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MOLECULAR PARAMETERS IN QSAR OF METHYLPHENYL QUINOLIN TRIAZOL DERIVATIVES BY MOLINSPIRATION

*** Alok Kumar Dash, Jhansee Mishra**

Institute of Pharmacy V.B.S.P.University Jaunpur, Uttarpradesh, India, 222003

***Corresponding Author: Alok Kumar Dash, E-mail: alokkudash@yahoo.co.in**

ABSTRACT

Various physiochemical parameters are known to be cross-correlated. Therefore, only variables or their combinations that have little co-variance should be used in a QSAR analysis. Molinspiration is perhaps best known as the distributor of the Java Molecular Editor (JME) in various forms, created by Peter Ertl at Novartis. It also publishes a wide range of chemical informatics software including mitools, a java program for calculating molecular properties. The chemical descriptor space whose convex hull is generated by a particular training set of chemicals is called the training set's applicability domain. Prediction of properties of novel chemicals that are located outside the applicability domain uses extrapolation, and so is less reliable (on average) than prediction within the applicability domain. For the methylphenylquinoline Triazol derivatives the best suitable receptor is Kinase inhibitor because all the derivative the value of Kinase comes out positive and it also near the 'O' value that means low energy is required.

Key Words: Molinspiration, QSAR, Kinase inhibitor, drug design.

INTRODUCTION

1.1 **Molinspiration**

Molinspiration is a chemical informatics software vendor based in Slovakia. Molinspiration is perhaps best known as the distributor of the Java Molecular Editor (JME) in various forms, created by Peter Ertl at Novartis. It also publishes a wide range of chemical informatics software including mitools, a java program for calculating molecular properties. mitools is used by ZINC.

A molecule editors a computer program for creating and modifying representations of chemical structures. Molecule editors can manipulate chemical structure representations in either a simulated two-dimensional space or three-dimensional space, via 2D computer graphics or 3D computer graphics, respectively. Two-dimensional output is used as illustrations or to query chemical databases. Three-dimensional output is used to build molecular models, usually as part of molecular modelling software packages. Database molecular editors such as Leatherface,[1] RECAP,[2] and Molecule Slicer[3] allow large numbers of molecules to be modified automatically according to rules such as 'deprotonate carboxylic acids' or 'break exocyclic bonds' that can be specified by a user. Molecule editors typically support reading and writing at least one file format or line notation. Examples of each include Molfile and simplified molecular input line entry specification (SMILES), respectively.

QSAR involves the derivation of mathematical formula which relates the biological activities of a group of compounds to their measurable physicochemical parameters. These parameters have major influence on the drug's activity. QSAR derived equation take the general form:

Biological activity= function(parameters)

Activity is expressed as log(1/c). C is the minimum concentration required to cause a defined biological response.

Quantitative structure–activity relationship models (QSAR models) are regression or classification models used in the chemical and biological sciences and engineering. Like other regression models, QSAR regression models relate a set of "predictor" variables (X)

to the potency of the response variable (Y), while classification QSAR models relate the predictor variables to a categorical value of the response variable.

In QSAR modeling, the predictors consist of physico-chemical properties or theoretical molecular descriptors of chemicals; the QSAR response-variable could be a biological activity of the chemicals. QSAR models first summarize a supposed relationship between chemical structures and biological activity in a data-set of chemicals. Second, QSAR models predict the activities of new chemicals.

Related terms include *quantitative structure–property relationships* (*QSPR*) when a chemical property is modeled as the response variable.[1][2] "Different properties or behaviors of chemical molecules have been investigated in the field of QSPR. Some examples are quantitative structure–reactivity relationships (QSRRs), quantitative structure–chromatography relationships (QSCRs) and, quantitative structure–toxicity relationships (QSTRs), quantitative structure–electrochemistryrelationships (QSERs), and quantitative structure–biodegradability relationships (QSBRs)." As an example, biological activity can be expressed quantitatively as the concentration of a substance required to give a certain biological response. Additionally, when physicochemical properties or structures are expressed by numbers, one can find a mathematical relationship, or quantitative structure-activity relationship, between the two. The mathematical expression, if carefully validated can then be used to predict the modeled response of other chemical structures.

1.2- Parameters

The parameter is the measure of the potential contribution of its group to a particular property of the parent drug.

