Journal of the Serbian Chemical Society
JSCS-info@shd.org.rs • www.shd.org.rs/JSCS
J. Serb. Chem. Soc. 86 (7–8) 625–637 (2021)
JSCS–5449
Original scientific paper

Quantitative structure–activity relationship modelling of influenza M2 ion channels inhibitors

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(Received 9 May 2020, revised 15 March, accepted 5 May 2021)

Abstract: A series of adamantane derivatives (rimantadine and amantadine) incorporating amino-acid residues are investigated by simplex representation of molecular structure (SiRMS) approach in order to found correlation between chemical structures of investigated compounds and obtained data for antiviral activity and cytotoxicity. The obtained data from QSAR analysis show that adamantane derivatives containing amino acids with short aliphatic non-polar residues in the lateral chain will have good antiviral activity against the tested virus A/H3N2, strain Hong Kong/68 with low cytotoxicity. QSAR experiments and *in vitro* data also show good correlation and reveal that modified adamantine derivatives including guanidated in the lateral chain amino acid and *β*-amino acids as substituents show low to none activity.

Keywords: QSAR study; molecular simplex; adamantine derivatives; amantadine; rimantadine; amino acids.

INTRODUCTION

Adamantane derivatives have been used successfully for the prevention and treatment of influenza A virus infection for more than 30 years.[1,2] The aminoadamantanes (amantadine and rimantadine) block M2 proton channel and thus stop virus replication. However, they are no longer effective because of widespread drug resistance. S31N is the predominant and amantadine-resistant M2 mutant, present in almost all of the circulating influenza A strains as well as in the pan-

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https://doi.org/10.2298/JSC200509036S

demic 2009 H1N1 and the highly pathogenic H5N1 flu strains.[3] Structural and biochemical studies of the S31N mutant showed that replacing ^{31}Ser, which is located in the helix–helix interface, with the bulkier Asn results insubstantially weaker helix–helix packing. Since the pocket is composed of residues from two adjacent TM helices, the stability and physical properties of the pocket depend on the dynamics and conformation of helical packing.[4] The M2 proton channel from influenza A virus, a prototype for a class of viral ion channels known as viroporins, conducts protons along a chain of water molecules and ionizable side-chains, including ^{37}His. Drugs inhibit proton conduction by binding to an aqueous cavity adjacent to M2's proton-selective filter, thereby blocking access of proton to the filter, and altering the energetic landscape of the channel and the energetics of proton-binding to ^{37}His. According to Gaiday *et al.* studied cage compounds inhibit the M2 ion channel by binding to the ^{37}His residue. The adamantane cage fits into a pocket formed by ^{41}Trp residue, while the hydrogen bond is formed between hydrogen atom of ammonium nitrogen and the nitrogen of histidine residue.[6] One of the possible approaches to restore the antiviral properties of this class of compounds is to incorporate more than one functional group in their molecule. Amino acids and peptides are promising alternative for such kind of modification because of their multi functionality.

Herein, we report the QSAR analysis of some adamantanes modified with different substituents and the role of specific modifications on the biological activity.

