MEDICINAL CHEMISTRY RESEARCH

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ORIGINAL RESEARCH

QSAR modeling of bis-quinolinium and bis-isoquinolinium compounds as acetylcholine esterase inhibitors based on the Monte Carlo method—the implication for Myasthenia gravis treatment

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Abstract The Monte Carlo method was used for quantitative structure–activity relationship modeling of bis-quinolinium and bis-isoquinolinium compounds as acetylcholine esterase inhibitors for a series of 36 compounds. quantitative structure–activity relationship models were calculated with the representation of the molecular structure by the Simplified Molecular Input-Line Entry System. One split into the training and test set was examined. The statistical quality of the developed model was good. The best calculated quantitative structure–activity relationship model had following statistical parameters: $r^2 = 0.8097$ for the training set and $r^2 = 0.9372$ for the test set. Structural indicators defined as molecular fragments responsible for increases and decreases in the inhibition activity were calculated. The computer-aided design of new compounds as potential acetylcholine esterase inhibitors with the application of defined structural alerts was presented.

Bis-quinolinium derivatives · Bis-isoquinolinium derivatives

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Introduction

Myasthenia gravis (MG) is an autoimmune disorder which results from the destruction of the post-synaptic membrane in the neuromuscular junction (Conti-Fine et al., 2006; Vincent et al., 2001). In most MG cases, human antibodies are produced to the nicotinic acetylcholine receptor (nAChR) (Tzartos et al., 1998; Vincent et al., 2003). An autoimmune attack to the endplate region of the neuromuscular junction resulting in reduced density of nAChR is initiated with these antibodies, which further leads to the destruction of the synaptic folds and the general simplification of the post-synaptic membrane. Reduced transmission in the neuromuscular junction results in a characteristic symptom of MG, that is, weakness of the striated muscles is caused by the decreased probability of the acetylcholine (ACh)–nAChR interaction (Santa et al., 1972). Acetylcholinesterase inhibitors can be used in the treatment of disorders with impaired cholinergic transmission, therefore the first-line treatment in early stages and in the mild forms of MG is based on peripheral inhibitors of AChE since they work by increasing the concentration of ACh in the synaptic junction and thus enhance the cholinergic transmission in spite of the nAChR depletion (Drachman, 1994; Lindstrom, 2000; Richman and Agius, 2003). It has to be noted that the application of AChE inhibitors is only a symptomatic approach and it does not resolve the original cause of the disease. The treatment of patients with MG is a complex task. The quality of life of patients with MG can be

**Fig. 1** Drugs used in *Myasthenia gravis* therapy
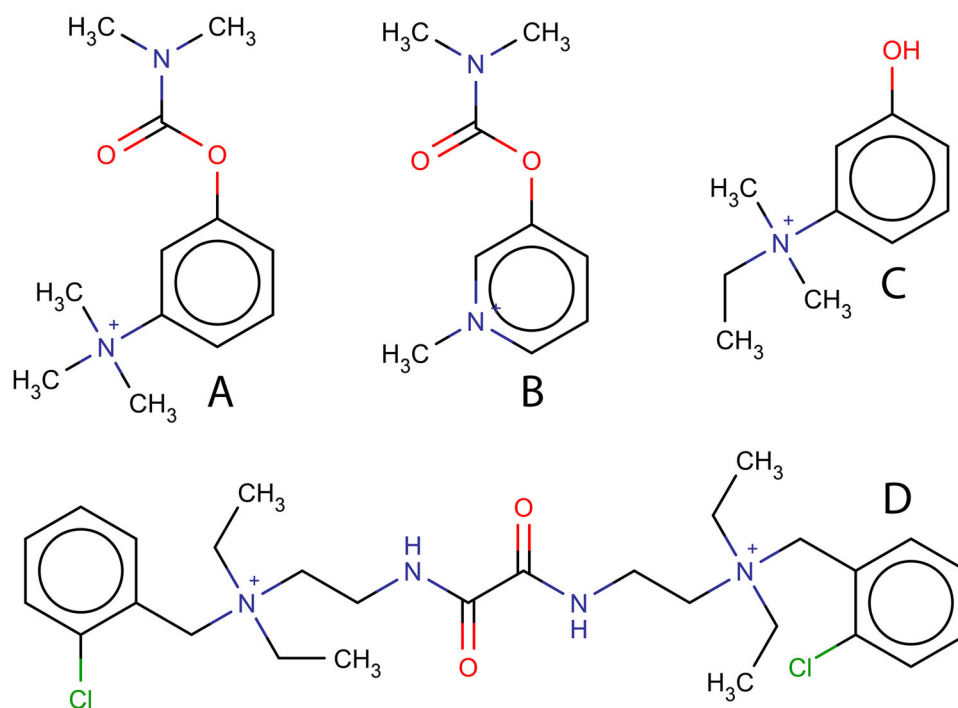
improved with the application of mild physical exercise. Therefore, physicians specialized in sports medicine, physiatrists and experts in sports in general can ease lives of MG patients and help them in continuous fight against this severe disorder (Lucia et al., 2007; Rubin and Hentschel, 2007). Most common drugs used in current MG therapy are presented in Fig. 1. Unfortunately, the use of these compounds often leads to the development of serious gastro-intestinal side effects, increased bronchial secretion, cardiac arrhythmia. Moreover, high intake of these compounds may lead to cholinergic crisis, characterized by even more severe weakness (Froelich and Eagle, 1996; Juel and Massey, 2007; Leigh et al., 2003). Considering the above-stated facts, the search is being continued for a far more effective AChE inhibitor that can be used in the treatment of MG.

