International Journal of Medical Science and Clinical Invention 9(4): 6067-6072, 2022
DOI:10.18535/ijmsci/v9i04.05
https://valleyinternational.net/index.php/ijmsci

Research Article,

Design and Qsar Studies of Benzimidazole Nucleus As Anti-Infective Agents

Sakharam Sirvi*[1], Deshbandhu joshi[2], Raghvendra Singh Bhadauria[3]

[1]Research Scholar, Department of Pharmaceutical chemistry, Shrinathji Institute of pharmacy, upali oden, Nathdwara, dist-Rajsamand (Raj.)-313301 INDIA
[2]Professor, Department of Pharmaceutical chemistry, Shrinathji Institute of pharmacy, upali oden, Nathdwara, dist-Rajsamand (Raj.)-313301 INDIA
[3]Principal, Department of Pharmaceutical chemistry, Shrinathji Institute of pharmacy, upali oden, Nathdwara, dist-Rajsamand (Raj.)-313301 INDIA
E-mail Address: choudharysakharam721@gmail.com

Abstract:

The objective of current study is to design, synthesize the benzimidazoles derivative and evaluate it for anti-malarialactivity by the recently developed Computer Aided Drug Designing techniques with development of new pharmacological active compounds However, a promising approach is needed to use these agents as templates for designing new derivatives with improved properties. The Aim of this project was thus to investigate the potential of the lead compound for future antimalrial drugs. . In order to accomplish this aim a range of synthetic derivatives of Benzimidazoles were prepared and biologically evaluated for Antimalarial activity. 2D Structure of all the designed compounds were draw with the help of chem Draw ultra-version 8.0.3 and exported to window of Chem 3D ultra version 8.0.3 Energy of all the 3D structures were minimized through MOPAC up to RMS gradient 0.001 and saved in MDL Mol file (.Mol) format.)]. In order to examine the predictive power of the QSAR models, the dataset was divided into training set consisting of 32 molecules and test set consisting of 8 compounds in such a way that the utilizing the diversity method in such a way that the structural diversity and a wide range of biological activity in the data set were added. The IC_{50} values were transformed to pIC_{50} in order to give numerically larger data values.

Keywords: Benzimidazole, CoMFA, CoMSIA, HQSAR and Docking

Introduction:

Benzimidazole and its derivatives are used in organic synthesis and vermicides or fungicides as they inhibit the action of certain microorganisms. Examples of benzimidazole [1] class fungicides include benomyl [1,2], carbendazim, chlorfenazole, cypendazole, debacarb, fuberidazole, furophanate, mecarbinzid, rabenzazole, thiabendazole, thiophanate [3].

Comparative Molecular Field Analysis is a 3D QSAR technique [4] based on data from known active molecules. CoMFA [4,5]can be applied, as it often is, when the 3D structure of the receptor is unknown. To apply CoMFA [4,5], all that is needed are the activities and the 3D structures of the molecules. Of course, activities have to be measured, but 3D structures can be determined either by measurement (crystal X-ray analysis) or by calculation from the 2D diagram [6] and (optionally) subsequent optimization.

Comparative Molecular Similarity Indices Analysis (CoMSIA) is known as one of the newer 3D QSAR methodology. This technique is most commonly used in drug discovery to find the common features that are important in binding to the relevant biological receptor. In this technique, both steric and electrostatic features, hydrogen bond donor, hydrogen bond acceptor and hydrophobic fields are considered. The fields

are evaluated by a PLS analysis [7] similar to the CoMFA formalism.

Material and Methods:

Designing of Compounds

On the basis of reported structure activity relationship of aminopyrido[1,2-a] benzimidazole analogues as an antifungal, QSAR studies using CoMFA, CoMSIA, HQSAR, and Molecular modeling [8, 9, 10] (Docking) studies twenty compounds were designed.