EXPERIMENTAL

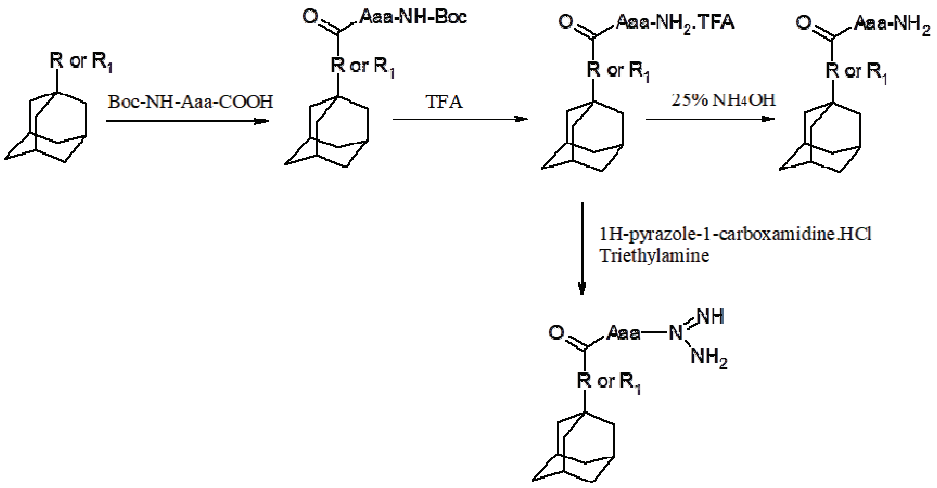
Chemical synthesis

Compounds aimed to this study were previously synthesized according to Scheme 1.

The synthetic protocol of target compounds was as follow: 3 mmol of 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate (TBTU) was dissolved in 15 mL CH_2Cl_2. Further, the corresponding Boc-$^{\alpha}$N-protected amino acid (3 mmol) and DIPEA (3.1 mmol) were added to a solution of TBTU. The obtained mixture was stirred at room temperature for 30 min and 3 mmol of rimantadine or amantadine and 3 mmol *N*,*N*-dimethylaminopyridine (DMAP) were also added. This mixture was stirred at room temperature for another 3 h, and then evaporated to dryness. After evaporation the obtained oil was purified by flash chromatography in system ethyl acetate:*n*-hexan (50:50 volume ratio).

1 eq. of Boc-$^{\alpha}$N-Aaa-amantadine or Boc-$^{\alpha}$N-Aaa-rimantadine was dissolved in 10-fold excess of trifuoroacetic acid (TFA) at 0 °C. The reaction mixture was stirred until fully deprotection of Boc-group under chromatographic control in systems chloroform-methanol (95:5 volume ratio). The excess of TFA evaporated and the obtained oil was dissolved in 10 mL methanol. Further 25 % ammonium hydroxide was added until the pH reached around 8. The solvent was evaporated under vacuum. Tha obtained crystals were dissolved in ethyl acetate and washed with 3×25 mL water. The organic layers were combined, dried on anhydrous Na_2SO_4 and solvent removed under vacuum. The yield of all compounds as well as ^{1}H- and ^{13}C-NMR analysis confirming their structures are given in Chayrov *et al.*[17]

For guanidated analogues synthesis the following procedure was used.



Scheme 1. Synthesis of amino acid derivatives of adamantine; R = $–NH_2$ is amantadine (Am), R = CH_3CHNH_2 is rimantadine (Rim), Aaa = amino acid; for amantadine Aaa = Ala; Phe; Phe(4-F); Val; for rimantadine Aaa = Ala; Gly; Ile; Leu; Phe; D-Phe(4-F); L-Phe(4-F); Val; beta-Ala; Tyr.

0.67 mmol of Boc-deprotected Aaa-rimantadine or Aaa-amantadine was dissolved in 2 mL of acetonitrile. Further to the obtained solution 1.00 mmol of 1*H*-pyrazole-1-carboxamidine hydrochloride and 2.0 mmol triethylamine were added. The reaction was run for 48 h at room temperature. At the end of the reaction time the solvent was evaporated under vacuum. The obtained crude oil was dissolved in 25 mL chloroform and washed several times with 5 % $NaHSO_4$ (pH 3). The organic layers were combined, dried with anhydrous Na_2SO_4 and solvent was evaporated under vacuum. The residue was crystalized in methanol/diethyl ether.

Biological studies

The results obtained by the realized biological tests[17] are presented in Table I.

