Quantitative Structure–Activity Relationship Studies of Anticancer Activity for Isatin (1H-indole-2,3-dione) Derivatives Based on Density Functional Theory

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ABSTRACT

To establish a QSAR of anticancer activity for Isatin derivatives, a series of Isatin derivatives were analyzed by principal component analysis, multiple linear regression, partial least squares and multiple nonlinear regression analysis. The authors proposed linear and nonlinear models and interpreted the activity of the compounds by multivariate statistical analysis. The proposed models were used to predict the activity of test set compounds, and an agreement between experimental and predicted values was verified. The applicability domain of MLR models was investigated using William’s plot to detect outliers and outsiders compounds. For the successful application of the developed models to predict new compounds, rigorous validation tests have been used in this direction. Additionally, the \( r_m^2 \) metrics have been used to ensure the close agreement of predicted response data with observed ones. The developed models have been used for designing some new Isatin derivatives with high predicted values of anticancer effect.

KEYWORDS
Anticancer, Cross Validation, Density Functional Theory, Isatin, Quantitative Structure–Activity Relation

INTRODUCTION

Isatin (1H-indole-2,3-dione) is an indole derivative and an important class of heterocyclic compounds found in many plants, such as Isatistinctoria, Calanthe discolor and Couroupitaguaianensis (Da Silva, Garden & Pinto, 2001). It is also found in humans as a metabolic derivative of adrenaline (Sonawane & Tripathi, 2013).

Isatin was first obtained as a product from chromic acid oxidation of indigo dye by Erdmann and Laurent (Erdmann, 1840; Laurent, 1840) in 1841, and their synthetic derivatives are important substrates used for the synthesis of a variety of heterocyclic compounds, and used as raw materials for drug synthesis. Isatin and its derivatives are well known therapeutic agents due to their wide range of pharmacological and biological activities including anticancer (Lee, Long, Murray et al., 2001; Chapman, Magee, Stukenbrok et al., 2002), anticonvulsant (Verma, Pandey, Singh et al., 2004), antiviral (Sriram Tanushree & Yogeeswari, 2004; Pirrung, Pansare, Sarma et al., 2005), antibacterial and antifungal (Chohan, Pervez, Rauf et al., 2004), anti-HIV and anti-inflammatory activities (Lashgari

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& Ziarani, 2011; Mishra & Bauerle, 2012; Walker, Kim & Nguyen, 2012). Isatins used as a starting point in the synthesis of oligomeric or polymeric structures which are used in the field of solar energy (Zhang, Fu, Xie et al., 2011), organic memory devices creation (Xu Li, Liu et al., 2011) and organic field effect transistors (Lei, Cao, Fan et al., 2011; Ashraf, Kronemeijer, James et al., 2012).

Many methodologies have been adopted to synthesize Isatin derivatives and to explore their possible role in the treatment of various diseases. Among these protocols, the method developed by Sand-Meyer is the oldest and the most frequently used for the synthesis of Isatin (Rehn, 2004). This method involves the reaction of aniline with chloral hydrate and hydroxylamine hydrochloride in aqueous sodium sulfate to form an isonitrosoacetanilide, which after isolation, when treated with concentrated sulfuric acid produces Isatin.

Looking at the literature, it can be seen that in particular, halogenated isatin derivatives have been reported to exhibit anticancer activity. 5-Bromo-3-o-nitrophenyl isatinhydrazone and 5-bromo-(2-oxo-3-indolinyl) thiazolidine-2,4-diones substituted by various Mannich bases were found to exhibit anticancer activity against Walker carcinoma-256 and P388 lymphocytic leukemia in mice, respectively (Esheba & Salama, 1985; Popp & Pajouhesh, 1983). 6-Bromo-2- methylthio-3H-indol-3-one, tyridolinenone, a brominated precursor to Tyrian purple, isolated from the egg masses of the Australian mollusk Dicathaisorbits has been reported as a cytotoxic marine compound (Westley, Vine, Benkendorff et al., 2006). 6-bromoisatin, a major decomposition product formed through the oxidation of tyriverdin (precursor of Tyrian purple), has been shown to have a weaker anti-cancer activity against a human lymphoma cell line in comparison with 6-Bromo-2- methylthio-3H-indol-3-one (Westley, Vine, Benkendorff et al., 2006; Benkendorff, Bremner & Davis, 2001). 5,7-Dibromoisatin, a significantly more potent as a cytotoxic than Isatin against U937 (human monocyte-like histiocytic lymphoma) cells (Vine, Locke, Ranson et al., 2007), its N-benzyl derivatives with more cytotoxicity toward these lymphoma cells and activity against a range of human cancer cell lines including a metastatic breast adenocarcinoma cell line (MDA-MB-231) (Vine, Locke, Ranson et al., 2007), and cytotoxic N-alkylhaloisatins are some examples of reported anticancer halogenated Isatins in recent researches (Vine, Locke, Ranson et al., 2007; Matesic, Locke, Bremner et al., 2008). In the recently approved drugs by FDA, a 5-fluoro-3-substituted-2-oxoindole, SU11248 (Sutent) is provided for the treatment of gastrointestinal stromal tumors and advanced renal-cell carcinoma (Prenen, Cools, Mentens et al., 2006; Motzer, Michaelson, Redman et al., 2006).

The experiment is a direct way to obtain the activity data of organic compounds, which has many deficiencies, such as the requirement of large trial organisms, high expense, long time duration, difference in measured value between different researchers. Consequently, it would be impossible to search the activity values of all organic compounds by experiments. As new compounds are springing up, other difficulties will also arise. Therefore, it is necessary to use the theoretical methods to make up the disadvantages of the experiment and to predict the data of compounds exactly.

With the rapid development of computer science and theoretical quantum chemical studies, one can speedily and precisely obtain the quantum chemical parameters of compounds by computation. These structural parameters along with the introduction of the quantitative structure-activity relationship (QSAR) models can increase the interpretability and predict the activity of new organic compounds. In this paper, the authors will focus on the anticancer activity of some Isatin derivatives.

In order to open a new way in anticancer drug research, a series of 40 Isatin derivatives were studied for their anticancer activity (Sabet, Mohammad, Sadeghi et al., 2010; Westley, Vine, Benkendorff et al., 2006; Matesic, Locke, Bremner et al., 2008). The aim of this study is to develop QSAR models able to correlate the structural features of the derivatives of Isatin with their anticancer activity. A variety of molecular descriptors were calculated to develop models with the studied activities
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