



Biodegradability Nature of Polybenzimidazole Analogs by Modulating Two Histidine Degradation Enzymes (Urocanase and Formiminoglutamase): *in silico* Approach

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Biodegradation pathway of substituted imidazole compounds has been reported to have close analogue to histidine degradation pathway. The present study carried out on four different types of polybenzimidazole (PBI) analogs such as *m*-PBI (where $n = 1, 2$ and 3), *p*-PBI (where $n = 1, 2$ and 3), pyridine-*m*-PBI (where $n = 1, 2$ and 3) and alkylated-*m*-PBI (where $n = 1, 2$ and 3). These polybenzimidazole analogs were evaluated on the docking behaviour of urocanase and formiminoglutamase (FIGase) using PatchDock. Besides, molecular physico-chemical, drug-likeness, ADME (absorption, distribution, metabolism and excretion analyses) were studied. ADME analysis showed that *m*-PBI (where $n = 1$) and pyridine-*m*-PBI (where $n = 1$) predicated to have cytochrome P450 (CYP1A2, CYP2C19, CYP2D6 and CYP3A4) inhibition effect. Docking studies revealed that alkylated-*m*-PBI (where $n = 2$) showed the least atomic contact energy (-123.83 kcal/mol) with that of urocanase. Similarly, *m*-PBI (where $n = 1$) showed the least ACE (-123.83 kcal/mol) with that of formiminoglutamase.

Keywords: Polybenzimidazole polymer, Molecular docking, Urocanase, Formiminoglutamase.

INTRODUCTION

Growths in science and technology, exclusively past 10 years, have augmented the quantity of artificial polymers fashioned universal a piece year. Around 140 million tons of artificial polymers are generated. The presence of materials in the atmosphere brings about significant difficulties, in addition to a test for wastewater management plants and contamination of groundwater and surface water. Artificial polymers are documented as main solid waste ecological contaminants [1].

Polybenzimidazoles (PBI) are linear aromatic heterocyclic polymers with benzimidazole repeating units, which exhibits excellent thermal stability, resistance to chemicals. Polybenzimidazoles have synthesized by condensation polymerization of 3,3',4,4'-tetraaminobiphenyl and aliphatic diacids or derivatives in the presence of polyphosphoric acid at higher temperature. The fundamental research work on these polymers

in the early stage development was carried out in Dupont and Hoechst Celanese Research Co by NASA and U.S. Air force Materials Laboratory [2-4]. Before the 1980s the majority of polybenzimidazole applications were restricted on fire blocking applications, thermal protective clothing, high temperature matrix resins and reverse osmosis membranes. Polybenzimidazole has been lengthily discovered in the area of membrane partitioning methodologies for fuel cells [5-7], nanofiltration [8], reverse osmosis [9], forward osmosis [10], metal extraction [11-13], protein extraction [14], nevertheless one major disadvantage of polybenzimidazole based polymer is difficult of liquefying it in mutual organic diluents. Polybenzimidazole has only limited solubility in a few highly polar and aprotic organic solvents such as dimethyl sulfoxide, *N,N*-dimethylacetamide, *N,N*-dimethylformamide and concentrated acids. These diluents are comparatively poisonous and explosive, which are dangerous to both operators and atmosphere. Furthermore, PBI has dissolving some superior circumstances, *i.e.*,

high pressure as well as high temperature, which is above the boiling point, these organic solvents also toxic in nature that causes environmental pollutions [15]. These limit the growth potential of polybenzimidazole based polymers but also non-degradable nature of these polymeric resins. Growing quantities of artificial polymers generated results in growing interest in polymer biodegradation.

In earlier studies, four types of polybenzimidazole based polymeric resins were investigated for the extraction of metal ions such as uranium, thorium, palladium and radioactive metals such as Am(III), Pu(IV), Eu(III) as a role of HNO₃ concentration and also investigated column chromatography separation of these metal ions from simulated waste solution. These results revealed that polybenzimidazole based polymer resins are suitable candidate for recovery of metal ions from actual nuclear waste materials [16]. But these polybenzimidazole polymeric resins were insoluble in organic solvents. Hence, there is a need for the alternative solvents or degradation pathways. The biodegradation pathway of imidazole ring compounds has been reported to have close analogues to the histidine degradation pathway. MetaCyc database (<http://metacyc.org>) has highlighted three important histidine catabolism/degradation pathways. Urocanase and formiminoglutamase (FIGase) are two key enzymes plays important role in histidine degradation pathway [17].