TABLE I. Data of biological tests of studied compounds; *CC* is cytotoxic concentration; *HNTC* is high-nontoxic concentration

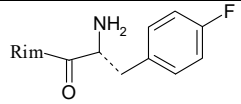
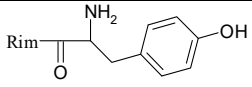
No.	Structural formula of compound (abbreviation)	CC_{50} / μM MDCK cells		*HNTC* / μM MDCK cells		IC_{50} / μM Against A/Hong Kong/68	log (IC_{50} / μM)
		Average	Class numb.	Average	Class numb.	Average	–
1	 (D-Phe(4-F)-Rim)	19.91	**1**	6.23	**1**	100.00	**2.00**
2	 (L-Tyr-Rim)	> 100	**0**	9.97	**1**	0.52	**–0.28**

TABLE I. Continued

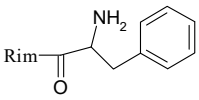
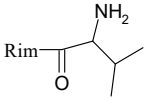
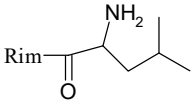
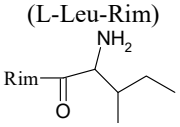
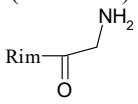
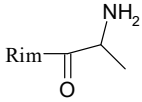
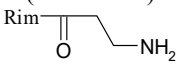
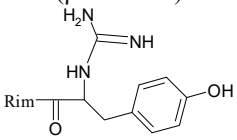
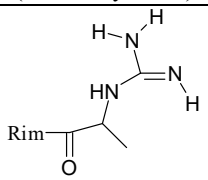
No.	Structural formula of compound (abbreviation)	CC_{50} / μM MDCK cells		*HNTC* / μM MDCK cells		IC_{50} / μM Against A/Hong Kong/68	log (IC_{50} / μM)
		Average	Class numb.	Average	Class numb.	Average	–
3	 (L-Phe-Rim)	21.93	**1**	4.75	**1**	100.00	**2.00**
4	 (L-Val-Rim)	70.33	**1**	10.20	**1**	100.00	**2.00**
5	 (L-Leu-Rim)	> 100	**0**	11.66	**1**	0.75	**–0.12**
6	 (L-Ile-Rim)	58.35	**1**	5.33	**1**	100.00	**2.00**
7	 (L-Gly-Rim)	> 100	**0**	13.89	**1**	0.11	**–0.96**
8	 (L-Ala-Rim)	> 100	**0**	14.65	**1**	1.53	**0.18**
9	 (β-Ala-Rim)	> 100	**0**	20.78	**1**	15.72	**1.20**
10	 (Gua-L-Tyr-Rim)	> 100	**0**	36.69	**1**	8.19	**0.91**
11	 (Gua-L-Ala-Rim)	> 100	**0**	> 100	**0**	41.90	**1.62**

TABLE I. Continued

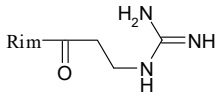
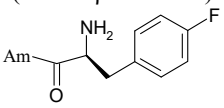
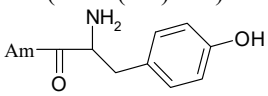
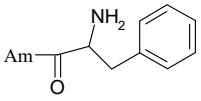
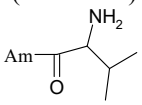
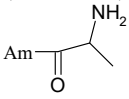
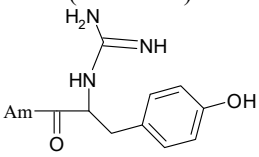
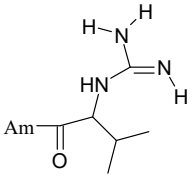
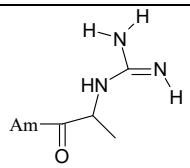
No.	Structural formula of compound (abbreviation)	CC_{50} / μM MDCK cells		*HNTC* / μM MDCK cells		IC_{50} / μM Against A/Hong Kong/68	log (IC_{50} / μM) –
		Average	Class numb.	Average	Class numb.	Average	
12	 (Gua-L-β-Ala-Rim)	> 100	**0**	> 100	**0**	100.00	**2.00**
13	 (L-Phe(4-F)-Am)	83.61	**1**	15.35	**1**	0.81	**–0.09**
14	 (L-Tyr-Am)	> 100	**0**	> 100	**0**	3.93	**0.59**
15	 (L-Phe-Am)	89.40	**1**	15.10	**1**	0.75	**–0.12**
16	 (L-Val-Am)	> 100	**0**	> 100	**0**	1.32	**0.12**
17	 (L-Ala-Am)	> 100	**0**	> 100	**0**	1.41	**0.15**
18	 (Gua-L-Tyr-Am)	> 100	**0**	> 100	**0**	59.71	**1.78**
19	 (Gua-L-Val-Am)	> 100	**0**	> 100	**0**	17.13	**1.23**

