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2D Quantitative Structure Activity Relationship Studies on Structurally Constrained Quinazoline Derivatives as Potent and Selective Histamine H3 Receptor Inverse Agonists

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In the present study 2D quantitative structure activity relationship (QSAR) study was performed on a new series of novel structurally constrained quinazoline derivatives for their H_3 receptor inverse agonistic activity. This series is reported by Tsuyoshi and Takashi. 2D quantitative structure activity relationship study was performed by using JChem. for Excel (version 5.3.6). Multiple linear regression analysis was performed, which was further evaluated with training and test set of compounds for prediction of activity. Several statistical regression expressions were obtained using multiple linear regression analysis. Matrix was used to evaluate each parameter for its contribution. R value was found 0.975 and correlation coefficient R_{sqr} was found 0.9567. The study indicated that topological parameters (Balaban index, harary index), thermodynamic descriptors (refractive index, dreiding energy) and topological parameter (Balaban index) and log P *etc*. play important role for the histamine receptor inverse agonistic activity.

Key Words: Quinazoline, Histamine, Multiple linear regression analysis, Inverse agonists, Histamine-3 receptors, Quantitative structure activity relationship analysis *etc*.

INTRODUCTION

Histamine is an endogenous antiepileptic so if released in central nervous system it helps in treatment of epilepsy. Histamine is produced by decarboxyalation of histidine and it has wide range of physiological and pathophysiological function in body[1]. It is one of the important chemical local mediator and neurotransmitter found in human body[2]. Histamine is a monoamine signaling molecule that acts *via* four G-protein-coupled histamine receptors; H_1, H_2, H_3 and H_4. H_1 histamine receptors are located on smooth muscles, endothelium and central nervous system. In tissue it causes vasodilation, bronchoconstriction, separation of endothelial cells and pain and itching due to insect stings. The primary receptors involved in allergic rhinitis symptoms, motion sickness and sleep regulationetc[3]. H_3 histamine receptor found on central nervous system and to a lesser extent peripheral nervous system. H_3 receptor antagonists thioperamide, clobenpropit, AQ0145 decreases the seizure susceptibility of electrically induced convulsion in mice. These compound acts by increasing endogenously released histamine in the brain. The anti convulsant effect of these compounds is antagonized by giving H_3 receptor agonists or H_1 receptor antagonist (mepyramine)[4,5]. These findings suggest that H_3 receptor antagonist and inverse agonists could represent a new approach to the development of anti epileptic drugs.

Histamine receptor and its ligands: Histamine-3 receptor is an auto and hetero-receptor (Fig. 1). Thus, its activation reduces, whereas blockade increases, not only the release of histamine but also several other neurotransmitter[6,7].

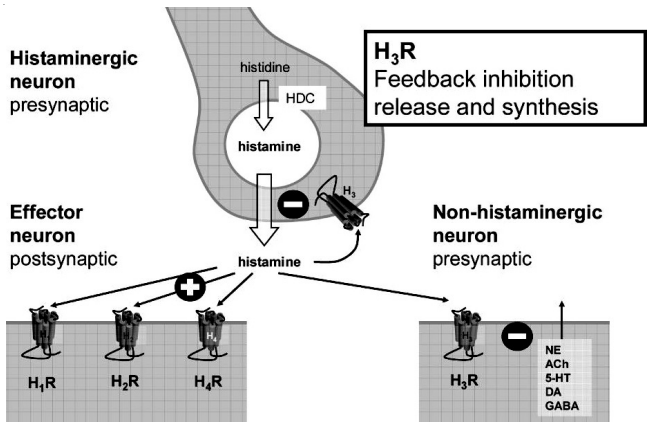

Fig. 1. H_3R auto- and hetero receptor function in the nervous system

H_3R agonists are derivatives of histamine. In these compounds replacement of imidazole moiety is not successful. N-methyl histamine is a potent agonist of histamine, imetit, imepip impentamine, proxyfen, GT-2331 are some other histamine-3 receptor agonists. Thioperamide was developed

as first potent selective H_3R antagonist later clobenpropit was discovered as inverse agonist. Now many H_3R antagonist and inverse agonist have been developed such as ABT-239, GT-216 UCL-1199 and various others[8]. Ligands are shown in Fig. 2.

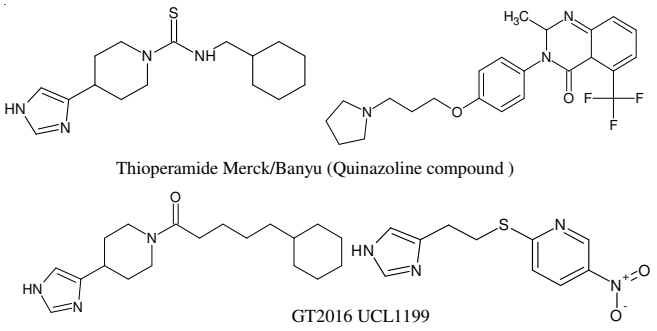

Fig. 2. Histamine receptor and its ligands

Objective: Recently, a new series of novel structurally constrained quinazoline derivatives has been reported by Tsuyoshi and Takashi[9]. In the present study, we tried to develop 2D QSAR of these compounds using multiple linear regression analysis and matrix for corelation.

