ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation Journal Home Page: www.ijrps.com

Molecular Modeling Studies of Benzimidazole Nucleus

Vijey Aanandhi M*[1], Anbhule Sachin J[2]

[1]Department of Pharmaceutical Chemistry and Analysis, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies (VISTAS) Pallavaram, Chennai - 600 117, Tamil Nadu, India

[2]Research Scholar, Department of Pharmaceutical Chemistry and Analysis, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies (VISTAS) Pallavaram, Chennai - 600 117, Tamil Nadu, India

Article History:

Received on: 09 Mar 2021
Revised on: 02 May 2021
Accepted on: 05 May 2021

Keywords:

Benzimidazole,
CoMFA,
CoMSIA,
HQSAR and Docking

ABSTRACT

For the identification of the lead compounds, a molecular docking tool is used. The little structure, namely Ligand, generally holds together the protein places. It describes a similar approach that utilizes to place over another three-dimensional structure of a probable drug on its prospective object sites. Given that, it was worthwhile to build a virtual library of benzimidazole derivatives to find lead structures to test against *C. Albicans*. The two-dimensional structure of all planned compounds was drawn by using the current version software and pass on to the software window. The energy of all three-dimensional structures was reduced by Molecular Orbital Package up to Root mean square gradient 0.001 and put aside in MDL Molfile (.Mol) format. To assess the likely potential of the Quantitative Structure-Activity Relationship models, the dataset was split into a training set comprising of 32 molecules and a test set of 8 molecules in such a way that the structural variety and an extensive range of biological action in the specific set were added. The IC50 values were transformed to pIC50 to give numerically larger data values.

*Corresponding Author

Name: Vijey Aanandhi M
Phone: +91 9840959519
Email: hodpchemistry@velsuniv.ac.in

ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v12i2.4740

Production and Hosted by

IJRPS | www.ijrps.com

INTRODUCTION

Benzimidazole and its descendant are treated in organic synthesis as vermicides or fungicides as they hamper the action of precise microorganisms. Examples of benzimidazole class fungicides include fuberidazole, cypendazole, chlorfenazole, rabenzazole, thiabendazole (Robl *et al.*, 2001; Kimura *et al.*, 1993). Comparative Molecular Field Analysis is a three-dimensional approach that depends on data from recognized functional compounds (Tanaka *et al.*, 1998). CoMFA can be employed, as it frequently is when the three-dimensional structure of the receptor is unspecified. To spread CoMFA, all that is required are the action and the 3D structures of the compounds (Terasawa *et al.*, 1998; Nakao *et al.*, 2001). By all means, the pursuit has to be determined, but the 3D structure can be discovered either by measurement (crystal X-ray analysis) or by calculation from the 2D diagram and future optimization (White *et al.*, 1996). CoMFA is recognized as one of the improved 3D QSAR methodologies. This approach is frequently used in drug invention to determine the regular features that are powerful in binding to the pertinent biological receptors. In this method, both steric and electrostatic attributes, hydrogen bond donor and acceptor, and hydrophobic field are contemplated. The fields are

assessed by a PLS analysis closer to the CoMFA formalism (Purchase and Holmes, 1997).

MATERIALS AND METHODS

Designing of Compounds

On the basis of the reported structure-activity relationship of aminopyrido[1,2-a] benzimidazole analogues as an antifungal, QSAR studies using CoMFA, CoMSIA, HQSAR (As shown in Table 1) and Molecular modeling (Docking) studies, twenty compounds were designed as shown in Figure 1. (Terasawa *et al.*, 1998; Li *et al.*, 1997; Purchase and White, 1996).