To our best of knowledge, there is no literature for predicting the degradability nature of polybenzimidazole based polymers. In present study, we have selected four PBIs with different units and evaluated on the docking behaviour of urocanase and formiminoglutamase (FIGase) biodegradation enzyme. The results analyzed using PyMOL software shown that the useful information to predict the biodegradable potential of polybenzimidazole based polymers. Furthermore, molecular physico-chemical, drug-likeness, absorption, distribution, metabolism and excretion analysis (ADME) were done.

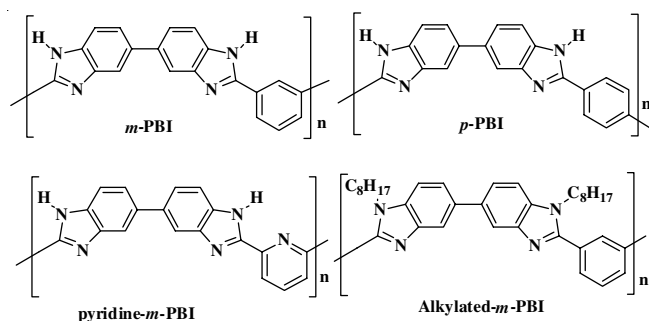


Fig. 1. Structure of synthesized polybenzimidazole polymeric resins

EXPERIMENTAL

Ligand preparation: Polybenzimidazole structures were drawn in ChemBioDraw Ultra 12.0 while molecular mechanic minimization of ligands carried out by ChemBio 3D Ultra 12.0, according to the reported procedure [18]. These structures were employed for further Patch Dock.

Target protein identification and preparation: The three dimensional (3D) structures of the Urocanase (PDB ID: 1UWL with resolution of 1.76 Å) and formiminoglutamase (FIGase) (PDB ID: 1XFK with resolution of 1.8 Å) were retrieved from

the Research Collaborator for Structural Bioinformatics (RCSB) Protein Data Bank (www.rcsb.org) [19]. A chain of these proteins was processed individually by removing another chain (B, C and D), ligands in addition to the crystallographically experimental water particles (water without hydrogen bonds). The protein mentioned above was prepared using UCSF Chimera software (www.cgi.ucsf.edu/chimera).

ADME and toxicity prediction by Komputer-Assisted technology analysis: ADME (absorption, distribution, metabolism and excretion) analysis was performed by Swiss ADME & TOPKAT analysis were done using Discovery Studio (Pondicherry University) ADME analysis was performed using six descriptors such as human intestinal absorption, aqueous solubility, blood-brain barrier, cytochrome P450 2D6, Plasma protein binding and hepatotoxicity. As for the TOPKAT analysis, five descriptors were used which includes aerobic biodegradability (AB), Ames mutagenicity, ocular irritancy, skin irritancy and skin sensitization.

Docking studies: Docking studies were carried out by the PatchDock online server (<http://bioinfo3d.cs.tau.ac.il/PatchDock>). PatchDock adopts geometry-based molecular docking algorithm method was used to recognize the binding scores, by binding residues atomic contact energy of the given ligands. The docking results were obtained through the email address. We also use to get uniform resource locator (URL), which provides the top 20 solutions in a table form *via* email. From these, the top one solution (the docked protein-ligand complex) was selected and downloaded in a database (pdb) file format. Further, the binding site analysis was carried out by PyMOL software (www.pymol.org).

RESULTS AND DISCUSSION

In general, biodegradation is a process in which environmental fate of a chemical can be assessed. In other words, it is the ability of any potent microorganisms to transform/use the harmful/hazards chemicals that enters the environment into non-hazardous/less hazards one. However, determining the biodegradation nature of compounds under *in vitro* condition is tedious and time consuming one [20]. To overcome these problem, molecular docking approaches has been explored in past years.