In modern drug design, quantitative structure–activity relationship (QSAR) modeling is widely used due to the fact that this powerful computational approach can make an early prediction of activity-related characteristics of drug candidates and eliminate compounds with undesired properties (Cherkasov et al., 2014; Dearden, 2016; Roy et al., 2015; Tropsha and Golbraikh, 2007). The main aim of QSAR modeling is to develop a simple mathematical equation that correlates a molecule's studied biological activity with its properties and molecular characteristics calculated as quantitative parameters–descriptors. Therefore, descriptors can be defined as entities that characterize specific information of a studied molecule in terms of numerical values associated with the chemical constitution for the correlation of the chemical structure with the

biological activity (Cronin and Schultz, 2003). When a QSAR model is built on geometry-dependent molecular descriptors, then the model development usually involves a relatively difficult calculation of the optimal molecular geometry which encompasses the application of high computational resources and a long time for computational experiments. For this reason, the conformation-independent 0D, 1D and 2D-QSPR methods emerge as an alternative approach for developing models based on the constitutional and topological molecular features of molecules (Ducho-wicz et al., 2012; Talevi et al., 2012). Descriptors calculated on the basis of molecular graphs are often used in QSAR modeling (Ivanciuc, 2013; Talevi et al., 2012). The simplified molecular input-line entry system (SMILES) can be considered as an alternative to molecular graphs and it can be used for defining of molecular structures (Toropov and Benfenati, 2007; Veselinović et al., 2015). One-variable QSAR models built up by the Monte Carlo optimization method based on SMILES descriptors have been published recently. One of the main advantages of this method in comparison to most commonly used QSAR models is the fact that it is not dependent on molecule conformation since it is based on constitutional and topological features of molecules. Moreover, QSAR models based on SMILES notation descriptors have similar or better statistical characteristics in comparison to 3D descriptors based QSAR models. All the above stated facts make QSAR modeling based on SMILES notation descriptors an attractive alternative to commonly used methods in drug design and discovery (Veselinović et al., 2015).

Fig. 2 General molecular
structures of studied compounds
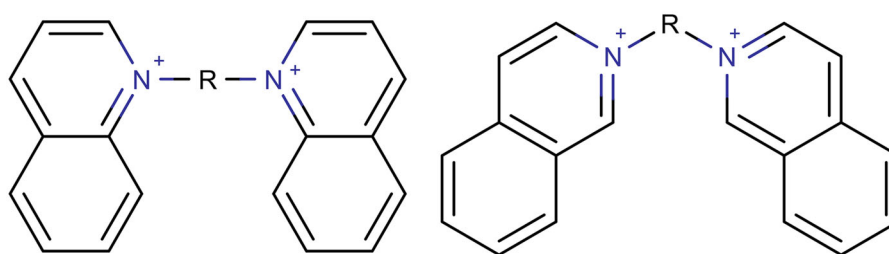
The aim of this study is to build a QSAR model based on
the SMILES notation optimal descriptors using the Monte
Carlo method for bis-quinolinium and bis-isoquinolinium
compounds as AChE inhibitors and to make an attempt to
define the molecular fragments responsible for the stated
inhibitory effect. Furthermore, we used the built model and
defined molecular fragments for the computer aided drug
design of new potentially promising AChE inhibitors.

Method

The data set

A QSAR model was developed for a series of 36 bis-qui-
nolinium and bis-isoquinolinium compounds acting as
AChE inhibitors (Komloova et al., 2011; Musilek et al.,
2011). General structures of these compounds are presented
in Fig. 2. Molecular structures of the studied compounds
were transformed into the canonical SMILES with the
ACD/ChemSketch program (ACD/ChemSketch v. 11.0).
To represent the pharmacological activity, pIC_{50} ($-\log IC_{50}$)
was used as a dependent variable for building both QSAR
models (Supplementary Table S1). Molecules with reported
zero activity were discarded from the model development.
The QSAR model for was built up for one random split (20
% of the compounds were used in the test set). The nor-
mality distribution plot of the whole dataset was checked
according to literature (Ojha and Roy, 2011).