TABLE I. Continued

No.	Structural formula of compound (abbreviation)	CC_{50} / μM		*HNTC* / μM		IC_{50} / μM	log (IC_{50} / μM)
		MDCK cells		MDCK cells		Against A/Hong Kong/68	
		Average	Class numb.	Average	Class numb.	Average	–
20	 (Gua-L-Ala-Am)	> 100	**0**	> 100	**0**	18.37	**1.26**
21	Am-H	> 100	**0**	n/a	**0**	0.39	**–0.41**
22	Rim-H	–	**–**	–	**–**	0.06	**–1.25**

QSAR calculations

In the present study the simplex representation of molecular structure (SiRMS) approach[7,8] was used for calculation of structural descriptors for all investigated compounds. The simplex approach is based on isolating and counting the number of molecular fragments (pairs, triples, quadruples of atoms).

Any molecule in the framework of SiRMS can be represented as a system of different specific fragments (simplexes) of fixed composition and topology. Various atomic characteristics can be used for the vertex differentiation in the simplex, such as the uniqueness of the atom (atom nature or a more detailed type), electronegativity, partial charge, lipophilicity, electronic polarizability (refraction), H-bond donor/acceptor potential, van der Waals interactions, *etc.* For atomic characteristics having real values (electronegativity, lipophilicity *etc*.) at the preliminary stage the range of values is divided into a certain number of groups G (G is a tuning parameter of models and can vary, as a rule from 3 to 7; see the example showing how using vertexes differentiation by atomic charges in Supplementary materials).

In addition, electronegativity, refraction, molecular weight and octan-1-ol–water partition coefficient (Log *P*) are calculated as integral characteristics that describe the whole molecule.

The calculation of descriptors was carried out at the 2D level of molecular structure representation. The 2D-QSAR models are the most popular in structure-property studies.[7,8] In this case only molecular topology is taken into account, i.e. all information is extracted from the structural formula.

The relationships between the calculated molecular descriptors and the studied properties of investigated molecules were established by methods of partial least squares (PLS)[9] and random forest (RF).[10]

The removal of highly correlated and constant descriptors, the trend vector method,[11] genetic algorithm (GA)[12] and the automatic variable selection (AVS) strategy[7] have all been used to select the descriptors in PLS. The removal of highly correlated descriptors is not necessary for PLS analysis since descriptors are reduced to a series of uncorrelated latent variables. This procedure frequently helps to obtain more adequate models. During this procedure one descriptor from each pair having a pair correlation coefficient r satisfying $|r|>0.90$ is eliminated. It was previously discovered[13] that descriptors involved in the best Trend Vector models (several decades of models with approximately identical quality) form a good subset for their subsequent usage in PLS. The noise elimination can be one of the more probable

explanations of the success of the trend vector procedure. GA is used as a tool for the selection of adequate PLS models. We used the small set of following algorithm parameters as mutation rate = 0.3, crossingover rate = 0.7, type of crossingover is double. Descriptors, from the best model obtained by a preliminary AVS procedure, are normally used as the starting "population". In this work we run GA only once. The GA is definitely not a tool for the elucidation of the global maximum or minimum, and very often subsequent AVS procedures and different enumerative techniques allow one to increase the quality of the PLS models obtained.

