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A Review on Computational Study of Tribulin Compound and its Derivatives: QSAR Studies

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ABSTRACT

Tribulin, also known as isatin, is an indole-derived organic compound with the formula $C_8H_5NO_2$. 1H-andole 3,2-dione (1H-indole-2,3-dione) is a derivative of indole, which are heterocyclic compounds. Tribulin is a monoamine oxidase and benzodiazepine receptor binding inhibitor with a low molecular weight. It was extracted from human plasma and animal brain after being heavily purified from human urine. Tribulin, or Isatin and its derivatives have attracted a lot of interest in recent years due to their chemotherapeutic potential. This review provides last details on the most active isatin derivatives that have been confirmed to have anticonvulsant, antianxiety, and antipsychoactive properties. these findings can lead to new molecular modifications that result in compounds with more desirable pharmacological properties, by using the quantitative structure-activity relationship (QSAR). The evaluation of the QSAR results depends on the correlation coefficient (r^2) and the cross validation coefficient (q^2), which are two of the most important factors that determine the strength of the mathematical model.

Keywords: Tribulin, indole, QSAR, biological activity.

Introduction:

1H-indole-2,3-dione, tribulin or isatin was initially acquired by Erdman and Laurent in 1841 as a product of an oxidation process. Indigo dye is mediated by HNO_3 and H_2CrO_4 acids [1,2] . Tribulin or Isatin compounds consist mainly of a pyrol ring attached to a benzene ring as in the following structure [3,4] .

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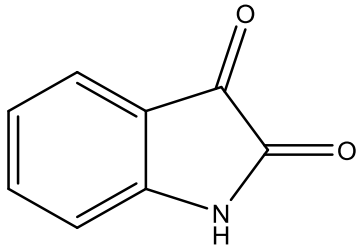

1H-indole-2,3-dione

1H-indole-2,3-dione is found in nature in many plants, genus Isatis, Calanth discolor, and Couroupita guianensis, and it is also found in the human body as metabolites of adrenaline derivatives [5-8].

This compound can be present naturally in plants of the genus Isatis, Calanthe discolor, and Couroupita guianensis -Aubl, as well as in the secretion of Bufo frogs' parotid gland. In addition it's a metabolic derivative of adrenaline in humans .

Tribulin or isatin was also got in plants, such as the melosatin alkaloids (methox phenylpentyl isatins) obtained from the Caribbean tumorigenic plant Melochia tomentosa. from fungi, contain substituted isatins. Streptomyces albus produced 6-(3'-methylbuten-2'-yl)isatin, and 5-(3’-methylbuten-2’-yl)isatin from Chaetomium globosum [9,10].

The study of QSAR is one of the most significant in modern chemistry because it allows the conversion of chemical compound properties and properties into mathematical equations that can be used in both theoretical and applied fields. QSAR is focused on defining the chemical compound, its molecular structure, and how its atoms bind to keep it stable, as well as analyzing its spatial position and obstruction, and determining its electronic and topographic characteristics, which give it physical and chemical properties that form a fingerprint.

The premise of QSAR techniques is that identical chemical-structures have the same properties, and it is the more variations among molecules, further difficult it is to compare their physical, and chemical properties, also the vital behaviors, while similarities between extremely similar molecules are much simpler. The software's implementation of QSAR to molecular modeling or (simulation), and drug design has resulted in the inclusion of computational chemistry approaches [11].

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Computational chemistry is concerned with determining the quantitative correlation of molecular configurations and behaviors using different chemometric methods. The QSAR technique's importance is the ability to figure out what a molecule's structural specifications are to display particular responses and predict the behavior of untested molecules, as well as the development of libraries on the internet [12].

Biological Activity:

1. Antimicrobial activity: The schiff bases for preparations of isatin and its derivatives are various compensators such as benzene-sulfonamide, quinoline is highly effective against germs and bacteria [13-15], and against fungi [16,17], as it occupies a wide field in the manufacture of a series of drugs for bacterias and fungi.

2. Anti-tuberculosis activity: Some scientists have been able to create tuberculosis-fighting compounds using fluoxin, ethyleneisatin, and derivatives [18].

3. Anticancer activity: The isatin analogs, benzothiazole, were prepared, which were effective against all types of cancer cells, but in varying proportions [19-22].

4. Anti-inflammatory activity: Preparation of a group of isatin derivatives such as triazolyisatins, isatinylidene and other derivatives resulting from compensation at different sites on the isatin ring has shown its efficacy against different types of infection to varying degrees [23-25].

5. Anti HIV activity: Isatin derivatives and analogs of aminoprimidine have shown efficacy against HIV [26,27].

6. Anticonvulsant activity: The anticonvulsant effect of various substances of indol such as 3- hydroxy-3-acetonyloxindole , which is prepared by combining isatin and acetone, has higher anticonvulsant activity than 3-hydroxyl-3-pehenacycloindole [28].

In addition to all of the above, isatin derivatives are effective against CNS Depressant Activity, (Central Nervous System Depression) [29,30], and isatin oximes were effective against different types of viruses [31-33]. Other Isatin derivatives also showed their effectiveness as antioxidant and antitumor [34-36].

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Due to its strong and different activity against many diseases therefore it played an important role in the pharmaceutical industry, as it became one of the most developed compounds of interest to chemists and pharmacists [37,38].