Various parameters used in QSAR studies are

1. Lipophilic parameters: partition coefficient, π-substitution constant

2. Polarizability parameters: molar refractivity, parachor

3. Electronic parameters: Hammet constant, dipole moment.

4. Steric parameters: Taft's constant.

1.2.1- Lipophilic parameters

Lipophilicity is partitioning of the compound between an aqueous and non-aqueous phase. Partition coefficient:

P = [drug] in octanol / [drug] in water

Typically over a small range of log P, e.g. 1-4, a straight line is obtained

e.g. log 1/C = 0.75 log P + 2.30

If graph is extended to very high log P values, then get a parabolic curve,

log 1/C = - k1 (log P) 2 + k 2 log P + k3

When P small, dominated by log P term

When P large, log P squared dominates & so activity decreases.

π-substituent constant or hydrophobic substituent constants:

The π-substituent constant defined by hansch and co-workers by the following equation.

px = log Px - log PH

A positive πvalue indicates that the πsubstituent has a higher lipophilicity than hydrogen and the drug favours the organic phase.

A negative πvalue indicates that the πsubstituent has a lower lipophilicity than hydrogen and the drug favours the aqueous phase.

1.2.2- Electronic parameters

The Hammett constant (σ);

s x = log (K x/K benzoic)

Electron Withdrawing Groups

Equilibrium shifts Right & K x >Kbenzoic

Since s x = log K x – log Kbenzoic, then s will be positive.

Hammett constant takes into account both resonance and inductive effects; thus, the value depends on whether the substituent is para or meta substituted -ortho not measured due to steric effects.

1.3- Steric substitution constant

- It is a measure of the bulkiness of the group it represents and it effects on the closeness of contact between the drug and receptor site. Much harder to quantitate
- Examples are: y Taft's steric factor (Es) (~1956), an experimental value based on rate constants
- Molar refractivity (MR)--measure of the volume occupied by an atom or group--equation includes the MW, density, and the index of refraction—
- Verloop steric parameter--computer program uses bond angles, van der Waals radii, bond lengths.

1.4-Hansch analysis

- Proposed that drug action could be divided into 2 stages: 1) Transport & 2) Binding
- Each of these stages depend upon the physical and chemical properties of the drug.
- Log 1/C = k1P = k 2 P 2 + k 3s + k 4Es + k 5
- Look at size and sign for each component of the equation.
- Accuracy depends on using enough analogs, accuracy of data, & choice of parameters
- Applications: used to predict the activity of an as yet unsynthesizedanalouge.

1.5- QSAR Application:-

QSAR models have been used for risk management. QSARS are suggested by regulatory authorities; in the European Union, QSARs are suggested by the REACH regulation, where "REACH" abbreviates "Registration, Evaluation, Authorisation and Restriction of Chemicals".

The chemical descriptor space whose convex hull is generated by a particular training set of chemicals is called the training set's applicability domain. Prediction of properties of novel chemicals that are located outside the applicability domain uses extrapolation, and so is less reliable (on average) than prediction within the applicability domain. The assessment of the reliability of QSAR predictions remains a research topic.

1. Equations are produced to predict relationship that properties may have on the mechanism/distribution of drug.

2. It is used for the prediction of biological activity.

3. QSAR include regression, pattern recognition techniques. QSAR is an equivalent to chemo metrics or multivariate statistical data analysis.

1.5.1-QSAR advantages

1. QSAR is important in drug development as it provide quantitative information relating properties of a compound to its activity.

2. QSAR provides a cost effective means of modifying drug molecules by insilico design and enhancement.

3. It quantify the relationship between structure and activity which provides an understanding of the effect of structure on activity.

4. There is also the potential of make predictions leading to the synthesis of novel analogous.

5. Care must be taken not to use extrapolation outside the range of the data set.

6. The result of QSAR can be used to help understanding interactions between functional groups in the molecules of greatest activity with those of their target.