QSAR model development and validation

The main concept of the QSAR modeling can be defined as
the following:

$$Endpoint = F(\text{Molecular Structure}) \tag{1}$$

The SMILES notation is one of the most convenient
molecule structure representations. In the presented QSAR
modeling, the SMILES notation is used for defining a
molecular optimal descriptor (DCW). DCW is calculated as
a function of the molecule's SMILES notation as shown in
Eq. 2:

$$DCW = F(\text{SMILES}) \tag{2}$$

Based on the SMILES notation, two types of optimal
descriptors defined can be defined. The first type of optimal
descriptors is a local SMILES attribute, defined as *SMILES
atoms*, a fragment of the SMILES notation which contains
one ('C', 'O', '#', etc.) or two symbols ('Cl', 'Br', '@@',
etc.) which cannot be examined separately. The simplest
way of defining a molecular DCW as a mathematical
function of SMILES atoms can be achieved with the
application of local SMILES attributes, as a mathematical
function of each character of the SMILES. Therefore, the
first and the simplest one SMILES notation based descriptor
is S_k (SMILES atom), a descriptor related to one SMILES
symbol (or two that cannot be separated). A linear combi-
nation of two or three SMILES atoms are descriptors
defined as SS_k and SSS_k (Veselinović et al., 2013, 2015).
The linear combination of the presented SMILES notation
based descriptors can be summarized in Eq. 3.

$$DCW(T, N_{epoch}) = \alpha \sum CW(S_k) + \beta \sum CW(SS_k)$$
$$+ \gamma \sum CW(SSS_k) \tag{3}$$

The inclusion of SMILES based descriptors in the QSAR
model development can be achieved with the application of
a simple rule—if the value of a coefficient is 1, then an
appropriate descriptor is included or if it is 0, then an
appropriate descriptor is discarded form the model building.
For this reason, coefficients α, β and γ from Eq. 3 are either
1 (yes) or 0 (no). In the presented QSAR model for AChE
inhibition all coefficients were 1, therefore all local
SMILES notation based descriptors were used in the model
development.

Each calculated optimal descriptor receives a numerical
value defined as the correlation weight (CW) with the
application of the Monte Carlo method. The applied Monte
Carlo method is based on a principle that suitable random
numbers are generated and further observed to see how that
fraction of numbers obeys some property/properties. The
application of iterative algorithms is used for the compu-
tation of obtaining and distribution of an unknown prob-
abilistic entity (Toropov et al., 2013). Therefore, the main
purpose of the Monte Carlo optimization process is the
calculation of the numerical data for the CW which gives
the maximal value of the correlation coefficient between the
endpoint and the optimal descriptor. The Monte Carlo

method is based on two parameters for the computation of stated numerical values—Threshold (T) and the Number of epochs (N_{epoch}). Threshold can be defined as the separator of calculated SMILES based descriptors into active and inactive with the application of the following principle: if the descriptor is active, then T has some numerical value; however, if the descriptor is inactive, then T has a fixed value of zero. The number of epochs (N_{epoch}) is related to the computational iterative process with one aim—to obtain the best statistical quality for the training set (Veselinović et al., 2013, 2015).

The linear regression approach is used as a method for developing a QSAR model after all CW are calculated (Eq. 4)

$$Endpoint = C_0 + C_1 \times DCW(Threshold, N_{epoch}) \qquad (4)$$

CORAL software was used for the development of the presented QSAR model (http://www.insilico.eu/coral). All local SMILES descriptors and global attributes (S_k, SS_k and SSS_k) were taken into consideration during the building of QSAR models. The search for the most predictive combination of T and N_{epoch} for all splits was performed from values 0–10 for T and 0–60 for N_{epoch}.

The main purpose of any QSAR modeling is to develop a robust model capable of predicting the properties of new molecules in an objective, reliable and precise manner (Roy, 2007). The application of three methods can be used for the assessment of robustness and reliability of a developed QSAR model (Roy et al., 2008): (a) internal validation or cross-validation using the training set compounds, (b) external validation using the test set compounds and (c) data randomization or Y-scrambling. This methodology was successfully applied for the validation of SMILES notation optimal descriptor based QSAR models (Veselinović et al., 2015).

