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REVIEW ARTICLE

Blood Brain Barrier and Alzheimer's Disease: Similarity and Dissimilarity of Molecular Alerts

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Abstract: ***Background*:** Blood brain barrier and Alzheimer's disease are interrelated. This interrelation is detected by physicochemical methods, pharmacological and electrophysiological analyses. Nature of the phenomenon is extremely complex. The description of this interrelation in mathematical terms is a very important task.

***Objective*:** The systematization of facts, which are described in the literature and related to interaction between processes, which influence Alzheimer's disease and blood brain barrier is the subject of this work. In addition, establishing of correlations between molecular features and endpoints, which are related to the treatment of Alzheimer's disease and blood brain barrier using the CORAL software are subjects of this work.

***Methods*:** The information on logically structured analysis is available in the literature and building up quantitative structure – activity relationships (QSARs) by the Monte Carlo method has been used to solve the task of systematization of facts related to the "treatment of Alzheimer's disease *vs*. blood brain barrier".

***Results*:** Comparison of agreements and disagreements of the available published papers together with the statistical quality of built up QSARs are results of this work.

***Conclusion*:** The facts from published papers and technical details of QSAR built up in this study give possibility to formulate the following rules: (i) there are molecular alerts, which are promoters to increase blood brain barrier and therapeutic activity of anti-Alzheimer disease agents; (ii) there are molecular alerts, which contradict each other.

Keywords: Alzheimer's disease, blood brain barrier, QSAR, monte carlo method, molecular alerts, CORAL software.

1. INTRODUCTION

Alzheimer's disease is a disorder of the central nervous system accompanied by memory deterioration, and progressive impairment of daily life activities. Aging of an organism is a biochemical process. Therefore, the injection of chemicals can influence this process. The blood-brain barrier is a major factor hindering the development of neurotherapeutics. Experimental methods of Blood Brain Barrier permeation determination as well as experimental definition of many other biomedical endpoints are cumbersome and expensive. Under such circumstances, computational approaches for the prediction of biomedical endpoints, in general, and computational methods for prediction of Blood Brain Barrier permeation, in particular are attractive alternatives of the direct experiment. Currently, there is no cure for Alzheimer's disease [1].

Being the most common form of dementia, Alzheimer's disease is currently affecting over 5.5 million people in the United States and more than 35 million worldwide [2, 3]. The hallmark of the disease is progressive cognitive decline that results in loss of language skills, difficulty in learning, loss of memory, and alterations in personality and mood [4-6].

There are some circumstances, which indicate the possible interrelation between processes related to Alzheimer's disease and Blood Brain Barrier [7-9]. It has been noticed that breakdown of the Blood Brain Barrier is a particularly important development in Alzheimer's disease progression [10-12].

According to the listed circumstances, the attractive paradigm to search agents versus Alzheimer's disease can be

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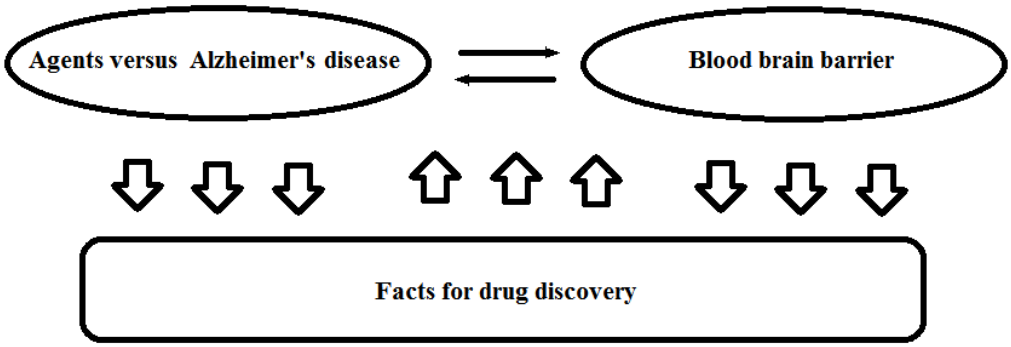

Fig. (1). Possible scheme to design agents versus Alzheimer's disease.

represented by scheme illustrated in Fig. (**1**). It is important to note that there are logical implications and interrelation between all the mentioned components of the paradigm.

2. ONTOLOGY

The information about the interaction between the elements of phenomena represented in Fig. (**1**) is very complex and unclear owing to dynamical and combinatorial aspects. The methods to represent this information in a format, which is convenient for understanding, should be regarded as methods of critical importance. One of the possible ways to construct a method of the above mentioned quality is the analysis of molecular alerts (features) able to influence the blood brain barrier and likely able to suggest the perspective list of molecular features valuable from the point of view of drug discovery oriented to define a group of agents versus Alzheimer's disease.

2.1. Task Definition: Interrelation Between Blood Brain Barrier and Alzheimer's Disease

Much of the underlying biology leading to Alzheimer's disease is unknown. Popular etiologic hypotheses have largely ignored the blood brain barrier as an important factor contributing to the pathologic hallmarks of this most common form of dementia. However, evidence identifying blood brain barrier dysfunction in Alzheimer's disease continues to escalate [13].

Normal ageing and Alzheimer's disease have many common features. In many ways, both conditions only differ by quantitative criteria. A variety of genetic, medical and environmental factors modulate the ageing-related processes leading to Alzheimer's disease. Thus, Alzheimer's disease is a metabolic disease [14]. The pathophysiological influence of microelements, including aluminum and iron, is highly controversial; at any rate, they may adversely affect of Alzheimer's disease progress [14].