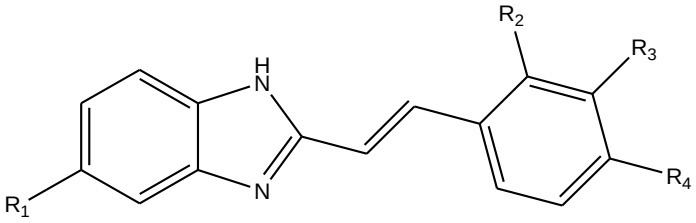

Table.1. Designed benzimidazole analogues on the basis of computational studies with their predicted

Compounds	CoMFA	CoMSIA	HQSAR
SRS- 01	4.5845	4.5796	4.85798
SRS - 02	4.6871	4.5871	4.5799
SRS - 03	5.2147	5.3214	5.6987
SRS - 04	5.3489	5.3217	5.2147
SRS - 05	5.3698	5.6874	5.3214
SRS - 06	5.8741	5.2879	6.2469
SRS - 07	5.6987	5.3297	5.2879
SRS - 08	5.2497	5.1264	5.3298
SRS - 09	6.2587	4.5478	6.2547
SRS - 10	5.2587	5.2558	5.5587
SRS - 11	5.2469	5.2167	5.2689
SRS - 12	5.2149	5.0240	5.0001
SRS - 13	5.3250	5.0219	5.0349
SRS - 14	5.6934	5.2149	5.1527
SRS - 15	5.2413	5.3241	5.2143
SRS - 16	5.2164	5.2143	5.2149
SRS - 17	5.0120	5.2010	5.0240
SRS - 18	5.2401	5.2497	5.2149
SRS - 19	5.2469	5.23	5.3497
SRS - 20	5.3697	5.2147	5.8797

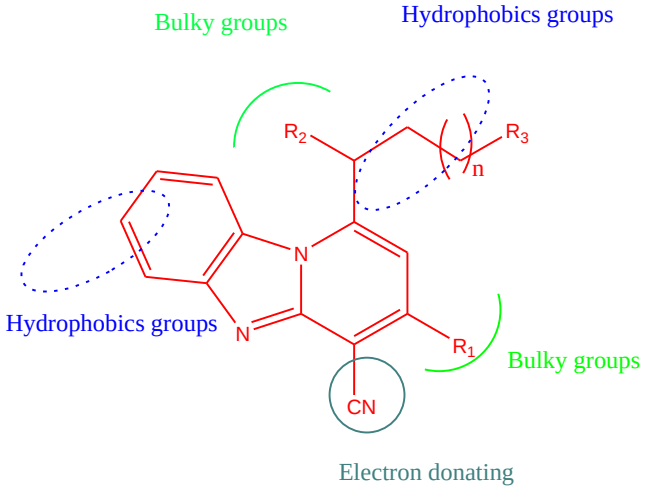

Fig. 1: Designing of Compound

Building of molecules using Chem Draw ultra and Chem 3D ultra:

2D Structure of all the designed compounds were draw with the help of chem Draw ultra-version 8.0.3 and exported to window of Chem 3D [11-14] ultra-version 8.0.3 Energy of all the 3D structures were minimized through MOPAC up to RMS gradient [11, 15] 0.001 and saved in MDL Mol file (.Mol) format.

Docking with Molegro Virtual Docker (MVD) version 5.0:

For the docking purpose protein model of *P. Falciferum* [16] was downloaded from protein data bank (PDB) Protein model of *P. Falciferum* (PDB code; 2ANL) were imported in the work space area. After this protein was prepared for the optimal docking, through an automatic procedure possible binding cavities were detected. From the docking wizard ligands were selected and the scoring function used is Moldock score [17-19] and rerank score. The search algorithm is taken as Moldock SE and number of run are taken 10 and max iterations were 1500 with population size 50 and with an energy threshold of 100. After the docking simulation is over the poses which were generated sorted by moldock score and rerank score. The rerank score function is computationally more expensive than the scoring function used during the docking simulation but it is generally better than the docking score [20] function at determing the best pose.

Table.2. Docking studies output MVD of the synthesized compounds.

Compounds	Mol Dock Score	Rerank Score	H-Bond interaction Energy [21] (Kcal/mol)
SRS- 01	-100.116	-82.8816	-3.3307
SRS - 02	-107.516	-88.0428	-1.09749
SRS - 03	-100.176	-83.1174	-3.17667
SRS - 04	-99.945	-83.2164	0
SRS - 05	-100.328	-83.19	-3.06724
SRS - 06	-98.6436	-80.5649	-1.80964
SRS - 07	-98.180	-79.1631	-2.38561
SRS - 08	-91.529	-76.746	0
SRS - 09	-117.34	-98.1904	-6.55914
SRS - 10	-90.41	-74.9213	0
SRS - 11	-112.59	-90.8293	-2.48909
SRS - 12	-105.179	-78.997	-2.24645
SRS - 13	-106.653	-85.6532	-2.41567
SRS - 14	-103.888	-85.3171	-2.5
SRS - 15	-115.047	-93.2363	-5.65478
SRS - 16	-104.192	-86.4478	-3.48502
SRS - 17	-115.434	-94.2198	-4.78329
SRS - 18	-112.272	-91.1066	0
SRS - 19	-112.604	-89.904	-3.64732
SRS - 20	-105.203	-85.6055	-3.42394
JE2_3151	-142.938	-112.281	-8.5462