According to the QSAR/QSPR OECD principles,[14] applicability domain (AD) of developed models was estimated. A ellipsoid model of structural space,[7] Williams plot[15] and tree AD approach[16] were used for AD estimation.

Within the framework of SiRMS approach it is possible to define the relative influence of the different physical and chemical factors on the character of the molecules interaction with the biological target.[7,8] For this purpose it is necessary to sum and compare absolute values of PLS regression coefficients of descriptors for all groups used for atom differentiation.

The clear interpretation is one of the advantages of SiRMS approach.[8] On the basis of developed QSAR models the influence of each atom over a particular property can be calculated. The contribution of each atom in the molecule can be defined as the ratio of the sum of PLS regression coefficients for all simplexes containing this atom to the number of atoms in the simplex. The atomic contribution depends on the number of simplexes that include this atom. The number of simplexes is not constant. It varies in different molecules depending on other constituents. Thus, this contribution is non-additive. The analysis of such information allows selecting different fragments which have negative or positive influence on a considered property.

The descriptors calculation and data analysis were performed using HiTQSAR software,[7] which was developed in the department of molecular structure and chemoinformatics of the A. V. Bogatsky Physico-chemical institute of National Academy of Sciences of Ukraine.

RESULTS AND DISCUSSION

During the first step of synthetic scheme Boc-$^{\alpha}$N-protected amino acid are bonded to rimantadine or amantadine. Next step is reaction of Boc-group deprotection with treatment with 10 fold excess of TFA. Finally target compounds are obtained as a free bases on their amino functions by treatment with 25 % ammonium hydroxide till pH around 8.

Thus using structures and results from biological investigations of target rimantadine and amantadine analogues QSAR analysis was carried out and the effects of the substituent on the *in vitro* cytotoxicity (CC_{50}), *HNTC* and antiviral activity (against human influenza virus A/H3N2 strain/Hong Kong/68) were also investigated.[17]

In this study we used a dataset consisting of 22 derivatives (13 are rimantadine derivatives and 9 – amantadine derivatives, Table I).

In addition, the derivatives Tyr-rimantadine, Ala-rimantadine, *β*-ala-Rimantadine, and Ala-amantadine, Val-amantadine, which exhibit the lowest cytotoxicity were guanidated using 1*H*-pyrazole-1-carboxamidine reagent (Scheme 1).[18]

All compounds were tested against human influenza virus A/H3N2 strain Hong Kong/68 and their activity is described by Chayrov *et al.*[17] The antiviral

activity against influenza virus strain A/H3N2 strain Hong Kong/68 *in vitro* of new analogs of amantadine and rimantadine conjugated with amino acids reveal that the highest antiviral activity combined with low cytotoxicity was demonstrated by the rimantadine derivative conjugated with the simplest in structure glycine. Moreover, glycyl-rimantadine presented a high stability profile after incubation in human plasma for 24 h. Interestingly, the analogues of amantadine with the amino acids L-phenylalanine and L-(4-F)-phenylalanine exhibited high activity although lower than those of the amantadine in the same concentration. In addition, amantadine and rimantadine analogues conjugated with guanidine showed low toxicity but they also exhibited low activity. The various aliphatic and aromatic amino acids as substitutes in the rimantadine molecule have no significant effect on antiviral activity. The use of β-alanine reduces antiviral activity. Guanidation of the rimantadine and amantadine analogues do not increase antiviral activity unlike guanidated oseltamivir analogues.

Using SiRMS approach for calculation of structural descriptors a total of about 2000 different structural characteristics were calculated for the investigated compounds.