1.5.2-QSAR disadvantages

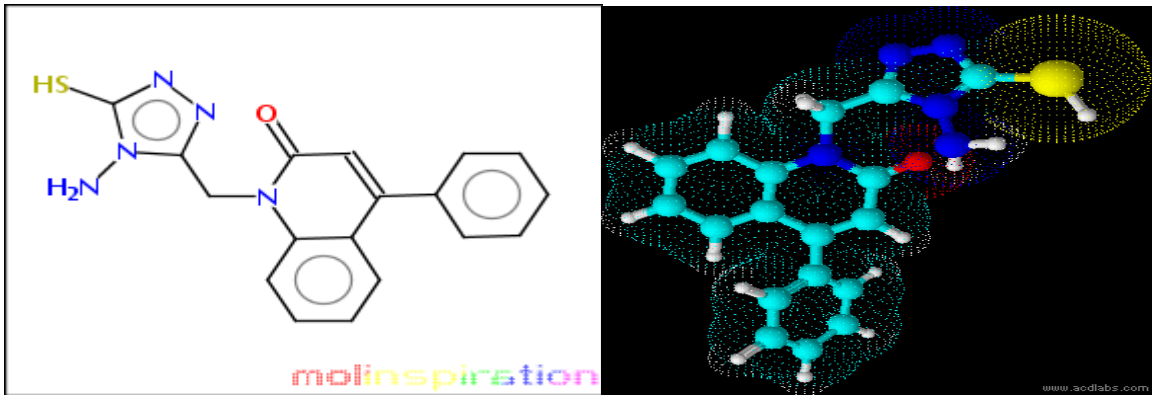
1. False correlation may arise through too heavy reliance being placed on biological data.

2. Experiments upon which QSAR analysis depends lack design in th strict sense of experimental design.

3. Many QSAR results cannot be used to confidently predict the most likely compounds of best activity.

4. Various physiochemical parameters are known to be cross-correlated. Therefore, only variables or their combinations that have little co-variance should be used in a QSAR analysis.

2- Compound code = A1



IUPAC NAME:

1-[(4-amino-5-sulfanyl-4H-1,2,4-triazol-3-yl)methyl]-4-phenylquinolin-2(1H)- One

Molecular formula:-$C_{18}H_{15}N_5O_5$

Molecular weight:-349.4096

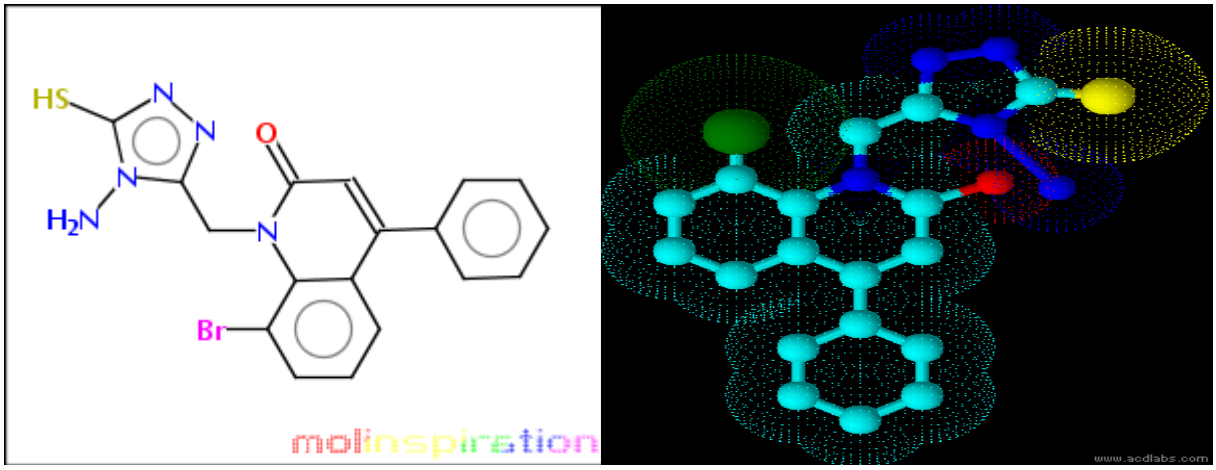
2.1-Physichochemical properties:-

Sr. No.	PROPERTIES	DATA
1	Log *p*	3.02
2	Molar refractivity	99.41 cm^3
3	Molar volume	242.00 cm^3
4	Parachor	679.5 cm3
5	Index of Refraction	1.758
6	Surface Tension	62.1 dyne/cm

2.2-Molinspiration bioactivity score:-

Sr. No.	PROPERTIES	DATA
1	GPCR ligand	***-0.40***
2	Ion channel modulator	***-0.61***
3	Kinase inhibitor	***0.08***
4	Nuclear receptor ligand	***-0.72***
5	Protease inhibitor	***-0.75***
6	Enzyme inhibitor	***-0.14***

3-Compound code = A2



IUPAC Name:-

1-[(4-amino-5-sulfanyl-4*H*-1,2,4-triazol-3-yl)methyl]-8-bromo-4-phenylquinolin-2(1*H*)-one

