Iranian Journal of Analytical Chemistry
Volume 7, Issue 1, March 2020 (64-69)

مجله ایرانی شیمی تجزیه
دوره۷، شماره ۱، فروردین ماه ۱۳۹۹ (۶۹-۶۴)

Molecular Design of N-Salicyloyl Tryptamine Derivatives Via Quantitative Structure-Property Relationship (QSPR) and Molecular Dynamic Simulation Methods

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Received: 19 January 2020 **Accepted:** 23 March 2020
DOI: 10.30473/ijac.2020.52687.1169

Abstract
N-salicyloyl tryptamine derivatives as anti-neuroinflammatory agents have a potent strategy to cure neuroinflammatory diseases including Alzheimer and Parkinson. Computational methods of quantitative structure properties relationships (QSPR) and molecular dynamics were successfully used to design of four novel N-salicyloyl tryptamine with improved properties. The QSPR model of five variables was presented to predict anti-neuroinflammatory activity of N-salicyloyl tryptamine derivatives. The quantum descriptors as Hartree Fock energy, ionization energy, softness, dipole moment and the thermal energy, were calculated with density functional theory at the B3LYP/6-311G level. Cross validation of multivariate linear regression (MLR) was used to build and evaluate the model QSPR. The model possesses coefficients of the highest squared correlation coefficient (R^2) of 0.900 for the training set and 0.817 for the test set. The statistical results exhibited high internal and external consistency as demonstrated by the validation methods. Three of designed compounds showed good pharmacokinetic properties by QSPR predictions. These results provided strong guidance for the discovery and design of novel potential anti-neuroinflammatory compounds. Also, the adsorption of the designed compounds on functionalized carbon nanotube (8, 0) was investigated using molecular dynamics simulation with COMPASS force field. Results indicated that the adsorption of designed N-salicyloyl tryptamine derivatives on f-CNT involves a partial π–π interaction and hydrogen bonding. The study of investigation the interactions of N-salicyloyl tryptamine with f-CNT (8, 0) can be useful for finding the main CNT-based carriers for these derrivatives.

Keywords
QSPR; N-Salicyloyl Tryptamine Derivatives; Dynamic Molecular; Density Functional Theory; Functionalized-Carbon Nanotube.

1. INTRODUCTION

One of an important defense mechanisms against damage toxins is Neuroinflammation, but persistent neuroinflammation can ultimately contribute to neurodegeneration, such as Parkinson or Alzheimer diseases and caused in neuronal death [1]. Hence, searching the multi-functional candidates is an imminent strategy of designing anti-neuroinflammation agents. As well as, salicylic acid derivatives have been introduced to alleviate neuroinflammation [2]. The mechanism of multi-functional agents may involve targeting Cyclooxygenase (COX), a key enzyme in fatty acid metabolism, a therapeutic target for treating neuroinflammation[3]. Also, N-salicyloyl tryptamine have been applied as anticonvulsant agents or anti-inflammatory, but it as anti-neuroinflammatory agents has not been reported [4]. To betterment and modification of anti-neuroinflammatory activities of N-salicyloyl tryptamine compounds, two kinds of derivatives which had different substituents (hydroxyl, amine) have been synthesized by Fan and coworkers [5]. They have been reported a series of N-salicyloyl tryptamine derivatives with multifunctional properties including radicals scavenging, COX inhibition, attenuating activation of glial cells, and attenuating neuronal damage.

Quantitative structure–property relationships (QSPR) is good tool for the modeling and prediction of physicochemical and biological properties of molecules and describes how a given physicochemical property varies as a function of molecular descriptors [6, 7]. QSPR and dynamic molecular simulations are commonly used computational technique that can speed up and save resources the process of designing better molecules [8]. QSAR modelling and electronic feature analysis of benzofuran salicylic acid derivatives as lymphoid tyrosine phosphatase (LYP) inhibitors has been studied by V. Suryanarayanan and coworkers [9]. An investigation on the quantitative structure-activity relationships of the anti-inflammatory activity of diterpenoid alkaloids have been done by Li and co-workers [10]. This research work was aimed at designing more effective N-salicyloyl tryptamine