The ranges of dividing the atom properties into intervals are, as already mentioned above, tuning characteristics and the following schemes were used in the calculation of simplex descriptors: electronegativity: A < 2.19 ≤ B < 2.5 ≤ C < 3 ≤ ≤ D, refraction: A < 1.5 ≤ B < 3 ≤ C < 8 ≤ D, atomic charge: A < –0.16 ≤ B < < –0.10 ≤ C < –0.04 ≤ D < 0.01 ≤ E < 0.07 ≤ F < 0.13 ≤ G, lipophilicity: A < –1.51 ≤ B < –0.96 ≤ C < –0.42 ≤ D < 0.13 ≤ E < 0.68 ≤ F < 1.23 ≤ G, VDW attraction: A < 50 ≤ B < 100 ≤ C < 250 ≤ D < 400 ≤ E < 650 ≤ F < 2000 ≤ G, VDW repulsion: A < 20.000 ≤ B < 32.000 ≤ C < 50.000 ≤ D < 100.000.

All atoms corresponding to the simplex vertices were also divided into three groups: A – acceptors of potential H-bond, D – donors of potential H-bond and I – indifferent ones.

On the first stage of this study, 2D QSAR model reflecting the structural influence of investigated compounds on their antiviral activity against human influenza (virus A/H3N2 strain Hong Kong/68) was developed. This model (Model A1) was used for interpretation, *i.e.*, for estimation of influence of different structural factors on investigated activity (on value of log IC_{50}), but this model was not intended for prediction of activity. Model A1 was built using the PLS method with two latent variables (based on 9 descriptors in the final) and with the following statistical characteristics: determination coefficient for the training set R^2 = = 0.88, coefficient of determination for cross-validation (leave-one-out) Q^2 = 0.77, standard error S(ws) = 0.35, S(cv) = 0.52 for training set and cross-validation, respectively. A "randomization" procedure (Y-Scrambling) was used to confirm the "non-randomness" of the developed QSAR model.[7] The statistical characteristics obtained using the Y-Scrambling procedure were lower in indices than in

the final model: R^2 (Y-scr) = 0.26 ± 0.03, Q^2 (Y-scr) = 0.10 ± 0.03. Thus, the non--randomness of the established relationship between the structure of the investigated compounds and their antiviral activity can be stated (see Supplementary material to this paper).

The analysis of obtained Model A1 testifies that, electrostatic (atomic charges) factors and lipophilicity have the largest influence on changing of antiviral activity (41 and 37 %, respectively). The relative influence of atom nature is 22 %.

As already mentioned above, on the basis of developed QSAR models the contribution of each atom in the molecule can be calculated. The analysis of such information allows selecting different fragments which have negative or positive influence on a considered property.

The sequence of mean relative influence of various substituents (R) for amantadine and rimantadine derivatives on antiviral activity (log IC_{50}) is shown on Fig. 1.