Several standard statistical metrics were used for validating the developed QSAR model, including the correlation coefficient (r^2), cross-validated correlation coefficient (q^2), standard error of estimation (s), mean absolute error (MAE), Fischer ratio (F) and root-mean-square error (RMSE). In addition, novel metrics (R_m^2 and MAE based metric) were used for further validation. Novel statistical metric (R_m^2) can be used to estimate true predictive potential of a developed QSAR model (Ojha et al., 2011; Roy et al., 2012). The calculation of this metric is based on the correlation between the observed and predicted values with (R^2) and without (R_0^2) intercept for the least squares regression lines as shown in eq. 5:

$$R_m^2 = R^2 - \left(1 - \sqrt{R^2 - R_0^2}\right) \qquad (5)$$

The main advantage of this metric is that it avoids the overestimation of the quality of prediction due to a wide

response (Y-range) since it does not consider the differences between individual responses and the training set mean. In addition, a scaled version of R_m^2 metric can be used in order to have a better estimation of QSAR model predictability. For calculating both R_m^2 and scaled version of R_m^2 metrics, an open-access web application "Rm2 calculator" is available at http://aptsoftware.co.in/rmsquare/. Finally, the mean absolute error (MAE) metric was used for the final estimation of the developed QSAR model prediction quality according to the published methodology (Roy et al., 2016). A software from http://teqip.jdvu.ac.in/QSAR_Tools/ web link was used for the calculation of the MAE based metric.

One of the most important features of all developed QSAR models is its applicability domain (AD). Molecules from the training set are used for this purpose. For all developed QSAR models, the AD is defined as biological, structural, or physicochemical space, knowledge, or information on which the model of the training set is developed and which can be used for predicting whether a developed QSAR model can be used on compounds which are not used in the model developing. Therefore, a defined AD can be applied for the assessment of the reliability of a developed QSAR model. If the application of the AD defines a studied compound as very different in comparison to all compounds from the training set, a reliable prediction of its property/activity is uncertain (Gadaleta et al., 2016; Gramatica, 2007). Considering QSAR models based on SMILES based descriptors, the difference between experimental and calculated values for a studied endpoint can be used for defining the AD with the application of $Delta(obs)$, d and $\overline{\overline{d}}$ (Toropov et al., 2011). For each molecule used in the QSAR study, $Delta(obs)$ is calculated as the difference between experimental and calculated values from a studied endpoint. d and $\overline{\overline{d}}$ are defined in Eqs. 6 and 7, respectively, where n is the number of studied compounds.

$$\overline{d} = \frac{\sum Delta(obs)}{n} \qquad (6)$$

$$d = \frac{\sum [Delta(obs) - Delta(calc)]^2}{n}. \qquad (7)$$

If $Delta(obs)$ of a studied compound belongs within the range $\overline{d} - d$ and $\overline{d} + d$, then it falls in the defined model AD. However, if compound's $Delta(obs)$ does not belong inside a defined range, then that compound does not belong in the defined AD. For this reason, the compound is considered as outlier, and it is discarded from the development of a QSAR model. The relation used for defining the AD is given in Eq. 8:

$$Delta(obs) \in (\overline{d} - d, \overline{d} + d) \qquad (8)$$

A defined methodology for the determination of the AD was successfully applied in the development of various

Table 1 The statistical quality of the developed QSAR model for bis-quinolinium and bis-isoquinolinium compounds as acetylcholine esterase inhibitors

	Training set					Test set				
	r^2	q^2	s	MAE	F	r^2	q^2	s	MAE	F
1 run	0.8097	0.7703	0.678	0.491	111	0.9372	0.8633	0.627	0.495	75
2 run	0.8078	0.7677	0.681	0.497	109	0.9465	0.8691	0.611	0.480	88
3 run	*0.8037*	*0.7627*	*0.689*	*0.497*	*106*	*0.9504*	*0.8740*	*0.575*	*0.460*	*96*
Av	0.8071	0.7669	0.683	0.495	109	0.9447	0.8688	0.604	0.478	83

r^2 correlation coefficient, q^2 cross-validated correlation coefficient, s standard error of estimation, *MAE* mean absolute error, *F* Fischer ratio, *RMSE* root-mean-square error, *Av* average value for statistical parameters obtained from three independent Monte Carlo optimization runs

Italics indicate the best Monte Carlo optimization run

Table 2 The criteria of predictability of the developed QSAR model related to the test set from three independent Monte Carlo optimization runs

	Normal				Scaled			
	r^2_m	$r^2_m(rev)$	$r^2_m(av)$	Δr^2_m	r^2_m	$r^2_m(rev)$	$r^2_m(av)$	Δr^2_m
1	0.7174	0.5718	0.6446	0.1455	0.6969	0.5517	0.6243	0.1452
2	0.7190	0.5800	0.6495	0.1390	0.6988	0.5596	0.6291	0.1392
3	0.7344	0.6100	0.6722	0.1244	0.7173	0.5947	0.6560	0.1226
Av	0.7236	0.5873	0.6554	0.1363	0.7043	0.5687	0.6365	0.1357

$r^2_m(rev)$ reverse r^2_m, $r^2_m(av)$ average r^2_m, *AV* average value for statistical parameters obtained from three independent Monte Carlo optimization runs

Each entry of submitted dataset is scaled as follows: Scaled Z(Observed or Predicted) = [Z - minimum of Observed]/[maximum of observed −minimum of Observed]

For an acceptable QSAR model, the value of $r^2_m(av)$ should be > 0.5 and Δr^2_m should be < 0.2 (Ojha et al., 2011; Roy et al., 2012)

QSAR models based on the Monte Carlo method and SMILES based descriptors (Veselinović et al., 2015).