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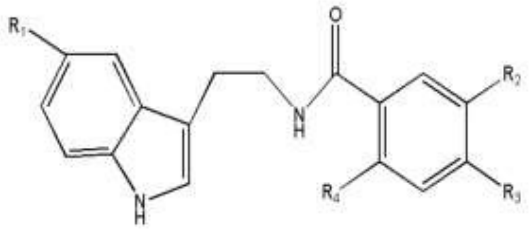
derivatives and to determine the dynamic binding strength of the f-CNT at different working conditions on. The stability of salicylic acid derivatives on the functionalized (8, 0) zigzag carbon nanotube as a drug delivery vehicle is studied within the formalism of the density functional theory calculations to understand the role of the pyrrolidine functional group in binding the adsorbed molecule to the drug delivery.

2. EXPERIMENTAL

The dataset of the N-salicyloyl tryptamine derivatives together with their anti-neuroinflammation agents values were selected from the literature [5] and used in this research work. The training set was used for the construction of the QSPR models while test sets were used to check the predictive ability of the generated models. The half maximal inhibitory concentration (IC50) values of N-salicyloyl tryptamine derrivatives represent the potential of a molecule in inhibiting a specific biological or biochemical function. The two dimensional structures of all the N-salicyloyl tryptamine derivatives (Fig. 1) were drawn with the Gauss view 5 software. Quantum chemical calculations are used to calculate electronic and quantum chemical descriptors, using the density functional theory (B3LYP/6-311G DFT) methods [11]. All calculations were done using Gaussian09 suite of program [12]. The quality assurance (reliability and predictive ability) of the developed QSPR model were accessed by internal (R^2, R^2 adj,) and external (R^2_{ext}) validation parameters. Furthermore, these validation parameters were contrasted and the base standard prescribed for the standard acceptable QSPR parameters [13].

2.2 Molecular dynamics simulation studies

Dynamics simulation calculations were performed to describe and determine the interaction between the N-salicyloyl tryptamine derivatives molecules and functionalized single carbon nanotube (8, 0). Molecular simulations are carried out by Material Studio (8.0) software [14]. The simulation approach consists of molecular dynamics and mechanics calculations utilizing the Forcite module [15]. The force field of the Condensed-phase Optimized Molecular Potentials for Atomistic Simulation Studies (COMPASS) is used for MD simulation, being one of the first ab initio force field methods validated and parameterized by the condensed-phase features [16].



Comp.	R1	R2	R3	R4	Comp.	R1	R2	R3	R4
1	H	H	H	3-Cl-2-Me-PhNH	14	OMe	H	H	NHPH
3	H	H	Me	OH	16	OH	H	H	NHPH
4	Me	H	H	OH	18	Cl	H	H	NHPH
5	H	Cl	H	Oh	19	Me	H	H	3-Cl-2-Me-PhNH
6	H	H	H	NHMe	20	OMe	H	H	3-Cl-2-Me-PhNH
7	H	H	OH	OH	22	H	H	H	2,3-di-Me-PhNH
8	Me	H	H	NHPh	23	H	H	H	OH
9	OH	H	H	OH	24	H	H	H	N(Me)2
11	H	Me	H	OH	25	OH	H	H	2,3-di-Me-PhNH
12	H	H	F	OH	26	H	H	H	NMePh
13	H	H	H	NHPh	27	OH	H	H	N(Me)2

Fig. 1. The structure of N-salicyloyl tryptamine derivatives

Table 1. Designed N-salicyloyl tryptamine derivatives and their predicted IC_{50}.

No.	R_1	R_2	R_3	R_4	Predicted IC_{50}
A	-OH	-Cl	-F	-NHPh	5271.6367
B	$-OCH_3$	$-CH_3$	-OH	$-N(Me)_2$	-3.8482
C	-Cl	-OH	-H	-NMePh	-9.8779
D	$-CH_3$	$-CH_3$	-H	-3-Cl-2-Me-PhNH	7.4025

In all the simulations, the temperature is equilibrated with the Andersen algorithm [17]. The dynamic simulation calculations were carried out after introducing the optimized N-salicyloyl tryptamine derivatives into the simulation vacuum slab of geometrically optimized hydrogen-containing f-SWCNT (8, 0). It can be seen in the Fig. 2. Using equation 1, the dynamic binding energy-strength was calculated for the f-SWCNT (8, 0) [18].