The application of gene transfer (*i.e.* macromolecular sequences of amino acids) can also be used to augment existing or provide new functions to cells in the hope that this will be of therapeutic benefit [15].

The Blood Brain Barrier is a dynamic and complex interface between the blood and the central nervous system regulating brain homeostasis. Major functions of the Blood Brain Barrier include the transport of nutrients and protection of the brain from toxic compounds. The nutrition of the brain involves small molecules like sugars, amino acids, vitamins, and trace elements. Large biomolecules, lipoproteins, peptide and protein hormones cross the Blood Brain Barrier by receptor-mediated transport [16]. Dysfunction in the transport of nutrients at the Blood Brain Barrier is described in several neurological disorders and diseases. The Blood Brain Barrier penetration of neuroprotective nutrients, especially the potential protective effect of polyphenols and alkaloids, on brain endothelium is well-known [16, 17].

Thus, the search for molecular features (fragments, 3D-isomerism, intramolecular and intermolecular quantum mechanical conditions) with apparent influence to blood brain barrier and destructed fragments of neurons can be a perspective for drug discovery.

2.2. Molecular Features which Influence to Blood Brain Barrier

Mechanistic interpretation for QSAR related to blood brain barrier usually based on physicochemical conditions such as octanol/water partition coefficient, isolated atomic energy [18], H-bond donor surface area, H-acceptor surface area [19], Rotatable bonds count, Hydrogen bond acceptor count [20]. There is influence of the presence of heavy atoms on the blood brain barrier and central nervous system [17]. The binding energy predictions were highly correlated with r^2=0.88, F=692.4, standard error of estimate =0.775, for selected blood brain barrier active/inactive compounds (n=93) [17].

Inhibition of efflux pumps present at the blood brain barrier by nutraceuticals and plant compounds can be carried out with a number of organic compounds such as Apigenin, Berbamine, Catechin, Chrysin, Rutin, *etc*. [16]. The rings are common attributes of these biologically active compounds [16]. Thus the six-membered rings are of molecular feature with influence on the blood brain barrier and central nervous system [16]. Presence of nitrogen in rings and size of linear molecular fragment connecting a couple of rings is also a molecular alert related to blood brain barrier [21].

2.3. Molecular Features which Influence the Alzheimer's Disease

Mechanistic interpretation for QSAR related to Alzheimer's disease is usually based on physicochemical and

biochemical conditions, such as molecular weight, total polar surface area hydrophilicity, absorption rate constants, *etc*., without molecular alerts [22]. However, modifiers of pharmacokinetics effects include molecular images such as 2-propan-water, acetone-water and the number of carbon atoms [22]. Chlorine and oxygen connected to six-membered rings, triple covalent bonds, as well as 3D-conformations can also be examined as structural alerts related to endpoints interrelated to Alzheimer's disease [23]. Finally, groups of five-membered and six-membered rings involve oxygen and nitrogen respectively, aspotential agents for treating Alzheimer's disease [24].

3. QSAR MODELS

3.1. Data

The binding affinity data (IC50 nM converted into negative decimal logarithm pIC50= $-\log_{10}$IC50) of 233 gamma-secretase inhibitors (potential agents for treatment Alzheimer's disease) are studied in the literature [25, 26]. The database for Blood brain barrier permeation (logBB) values for 291 substances is available from the literature [27].

3.2. Optimal Descriptor

A model for biological activity is building up as one-variable correlation

$$Activity = C_0 + C_1 \times DCW(T^*, N^*) \quad (1)$$

The C_0 and C_1 are regression coefficients (intercept and slope) calculated with the Least squares method. "T" is threshold to define rare features extracted from SMILES. For instance, if T=3, all features which have prevalence less than 3 in the training set are considered as rare. The rare features are not used to build up a model (their correlation weights are zero). N is the number of epochs of the Monte Carlo optimization for correlation weights of molecular features involved in the modelling process. The T* and N* are values of the T and N which give the best statistical characteristics for model calculated with Eq. 1 for the calibration set.

The optimal descriptor of correlation weights (DCW) of different molecular features extracted from simplified molecular input-line entry system (SMILES) [28] and from molecular graph:

$$DCW(T^*, N^*) = DCW_{graph}(T^*, N^*) + DCW_{SMILES}(T^*, N^*) \quad (2)$$

where

$$DCW_{SMILES}(T^*, N^*) = CW(HARD) + \sum CW(S_k) + \sum CW(SS_k) \quad (3)$$

$$DCW_{graph}(T^*, N^*) = CW(C3) + CW(C4) + CW(C5) + CW(C6) + CW(C7) \quad (4)$$

Twelve symbols for registration of molecular features extracted from SMILES are reserved in the program for possible modifications in the future.

Example of the molecular features extracted from SMILES and represented by twelve symbols is shown in Table **1**. The C3 – C7 are situations in a molecular system related to the presence (absence) of three-membered, four-membered, five-membered, six-membered and seven-membered rings. Table **2** represents general scheme of the representation of different situations related to rings by twelve symbols.

The CW(x) is the correlation weights for a molecular feature x. The correlation weights are calculated with the Monte Carlo method optimization. The CORAL software is available for the calculations [29]. The optimal correlation weights give maximal correlation coefficient value between experimental and predicted activity for the training set. The predictive potential of the model should be checked up with external validation set [29]. The detailed description of the CORAL software is available on the Internet (http://www.insilico.eu/coral).

3.4. Predictive Models Built up with the CORAL Software

Three different splits into the training and validation set were studied for the binding affinity data on gamma-secretase inhibitors (pIC50), and were also studied for Blood brain barrier permeation (logBB). It is to be noted that the training set for the CORAL models is structured into training, invisible and calibration sets [30, 31].