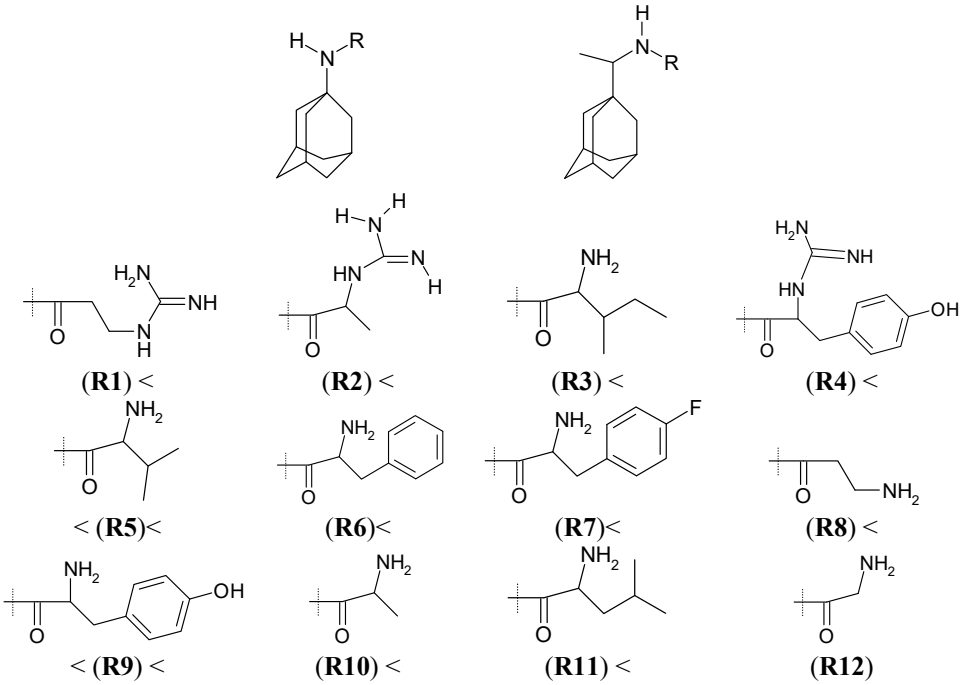


Fig. 1. Averaged relative influence of substituents (R) for amantadine and rimantadine derivatives on antiinfluenza activity (log IC_{50}) by the Model A1.

In addition, the influence of identical substituents for amantadine and rimantadine derivatives was estimated separately:

a) for amantadine: R2 < R4 < R5 < R6 <R7 < R9 < R10;

b) for rimantadine:R2 < R5 < R6 <R7 < R4 < R10 < R9.

In general, the sequence of changes in the relative influence of the substituents is the same for derivatives of amantadine and rimantadine, a noticable difference can only be noted for hydroxyl-containing substituents R4 and R9. Averaged relative influence of Rim- and Am-centers on antiinfluenza activity by the Model A1 equals 0.75 and –0.19, respectively.

RF model was developed for estimation of the predictive ability of the QSAR model. RF models were constructed according to the described original RF algorithm.[10] RF is an ensemble of single decision trees.[16] Each tree has been grown as: a) A bootstrap sample, which will be a training set for the current tree, is produced from the whole training set of N compounds. Compounds which are not in the current tree training set are placed in an out-of-bag (OOB) set (OOB set size is ~N/3); b) the best split by classification and regression tree (CART) algorithm[10] among the m randomly selected descriptors from whole set of M ones in each node is chosen. The value of m is just one tuning parameter for which RF models are sensitive; c) each tree is grown to the largest possible extent (there is no pruning).

RF model (Model A2) was built using the descriptor's set from Model A1. Obtained model (trees count = 50, randomly selected descriptors count = 3) has following statistical characteristics: determination coefficient for the training set $R^2_{(ws)}$ = 0.95, coefficient of determination for out-of-bag (OOB) set $R^2_{(OOB)}$ = = 0.65, $RMSE_{(ws)}$ = 0.26, $RMSE_{(oob)}$ = 0.62. The characteristics of the OOB just reflect the predictive ability of the QSAR model, which can be considered satisfactory. The greater accuracy of prediction is observed for compounds with medium activity (see Supplementary material).

Further in this study, QSAR models reflecting the structural influence of the investigated compounds on their cytotoxicity (CC_{50}) and *HNTC* were developed. The cytotoxicity data (CC_{50}) show (Table I) that among the 21 compounds, only 6 exhibit cytotoxicity (CC_{50} values are less than 100). For *HNTC* data were found that among the 21 compounds, only 12 exhibit activity (property values are less than 100).

Thus, the original activity values were coded as follows: 1-active (property < < 100) and 0-inactive (property > 100). In these cases RF method was used for decision of classification tasks.

