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Qsar Study Of Some Nnrtis Of 2, 4, 5-Trisubstituted Thiazole Derivatives

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ABSTRACT: Acquired Immuno Deficiency Syndrome (AIDS) is a viral disease caused by Human Immuno deficiency Virus. The approache for the treatment of HIV infections used NNRTIs inhibitors for HIV type-1. The structure-based approaches may be useful for the design and discovery of new HIV-1 RT inhibitors compounds. QSAR activity focuses on the chemical compound influencing the activity and the allowing synthesis of selective potential structure molecules. Pharmacophore optimization of Thiazole nucleus as non-nucleoside reverse transcriptase inhibitors using 2D QSAR. Material & Method: We have developed quantitative structure–activity relationship (QSAR) models for 18 non-nucleoside HIV- 1 reverse transcriptase inhibitors (NNRTIs) of the 2,4,5-Trisubstituted thiazole derivatives. Studies were carried out on using BuildQSAR Software using Multiple Linear Regression (MLR) Analysis. QSAR studies indicated the requirement of certain physicochemical parameters and GFE, Henry law, lop p and total energy these descriptors are increase the biological activity of the proposed compound for better Anti HIV activity.

KEY WORDS: Molecular Modeling, 2d Qsar, AIDS, Anti –HIV, Pharmacophore, non-nucleoside reverse transcriptase inhibitors (NNRTIs)

I. INTRODUCTION:

The designing of NNRTIs inhibitors for HIV type-1 is one of the approache for the treatment of HIV infections(1). The HIV-1NNRTIs non-nucleoside reverse transcriptase inhibitors constitute a drug class which includes nevirapine, delavirdine, efavirenz, etravirine, and rilpivirine approved for clinical use. The efficiency of many of these drugs has been undermined by drug-resistant variants of HIV-1 RT, and therefore becomes unavoidable to designing of novel drugs to resistance[(2)]. "The drug design strategies include medicinal chemistry, computational chemistry and pharmacological approaches. In particular, computational modeling approaches, including machine learning, empirical descriptors-based, force-field and hybrid quantum mechanics/molecular mechanics-based methods are used for new drug discovering the new compound". These methods have a major impact on the efforts to guidance the designing new drug discovery and its help to making next generation of NNRTIs its give help to fight to multidrug resistance[(3-5).]

QSAR methods provide information about the basic physicochemical properties as well as the biological and human health effects of chemicals before they reach into the market for public use. In this aspect, application of QSAR methods along with structure-based approaches may be useful for the design and discovery of new HIV-1 RT inhibitors compounds. QSAR activity focuses on the chemical compound influencing the activity and the allowing synthesis of selective potential structure molecules[(6-7).]

Quantitative structure activity relationships (QSARs) are among the most widely used techniques in rational drug design, which finds the mathematical relationship between physicochemical properties of compounds and their experimentally determined biological activities. The derived QSAR model can be subsequently used for predict the biological activity of new compound which is synthesis[(8).] The QSAR model can enhances understanding of the specifics of drug action. QSAR study of new compound increase the success with less time and cost in drug synthesis.

II. MATERIAL AND METHODS: INSILICO STUDY

ACD/ChemSketch[(9)]

ACD/ChemSketch is a molecular modelling program used to create and modify images of chemical structures. Also, there is a software that allows molecules and molecular models displayed in two and three dimensions, to understand the structure of chemical bonds and the nature of the functional groups.Chemical structures and SMILE notations of the compounds were

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obtained by using ACD labs ChemSketch version12.0 (https://www.acdlabs.com/resources/freeware/chemsketch/)

Chemoffice 16.0

Chemoffice provides computational tools bases on the molecule modeling for optimizing model, molecular dynamics and calculating single point energies of the molecules. These structures of compound were draws in chemoffice 16.0. Chemoffice package has provision for the energy minimization, geometry optimization and QSAR properties calculation.

BuildQSAR

BuildQSAR is a free program designed to help the QSAR practitioner on the task of building and analyzing quantitative models through regression analysis. The main part of the program is a spreadsheet, in which the user can enter with the data set composed by the structure definition of the compounds, one or more types of biological activity values and many physicochemical properties.

Lead Compound:

The main compound is the thiazole and attach the other functional group the lead compound is shown in fig.1.

The lead compound is 5-benzyl-N-((2,3-dihydrobenzofuran-5-yl)methyl)-4-phenylthiazol-2-amine

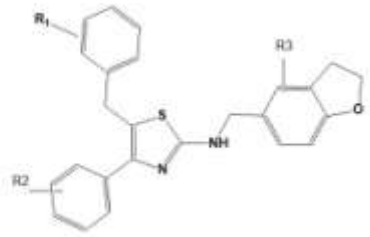

Fig. 1

Proposed Compounds:

Table :1 list of the proposed series of compound of 2,4 and 5 postion of thiazole compound.