Computational experiments have shown that efficacy of the "training" can be improved by means of special set which permanently checks the absence of overtraining. This set can be named as "passive training set" or "invisible training set".

In other words, there are two ways to use a "total" training set to build up correlation "descriptor - endpoint":

Traditional scheme: all compounds of the total training set are taken into the Monte Carlo optimization process. Result will be the maximal correlation coefficient between optimal descriptor and endpoint for all total training set.

Balance of correlations: The first half of the total training set is involved in the Monte Carlo optimization process. However, second half is not involved in the process. In this case, the result will be maximal correlation coefficient between the optimal descriptor and endpoint for the first half of compounds, whereas second half of compounds will give hint whether the correlation is objective or this correlation is preferable solely for the first active half of compounds.

Thus, the balance of correlation is building up a QSAR model with the following participants:

(i) The training set is "builder of the model";

(ii) The invisible training set is the "inspector of the model"; the inspector must detect and stop the process of the overtraining;

(iii) The calibration set is an expert; the expert must declare, "Model is ready";

(iv) The validation set is the appraiser of real predictive potential of the model.

Table 1. Examples of representation of SMILES attributes by means of twelve symbols [SMILES = "NC(SCCF)=N"].

ID	Comment	1	2	3	4	5	6	7	8	9	10	11	12
1	Representation of S_k	**N**	.	.	.	.	.	.	.	.	.	.	.
		C	.	.	.	.	.	.	.	.	.	.	.
		(*	.	.	.	.	.	.	.	.	.	.	.
		S	.	.	.	.	.	.	.	.	.	.	.
		C	.	.	.	.	.	.	.	.	.	.	.
		C	.	.	.	.	.	.	.	.	.	.	.
		F	.	.	.	.	.	.	.	.	.	.	.
		(	.	.	.	.	.	.	.	.	.	.	.
		=	.	.	.	.	.	.	.	.	.	.	.
		N	.	.	.	.	.	.	.	.	.	.	.
2	Representation of SS_k	**N**	.	.	.	**C**	.	.	.	.	.	.	.
		C	.	.	.	**(**	.	.	.	.	.	.	.
		S	.	.	.	**(**	.	.	.	.	.	.	.
		S	.	.	.	**C**	.	.	.	.	.	.	.
		C	.	.	.	**C**	.	.	.	.	.	.	.
		F	.	.	.	**C**	.	.	.	.	.	.	.
		F	.	.	.	**(**	.	.	.	.	.	.	.
		=	.	.	.	**(**	.	.	.	.	.	.	.
		N	.	.	.	**=**	.	.	.	.	.	.	.
			=	#	@	N	O	S	P	F	Cl	Br	I
3	Definition of HARD attribute	**$**	**1**	**0**	**0**	**1**	**0**	**1**	**0**	**1**	**0**	**0**	**0**

*)Brackets are the representation of molecular branching and used only "without".

Table 2. Definition of SMILES attributes related to the presence of rings.

	1	2	3	4	5	6	7	8	9	10	11	12
Ring status	**C**	**x**	**.**	**.**	**.**	**a**	**h**	**.**	**y**	**.**	**.**	**.**

The **x** is the size of rings *i.e.* **x**=3, 4, 5, 6, 7; If there are aromatic rings then **a**='A', otherwise **a**='.'; If there are heteroatoms in rings then **h**='H', otherwise **h**='.'; The **y** is the number of rings *i.e.* **y**=0, 1, 2, …

The advantage to this approach is the possibility of building up a model solely from 2D data on the molecular structure represented by SMILES with the interpretation of influence of different molecular features extracted from SMILES. However, there are some disadvantages of the approach. In particular, the Monte Carlo optimization is not a fast calculation especially for large datasets. In addition, some of the SMILES fragments do not have transparent physical meaning (*e.g*. symbols "[", "@", dots, *etc*.).

The models, which were built up with the balance of correlations, are as follows:

Binding Affinity of Gamma-secretase Inhibitors *(Potential Agents for Treatment Alzheimer's Disease*)

Split 1

pIC_{50} = 1.2942501 (± 0.0382248) + 0.1606057 (± 0.0009709) * DCW(1,15) (5)

n=62, r^2=0.8258, RMSE=0.623, F=284 (training set)

n=71, r^2=0.6856, RMSE=0.727 (invisible training set)

n=51, r^2=0.6810, RMSE=0.751 (calibration set)

n=49, r^2=0.7752, RMSE=0.733 (validation set)

Table 3. Lists of stable promoter of increase (all correlation weights are positive) or decrease (all correlation weights are negative) for pIC50 and logBB.