After defining the AD, the molecule 14 from the research reported by Musilek et al. was defined as outlier and it was discarded from the model development.

Results and discussion

Table 1 shows the statistical quality of the built QSAR model for bis-quinolinium and bis-isoquinolinium compounds acting as AChE inhibitors. The presented results reveal that there is the reproduction of the statistical quality for the calculated model in three independent runs of the Monte Carlo optimization. Furthermore, the results from Table 1 show that the predictability is good. In order to further assess the quality of the developed QSAR model, novel statistical metric was used according to published methodologies and the results are presented in Table 2. The presented QSAR model for IC_{50} is satisfactory from the point of view of new criteria (Ojha et al., 2011; Roy et al., 2012). Supplementary Table S2 shows Y-randomization (Ojha and Roy, 2011) which also confirms the robustness of

the suggested models. MAE based metric revealed that the developed QSAR model is "moderate", what classified this model as valid. The search for preferable T and N_{epoch} revealed that preferable T is 2 and preferable N_{epoch} 10. Figure 3 graphically presents the best Monte Carlo optimization run (the highest value for r^2) for the developed QSAR model.

$DCW(T,N_{epoch})$ for compounds in the training and test sets are calculated as described in the Method section of this manuscript. The application of the above-mentioned T and the N_{epoch} gives the following model for the pIC_{50} calculated according to Eq. 4:

$$pIC_{50} = -13.7073\,(\pm 0.4666) + 0.1431\,(\pm 0.0036) \\ \times DCW(2, 10)$$
(9)

According to the calculated correlation weights (CW), the values of molecular features (SA_k) from three Monte Carlo optimization runs, SA_k can be classified as promoters of increase or promoters of decrease of a studied activity, and as undefined molecular features. A simple rule is applied for this classification: if the $CW(SA_k)$ obtained from

Fig. 3 Graphical representation of the developed QSAR model for bis-quinolinium and bis-isoquinolinium derivates as acetylcholine esterase inhibitors
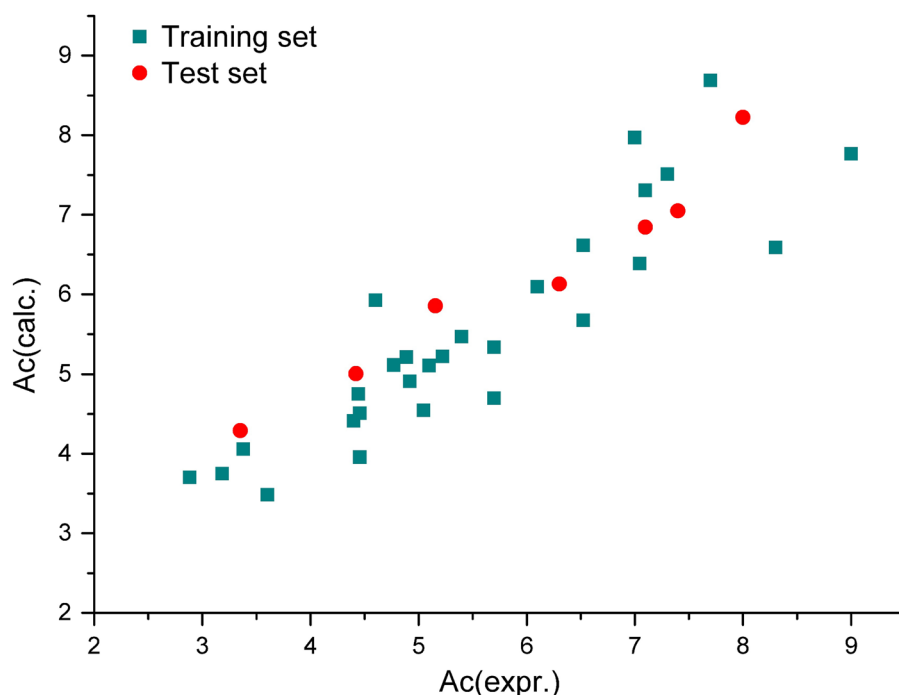
three independent Monte Carlo optimization runs is positive then that SA_k is the promoter of increase, likewise if the $CW(SA_k)$ from three independent Monte Carlo optimization runs is negative then that SA_k is the promoter of decrease; if there are both positive and negative values of the $CW(Sk)$ in three runs of the Monte Carlo optimization process, then that SA_k is undefined (Veselinović et al., 2015). The list of all SA_k, with the correlation weights for three runs of the Monte Carlo optimization process of the built QSAR model for maleimide derivatives is given in Supplementary Table S3. The built QSAR model represented with Eq. 5 has the mechanistic interpretation as well as calculated SA_k which can be further defined as molecular fragments. According to the presented data, several important SA_ks that can be classified as promoters of pIC_{50} value decrease are $O…C…C…$ (ethoxy group) and $C………..$ (methyl group) while several important SA_ks that can be classified as promoters of pIC_{50} value increase are $= ………..$ (double bond), $C… = …….$ and $C… = …C…$ (double bond on a carbon atom), $C…/……..$, $C…/…C…$, $/………..$, $\………..$ and $\…C…….$ both *cis* and *trans* conformations, $O………..$ (sp^3 hybridized oxygen atom), $O…C…….$ (methoxy group), $C…C…….$ (ethyl group), etc. The obtained findings are in accordance with the results of SAR findings from published data (Komloova et al., 2011; Musilek et al., 2011).