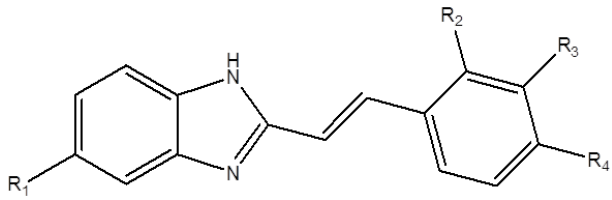

Figure 1: Designed benzimidazole structure

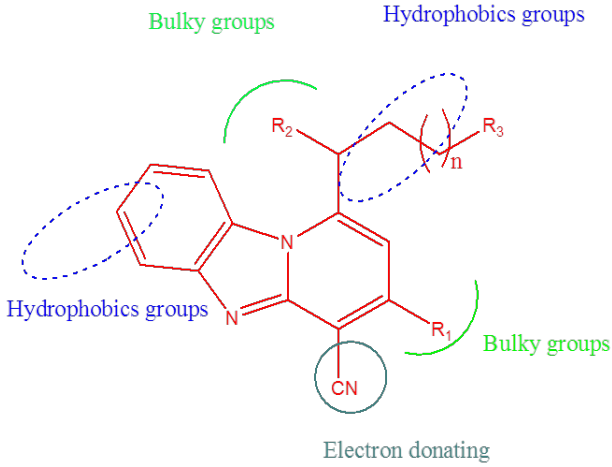

Figure 2: Designing of Compound

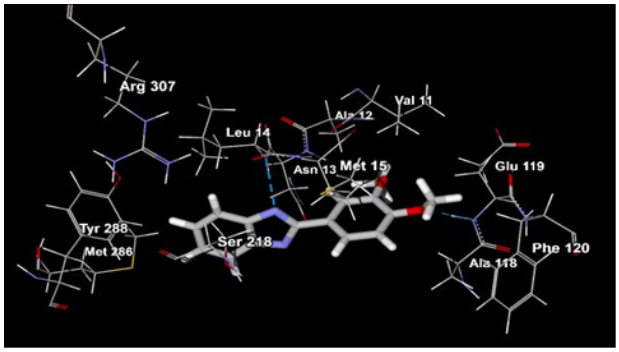

Figure 3: Compound SY-07

The construction of the compounds with the help of Chem Draw ultra and Chem 3D ultra

The two-dimensional structure, as shown in Figure 2, of all planned molecules were drawn by using

