**, **4, 7, 8,** and **9** were found to possess moderate bioactivity scores, ADMET properties, druglikeness, non-toxicity and can be act as good oral drug. It is also found that the designed molecules having amino, methyl and ethyl group as substituent showed good predicted bioactivities. Based on, *in-silico* studies and some structural modifications, design of new benzimidazole derivatives is possible, which will help to modify receptor binding and toxicity profiles. In future, synthesis and antimicrobial activity screening of the molecules which showed good predicted bioactivity is possible and it is a green chemistry approach.

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