In earlier studies, we have prepared four different polybenzimidazole based polymers for metal extraction purpose, that resins are insoluble in organic solvents and non-degradable in nature, therefore need for the degradation pathways. In present study, four polybenzimidazole polymers with different units has selected, it could be beneficial to know the physico-chemical and drug-likeness properties of these polybenzimidazole polymers before carry out docking studies. Lipinski's rule of five was applied and additional helps to determine whether a principal composite having a certain pharmacological and biological actions might be done into an orally lively drug for human [21]. Violation of the Lipinski's rule of five is when logA > 5, MW > 500, number of N, O (hydrogen bond receptor) > 10, number of OH and NH (hydrogen bond donor) > 5 and number of the rotatable bond (rotb) > 15. *m*-PBI, *p*-PBI single unit has shown 1 violations, *m*-PBI, *p*-PBI, *py-m*-PBI double unit and alkylated-*m*-PBI

single and second unit has shown 2 violation. In addition, alkylated-*m*-PBI third unit showed 3 violation and rest of other PBIs third unit showed 4 violations and py-*m*-PBI single unit exhibited there is no violation. All the PBIs have above 500 MW except *m*-PBI, *p*-PBI and py-*m*-PBI single unit, in addition, all the PBIs showed above 5 log A value (Table-1). These results shows that all PBIs does not obey the Lipinski's rule.

The drug-likeness score, if the score is > 0 is active, -5.0 to -0.0 is moderate active and < -5.0 is inactive [22]. *m*-PBI,

p-PBI, py-*m*-PBI and alkylated-*m*-PBI single unit showed bioactive score in five descriptions. *m*-PBI, *p*-PBI, py-*m*-PBI and alkylated-*m*-PBI second and third units showed moderate bioactive score in all descriptions (Table-2). ADME prediction is also required before carrying out docking studies and which is commonly accepted in the primary step of medicine finding, drug screening, drug design, owing to its unique characteristic nature [23]. Table-3 showed the ADME profile of the PBI with different units. *m*-PBI, *p*-PBI, Py-*m*-PBI single unit have shown

TABLE-1
MOLECULAR PHYSICO-CHEMICAL DESCRIPTORS ANALYSIS OF FOUR PBIs WITH DIFFERENT UNITS USING MOLINSPIRATION ONLINE SOFTWARE TOOL

Polymer resins*	log A ^a	TPSA ^b	Natoms ^c	MW ^d	noN ^e	nOH NH ^f	Nviolations ^g	Nroth ^h	Volume ⁱ
<i>m</i> -PBI, 1Unit	5.87	57.37	27	352.44	4	2	1	3	326.43
<i>m</i> -PBI, 2 Unit	9.34	114.73	51	660.78	8	4	2	6	590.29
<i>m</i> -PBI, 3 Unit	10.17	172.10	75	969.13	12	6	4	9	854.16
<i>p</i> -PBI, 1 Unit	5.89	57.37	27	352.44	4	2	1	3	326.43
<i>p</i> -PBI, 2 Unit	9.19	114.73	50	646.76	8	4	2	5	573.49
<i>p</i> -PBI, 3 Unit	10.11	172.10	74	955.10	12	6	4	8	837.36
Py- <i>m</i> -PBI, 1 Unit	4.35	70.26	27	353.43	5	2	0	3	322.27
Py- <i>m</i> -PBI, 2 Unit	8.23	140.52	51	662.76	10	4	2	6	581.98
Py- <i>m</i> -PBI, 3 Unit	9.68	210.77	75	972.09	15	6	4	9	841.69
Alkyl- <i>m</i> -PBI, 1 Unit	9.78	35.65	43	576.87	4	0	2	17	595.54
Alkyl- <i>m</i> -PBI, 2 Unit	10.89	71.30	83	1109.65	8	0	2	34	1128.52
Alkyl- <i>m</i> -PBI, 3 Unit	11.40	106.96	123	1642.42	12	0	3	51	1661.49

^aOctanol-Water partition coefficient, ^bPolar surface area, ^cNumber of non-hydrogen atoms, ^dMolecular weight, ^eNumber of hydrogen bond acceptors [O and N atoms], ^fNumber of hydrogen bond donors [OH and NH groups], ^gNumber of Rule of 5 violations, ^hNumber of rotatable bonds, ⁱMolecular volume; *Unit 1, 2, 3 is n 1, 2 and 3.