The analysis of SA_k presented in Supplementary Table. S3 can be useful in the search and computer aided design of novel derivatives with desired pIC_{50} values. The structures of novel compounds obtained by molecular modeling are presented in Fig. 4.

The molecule 37 from dataset was selected as a template for the molecular design. One of the goals of the presented molecular design was to obtain molecules with higher pIC_{50} values in comparison to the template molecule, since higher pIC_{50} values mean that a lower concentration is needed to inhibit 50 % of an enzyme. Molecular structures presented as the SMILES notation of designed molecules and their calculated pIC_{50} values obtained with the application of built QSAR model for compounds (Eq. 5) are presented in Table 3.

Table 4 presents an example of the calculation of DCW(2,10) for the template molecule A. When Eq. 5 is applied for calculating DCW, the resulting endpoint value (pIC_{50}) is 6.6140. In the molecule A1+ two more carbon atoms were added to the molecule. In the molecule A1+ one more SA_k was added in comparison to the molecule A, $C…C…….$ (ethyl group), defined as the promoter of Ac increase. For this reason, the molecule A1+ has the calculated Ac value of 7.6291. The molecule A2+ has two more carbon atoms in comparison to the molecule A1+ and also a higher value of Ac (8.5491). The molecule A3+ has substituted one carbon atom with oxygen which leads to the introduction of $O…C…….$ SA_k, also defined as the promoter of increase. The calculated value for the molecule A3+ Ac was 7.8063. Molecules A4+ and A5+ represent two stereo isomers. Since both have promoters of Ac increase, their values for the calculated Ac were 7.9879 and 7.7828, respectively. Results suggest that *trans* isomer is favorable in comparison to *cis* since it has a higher value for the calculated Ac.