Molecular formula:-C18H14BrN5OS

Molecular weight:-428.30566

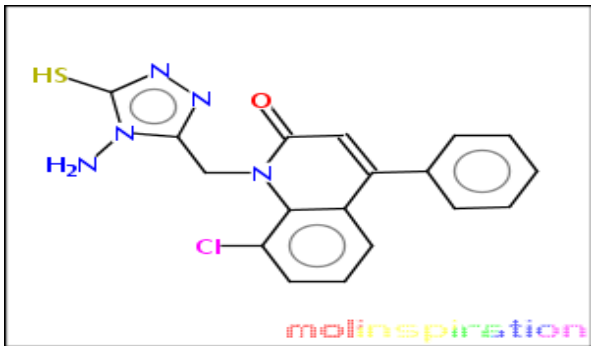
3.1-Physichochemical properties:-

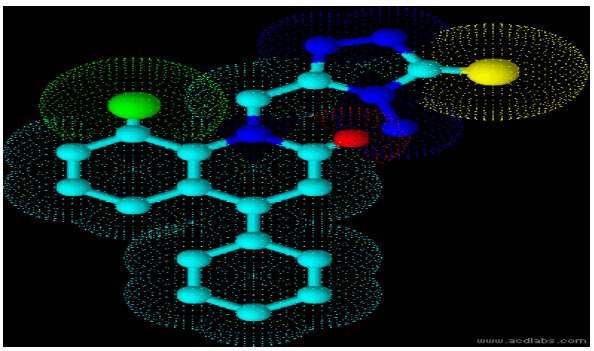
Sr. No.	PROPERTIES	DATA
1	Log *p*	3.78
2	Molar refractivity	99.63 cm^3
3	Molar volume	254.5 cm^3
4	Parachor	723.0cm3
5	Index of Refraction	1.781
6	Surface Tension	65.1dyne/cm

3.2Molinspiration bioactivity score:-

Sr. No.	PROPERTIES	DATA
1	GPCR ligand	***-0.48***
2	Ion channel modulator	***-0.74***
3	Kinase inhibitor	***0.05***
4	Nuclear receptor ligand	***-0.81***
5	Protease inhibitor	***-0.76***
6	Enzyme inhibitor	***-0.22***

4- Compound code = A3





IUPAC Name:-

1-[(4-amino-5-sulfanyl-4*H*-1,2,4-triazol-3-yl)methyl]-8-chloro-4-phenylquinolin-2(1*H*)-one

Molecular formula:-C18H14CIN5OS

Molecular weight:-483.85466

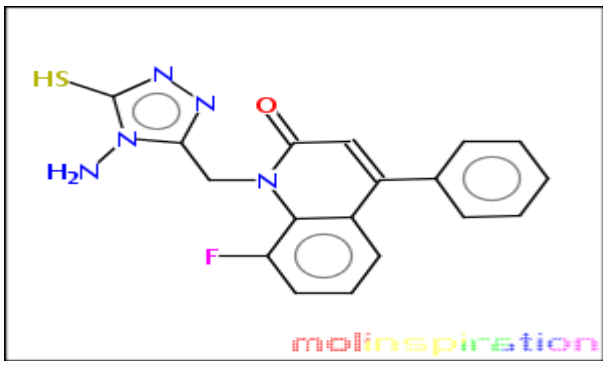
4.1-Physichochemical properties

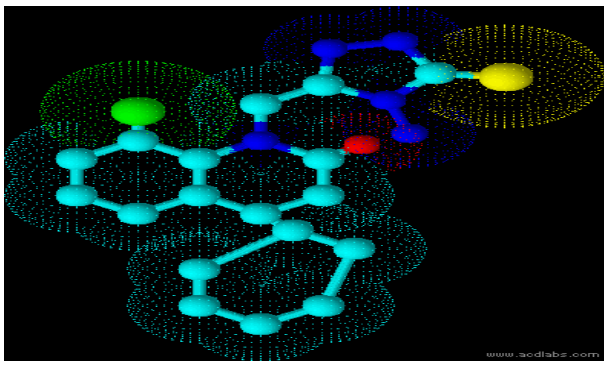
Sr. No.	PROPERTIES	DATA
1	Log *p*	3.65
2	Molar refractivity	104.01cm^3
3	Molar volume	251.02 cm^3
4	Parachor	708.3cm3
5	Index of Refraction	1.766
6	Surface Tension	63.1dyne/cm