TABLE-2
DRUG-LIKENESS PROPERTY ANALYSIS OF 4 PBIs WITH DIFFERENT UNITS USING MOLINSPIRATION ONLINE SOFTWARE TOOL

Polymer resins	GPCR* ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
<i>m</i> -PBI, 1Unit	0.31	0.17	0.34	-0.01	0.02	0.21
<i>m</i> -PBI, 2 Unit	-0.60	-1.50	-0.99	-1.24	-0.45	-0.99
<i>m</i> -PBI, 3 Unit	-3.70	-3.79	-3.77	-3.81	-3.65	-3.74
<i>p</i> -PBI, 1 Unit	0.29	0.16	0.31	-0.04	-0.00	0.19
<i>p</i> -PBI, 2 Unit	-0.52	-1.36	-0.83	-1.12	-0.38	-0.87
<i>p</i> -PBI, 3 Unit	-3.69	-3.78	-3.75	-3.80	-3.63	-3.73
Py- <i>m</i> -PBI, 1 Unit	0.48	0.34	0.54	-0.04	0.18	0.36
Py- <i>m</i> -PBI, 2 Unit	-0.52	-1.45	-0.92	-1.28	-0.37	-0.90
Py- <i>m</i> -PBI, 3 Unit	-3.68	-3.78	-3.75	-3.81	-3.64	-3.73
Alkyl- <i>m</i> -PBI, 1 Unit	0.10	-0.45	-0.15	-0.30	-0.05	-0.13
Alkyl- <i>m</i> -PBI, 2 Unit	-3.82	-3.88	-3.88	-3.90	-3.80	-3.85
Alkyl- <i>m</i> -PBI, 3 Unit	-4.05	-4.07	-4.07	-4.08	-4.04	-4.05

*GPCR- G Protein coupled receptors

TABLE-3
ADME ANALYSIS OF TRIAZOLE DERIVATIVES USING SWISS ADME ONLINE TOOL

Polymer resin	GI (%)	BBB#	**P-gp	*CYP1A2	*CYP2C19	*CYP2C9	*CYP2D6	*CYP3A4	@log Kp
<i>m</i> -PBI, 1Unit	High	No	Yes	Yes	Yes	No	Yes	Yes	-4.52
<i>m</i> -PBI, 2 Unit	Low	No	No	No	No	No	No	No	-3.50
<i>m</i> -PBI, 3 Unit	Low	No	Yes	No	No	No	No	No	-2.48
<i>p</i> -PBI, 1 Unit	High	No	Yes	Yes	Yes	No	Yes	Yes	-4.52
<i>p</i> -PBI, 2 Unit	Low	No	No	No	No	No	No	No	-3.72
<i>p</i> -PBI, 3 Unit	Low	No	Yes	No	No	No	No	No	-2.70
Py- <i>m</i> -PBI, 1 Unit	High	No	Yes	Yes	Yes	No	Yes	Yes	-5.23
Py- <i>m</i> -PBI, 2 Unit	Low	No	No	No	No	No	No	No	-4.93
Py- <i>m</i> -PBI, 3 Unit	Low	No	Yes	No	No	No	No	No	-4.63
Alkyl- <i>m</i> -PBI, 1 Unit	Low	No	Yes	Yes	No	No	No	Yes	-1.20
Alkyl- <i>m</i> -PBI, 2 Unit	Low	No	Yes	No	No	No	No	No	-3.14
Alkyl- <i>m</i> -PBI, 3 Unit	Low	No	Yes	No	No	No	No	No	-7.48

%-Gastrointestinal, #-Blood-brain barrier permeant, **-P-gp-P-glycoprotein substrate, CYP-Cytochrome P450, 8 Inhibitor, @-Skin Permeation (cm/s).