QSAR Studies of Tribulin as Isatin:

Many scholars have used theoretical analyses and computational calculations to do extensive analysis on the isatin and its derivatives. Numerous varied descriptors of these compounds and their substitutes, each according to their biological activity. These compounds have been studied by linking theoretical descriptors with their biological activity, which is known as the quantitative structure-activity relationship, (QSAR). We will review the most important of theoretical studies and their results:

In 2008, *Sharma* studied 25 compounds of isatin derivatives as he designed two models based on the two models on two descriptors. The statistical results of the first model were $r^2 = 0.857$, $q^2 = 0.821$, and the second model have $r^2 = 0.896$, $q^2 = 0.867$ [39].

In 2009, Wang and his assistants studied 59 isatin complexes, as it depended on 44 complexes to design 4 theoretical models. The first and second were based on 4 descriptors and the values of $r^2= 0.971$, $q^2= 0.925$ and $r^2= 0.968$, and $q^2= 0.910$ respectively. In the third and fourth models, 5 descriptors were used and the values of $r^2= 0.979$, $q^2= 0.945$ and $r^2= 0.967$, $q^2= 0.898$ respectively [40].

A theoretical study of isatin derivatives was also completed in 2010 by many researchers. Moorthy and his assistants designed two models through the theoretical study. The first was by using two descriptors and the values of $r^2= 0.87$, $q^2= 0.79$. The second model was using three descriptors and the values of $r^2= 0.84$, $q^2= 0.65$ appeared [41]. In the same year, another group of isatin derivatives was studied, Sabet and his assistants designed a model consisting of 4 descriptors with values of $r^2= 0.92$, $q^2= 0.90$ [42] .

Wang and his assistants designed two models, the first containing 5 descriptors of 19 compounds of isatin and its derivatives, and obtained values of $r^2= 0.928$, $q^2= 0.498$. The other model included 6 descriptors and the values of $r^2= 0.957$, $q^2=0.535$ [43].

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In 2013, Riham designed a model with 3 descriptors and obtained values of r^2= 0.903, q^2= 0.812 [44].

Isatine compounds and their derivatives were studied in 2014 by the researcher Kumar and his assistants, and they designed only two models with one descriptor of each model only for 28 compounds, and the results of r^2= 0.702, q^2= 0.639, While the second model has r^2= 0.541, q^2= 0.454. In addition, Kumar and his assistants also reached, by studying 14 compounds of isatin derivatives, to five mathematical models for different biological activities. The values of r^2 ranged between (0.519-0.960), and the values of q^2 ranged between (0.272-0.945) [45].

Boukarai had conducted a theoretical study of 47 isatin substitutes and derivatives in 2015 and designed a model that includes 5 descriptors with a value of r^2= 0.884 [46] .

While in 2019, Allangba and et al. studied 15 compounds of isatin chalcones. They designed a model that includes two descriptors, and the value of r^2 = 0.93 [47] .

Also in 2019 Srour and his workers syntheses of some new dispiro[indene-2,3′-pyrrolidine-2′,3″-indoline]-1,2″(3H)-dione as a result of decarboxylative condensation of isatines, then they study their activity by QSAR, using 26 compounds and 5 descriptors to make the mathematical model. the result was r^2=0.893 [48] .

Chemchem and et al. researched theoretically twelve isatin (Schiff bases) compounds made by reacting isatin and 5-bromoisatin with various anilines using green chemistry in the year 2020. When they used nine compounds, they gave the model's equation with three descriptors and the correlation coefficient r^2 = 0.7181[49] .

Recently, 30 different (QSAR) models of isatin-based oxadiazole derivatives were progressing using (CoMFA), and (CoMSIA), straightly. To study the chemical biological interaction of isatin-based oxadiazole derivatives as a Thymidine Phosphorylase (TP) inhibitor. The optimum (CoMFA), model had r^2 and q^2 of 0.920 and 0.697, while the best (CoMSIA), model had $r^2$and $q^2$of 0.912 and 0.692, respectively [50].

We can say that the efficiency of the model equation depends on the number of descriptors as well as the statistical criteria, The more details, data, and the fewer descriptors, the more efficient the calculation becomes, i.e. closer to mathematics.

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As previously said, statistics is an approximate approach as compared to mathematics.

Conclusion:

In drug screening and architecture, computational approaches have become increasingly important. Drug binding sites on target macromolecules can be identified and drug activity mechanisms can be elucidated using multiscale biomolecular simulations. Virtual scanning can scan large chemical databases for Tribulin (Isatin) compounds quickly and efficiently.

The numerous QSAR approaches were briefly explored in this review. Despite the fact that these methodologies have certain drawbacks, they have a lot of uses in the biological activities of Tribulin (Isatin) compounds. QSAR is a valuable medicinal chemistry method for quantitatively and retrospectively understanding structure-activity relationships, as well as developing synthetic guidance that leads to rational and experimentally testable hypotheses. Before applying predictive models to real-world scenarios, it's important to understand the fundamental shortcomings of QSAR methodologies to prevent misuse and misinterpretation. Moreover, the problems with alignment dependence and conformational flexibility, in particular, must be taken into account. A thorough understanding and error-free application of QSAR modeling would undoubtedly help medicinal chemists prioritize their experimental activities and increase experimental hit rates significantly.

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