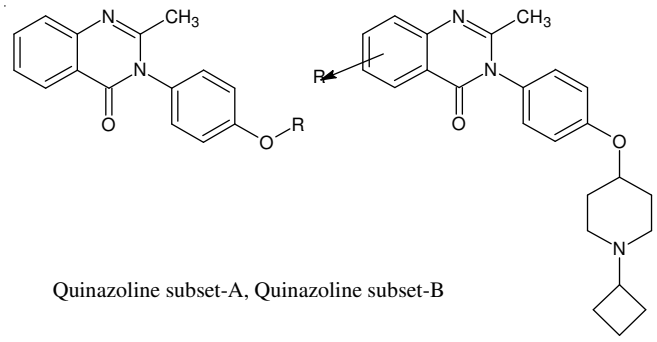

Fig. 3. Structures of quinazolines

EXPERIMENTAL

The series of quinazoline derivatives (Fig. 3) was taken from the reported work of Tsuyoshi and Takashi[9]. The IC_{50} (half maximal inhibitory concentration) values were converted to negative logarithmic data (pIC_{50}) for QSAR analysis. The correlation was sought between histamine-3 receptor inverse agonistic activity and various physicochemical parameters such as hydrophobic parameters (Log P, Log D), polarizability parameters (molecular polarizability), topological parameters (balaban index, randic index, harary index). Stepwise multiple linear regression analysis method was used for analysis. Following statistical parameters were considered to select the statistical significance of QSAR models correlation coefficient (r), standard deviation (SD), coefficient of determination (r^2), adjscent correlation(r^2) and standard error of estimate.

RESULTS AND DISCUSSION

The given series has two different subsets A compound no **1-17** and subset B having **22-39**. The both subsets have quinazolinone structure, in subset-A substituents are attatched to phenoxy fragment and in subset-B the substituents are attatched to aryl moiety. In subset-A compound no. **2** could not subjected to QSAR analysis due to approximate IC_{50} value. All the **38** compounds were subjected to QSAR analysis excluding compound no. **2** due to above mentioned reason.

The subset-A gave various equations, but no single equation is significant for histamine-3 receptor inverse agonist activity. Model showing highiest co-relation among them is:

PIC_{50} = 2.704 - (0.409* LogP) N = 16.00 Model-1

R = 0.285, R_{sqr} = 0.0811, A_{dj} R_{sqr} = 0.0155

The subset-B gave various equations, model showing highest co-relation among all for histamine-3 receptor inverse agonist activity was found to be as follows:

PIC_{50} = 86.973-(50.196* Balaban index)-(0.395* Platt index)

N = 20.000 Model-2

R = 0.759, R_{sqr} = 0.576, A_{dj} R_{sqr} = 0.526

Two subsets were combined together uisng topological parameteres amd molecular polarizability and resultant series of compound were subjected to multiple linear regression analysis. Multiparameteric models gave significant correlations.

Based on corelation cofficients following models were selected for histamine-3 receptor inverse agonist activity.

PIC_{50} = 7.258 - (0.289* Balaban index) + (0.121* MPol)-(0.122* Platt index)

N = 37 Model-3

R = 0.615, R_{sqr} = 0.379, A_{dj} R_{sqr} = 0.322

This model was unable to explain the activity of some compounds based on scores and calculations, R_{sqr} is also less, than after removing these compounds following equation was obtained.

PIC_{50} = 16.640-(4.152* Balaban index)+(0.172* MPol)-(0.204* Platt index)

N = 35.000, R = 0.633, R_{sqr} = 0.401, A_{dj} R_{sqr} = 0.343 Model-4

This model again was unable to explain the activity of some compounds based on scores and calculations, R_{sqr} is also less, than after removing these compounds following equation was obtained.

PIC_{50} = 16.007-(3.360* Balaban index)+(0.201* MPol)-(0.219* Platt index)

N = 33.000, R = 0.683, R_{sqr} = 0.466, A_{dj} R_{sqr} = 0.411 Model-5

Standard error of estimate = 0.598

In model-5 R value increased from 0.63 to 0.68. R_{sqr} also increased and standard error of estimate is also very low which shows the model is significant.

To get good correlation cofficient outlier based on statistical parameteres some compounds were removed and final equation was obtained as follows:

PIC_{50} = 357.272-(126.437* Balaban index) + (2.371* Harary index)-(1.999* Platt index)-(21.904* Refractive index) Model-6

N = 17, R = 0.975, R_{sqr} = 0.950, A_{dj} R_{sqr} = 0.933

Standard error of estimate = 0.185

For model-6 leave one out (LOO) cross validation was performed fo predictivity and values of Q square, S_{PRESS} were found satisfactory.

Q^2 = 0.6251, S_{PRESS} = 0.4969, S_{DEP} = 0.39

Study revealed that mainly topological parameters such as balaban index, refractive index and platt index contributed negatively to the biological activity whereas harary index contributed positively to the biological activity. The Q^2 value revealed that results are not based on chance correlation. The correlation matrix and predicted biological activity for model-

6 are given in Table-1. Fig. 4 shows the graph of observed and predicted biological activity.

TABLE-1
CORRELATION MATRIX FOR MODEL-6

	BI	HI	PI	RI
BI	1			
HI	0.85	1		
PI	0.75	0.93	1	
RI	0.83	0.97	0.83	1

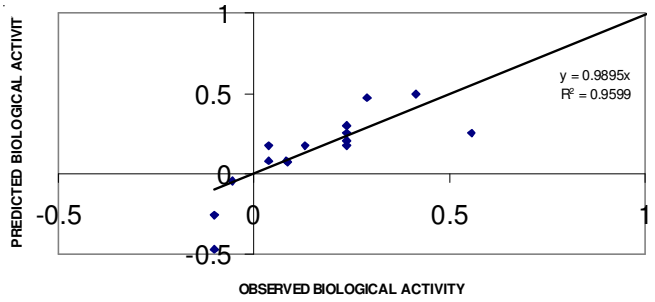

Fig. 4. Graph of observed and predicted biological activity

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