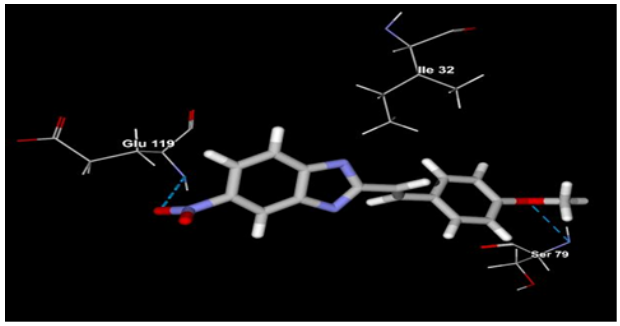

Figure 4: Compound SY-11

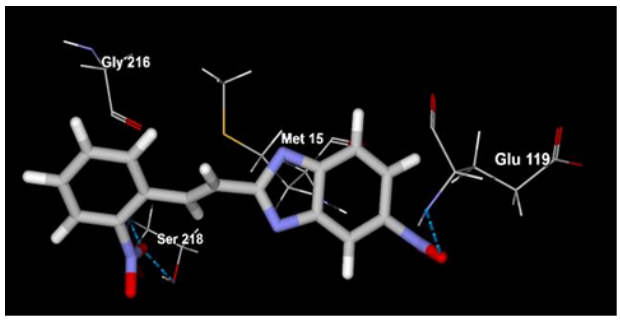

Figure 5: Compound SY-16

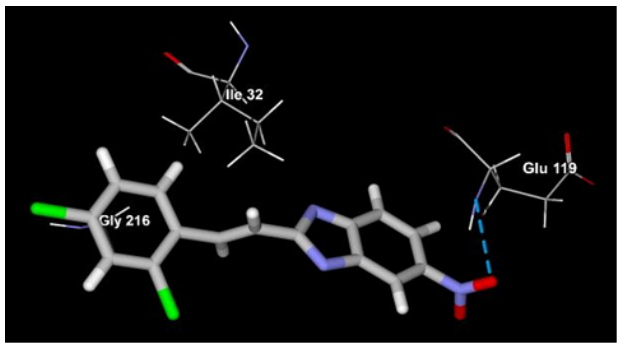

Figure 6: Compound SY-18

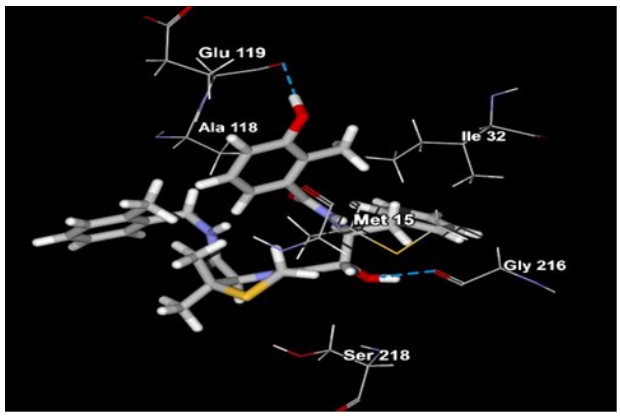

Figure 7: Reference Ligand

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

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

Table 2: Docking studies output MVD of the synthesized compounds

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

Chem Draw ultra-version 8.0.3 and exported to the window of Chem three-dimensional ultra-version 8.0.3 (Roth *et al.*, 1995; Wilde *et al.*, 1995; Drumm and Deininger, 2007). The energy of all 3D structures was minimized through MOPAC up to RMS gradient 0.001 and saved in MDL Mol file (.Mol) format (Kazimierczuk and Shugar, 1989).

Docking accompanied by MVD 5.0

For the docking reason protein model of *Candida Albicans* was selected from the protein data bank. The protein model of *Candida Albicans* (6T1O) was bringing in a workspace area (Kazimierczuk *et al.*, 2002). Subsequently, proteins were making ready for optimum docking through an automated procedure, likely binding cavities were detected. From the docking wizard, the ligand was chosen and the scoring function utilized is Moldock score and rerank score, as shown in Table 2. (Kazimierczuk *et al.*, 2002; Tiwari, 2006). The search algorithm is considered as Moldock SE, and the number of the run is utilized 10 and maximum interaction were 1500 accompanied by size 50 and with an energy threshold of 100. Following docking simulation is over the poses which were generated sorted by Moldock score and rerank score. The rerank score function is computationally extra costly than the scoring function utilized during the docking simulation, but it is normally superior to the docking score function at determining the greatest pose (Furniss *et al.*, 1989).

Interaction study of the designed molecule

Steric and electrostatic attributes hydrogen bond donor and acceptor, hydrophobic fields study was performed as shown in Figure 3, Figure 4, Figure 5, Figure 6 and Figure 7.

The compound SY-07 shows hydrogen bond interaction between Leu 14 and shows steric interaction between Glu 119, Met 15 and Ser 218 as compared to the reference.

The compound SY-11 shows hydrogen bond interaction between Glu 119, Ser 79 and shows steric interaction of lie 32.

The compound SY-16 Shows hydrogen bond interaction between Ser 216, Glu119 and shows steric interaction between Met15, Gly 216.

The compound sy-18 shows hydrogen interaction of Glu 119 and shows steric interaction lie 32 and Gly 216.

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

The above method is most frequently used in drug invention to find usual features that are significant in binding to the pertinent living receptors. In this approach, steric and electrostatic attributes, hydrogen bond donor and acceptor, hydrophobic fields was contemplated. Twenty compounds were designed in which heterocyclic ring is substituted at NH group of Substituted ortho-phenylenediamine moiety while some compound is also bearing chloro and nitro group on the para position of the aromatic ring. Based on this novel designed strategy, the library was docked into *C. albicans*; fifteen compounds were selected for the synthesis based on their mol dock scores, rerank scores and hydrogen bond interactions.

ACKNOWLEDGEMENT

The authors are thankful to the Vels Institute of Science, Technology & Advanced Studies (VISTAS) and its management for providing research facilities and encouragement. I take pleasure to express my sincere thanks to H.S.B.P.V.T' GOI, College of Pharmacy, Kashti, for valuable support.

Conflict of Interest

The authors declare that they have no conflict of interest for this study.

Funding Support

The authors declare that they have no funding support for this study.

REFERENCES

Drumm, J. E., Deininger, D. D. 2007. Facile Preparation of Fused Ring Azolylureas. *Tetrahedron letters*, 48(31):5535–5538.

Furniss, B. S., Hannaford, A. J., Tatchell, A. R. 1989. Vogel's Textbook of Practical Organic Chemistry, 5th Edn, Pearson Education. page 1514, London. ISBN: 9788177589573.

Kazimierczuk, Z., Shugar, D. 1989. Preparation and Properties of the 5,6- and 4,6(5,7)-Dinitro Derivatives of Benzimidazole and their 1-β-D-Ribofuranosides. *Nucleosides and Nucleotides*, 8(8):1379–1385.