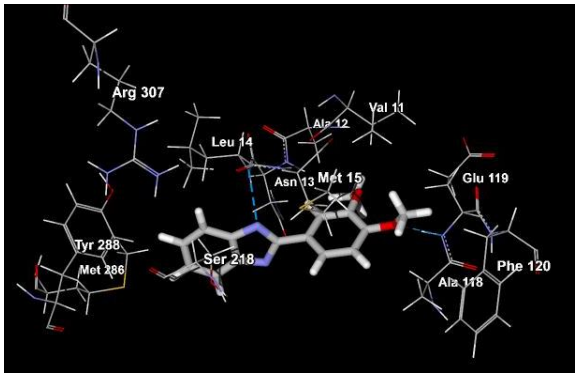

Fig. 2: Compound SRS -07 – The compound SRS -07 shows hydrogen bond interaction between Leu 14 and shows steric interaction between Glu 119, Met 15 and Ser 218 as compared to reference.

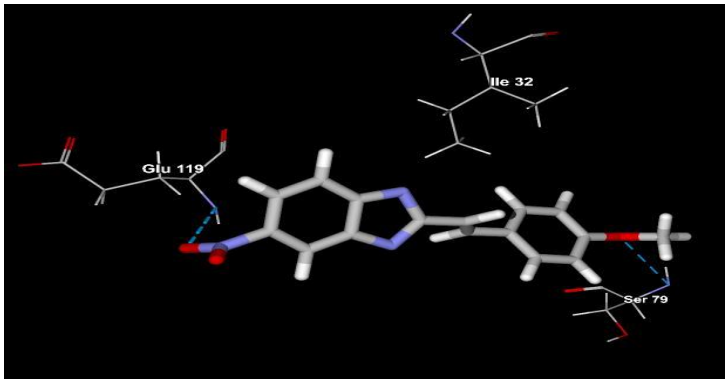

Fig. 3 : Compound SRS -11– The compound SRS -11 shows hydrogen bond interaction between Glu 119, Ser 79 and shows steric interaction of lie32.

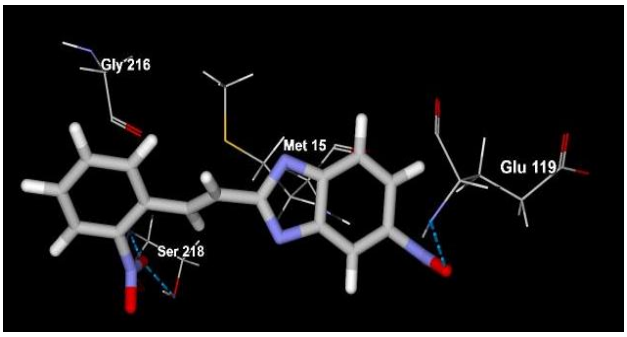

Fig. 4 : Compound SRS -16 – The compound SRS -16 Shows hydrogen bond interaction between Ser 216, Glu119 and shows steric interaction between Met15,Gly 216.

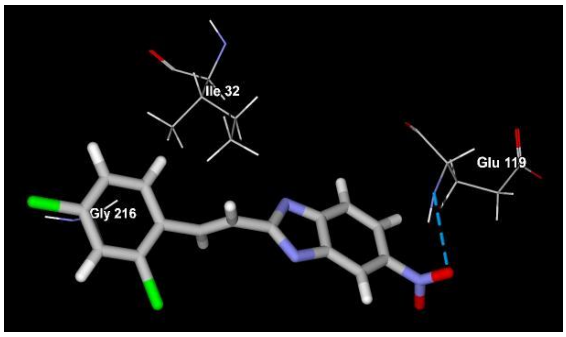

Fig. 5 : Compound SRS -18 – The compound SRS -18 shows hydrogen interaction of Glu 119 and shows steric interaction lie 32 and Gly 216.