No.	Feature, F	CW(F) Run 1	CW(F) Run 2	CW(F) Run 3	Training Set	Invisible Training Set	Calibration Set
	pIC50, split 1						
1	1.....	0.24936	0.81527	1.00426	62	71	51
2	O...(.....	1.81598	2.00425	2.94093	62	71	51
3	O...=.....	0.62907	0.75437	1.18718	62	71	51
4	C3.....0...	1.74618	3.12552	2.49983	60	71	51
5	C4.....0...	3.12573	4.43867	1.99580	60	71	51
6	C...(.....	0.68970	0.62551	0.25068	59	62	43
7	C...1.....	1.37112	1.12572	1.43837	59	61	43
8	c...(.....	1.25445	1.43762	1.37518	57	63	46
9	c...1.....	0.37510	0.68855	0.24748	55	65	47
10	N...(.....	0.43569	0.12723	0.12950	50	54	38
11	1...(.....	0.62013	0.37156	0.50154	41	46	28
12	N...C.....	0.74564	0.93512	0.62564	41	43	29
13	S.....	1.87883	1.44122	2.56649	40	43	33
14	[...C.....	2.87716	1.68980	1.75250	38	34	25
15	F.....	0.68765	0.74914	0.37233	37	38	28
16	C5.....0...	4.87431	4.87313	3.87512	36	40	31
1	(.....	-0.50046	-0.62885	-0.05899	62	71	51
2	=...(.....	-0.37242	-0.24593	-0.56678	62	69	51
3	=.....	-2.24798	-1.12583	-2.05997	62	71	51
4	C.....	-0.56673	-0.56218	-0.50032	62	71	51
5	c.....	-0.06497	-0.18722	-0.31242	62	71	51
6	c...c.....	-0.56687	-0.49790	-0.81516	62	71	51
7	N.....	-0.68973	-1.12750	-0.68769	54	62	41
8	(...(.....	-0.74772	-1.12089	-1.81062	39	44	34
9	[...H.....	-1.56676	-1.25190	-0.31208	38	34	25
10	Cl..(.....	-0.24951	-0.56565	-0.62721	35	27	26
11	C...=.....	-2.37058	-2.74693	-3.44246	26	30	14
12	H...@@.....	-1.06063	-0.37158	-1.43490	21	21	13
13	[...@.....	-2.31200	-2.81686	-1.50485	19	11	9
14	=...1.....	-1.31479	-1.74616	-1.00456	9	15	10
15	[...N.....	-0.43407	-2.19238	-1.93745	9	12	6
16	C6...AH.4...	-3.74966	-2.99712	-2.99987	8	6	5

(Table 3) contd….

No.	Feature, F	CW(F) Run 1	CW(F) Run 2	CW(F) Run 3	Training Set	Invisible Training Set	Calibration Set
	pIC50, split 2						
1	1.....	0.37791	0.75136	0.50087	66	67	50
2	O.....	1.93510	2.31473	1.06252	66	67	50
3	C...(.....	0.06720	0.43483	0.62375	61	61	45
4	C...1.....	1.56744	1.62065	1.75150	61	58	43
5	c...(.....	1.56080	1.18804	1.75301	60	60	46
6	N...(.....	0.50498	0.62805	0.43364	54	49	36
7	C...C.....	0.37205	0.62336	0.37277	51	58	42
8	2.....	0.43523	0.56398	0.12820	45	51	32
9	C5.....0...	6.00472	5.99545	6.25140	43	36	34
10	N...C.....	1.37968	1.68793	1.87623	39	41	27
11	[...C.....	0.12456	0.49768	1.80975	37	38	23
12	[...H.....	1.62581	0.69162	1.00379	37	38	23
13	c...2.....	0.99918	0.56194	1.12751	35	36	24
14	F.....	0.49877	0.44089	1.30846	34	37	28
15	F...(.....	0.62920	0.69236	0.37820	33	35	27
16	S.....	3.12476	2.87269	3.37296	33	43	31
1	(.....	-0.55900	-0.55795	-1.06147	66	67	50
2	=.....	-0.31255	-1.99752	-1.87560	66	67	50
3	C.....	-0.24649	-0.62194	-0.37101	66	67	50
4	C3.....0...	-4.12984	-4.74520	-3.49783	66	66	49
5	c.....	-0.43299	-0.12822	-0.37044	66	67	50
6	c...c.....	-0.56748	-0.50425	-0.99606	66	67	50
7	N.....	-1.25121	-1.12588	-1.00118	57	60	39
8	H.....	-1.37596	-0.25167	-1.18672	37	38	23
9	c...C.....	-0.37586	-0.37213	-0.49682	37	38	25
10	[...(.....	-1.37164	-1.62892	-0.87345	35	35	22
11	(...(.....	-1.00341	-1.05836	-0.99682	32	44	32
12	C...=.....	-1.87617	-0.49606	-0.87942	26	28	23
13	C...@@.....	-1.93993	-0.24818	-0.05935	23	21	15
14	[...1.....	-0.25399	-0.87790	-0.06226	22	25	17
15	$10011100100	-1.24578	-1.56069	-1.81534	13	10	7
16	C7...A..1...	-0.24768	-1.18849	-0.62114	11	21	10
	pIC50, split 3						
1	1.....	0.80782	0.12046	1.00472	61	63	55
2	=...(.....	0.80859	0.43861	1.24558	61	63	53
3	O...(.....	2.81151	2.62129	2.31681	61	63	55

(Table 3) contd….