TABLE-4
 TOXICITY PREDICATION ANALYSIS OF PBI ANALOGUES USING DISCOVERY STUDIO SOFTWARE

S. No.	Polymer resin	AB ⁺	AM ⁺⁺	O [#]	SI ^{##}	SS ⁺	OT ⁺⁺
1	<i>m</i> -PBI, 1Unit	Non-degradable	Non-mutagen	Irritant	Irritant	Sensitizer	81.206
2	<i>m</i> -PBI, 2 Unit	Degradable	Non-mutagen	Irritant	Irritant	Sensitizer	16.792
3	<i>m</i> -PBI, 3 Unit	Degradable	Non-mutagen	Irritant	Irritant	Sensitizer	2.709
4	<i>p</i> -PBI, 1 Unit	Non-degradable	Non-mutagen	Irritant	Irritant	Non-Sensitizer	35.606
5	<i>p</i> -PBI, 2 Unit	Degradable	Non-mutagen	Irritant	Irritant	Non-Sensitizer	11.036
6	<i>p</i> -PBI, 3 Unit	Degradable	Non-mutagen	Irritant	Irritant	Sensitizer	2.479
7	Py- <i>m</i> -PBI, 1 Unit	Non-degradable	Non-mutagen	Irritant	Irritant	Sensitizer	30.815
8	Py- <i>m</i> -PBI, 2 Unit	Degradable	Non-mutagen	Irritant	Irritant	Sensitizer	9.612
9	Py- <i>m</i> -PBI, 3 Unit	Degradable	Non-mutagen	Irritant	Irritant	Sensitizer	24.589
10	Alkyl- <i>m</i> -PBI, 1 Unit	Degradable	Non-mutagen	Irritant	Irritant	Sensitizer	7.103
11	Alkyl- <i>m</i> -PBI, 2 Unit	Degradable	Non-mutagen	Irritant	Irritant	Sensitizer	1.578
12	Alkyl- <i>m</i> -PBI, 3 Unit	Degradable	Non-mutagen	Irritant	Irritant	Sensitizer	2.340

(AB⁺ - Aerobic biodegradability; AM⁺⁺ - Ames mutagenicity; OI[#] - Ocular irritancy; SI^{##} - Skin irritancy; SS⁺ - Skin sensitization; OT⁺⁺ - Oral toxicity, g/kg-body weight).

higher gastrointestinal (GI) absorption effect. On the other hand rest of the PBIs different unit has exhibited low gastrointestinal (GI) absorption effect. *m*-PBI, *p*-PBI, py-*m*-PBI single unit has predicted to CYP 1A2, CYP 2C19, CYP 2D6 and CYP 3A4 inhibition effect and *m*-PBI, *p*-PBI, py-*m*-PBI, alkylated-*m*-PBI third unit has predicted to have P-glycoprotein substrate inhibition effect.

The toxicity profile of polybenzimidazole analogous are listed in the Table-4, which shows *m*-PBI, *p*-PBI, py-*m*-PBI single unit non-degradable towards AB nature, on the other hand remaining PBIs units are degradable in nature. All the PBIs has shown ocular/eye irritancy and skin irritancy in humans.

Urocanate is first metabolic in the histidine degradation pathway, which is converted into 4-imidazolone-5-propionate by the enzymatic action of urocanase [24]. Urocanase has reported in bacteria, vegetables/mammals and plants. The pyridine based-*m*-PBI shown the highest atomic contact energy (-368.86 kcal/mol) and alkylated-*m*-PBI exhibited least ACE (-123.83 kcal/mol) with that of *P. putida* urocanase. The present finding is in good agreement with earlier report, where all PBIs single units are minimum degradable nature, but two or more units are degradable, while increasing the polymer chain length increasing the degradation ability. Alkylated-*m*-PBI third unit interacted with Asp 204 amino acid residue (Table-5) whereas Kessler *et al.* [24] reported that Asp 204 amino acid involves in acid-base catalytic reaction and Tyr 52 amino acid residue stabilize the positive charge of the substrate.