For the first case since the dataset is unbalanced, *i.e.*, the count of active and inactive molecules is significantly different, a special procedure for balance was used. The count of inactive molecules was constant (15 molecules) and the count of active ones was duplicated. In the first series, 6 active molecules (all of active and inactive – 21 molecules) were used for developed Model B1 **(**trees count = 100, randomly selected descriptors count = 5); in the second series the count of active molecules was increased twofold, *i.e.*, 12 active molecules (a total of 27

molecules) were used for developed Model B2 (trees count = 150, randomly selected descriptors count = 13). The resulting QSAR models for the training set showed an unmistakable classification. The predictive ability of the QSAR models was evaluated using the "out-of-bag" (OOB) procedure. The quality of the classification models was assessed according to the following statistical characteristics: Matthew's correlation coefficient (*MCC*), specify (*SPC*), accuracy (*ACC*) and sensitivity (*SEN*):

$$MCC = \frac{(TP \cdot TN + FP \cdot FN)}{\sqrt{(TP + FP)(TP + FN)(TN + FP)(TN + FN)}}$$

$$SPC = \frac{TN}{(TN + FP)}$$

$$ACC = \frac{(TP + TN)}{(TP + TN + FP + FN)}; \; SEN = \frac{TP}{(TP + FN)}$$

where *TP* – true positive, *TN* – true negative, *FP* – false positive, *FN* – false negative.

The obtained data are presented in Table II.

TABLE II. Statistical parameters for classification models for CC_{50} (Models B1 and B2) and HNTC (Model B3) for "out-of-bag" set

Model	Set	*MCC*	*ACC*	*SPC*	*SEN*
B1	6 + 15 = 21	0.77	0.90	0.88	1
B2	12 + 15 = 27	0.86	0.93	0.93	0.92
B3	12 + 9 = 21	0.81	0.90	0.89	0.91

As it can be seen from Table II, the balancing of models leads to a significant quality improvement. Model B2 could be considered as the most appropriate.

For *HNTC* data the duplication procedure was not used, since the dataset is more balanced (active molecules 12 and inactive 9). Model B3 (trees count = = 150, randomly selected descriptors count = 20) was also built for *HNTC* dataset, statistical parameters are shown in Table II.

As can be seen from this table, the statistical characteristics of models B1––B3 are quite acceptable.

It should be noted that all molecules are in domain applicability (DA) of Models A1, A2 and B1–B3.

CONCLUSION

The realized QSAR studies have found good compliance between theoretical predictions and in vitro revealed activity and cytotoxicity. Compounds 2, 5 and 7 have both good antiviral activity against tested virus A/H3N2, strain Hong Kong/68 combined with low cytotoxicity which is in a perfect correlation with QSAR pre-

diction studies. All guanidated derivatives have lower activity according to both QSAR investigation and in vitro assay. Based on the obtained results we can conclude that more bulky side chain residues are not tolerated by the mechanism of interaction with M2 ion channels of influenza virus. Unfortunately, the same conclusion is revealed for structures creating less conformational freedom including *β*-amino acids as moiety in the lateral chain of amantadine and rimantadine.

SUPPLEMENTARY MATERIAL

Additional data are available electronically at the pages of journal website: https://www.shd-pub.org.rs/index.php/JSCS/index, or from the corresponding author on request.

И З В О Д

МОДЕЛОВАЊЕ КВАНТИТАТИВНОГ ОДНОСА СТРУКТУРА–АКТИВНОСТ ИНХИБИТОРА М2 ЈОНСКОГ КАНАЛА ВИРУСА ГРИПА

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Серија нових деривата адамантана који садрже фрагменте аминокиселина испитана је користећи метод симплекс представљања молекулских структура (енг. simplex representation of molecular structure, SiRMS) са циљем да се утврди однос између хемијске структуре испитиваних једињења и резултата антивиралне и цитотоксичне активности. Добијени резултати QSAR анализе показују да ће деривати адамантана који садрже аминокиселине кратких неполарних алифатичних група у бочном низу имати добре антивиралне активности према A/H3N2 сoју Hong Kong/68 вируса као и малу цитотоксичност. QSAR експерименти и резултати in vitro активности показују добру корелацију и указују да деривати који садрже гуанидо фрагмент у бочном низу и *β*-аминокиселину као супституент, имају малу или не показују активност.

(Примљено 9. маја 2020, ревидирано 15. марта, прихваћено 6. маја 2021)

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