Kazimierczuk, Z., Upcroft, J. A., Upcroft, P., Górska, A., Starościak, B., Laudy, A. 2002. Synthesis, antiprotozoal and antibacterial activity of nitro- and halogeno-substituted benzimidazole derivatives. *Acta Biochimica Polonica*, 49(1):185–195.

Kimura, T., Takase, Y., Hayashi, K. 1993. 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*, 36(11):1630–1640.

Li, H.-Y., DeLucca, I., Boswell, G. A., Billheimer, J. T., Drummond, S., Gillies, P. J., Robinson, C. 1997. 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*, 5(7):1345–1361.

Nakao, K., Kubota, H., Yasuhara, M. 2001. Novel Hydroxyphenylurea Dual inhibitor Against Acyl-CoA: cholesterol Acyltransferase (ACAT) and Low-Density Lipoprotein (LDL) Oxidation as Antiatherosclerotic Agent. *Bioorganic & medicinal chemistry*, 9(4):853–861.

Purchase, C. F., White, A. D. 1996. Tetrazole-substituted ureas as inhibitors of Acyl- CoA: Cholesterol O-Acyltransferase (ACAT). *Bioorganic & medicinal chemistry letters*, 6(15):1753–1758.

Purchase, T. S., Holmes, A. 1997. Inhibitors of Acyl-CoA: Cholesterol Acyltransferase: Novel Trisubstituted Ureas as Hypocholesterolemic agents. *Bioorganic & medicinal chemistry*, 5(4):739–747.

Robl, J. A., Sulsky, R., Sun, C., Simpkins, L. M., Wang, T., Dickson, J. K. 2001. A Novel Series of Highly Potent Benzimidazole-Based Microsomal Triglyceride Transfer Protein Inhibitors. *J. Med. Chem*, 44(6):851–856.

Roth, B. D., Roark, W. H., Picard, J. A., Stanfield, R. L., Bousley, R. F., Anderson, M. K., Hamelehle, K. L., Homan, R., Krause, B. R. 1995. Inhibitors of acyl-coa:cholesterol acyltransferase (ACAT). 15. sulfonylurea inhibitors with excellent hypocholesterolemic activity in vivo. *Bioorganic & Medicinal Chemistry Letters*, 5(20):2367–2370.

Tanaka, A., Terasawa, T., Hagihara, H., Sakuma, Y., Ishibe, N., Sawada, M., Takasugi, H., Tanaka, H. 1998. Inhibitors of acyl-CoA: cholesterol O-acyltransferase (ACAT). Part 1: Identification and structure-activity relationships of a novel series of substituted N-alkyl-N-biphenylylmethyl-N′-arylureas. *Bioorganic & Medicinal Chemistry*, 6(1):15–30.

Terasawa, T., Tanaka, A., Hagihara, H., Sakuma, Y., Ishibe, N., Sawada, M., Takasugi, H., Tanaka, H. 1998. Inhibitors of Acyl-CoA:CholesterolO-Acyltransferase. 2. Identification and Structure−Activity Relationships of a Novel Series ofN-Alkyl-N-(heteroaryl-substituted benzyl)-N'-arylureas1. *Journal of Medicinal Chemistry*, 41(13):2390–2410.

Tiwari, A. K. 2006. Synthesis and antiviral activities of N-substituted 2- substituted - benzimidazole derivatives. *Indian journal of chemistry*, 45(2):489–493.

White, A. D., Creswell, M. W., Chucholowski, A. W., Blankley, C. J., Wilson, M. W., Bousley, R. F., Essenburg, A. D., Hamelehle, K. L., Krause, B. R., Stanfield, R. L., Dominick, M. A., Neub, M. 1996. Heterocyclic Ureas: Inhibitors of Acyl-CoA:CholesterolO-Acyltransferase as Hypocholesterolemic Agents1. *Journal of Medicinal Chemistry*, 39(22):4382–4395.

Wilde, R. G., Billheimer, J. T., Germain, S. J., Gillies, P. J., Higley, C. A., Kezar, H. S., Maduskuie, T. P., Shimshick, E. S., Wexler, R. R. 1995. Acyl CoA:cholesterol acyltransferase (ACAT) inhibitors: ureas bearing heterocyclic groups bioisosteric for an imidazole. *Bioorganic & Medicinal Chemistry Letters*, 5(2):167–172.