Fig. 4 The molecular design of perspective acetylcholine esterase inhibitors using the QSAR model calculated with Eq. (5) and SA$_k$s calculated using the Monte Carlo method
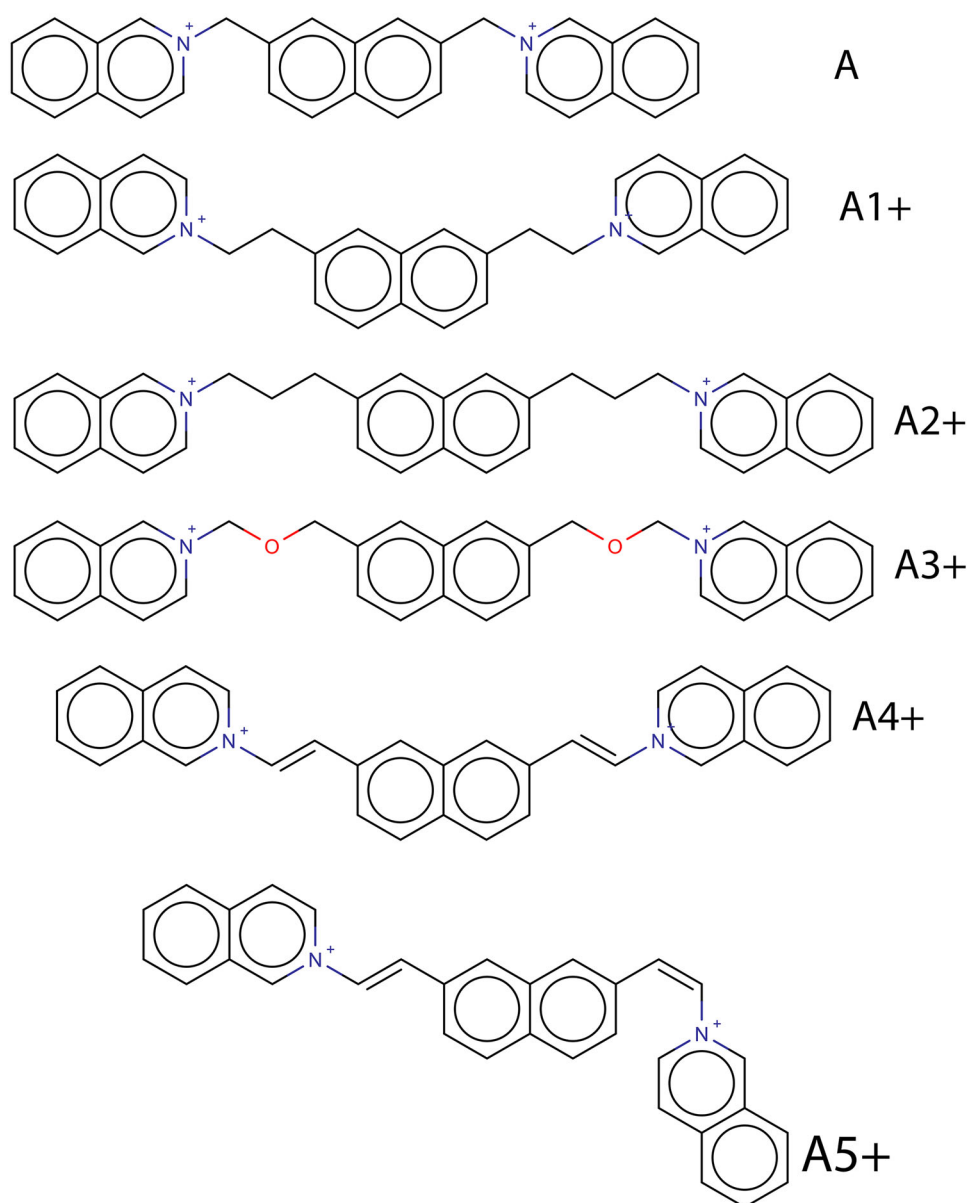
Table 3 The SMILES notation and Ac values calculated using Eq. (9) for compounds designed with the application of the results of QSAR modeling obtained in this study

Molecule	SMILES notation	Ac (calc.)
A	c1c6ccccc6cc[n+]1Cc4cc5cc(C[n+]2cc3ccccc3cc2)ccc5cc4	6.6140
A1+	c1c6ccccc6cc[n+]1CCc4cc5cc(CC[n+]2cc3ccccc3cc2)ccc5cc4	7.6291
A2+	c1c6ccccc6cc[n+]1CCCc4cc5cc(CCC[n+]2cc3ccccc3cc2)ccc5cc4	8.5491
A3+	c1c6ccccc6cc[n+]1COCc4cc5cc(COC[n+]2cc3ccccc3cc2)ccc5cc4	7.8063
A4+	c1c6ccccc6cc[n+]1/C=C/c4cc5cc(/C=C/[n+]2cc3ccccc3cc2)ccc5cc4	7.9879
A5+	c1c6ccccc6cc[n+]1\C=C/c4cc5cc(\C=C/[n+]2cc3ccccc3cc2)ccc5cc4	7.7828

Conclusion

QSAR models for bis-quinolinium and bis-isoquinolinium compounds as acetylcholine esterase inhibitors were built. The Monte Carlo optimization process incorporated within

CORAL software was capable to be an efficient tool to build up a robust model of good statistical quality. The predictive potential of the applied approach was tested and the robustness of the model was proven with different methods. The SMILES attributes, defined as SMILES
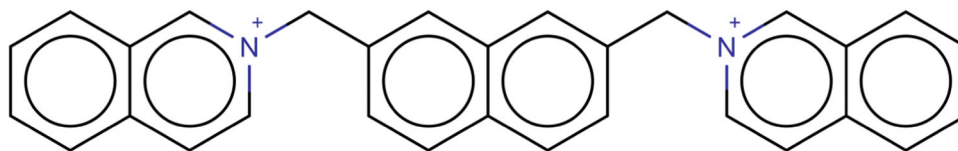
Table 4 The example of DCW(2,10) calculation
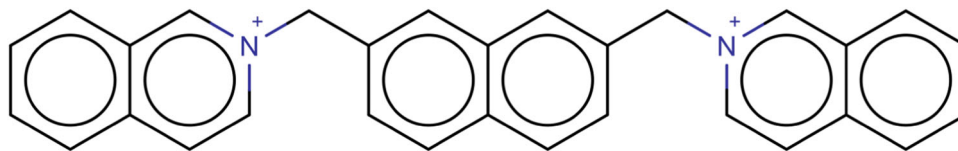
SMILES notation: c1c6ccccc6cc[n+]1Cc4cc5cc(C[n+]2cc3ccccc3cc2)ccc5cc4