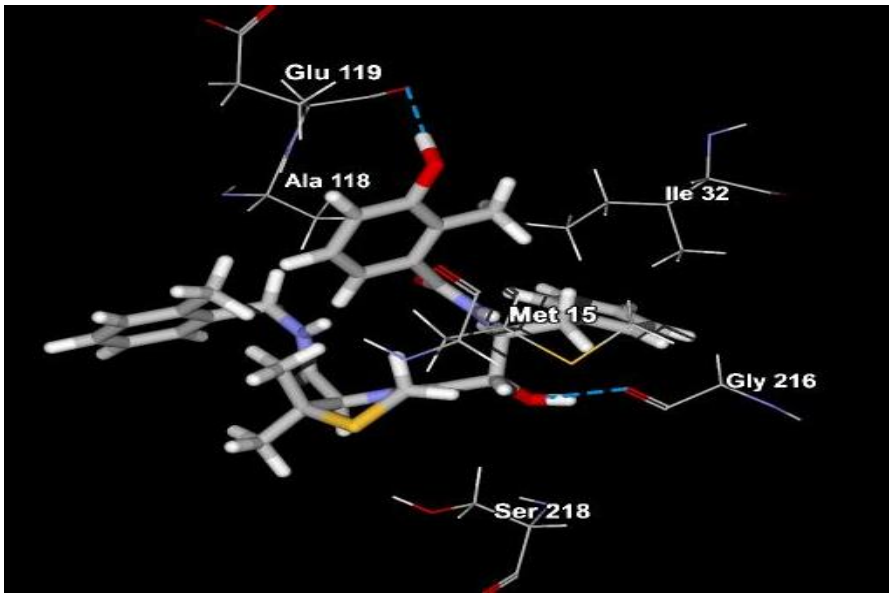

Fig. 6: Reference Ligand – The reference ligand shows hydrogen interaction between Gly 216, Glu 119 and shows steric interaction between Met 15, Ser 218, lie 32 and Ala 118.

Conclusion:

This technique is most commonly used in drug discovery to find the common features that are important in binding to the relevant biological receptor. In this technique, both steric and electrostatic features, hydrogen bond donor, hydrogen bond acceptor and hydrophobic fields are considered. Twenty compounds were designed in which heterocyclic ring is substituted at NH group of Substituted ortho-phenylenediamine moiety while some compound also bearing chloro and nitro group on para position of aromatic ring. Based on this novel designed strategy, the library was docked fifteen compounds were selected for the synthesis based on their mol dock scores, rerank scores and hydrogen bond interactions.

Acknowledgement: Author was thankful to Mr. Mangi Lal Choudhary sir for provided docking Software for study.

Conflict of interest: Author has no conflict of interest.

References:

[1] Kimura T, Takase Y, and Hayashi K, "Structure-Activity Relationship of N-[2- (Dimethy1amino)-6-[3-(5-methyl-4-phenyl-1H-imidazol-1-yl)propoxy]phenyl]-N'- pentylurea And Analogues. Novel

Potent Inhibitors of Acyl-CoA: Cholesterol *O*Acyltransferase with Antiatherosclerotic Activity", *J. Med. Chem.,* 1993, 36, 1630- 1640.

[2] Robl JA, Sulsky R, Sun C, Simpkins LM, Wang T, and Dickson JK, "A Novel Series of Highly Potent Benzimidazole-Based Microsomal Triglyceride Transfer Protein Inhibitors", *J. Med. Chem.*, 2001, 44, 851-856.

[3] White AD, Creswell MW, and Chucholowski AW, "2-Azetidinone Cholesterol Absorption Inhibitors: Structure-Activity Relationships on the Heterocyclic Nucleus", *J. Med. Chem.*, 1996, 39, 4382-4395.

[4] Tanaka A, Terasawa T, Hagihara H, and Sakuma Y, "Inhibitors of acyl-CoA: cholesterol *O*-acyltransferase (ACAT): Identification and structure-activity relationships of a novel series of substituted N-alkyl-N-biphenylylmethyl-N'- arylureas", *Bioorganic & medicinal chemistry*, 1998, 6, 15-30.

[5] Nakao K, Kubota H, and Yasuhara M, "Novel Hydroxyphenylurea Dual inhibitor Against Acyl-CoA: cholesterol Acyltransferase (ACAT) and Low Density Lipoprotein (LDL) Oxidation as Antiatherosclerotic Agent", *Bioorganic & medicinal chemistry*, 2001, 9, 853-861.