Similarly, the docking studies and binding site analysis in Table-6 shows that pyridine based-*m*-PBI third unit have highest ACE (-560.67 kcal/mol), while *m*-PBI single unit have least ACE (-120.86 kcal/mol) values with that of *V. cholera* FIGase. The present finding was in good agreement with earlier report, where *m*-PBI single unit exhibited minimum degradation and pyridine based-*m*-PBI shown maximum degradation. These results might suggest that *m*-PBI single unit strongly exhibit FIGase activity and thus leads to minimum degradation. These studies Asp 89 & 321 amino acid residue has been shown by three PBIs, namely, *m*-PBI single unit, *p*-PBI single unit and pyridine based-*m*-PBI.

 TABLE-5
 BINDING SITE ANALYSES OF POLYBENZIMIDAZOLE (PBI) ANALOGS WITH THAT OF UROCANASE USING PATCHDOCK

S. No.	Polymer resin	-ACE (-kcal/mol)	Interaction of amino acid residue	Bond distance (Å)
1	<i>m</i> -PBI, 1Unit	285.30	Ser266	2.15
2	<i>m</i> -PBI, 2 Unit	263.63	Tyr	2.10
			Gln199	3.09
3	<i>m</i> -PBI, 3 Unit	162.75	Gln41	2.69
			Ser402	2.96
			Ser402	2.77
4	<i>p</i> -PBI, 1 Unit	314.32	Gln264	3.23
			Ser266	3.04
5	<i>p</i> -PBI, 2 Unit	242.96	Gln199	1.84
6	<i>p</i> -PBI, 3 Unit	183.49	Gln399	2.13
			Arg13	3.26
7	Py- <i>m</i> -PBI, 1 Unit	334.40	Gln264	2.94
			Ser266	3.09
8	Py- <i>m</i> -PBI, 2 Unit	142.46	Gln208	3.36
9	Py- <i>m</i> -PBI, 3 Unit	368.86	Ser402	3.47
			Gln41	3.23
			Ala14	2.98
10	Alkylated- <i>m</i> -PBI, 1 Unit	358.86	Ser266	3.26
			Asn45	3.36
11	Alkylated- <i>m</i> -PBI, 2 Unit	123.83	No interaction	Nil
12	Alkylated- <i>m</i> -PBI, 3 Unit	194.52	Asp204	3.45
			Gln480	2.33

Conclusion

In the present study, all the tested PBI derivative different units have shown to dock with both targeted enzymes. However, *p*-PBI second unit and alkylated-*m*-PBI single unit does not interact with amino acid residues of FIGase also alkylated-*m*-PBI second unit does not interact with amino acid residues of Urocanase. The toxicity profile of PBI derivatives shows *m*-PBI, *p*-PBI and pyridine-*m*-PBI single unit non-degradable towards AB nature. But others are degradable in nature. These observation suggested that all the polybenzimidazole based polymer were degraded using these two degradation enzymes.

TABLE-6
BINDING SITE ANALYSES OF POLYBENZIMIDAZOLE (PBI)
ANALOGS WITH THAT OF FORMIMINOGLUTAMASE (FIGase)
USING PATCHDOCK

S. No.	Polymer resin	-ACE (-kcal/mol)	Interaction of amino acid residue	Bond distance (Å)
1	m-PBI, 1 Unit	120.86	Asp284	2.72
			Asp321	2.43
			Glu328	2.80
2	m-PBI, 2 Unit	305.73	Gly12	3.20
3	m-PBI, 3 Unit	276.71	Arg58	2.46
			Arg173	3.26
			Ser205	2.96
4	p-PBI, 1 Unit	179.20	Asp89	3.12
			Leu90	3.22
5	p-PBI, 2 Unit	520.11	No interaction	Nil
6	p-PBI, 3 Unit	416.73	Thr10	1.92
			Leu90	3.19
			Asn92	3.16
7	Py-m-PBI, 1 Unit	167.43	Asp89	3.27
8	Py-m-PBI, 2 Unit	560.67	Arg24	3.06
9	Py-m-PBI, 3 Unit	229.82	Glu57	2.57
			Arg58	2.11 & 3.31
			Thr164	2.31
10	Alkylated-m-PBI, 1 Unit	150.33	No interaction	Nil
11	Alkylated-m-PBI, 2 Unit	342.63	His159	2.91
			Ser205	3.26
12	Alkylated-m-PBI, 3 Unit	545.43	Arg317	2.36

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CONFLICT OF INTEREST

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

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