DCW = 141.95901

Ac (calc.) = 6.6140

SA_k	$CW(SA_k)$	SA_k	$CW(SA_k)$	SA_k	$CW(SA_k)$
c……...	0.4965	c…1……	0.6605	c…1…c…	1.7547
1……...	1.5594	c…1……	0.6605	6…c…1…	0
c……...	0.4965	c…6……	1.3086	c…6…c…	0.81
6……...	1.0634	c…6……	1.3086	c…c…6…	0.504
c……...	0.4965	c…c……	0.0585	c…c…c…	0.3147
c……...	0.4965	c…c……	0.0585	c…c…c…	0.3147
c……...	0.4965	c…c……	0.0585	c…c…c…	0.3147
c……...	0.4965	c…c……	0.0585	c…c…6…	0.504
c……...	0.4965	c…6……	1.3086	c…6…c…	0.81
6……...	1.0634	c…6……	1.3086	c…c…6…	0.504
c……...	0.4965	c…c……	0.0585	c…c…[…	1.2457
c……...	0.4965	c…[……	2.3761	n…[…c…	1.9356
[……...	3.3775	n…[……	2.2235	[…n…+…	2.1298
n……...	0.6571	n…+……	1.7468	n…+…[…	2.7159
+……...	2.4989	[…+……	2.3774	1…[…+…	0.6532
[……...	3.3775	[…1……	1.3789	[…1…C…	0.8799
1……...	1.5594	C…1……	1.6548	c…C…1…	−0.6827
C……...	0.1208	c…C……	−0.4031	C…c…4…	0.3784
c……...	0.4965	c…4……	1.0983	c…4…c…	2.1859
4……...	1.7489	c…4……	1.0983	c…c…4…	1.7482
c……...	0.4965	c…c……	0.0585	c…c…5…	0.3445
c……...	0.4965	c…5……	0.0361	c…5…c…	0.0036
5……...	0.2226	c…5……	0.0361	c…c…5…	0.3445
c……...	0.4965	c…c……	0.0585	c…c…(…	0.5026
c……...	0.4965	c…(……	1.0638	c…(…C…	0.248
(……...	−0.407	C…(……	0.4727	[…C…(…	0.3785
C……...	0.1208	[…C……	1.9639	n…[…C…	2.3776
[……...	3.3775	n…[……	2.2235	[…n…+…	2.1298
n……...	0.6571	n…+……	1.7468	n…+…[…	2.7159
+……...	2.4989	[…+……	2.3774	2…[…+…	1.5964
[……...	3.3775	[…2……	0.8109	c…2…[…	1.7479
2……...	1.9409	c…2……	1.4711	c…c…2…	1.9706
c……...	0.4965	c…c……	0.0585	c…c…3…	0.909
c……...	0.4965	c…3……	0.8157	c…3…c…	0.2487
3……...	2.3075	c…3……	0.8157	c…c…3…	0.909
c……...	0.4965	c…c……	0.0585	c…c…c…	0.3147
c……...	0.4965	c…c……	0.0585	c…c…c…	0.3147

Table 4 continued

SMILES notation: c1c6ccccc6cc[n+]1Cc4cc5cc(C[n+]2cc3ccccc3cc2)ccc5cc4

DCW = 141.95901

Ac (calc.) = 6.6140

SA$_k$	CW(SA$_k$)	SA$_k$	CW(SA$_k$)	SA$_k$	CW(SA$_k$)
c………..	0.4965	c…c…….	0.0585	c…c…c…	0.3147
c………..	0.4965	c…c…….	0.0585	c…c…3…	0.909
c………..	0.4965	c…3…….	0.8157	c…3…c…	0.2487
3………..	2.3075	c…3…….	0.8157	c…c…3…	0.909
c………..	0.4965	c…c…….	0.0585	c…c…2…	1.9706
c………..	0.4965	c…2…….	1.4711	c…2…(…	2.8476
2………..	1.9409	2…(…….	2.1865	c…(…2…	2.1876
(………..	−0.407	c…(…….	1.0638	c…c…(…	0.5026
c………..	0.4965	c…c…….	0.0585	c…c…c…	0.3147
c………..	0.4965	c…c…….	0.0585	c…c…5…	0.3445
c………..	0.4965	c…5…….	0.0361	c…5…c…	0.0036
5………..	0.2226	c…5…….	0.0361	c…c…5…	0.3445
c………..	0.4965	c…c…….	0.0585	c…c…4…	1.7482
c………..	0.4965	c…4…….	1.0983		
4………..	1.7489				

notation based molecular descriptors, which are promoters of IC$_{50}$ increase/decrease were identified. The suggested modeling process and computer aided drug design were based on computational experiments with the application of statistically stable structural alerts (promoters of increase or decrease of IC$_{50}$). This approach can be applied in the search for new potential acetylcholine esterase inhibitors.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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