No.	Feature, F	CW(F) Run 1	CW(F) Run 2	CW(F) Run 3	Training Set	Invisible Training Set	Calibration Set
	pIC50, split 3						
4	O...=.....	0.93514	1.43913	0.68355	61	63	55
5	c.....	0.06327	0.00247	0.12191	61	63	55
6	C...1.....	0.81487	1.06109	1.12812	58	60	46
7	c...(.....	0.68932	0.75280	0.93721	57	59	47
8	c...1.....	0.06090	0.30887	0.37182	53	58	51
9	N...(.....	0.37516	0.87510	1.68538	50	48	43
10	2.....	0.94011	1.18721	1.05999	48	43	36
11	[...C.....	1.18350	0.74643	1.12063	39	35	26
12	N...C.....	1.25462	1.31352	1.62911	37	42	33
13	S.....	1.24827	2.00081	0.93984	36	39	36
14	C5.....0...	3.43701	5.50479	6.44186	35	37	34
15	F...(.....	1.12015	0.55846	1.12187	35	33	27
16	S...(.....	1.99622	1.55892	1.68773	33	37	34
1	(.....	-0.37339	-0.06365	-0.62191	61	63	55
2	=.....	-1.62730	-2.31258	-2.12289	61	63	55
3	C.....	-0.37397	-0.69070	-0.56000	61	63	55
4	c...c.....	-0.62350	-0.50475	-1.12573	61	63	55
5	N.....	-1.12086	-1.31212	-2.06263	54	53	48
6	C...C.....	-0.24581	-0.06071	-0.37304	48	47	46
7	[...H.....	-0.44110	-0.30958	-1.24568	39	35	26
8	@@.....	-0.87191	-0.19206	-0.62280	30	20	14
9	C...=.....	-1.75324	-1.80866	-1.87391	28	25	22
10	[...1.....	-0.12014	-0.56717	-0.31449	24	22	18
11	[...@.....	-2.05908	-1.00253	-0.12596	16	10	13
12	C7...A..1...	-1.06160	-1.43859	-0.62483	15	16	14
13	$10011100100	-0.62031	-0.25133	-2.50400	9	12	7
14	[...2.....	-1.31346	-1.43451	-0.75249	9	8	7
15	C6...AH.4...	-0.94103	-2.06365	-1.55992	8	7	7
16	S...C.....	-1.12210	-1.62776	-1.19212	8	1	1
	LogBB, split 1						
1	C.....	0.69000	0.44177	0.44099	101	102	42
2	C4.....0...	1.44233	1.93619	0.87009	100	104	43
3	C3.....0...	9.24711	8.24931	6.37970	99	102	43
4	C...C.....	0.18958	0.24932	0.31713	90	88	41
5	C...(.....	1.06715	0.74746	1.24582	87	91	35
6	C...1.....	0.50407	0.68784	0.99825	80	76	26

(Table 3) contd….

No.	Feature, F	CW(F) Run 1	CW(F) Run 2	CW(F) Run 3	Training Set	Invisible Training Set	Calibration Set
	LogBB, split 1						
7	C...=.....	1.06451	1.00467	0.93251	80	80	24
8	C5.....0...	5.18616	4.87599	3.06013	66	70	32
9	N...C.....	1.06163	1.25062	1.05830	61	59	20
10	N...(.....	1.87440	1.80861	1.50002	50	50	16
11	O...=.....	3.74850	3.12144	3.50390	45	49	17
12	O...C.....	1.87390	1.62698	1.50087	42	35	10
13	=...2.....	1.31662	2.37411	1.93516	41	37	12
14	C...3.....	1.56423	0.24589	0.69105	36	43	10
15	$10011000000	3.49649	2.87644	4.06526	32	23	7
16	C5....H.1...	0.93855	0.49718	0.24570	29	28	11
1	=.....	-1.94237	-2.00425	-1.12592	89	86	30
2	(.....	-1.94146	-1.44173	-1.93644	88	91	35
3	N.....	-1.69081	-1.80786	-1.68985	74	69	22
4	O.....	-3.93612	-3.12302	-3.87867	66	69	27
5	=...(.....	-0.87699	-0.37408	-0.56436	62	58	23
6	C...2.....	-1.87318	-2.18807	-1.87392	60	59	16
7	O...(.....	-1.74592	-1.74659	-1.50041	43	49	19
8	2...(.....	-2.06074	-0.87009	-1.37681	36	35	10
9	N...=.....	-1.62360	-1.50313	-2.12455	30	35	11
10	=...3.....	-0.68502	-0.93424	-1.18858	26	29	8
11	N...2.....	-2.81032	-1.19035	-2.12915	24	19	6
12	[.....	-0.81319	-1.12785	-1.31036	10	8	3
13	=...4.....	-1.31236	-0.81692	-0.68350	9	19	5
14	N...H.....	-1.12172	-0.87838	-1.62984	7	6	3
15	[...C.....	-2.87947	-2.75490	-2.06543	7	5	3
16	Br.....	-0.49505	-0.49665	-1.94093	6	2	2
	LogBB, split 2						
1	C3.....0...	10.87070	9.99674	11.00131	103	103	41
2	C.....	0.12071	0.12533	0.37494	101	106	41
3	C...C.....	0.93320	0.87535	0.50239	89	96	37
4	C...(.....	1.19210	1.25322	0.62690	83	93	36
5	C...=.....	0.37918	1.37448	0.44201	80	86	24
6	1.....	1.49679	0.12476	1.06684	74	88	26
7	C...1.....	1.18368	1.49925	1.56002	74	88	26
8	C5.....0...	4.25337	4.68880	4.12680	68	66	36
9	N...C.....	1.74585	1.50379	1.31711	61	68	19

(Table 3) contd….