4.2-Molinspiration bioactivity score:-

Sr. No.	PROPERTIES	DATA
1	GPCR ligand	***-0.39***
2	Ion channel modulator	***-0.60***
3	Kinase inhibitor	***0.09***
4	Nuclear receptor ligand	***-0.70***
5	Protease inhibitor	***-0.72***
6	Enzyme inhibitor	***-0.10***

5- Compound code = A4





IUPAC Name:-

1-[(4-amino-5-sulfanyl-4*H*-1, 2, 4-triazol-3-yl) methyl]-8-fluoro-4-phenylquinolin-2(1*H*)-one

Molecular formula:-C18H14FN5OS

Molecular weight:-367.4000632

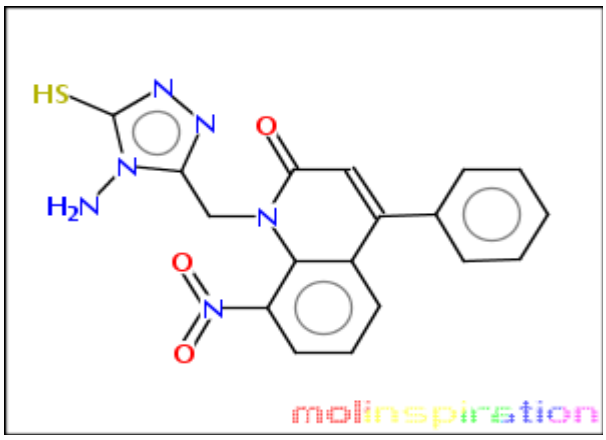
5.1-Physichochemical properties:-

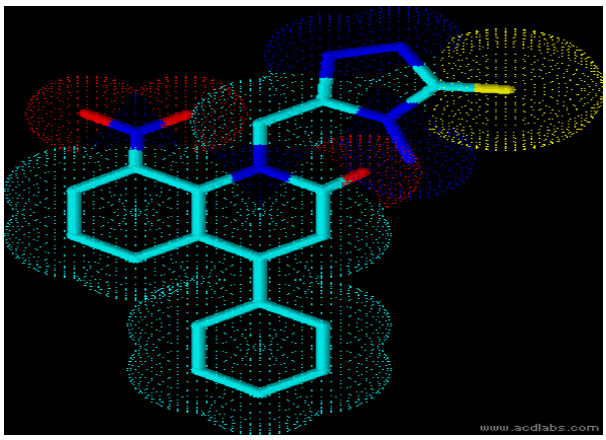
Sr. No.	PROPERTIES	DATA
1	Log *p*	3.14
2	Molar refractivity	99.28cm^3
3	Molar volume	244.8 cm^3
4	Parachor	379.7cm3
5	Index of Refraction	1.744
6	Surface Tension	59.3dyne/cm

5.2-Molinspiration bioactivity score:-

Sr. No.	PROPERTIES	DATA
1	GPCR ligand	***-0.30***
2	Ion channel modulator	***-0.56***
3	Kinase inhibitor	***0.07***
4	Nuclear receptor ligand	***-0.75***
5	Protease inhibitor	***-0.74***
6	Enzyme inhibitor	***-0.07***

6- Compound code = A5





IUPAC Name:-

1-[(4-amino-5-sulfanyl-4*H*-1,2,4-triazol-3-yl)methyl]-8-nitro-4-phenylquinolin-2(1*H*)-one

MOLECULAR FORMULA:-C18H14N6O3S

MOLECULAR WEIGHT:-394.40716

6.1- Physichochemical properties:-

Sr. No.	PROPERTIES	DATA
1	Log *p*	2.93
2	Molar refractivity	105.07cm^3
3	Molar volume	247.2 cm^3
4	Parachor	725.0cm3
5	Index of Refraction	1.793
6	Surface Tension	73.8dyne/cm

6.2-Molinspiration bioactivity score:-

Sr. No.	PROPERTIES	DATA
1	GPCR ligand	***-0.44***
2	Ion channel modulator	***-0.58***
3	Kinase inhibitor	***-0.08***
4	Nuclear receptor ligand	***-0.80***
5	Protease inhibitor	***-0.73***
6	Enzyme inhibitor	***-0.14***

7-DISCUSSION AND RESULT

From the above comparative graph we can conclude that for the methylphenylquinoline Triazol derivatives the best suitable receptor is Kinase inhibitor because all the derivative the value of Kinase comes out positive and it also near the 'O' value that means low energy is required. So we can say that the Kinase Inhibiter is used during the action of Methylphenylquinoline Triazol derivative drugs.

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