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Applied Chemistry

Elixir Appl. Chem. 144 (2020) 54535-54536

ISSN: 2229-712X

Pharmacophore Analysis for Anti-Malarial Activity of Pyrido[1,2- A] Benzimidazoles

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ARTICLE INFO

Article history:

Received 29 May 2020;
Received in revised form: 30 June 2020;
Accepted: 10 July 2020;

Keywords

Anti-malarial,
Pyrido[1,2-a]Benzimidazole,
Pharmacophore Modeling.

ABSTRACT

The present work is an attempt to identify key structural features that govern the anti-malarial activity of Pyrido[1,2-a]benzimidazoles using pharmacophoric analysis. The work is based on a dataset of fifty-six molecules comprising diverse derivatives of Pyrido[1,2-a]benzimidazole. The structures were drawn, optimized and aligned using standard protocol. The final model was developed using aligned molecules. The analysis reveals that the anti-malarial activity of Pyrido[1,2-a]benzimidazoles is related with features. The analysis points out that in future modifications these features should be retained.

Introduction

Malarial is a deadly and vector borne disease with high economic burden on developing countries from Asia, Africa and South America. It is still a major cause of mortality in many countries[1-4]. Even though, treatments are available to control this fatal disease, but emergence of resistance against existing drugs like Chloroquine, etc. is an issue which should be addressed in time. The process of developing a new drug is a long and costly process[1-4]. To speed up this process, modern techniques like Pharmacophore modeling, molecular docking, etc. could be used. These methods are cheaper and time saving[2-4].

Recently, Singh *et al.*[1] Synthesized and screened a good number of Pyrido[1,2-a]benzimidazole derivatives. The results showed that Pyrido[1,2-a]benzimidazole could be used as a core to develop new drug for malaria. Even though, structure activity relationships were discussed by them, no attempt was executed to develop a pharmacophore model. A pharmacophore model will be useful to get idea about common features as well as features responsible for change in activity profile of Pyrido[1,2-a]benzimidazoles. Therefore, in the present work, we have performed pharmacophoric analysis to achieve this goal.

Experimental methodology[5-11]:

Dataset selection: The dataset comprises fifty-six derivatives of Pyrido[1,2-a]benzimidazole[1]. The presence of substituents at different positions ensures the covering of broad chemical space. The activity against NF54 cell lines reported as IC50 has been used for the present work. The five most and least active molecules have been presented in Table 1.

Structure generation, Optimization and Alignment:

The SMILES notations provided by Singh et al. were used to generate 3D-structures for all the molecules using OpenBabel. The 3D-structures were then optimized using MMFF94 force filed using OpenBabel. The optimized structures were then aligned using Open3DAlign. The aligned structures were used for generation of final pharmacophore model using pyMOl and its plugin 'LIQUID'[5-11].

Table 1. Five most and least active molecules used in the present work.

Compound ID	SMILES notation	NF54 IC50
1	ClC1=CC(N=C2N3C(NCCNCC)=CC(C4=CC=C(C(F)(F)F)C=C4)=C2C#N)=C3C=C1Cl	0.02
2	ClC1=CC(N=C2N3C(NCCNCC)=CC(C4=CC=C(C(F)(F)F)C=C4)=C2C#N)=C3C=C1	0.03
3	ClC1=CC2=C(N=C3N2C(NCCNCC)=CC(C4=CC=C(C(F)(F)F)C=C4)=C3C#N)C(Cl)=C1	0.03
4	OC(CC1)CN1CCNC2=CC(C3=CC=C(C(F)(F)F)C=C3)=C(C#N)C(N42)=NC5=C4C=CC=C5	0.04
5	ClC1=C(Cl)C=C(N=C2N3C(NC4CCN(C)CC4)=CC(C5=CC=C(C(F)(F)F)C=C5)=C2C#N)C3=C1	0.05
6	O=S(CCC1NC2=CC(C3=CC=C(C(F)(F)F)C=C3)=C(C#N)C4=NC5=CC=CC=C5N42)(CC1)=O	7.81
7	OC(C1)CCN1C2=CC(C3=CC=C(C(F)(F)F)C=C3)=C(C#N)C4=NC5=CC=CC=C5N42	8.48
8	O=S(NCCNC1=CC(C2=CC=C(C(F)(F)F)C=C2)=C(C#N)C(N31)=NC4=C3C=CC=C4)(C)=O	9.1
9	O=C(C)NCCNC1=CC(C2=CC=C(C(F)(F)F)C=C2)=C(C#N)C(N31)=NC4=C3C=CC=C4	16.42
10	OC(C1)CN1C2=CC(C3=CC=C(C(F)(F)F)C=C3)=C(C#N)C4=NC5=CC=CC=C5N42	21.32

Results and Discussions

The present pharmacophoric analysis led to generation of a pharmacophore model. For the sake of convenience and understanding, the pharmacophore models are molecule number 1 and 10 have been presented as representatives in figure 1 and 2.