No.	Feature, F	CW(F) Run 1	CW(F) Run 2	CW(F) Run 3	Training Set	Invisible Training Set	Calibration Set
	LogBB, split 2						
10	2.....	1.37069	0.93599	0.87107	56	71	15
11	=...1.....	1.00094	1.00452	1.18761	48	61	19
12	N...(.....	2.00333	2.24552	1.81625	47	50	18
13	O...=.....	3.62311	3.49517	3.37670	42	52	19
14	=...2.....	1.18866	0.62164	0.18527	40	45	11
15	C...3.....	1.31047	0.87676	1.31327	38	47	9
16	O...C.....	2.12437	2.25455	1.81321	36	40	12
1	C4.....0...	-0.49732	-0.50309	-0.50008	103	106	41
2	C7.....0...	-3.50133	-3.24763	-2.87060	90	88	34
3	=.....	-1.12942	-2.24834	-1.31595	85	96	28
4	(.....	-1.62048	-1.81308	-1.18864	84	94	36
5	N.....	-2.49537	-2.68449	-2.25354	70	78	23
6	O.....	-3.62711	-4.25421	-3.56712	64	75	28
7	=...(.....	-2.18783	-0.74894	-1.93659	56	71	23
8	C...2.....	-2.49624	-2.30834	-1.81363	56	70	15
9	O...(.....	-2.12646	-1.87628	-2.00250	41	54	18
10	N...=.....	-1.12893	-0.99861	-0.99789	37	34	5
11	2...(.....	-1.75032	-0.75119	-0.49969	35	43	8
12	=...3.....	-1.00262	-0.62848	-0.25161	27	32	7
13	N...2.....	-2.00309	-0.24532	-0.87223	22	29	5
14	S.....	-0.80988	-2.37982	-1.12535	16	17	3
15	=...4.....	-2.24740	-0.99940	-1.12895	12	17	3
16	[...C.....	-3.81523	-3.37811	-2.81052	8	6	2
	LogBB, split 3						
1	C.....	0.00132	0.19167	0.25322	103	104	40
2	C3.....0...	9.74655	10.49769	9.50124	102	104	40
3	C...C.....	1.00004	1.25242	1.00283	92	97	33
4	C...(.....	0.50101	1.37191	1.00401	90	89	35
5	C...1.....	1.31706	1.00284	1.49553	77	83	27
6	C...=.....	0.55849	1.49910	0.06478	76	87	25
7	C5.....0...	6.00291	4.74699	5.25173	71	66	32
8	N...C.....	1.24857	0.87346	1.62565	61	63	21
9	N...(.....	0.75396	1.37567	1.68298	58	43	17
10	O...=.....	1.50315	2.50127	1.49589	49	45	18
11	=...2.....	3.25269	1.68316	2.25396	38	45	12
12	3.....	1.62996	0.75194	0.74545	36	45	10

(Table 3) contd….

No.	Feature, F	CW(F) Run 1	CW(F) Run 2	CW(F) Run 3	Training Set	Invisible Training Set	Calibration Set
	LogBB, split 3						
13	C...3.....	0.00153	0.25042	0.74564	36	45	10
14	1...(.....	1.87609	2.19099	3.00002	34	27	14
15	C6.....0...	2.50113	4.75479	4.37791	33	27	16
16	O...C.....	0.62800	0.49543	0.74706	31	37	14
1	(.....	-0.50197	-1.74939	-1.25398	92	89	35
2	C7.....0...	-3.00432	-2.24765	-2.50016	92	86	35
3	=.....	-1.74993	-2.19227	-0.93260	84	93	30
4	N.....	-1.50133	-2.62558	-3.30976	69	75	24
5	=...(.....	-0.37305	-0.00161	-0.68413	66	63	18
6	O.....	-3.49561	-3.49608	-3.05869	66	69	28
7	C...2.....	-1.25479	-1.19206	-1.56163	55	66	17
8	O...(.....	-1.62599	-1.87859	-2.25388	46	48	15
9	2...(.....	-1.25291	-1.75055	-2.00114	37	36	11
10	N...=.....	-3.00207	-2.49735	-2.24940	31	34	10
11	C5....H.1...	-0.31727	-0.62372	-0.06462	29	29	6
12	=...3.....	-1.25013	-2.25139	-0.31558	27	29	6
13	(...(.....	-1.49562	-1.56378	-2.00367	23	16	7
14	N...2.....	-2.18457	-2.87062	-2.50423	23	24	8
15	[.....	-0.44089	-0.31661	-0.31291	8	11	3
16	[...H.....	-0.75060	-0.74589	-0.12414	8	6	2

Split 2

pIC_{50} = 3.2737064 (± 0.0326601) + 0.1974723 (± 0.0013567) * DCW(1,15) (6)

n=66, r^2=0.7711, RMSE=0.694, F=216 (training set)

n=67, r^2=0.7702, RMSE=0.703 (invisible training set)

n=50, r^2=0.7258, RMSE=0.718 (calibration set)

n=50, r^2=0.7676, RMSE=0.645 (validation set)

Split 3

pIC_{50} = 2.1408654 (± 0.0416128) + 0.1757965 (± 0.0012683) * DCW(1,15) (7)

n=61, r^2=0.7725, RMSE=0.665, F=200 (training set)

n=63, r^2=0.7724, RMSE=0.756 (invisible training set)

n=55, r^2=0.7610, RMSE=1.11 (calibration set)

n=54, r^2=0.7753, RMSE=0.882 (validation set)

Blood Brain Barrier Permeation (logBB)

Split 1

Log(BB) = -0.8609358 (± 0.0066439) + 0.0537248 (± 0.0003448) * DCW(1,15) (8)

n=101, r^2=0.7438, RMSE=0.286, F=287 (training set)

n=104, r^2=0.7540, RMSE=0.331 (invisible training set)

n=43, r^2=0.9141, RMSE=0.198 (calibration set)

n=43, r^2=0.8592, RMSE=0.240 (validation set)

Split 2

Log(BB) = -0.9164493 (± 0.0072757) + 0.0385240 (± 0.0002497) * DCW(1,10) (9)

n=103, r^2=0.6830, RMSE=0.350, F=218 (training set)

n=107, r^2=0.6828, RMSE=0.330 (invisible training set)

n=41, r^2=0.8350, RMSE=0.229 (calibration set)

n=40, r^2=0.8310, RMSE=0.319 (validation set)

Split 3

Log(BB) = -0.5038388 (± 0.0053701) + 0.0231569 (± 0.0001622) * DCW(1,10) (10)

n=104, r^2=0.6388, RMSE=0.359, F=180 (training set)

n=105, r^2=0.6477, RMSE=0.389 (invisible training set)

n=41, r^2=0.8344, RMSE=0.275 (calibration set)

n=41, r^2=0.7273, RMSE=0.274 (validation set)

Table 4. Molecular features which have the same effect for pIC50 (denoted 1) and logBB (denoted 2).