COMPOUND	R1	R2	R3	IC50 µm
1	2-OCH3,5-F	3,5 F	3H,	0.236
2	3-CI,5-F	2-F,4-CI	4H,	0.161
3	2-6-CI,4-OCH3	2-OCH3,4-6 CI	6H,	0.861
4	2-6 OCH3	2-4 CI	5H,	0.204
5	3-5 F	2-4 CI,6-F	3H,	0.191
6	2-6 CI,4-OCH3	3-OCH3,6-F	2H,	0.256
7	2-OCH3,5-CI	2-F	4OCH3,	0.072
8	2-6 CI,4-OCH3	2-4 CI	2OCH3,	0.196
9	2-4 OCH3	2-6 CI,4-F	5OCH3,	0.132
10	2-OCH3,3-5 F	2-OCH3,4-6 F	5OCH3,	0.298
11	2-6 CI	2-CI,4-6 F	3OCH3,	0.191
12	2-5 OCH3,	4-6 F	6OCH3,	0.147
13	3-5 F,4-OCH3	2-4 CI	2H,	0.246
14	2-6 CI,4- OCH3	2-OCH3	2H,	0.13
15	4-CI	4- CI	3H,	0.302
16	4-F,	2-OCH3	3H,	0.21
17	4-OCH3	2-OCH3,4-CI	2H,	1.88
18	2-OCH3,5-CI	4-F	2H	0.051

III. RESULT AND DISCUSSION:

In order to develop QSAR between anti hiv activity as dependent variables and substituent's constant as independent variables, multiple liner regression analysis of data was done and equations were obtained.

Model 01 : QSAR Equation

BA: + 0.4602 (± 1.5763) STRETCH + 0.0245 (± 0.4916) BEND - 1.5904 (± 6.8830) STRCH

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BEND - 0.0279 (± 0.0541) TORSION + 0.0100 (± 0.3421) NON 1,4 VDW - 1.4412 (± 4.9127

Model 02 : QSAR Equation

BA: + 0.0998 (± 0.1567) GFE + 248.2927 (± 389.9072) henry law + 289.2498 (± 454.3143) log P - 39.8710 (± 62.6425) Mol REf - 0.0070 (± 0.1828) 1,4 vdw - 134.5060 (± 209.1388)

Model 03 : QSAR Equation

BA: + 0.2410 (± 1.3183) strch - 0.0497 (± 0.2282) bend - 0.0285 (± 0.0954) 1,4 vdw - 0.0095 (± 0.0282) total energy + 0.0397 (± 0.2782) log p + 1.2603 (± 3.5207)

The QSAR equation of Proposed series of compound given equation 1,2, and 3 studied and that equation gives the near same activity of the given series of compound to proposed compound. The compound are in equation the NON 1,4 VDW, STRETCH, BEND, GFE, Henry law, lop p and total energy these descriptors are increase the biological activity of the proposed compound . The biological activity of given equations are 70%84 and 63% are given respectively.

the best model the suitable change on the substitution at R by certain functional group which increase the volume contain within the molecular surface as well as the molecular weight which may lead to enhanced of the anti hiv activity.

IV. CONCLUSION:

Quantitative structure activity relationship (QSAR) is an area of computational research that construct models to correlate and predict biological properties from structural parameters of existing molecules. Such models can play an important role in lead structure optimization. The QSAR study shows that electronic, shape and topological descriptors are responsible for describing activity of 2,4,5-Trisubstituted Thiazole Derivatives. The QSAR model is statiscally and chemically sound with exceptional predictive power as proven from the predict activity of test set of compound.

Research is focus on derivatives of 2,,4,5-Trisubstituted thiazole . The qsar equations the descriptors give more biological activity of compound. Major descriptors like SOD, Total Valence Connectivity, Shape Attribute Mol Refractivity, log p ,1,4 VDW , Molecular Topological Index are activity show in equation 1,2,and 3 in proposed compound. The positions of the electron donor compound are given more effect to give the biological compound.

In the proposed compound the non 1,4 vdw, stretch, bend, gfe, Henry law, lop p and total energy these descriptors are increase the biological activity of the proposed compound . The biological activity of given equations are 70%,84 and 63% are given respectively

The best model the suitable change on the substitution at R by certain functional group which increase the volume contain within the molecular surface as well as the molecular weight which may lead to enhanced of the anti hiv activity.

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