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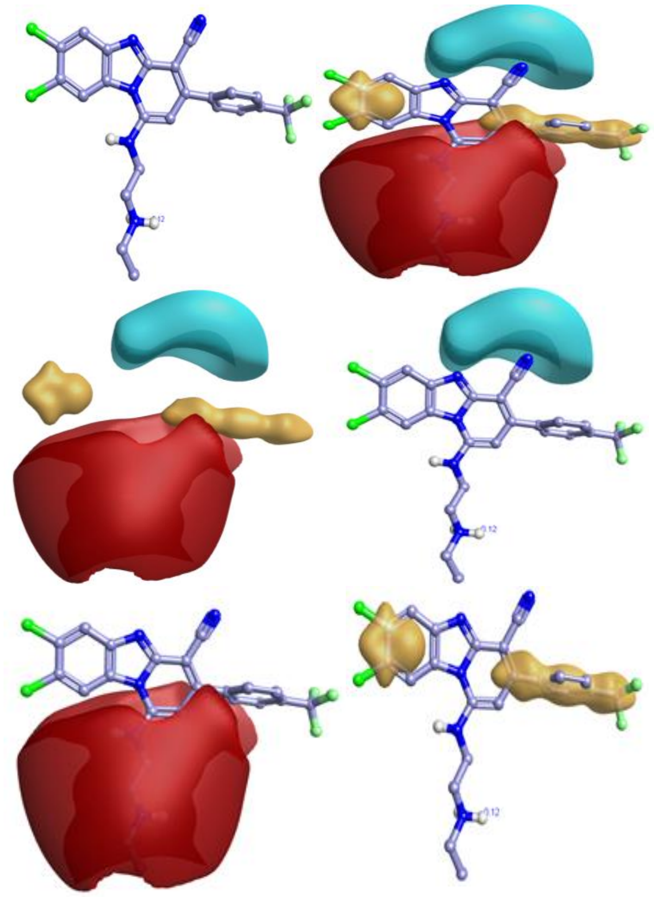

Figure 1. Pharmacophore pattern for most active molecule 1. (Red- positive charged, Blue-negative charged, Yellow- Hydrophobic region)

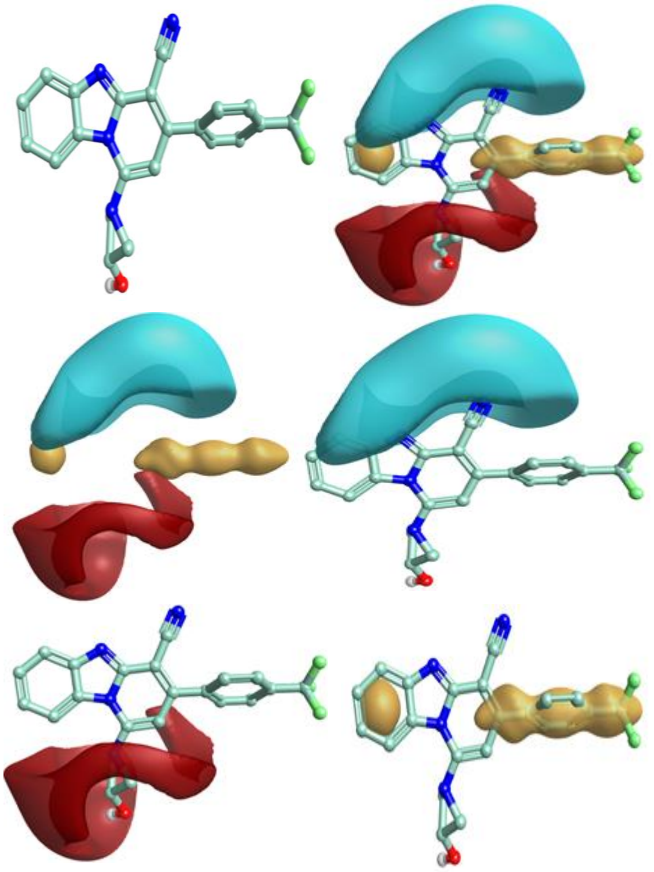

Figure 2. Pharmacophore pattern for least active molecule 10.(Red- positive charged, Blue-negative charged, Yellow- Hydrophobic region).

A comparison of figure 1 and 2 indicates that he most and least active molecules 1 and 10 have good differences in their pharmacophoric patterns. The most active molecules has a large positive region present below the Pyrido[1,2-a]benzimidazole ring. Another difference is with respect to the size of hydrophobic region present due to Chlorine atoms attached to aromatic ring of molecule 1 on the Pyrido[1,2-a]benzimidazole moeity. Therefore, in future optimizations, these regions should be retained to have good activity.

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