The binding energy ($E_{binding}$) between the N-salicyloyl tryptamine derivatives and the f-CNT can be calculated using the following formula:

$$E_{binding} = E_{total} - E_{\text{f-SWCNT}} - E_{NST} \quad (1)$$

Where, $E_{binding}$ represents the energy of the adsorption structure, $E_{\text{f-SWCNT}}$ shows the energy of f-WCNT, and E_{NST} denotes the energy of one isolated dopamine molecule. All values of energies are obtained by optimization of the geometry structure.

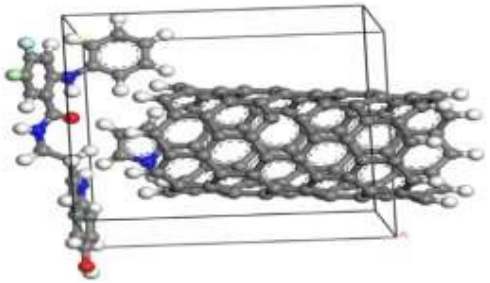


Fig. 2. The optimized structure of the f-CNT and designed compound (A).

3. RESULTS AND DISCUSSION

3.1. Analysis and validation

To propose a mathematical model and to quantitatively evaluate the substituent's physicochemical effects on IC50 for the set consisting of N-salicyloyl tryptamine derrivatives, we submitted the data matrix that was composed of the 12 variables that corresponded to the training set to a descendent multiple regression analysis. The decreasing study of MLR based on the elimination of descriptors aberrant until a valid model. This method used the coefficients R, R^2, MSE and F-values to select the best regression performance, where r is the correlation coefficient; r^2 is the coefficient of determination; MSE is the mean squared error; and F is the Fisher F-statistic.

The selected descriptors are: the Hartree Fock energy (HF), ionization energy ($I=-E_{HOMO}$), softness (σ), dipole moment (DM) and the thermal energy (Et). The QSPR model built using the multiple linear regression (MLR) method is represented by the following equation:

$$IC_{50} = 0.016 * (HF) + 359.378 * (I) + 2.486 * (\sigma) - 3.251 * (\text{DM}) + 0.02 * (\text{Et}) - 66.028 \quad (2)$$

Therefore, we can conclude, with confidence, that the model brings a significant amount of information. The elaborated QSPR model reveals that the IC50 could be explained by a number of electronic factors (I, σ and HF). The negative correlation of these factors with the IC50 in equation 1 shows that an increase in the values of these factors implies a decrease in the value of IC50. The predicted IC50 values calculated from equation 2 using the optimal MLR model are given in Table 1 for design compounds.

3.2. Dynamic molecular simulation generation and analysis

Dynamic molecular simulation calculations were carried out between all the designed molecules on the functionalized single carbon nanotube (8, 0) to determine the dynamic binding energies using Eq. (1). The four novel designed anti-neuroinflammatory agents with serial number of 1,2,3,4 were found to have dynamic binding strength of –29.83 kcal/mol, -35.72 kcal/mol, -38.72 kcal/mol and -26.32kcal/mol respectively. According to our theoretical calculations, the negative sign of the calculated binding energy shows all functionalized configurations are energetically stable. Also, it can be concluded that the interaction between the designed N-salicyloyl tryptamine derivatives and f-SWCNT demonstrates a weak chemisorption characteristic in nature. The negative binding energy corresponds to favorable binding of N-salicyloyl tryptamine derivatives to the functionalized nanotube and presence of the active sites available for hydrogen bond formation facilitates better drug binding to the nanotube. The results presented in this paper indicate that pyrrolidine functionalized carbon nanotube seems to be a novel material for drug delivery applications.