	1	1	1	2	2	2	TRN1*	iTRN1	CLB1	TRN2	iTRN2	CLB2
pIC50-split1-logBB-split1												
O...=.....	+	+	+	+	+	+	62	71	51	45	49	17
C3.....0...	+	+	+	+	+	+	60	71	51	99	102	43
C4.....0...	+	+	+	+	+	+	60	71	51	100	104	43
C...(.....	+	+	+	+	+	+	59	62	43	87	91	35
C...1.....	+	+	+	+	+	+	59	61	43	80	76	26
N...(.....	+	+	+	+	+	+	50	54	38	50	50	16
1...(.....	+	+	+	+	+	+	41	46	28	25	29	14
N...C.....	+	+	+	+	+	+	41	43	29	61	59	20
C5.....0...	+	+	+	+	+	+	36	40	31	66	70	32
N...1.....	+	+	+	+	+	+	36	33	22	23	23	6
O...C.....	+	+	+	+	+	+	22	23	20	42	35	10
(.....	-	-	-	-	-	-	62	71	51	88	91	35
=...(.....	-	-	-	-	-	-	62	69	51	62	58	23
=.....	-	-	-	-	-	-	62	71	51	89	86	30
N.....	-	-	-	-	-	-	54	62	41	74	69	22
pIC50-split1-logBB-split2												
1.....	+	+	+	+	+	+	62	71	51	74	88	26
O...=.....	+	+	+	+	+	+	62	71	51	42	52	19
C3.....0...	+	+	+	+	+	+	60	71	51	103	103	41
C...(.....	+	+	+	+	+	+	59	62	43	83	93	36
C...1.....	+	+	+	+	+	+	59	61	43	74	88	26
N...(.....	+	+	+	+	+	+	50	54	38	47	50	18
1...(.....	+	+	+	+	+	+	41	46	28	33	28	14
N...C.....	+	+	+	+	+	+	41	43	29	61	68	19
F.....	+	+	+	+	+	+	37	38	28	21	11	5
C5.....0...	+	+	+	+	+	+	36	40	31	68	66	36
N...1.....	+	+	+	+	+	+	36	33	22	26	27	5
O...C.....	+	+	+	+	+	+	22	23	20	36	40	12
(.....	-	-	-	-	-	-	62	71	51	84	94	36
=...(.....	-	-	-	-	-	-	62	69	51	56	71	23
=.....	-	-	-	-	-	-	62	71	51	85	96	28
N.....	-	-	-	-	-	-	54	62	41	70	78	23
pIC50-split1-logBB-split3												
O...=.....	+	+	+	+	+	+	62	71	51	49	45	18
C3.....0...	+	+	+	+	+	+	60	71	51	102	104	40

(Table 4) contd….

	1	1	1	2	2	2	TRN1*	iTRN1	CLB1	TRN2	iTRN2	CLB2
pIC50-split1-logBB-split3												
C...(.....	+	+	+	+	+	+	59	62	43	90	89	35
C...1.....	+	+	+	+	+	+	59	61	43	77	83	27
N...(.....	+	+	+	+	+	+	50	54	38	58	43	17
1...(.....	+	+	+	+	+	+	41	46	28	34	27	14
N...C.....	+	+	+	+	+	+	41	43	29	61	63	21
C5.....0...	+	+	+	+	+	+	36	40	31	71	66	32
O...C.....	+	+	+	+	+	+	22	23	20	31	37	14
(.....	-	-	-	-	-	-	62	71	51	92	89	35
=...(.....	-	-	-	-	-	-	62	69	51	66	63	18
=.....	-	-	-	-	-	-	62	71	51	84	93	30
N.....	-	-	-	-	-	-	54	62	41	69	75	24
(...(.....	-	-	-	-	-	-	39	44	34	23	16	7
pIC50-split2-logBB-split1												
C...(.....	+	+	+	+	+	+	61	61	45	87	91	35
C...1.....	+	+	+	+	+	+	61	58	43	80	76	26
N...(.....	+	+	+	+	+	+	54	49	36	50	50	16
C...C.....	+	+	+	+	+	+	51	58	42	90	88	41
C5.....0...	+	+	+	+	+	+	43	36	34	66	70	32
N...C.....	+	+	+	+	+	+	39	41	27	61	59	20
O...C.....	+	+	+	+	+	+	22	18	19	42	35	10
(.....	-	-	-	-	-	-	66	67	50	88	91	35
=.....	-	-	-	-	-	-	66	67	50	89	86	30
N.....	-	-	-	-	-	-	57	60	39	74	69	22
pIC50-split2-logBB-split2												
1.....	+	+	+	+	+	+	66	67	50	74	88	26
C...(.....	+	+	+	+	+	+	61	61	45	83	93	36
C...1.....	+	+	+	+	+	+	61	58	43	74	88	26
N...(.....	+	+	+	+	+	+	54	49	36	47	50	18
C...C.....	+	+	+	+	+	+	51	58	42	89	96	37
2.....	+	+	+	+	+	+	45	51	32	56	71	15
C5.....0...	+	+	+	+	+	+	43	36	34	68	66	36
N...C.....	+	+	+	+	+	+	39	41	27	61	68	19
F.....	+	+	+	+	+	+	34	37	28	21	11	5
O...C.....	+	+	+	+	+	+	22	18	19	36	40	12
(.....	-	-	-	-	-	-	66	67	50	84	94	36
=.....	-	-	-	-	-	-	66	67	50	85	96	28
N.....	-	-	-	-	-	-	57	60	39	70	78	23

(Table 4) contd….