[6] White AD, Creswell MW, and Chucholowski AW, "Heterocyclic ureas: inhibitions of Acyl-CoA: Cholesterol *O*-Acyltransferase as hypocholesterolemic agents", *J. Med. Chem.*, 1996, 39, 4382-4395.

[7] Purchase TS, and Holmes A, "Inhibitors of Acyl-CoA: Cholesterol Acyltransferase: Novel Trisubstituted Ureas as Hypocholesterolemic agents", *Bioorganic & medicinal chemistry*, 1997, 5(4), 739-747.

[8] Tanaka A, Terasawa T and Takasugi H, "Identification and Structure-Activity Relationships of a Novel Series of *N*-Alkyl-*N*-(heteroaryl-substituted benzyl)-*N*'- arylureas", *J. Med. Chem.*, 1998, 41, 2390-2410.

[9] Hui-Yin Li, Delucca I and Boswell GA, "Design, synthesis and structure-activity relationship studies of Novel 4,4-Bis(trifluoromethyl)imidazolines as Acyl-CoA: cholesterol Acyltransferase (ACAT) inhibitors and antihypercholesterolemic agents", *Bioorganic & medicinal chemistry*, 1997, 5(7), 1345-1361.

[10] Purchase II CF and White AD, "Tetrazole-substituted ureas as inhibitors of Acyl- CoA: Cholesterol *O*-Acyltransferase (ACAT). A Novel preparation of ureas from weakly nucleophilic amines", *Bioorganic & medicinal chemistry letters*, 1996, 6(15), 1753-1758.

[11] Roth BD, Roark WH and Picard JA, "Inhibitors of Acyl-CoA: Cholesterol Acyltransferase (ACAT): Sulfonylurea inhibitors with excellent hypocholesterolemic activity in-vivo", *Bioorganic & medicinal chemistry letters*, 1995, 5(20), 2367-2370.

[12] Wilde RG, Billheimer JT and Germain SJ, "Acyl-CoA: Cholesterol Acyltransferase (ACAT) inhibitors: Ureas bearing heterocyclic groups Bioisosteric for an imidazole", *Bioorganic & medicinal chemistry letters*, 1995, 5(2), 197-172.

[13] Drumm JE and Deininger DD, "Facile preparations of fused ring azolylureas", *Tetrahedron letters*, 2007, 48, 5535-5538.

[14] synthesis of benzimidazole- Wikipedia, the free encyclopedia http:// benzimidazole.net/synthesis.html

[15] Kazimierczuk, Z. & Shugar, D. (1989) Preparation and properties of the 5,6- and 4,6-dinitro derivatives of benzimidazole and their 1-beta-D-ribofuranosides. *Nucleosides, Nucleotides.* 8, 1379–1385

[16] Zygmunt Kazimierczuk Synthesis, antiprotozoal and antibacterial activity of nitro- andhalogeno-substituted benzimidazole derivatives Acta biochemical polonica vol 49 No.1 1/2002 pp. 185-195

[17] ashish kumar tiwari synthesis and antiviral activities of N-substituted 2- substituted –benzimidazole derivatives Indian journal of chemistry vol 35B feb, 2006 pp. 489-493.

[18] P.B. Thakare, A.J. Asnani, "Recent Advances and Potential Pharmacological Activities of Benzimidazole Derivatives", International Journal of Research in Pharmaceutical and Biomedical sciences, Apr-Jun 2011, *2(2)*, 695-700

[19] Furniss B.S. ,Hannaford A.J. and Tatchell A.R., vogel‟s Textbook of Practical Organic Chemistry,5th Edn, Pearson Education, London,2007,pp.691-92,705,709- 10,723,991-92,996,1229,1261-62

[20] P.B. Thakare, A.J. Asnani, "Recent Advances and Potential Pharmacological Activities of Benzimidazole Derivatives", International Journal of Research in Pharmaceutical and Biomedical sciences, Apr-Jun 2011, *2(2)*, 695-700

[21] Furniss B.S. ,Hannaford A.J. and Tatchell A.R., vogel‟s Textbook of Practical Organic Chemistry,5th Edn, Pearson Education, London,2007,pp.691-92,705,709- 10,723,991-92,996,1229,1261-62