4. CONCLUSION

QSPR and MD methods were used to design four novel N-salicyloyl tryptamine derivatives. By defining the quantum descriptors in the regression model, we finalize that the decreased dipole moment (DM) as well as the increased values of Hartree Fock energy (HF), ionization energy ($I=-E_{HOMO}$), softness (σ) and the thermal energy (Et). are valid for the larger activity of the studied compounds (Table 1) gau. The anti-neuroinflammatory improved properties (5271.6367, -33.8482, -9.8799 and 7.4025) of our designed compounds were calculated. IC50 values of A and C designed derivatives are positive while IC50 values of B and D designed compounds are negative. The first designed compound (A) due to electronegative groups, has good activity Moreover, the result of molecular dynamics simulations in which C compound with

the most promised binding dynamic energy of (-38.72kJ/mol kcal/mol was found to be dynamically bound better on the simulated f-CNT(8,0). This research will help designing new N-salicyloyl tryptamine derivatives with improved properties. Results indicated that the adsorption of designed N-salicyloyl tryptamine derivatives on f-CNT involves a partial π–π interaction and hydrogen bonding, our results suggest that altering the functionalization of the nanotube surface can affect the drug–nanotube interaction. The results reported here should aid attempts to optimize the design of novel f-CNT-based drug carriers.

Acknowledgments
We gratefully thank Payam Noor University for financial support. The authors would like to express their appreciations to department of chemistry this university for providing research facilities.

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طراحی مولکولی مشتقات N سالیسیلول تریپتامین با استفاده از روش‌های رابطه کمی خواص- ساختار و شبیه‌سازی دینامیک مولکولی

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تاریخ دریافت: ۲۹ دی ۱۳۹۸ تاریخ پذیرش: ٤ فروردین ۱۳۹۹

چکیده

مشتقات N سالیسیلول تریپتامین به‌عنوان عامل های ضدحساسیت عصبی دارای پتانسیل درمانی بیماری های الزایمر و پارکینسون می‌باشند. روش¬های محاسباتی روابط کمی خواص- ساختار(QSPR) و شبیه‌سازی دینامیک مولکولی برای طراحی چهار ترکیب جدید مشتقات N سالیسیلول تریپتامین بصورت موفقیت‌آمیز استفاده گردید. مدل QSPR پنج متغیره برای پیش‌بینی خواص و فعالیت ضد التهاب عصب مشتقات N سالیسیلول تریپتامین ارائه گردید. توصیف گرهای کوانتومی مانند، انرژی هارتری فاک، انرژی یونش، ممان دوقطبی و انرژی گرمایی با استفاده از روش نظریه تابعیت چگالی در سطح B3LYP/6-311G محاسبه گردید. اعتبارسنجی متقابل رگرسیون خطی چند متغیره MLR برای طراحی مدل QSPR استفاده گردید. مدل دارای بالاترین ضریب همبستگی R^2 برابر ۰/۹۰۰برای سری آموزش و ۰/۸۱۷ برای سری تست می‌باشد. نتایج آماری سازگاری داخلی و خارجی بالایی را بوسیله روش‌های اعتبار سنجی نشان می‌دهد. سه مورد از ترکیبات طراحی شده، خواص دارویی خوبی را با مدل QSPR ارائه می‌دهند و می‌تواند راهنمای مناسبی برای کشف و طراحی ترکیبات جدید با خاصیت ضد التهابی عصبی را فراهم می‌نماید. همچنین جذب ترکیبات طراحی شده بر روی نانولوله کربنی (۸و۰) عامل‌دار با استفاده از شبیه‌سازی دینامیک مولکولی ومیدان نیرو COMPASS انجام گردید. نتایج جذب مشتقات طراحی شده بر نانولوله کربنی (۸و۰) عامل‌دار نشان داد که برهمکنش‌ها می‌توانند شامل برهمکنش‌های جزئی π–π و پیوندهای هیدروژنی باشند. مطالعه برهمکنش این ترکیبات با نانولوله کربنی (۸و۰) عامل‌دار جهت یافتن حامل‌های دارویی پایه نانولوله کربنی برای این مشتقات، می‌تواند مناسب باشد.

واژه‌های کلیدی

روابط کمی خواص- ساختار (QSPR)؛ مشتقات N سالیسیلول تریپتامین؛ دینامیک مولکولی؛ نظریه تابعیت چگالی؛ نانولوله کربنی عامل‌دار.