	1	**1**	**1**	**2**	**2**	**2**	**TRN1***	**iTRN1**	**CLB1**	**TRN2**	**iTRN2**	**CLB2**
pIC50-split2-logBB-split3												
C...(.....	+	+	+	+	+	+	61	61	45	90	89	35
C...1.....	+	+	+	+	+	+	61	58	43	77	83	27
N...(.....	+	+	+	+	+	+	54	49	36	58	43	17
C...C.....	+	+	+	+	+	+	51	58	42	92	97	33
C5.....0...	+	+	+	+	+	+	43	36	34	71	66	32
N...C.....	+	+	+	+	+	+	39	41	27	61	63	21
O...C.....	+	+	+	+	+	+	22	18	19	31	37	14
(.....	-	-	-	-	-	-	66	67	50	92	89	35
=.....	-	-	-	-	-	-	66	67	50	84	93	30
N.....	-	-	-	-	-	-	57	60	39	69	75	24
(...(.....	-	-	-	-	-	-	32	44	32	23	16	7
pIC50-split3-logBB-split1												
O...=.....	+	+	+	+	+	+	61	63	55	45	49	17
C...1.....	+	+	+	+	+	+	58	60	46	80	76	26
N...(.....	+	+	+	+	+	+	50	48	43	50	50	16
N...C.....	+	+	+	+	+	+	37	42	33	61	59	20
C5.....0...	+	+	+	+	+	+	35	37	34	66	70	32
N...1.....	+	+	+	+	+	+	32	31	29	23	23	6
(.....	-	-	-	-	-	-	61	63	55	88	91	35
=.....	-	-	-	-	-	-	61	63	55	89	86	30
N.....	-	-	-	-	-	-	54	53	48	74	69	22
pIC50-split3-logBB-split2												
1.....	+	+	+	+	+	+	61	63	55	74	88	26
O...=.....	+	+	+	+	+	+	61	63	55	42	52	19
C...1.....	+	+	+	+	+	+	58	60	46	74	88	26
N...(.....	+	+	+	+	+	+	50	48	43	47	50	18
2.....	+	+	+	+	+	+	48	43	36	56	71	15
N...C.....	+	+	+	+	+	+	37	42	33	61	68	19
C5.....0...	+	+	+	+	+	+	35	37	34	68	66	36
N...1.....	+	+	+	+	+	+	32	31	29	26	27	5
(.....	-	-	-	-	-	-	61	63	55	84	94	36
=.....	-	-	-	-	-	-	61	63	55	85	96	28
N.....	-	-	-	-	-	-	54	53	48	70	78	23
pIC50-split3-logBB-split3												
O...=.....	+	+	+	+	+	+	61	63	55	49	45	18
C...1.....	+	+	+	+	+	+	58	60	46	77	83	27
N...(.....	+	+	+	+	+	+	50	48	43	58	43	17

(Table 4) contd….

	1	1	1	2	2	2	TRN1*	iTRN1	CLB1	TRN2	iTRN2	CLB2
pIC50-split3-logBB-split3												
N...C.....	+	+	+	+	+	+	37	42	33	61	63	21
C5.....0...	+	+	+	+	+	+	35	37	34	71	66	32
(.....	-	-	-	-	-	-	61	63	55	92	89	35
=.....	-	-	-	-	-	-	61	63	55	84	93	30
N.....	-	-	-	-	-	-	54	53	48	69	75	24

*)TRN1, iTRN1 and CLB1 are the numbers of a feature in the training, invisible training and calibration sets for endpoint 1; TRN2, iTRN2 and CLB2 mean the same for endpoint 2.

Table 5. Molecular features which have the opposite effect for pIC50 (denoted 1) and logBB (denoted 2).

	1	1	1	2	2	2	TRN1*	iTRN1	CLB1	TRN2	iTRN2	CLB2
pIC50-split1-logBB-split1												
O...(.....	+	+	+	-	-	-	62	71	51	43	49	19
2...(.....	+	+	+	-	-	-	31	33	18	36	35	10
C.....	-	-	-	+	+	+	62	71	51	101	102	42
C...=.....	-	-	-	+	+	+	26	30	14	80	80	24
pIC50-split1-logBB-split2												
O...(.....	+	+	+	-	-	-	62	71	51	41	54	18
C4.....0...	+	+	+	-	-	-	60	71	51	103	106	41
2...(.....	+	+	+	-	-	-	31	33	18	35	43	8
C7.....0...	+	+	+	-	-	-	28	21	22	90	88	34
C.....	-	-	-	+	+	+	62	71	51	101	106	41
C...=.....	-	-	-	+	+	+	26	30	14	80	86	24
pIC50-split1-logBB-split3												
O...(.....	+	+	+	-	-	-	62	71	51	46	48	15
2...(.....	+	+	+	-	-	-	31	33	18	37	36	11
C7.....0...	+	+	+	-	-	-	28	21	22	92	86	35
C.....	-	-	-	+	+	+	62	71	51	103	104	40
C...=.....	-	-	-	+	+	+	26	30	14	76	87	25
pIC50-split2-logBB-split1												
O.....	+	+	+	-	-	-	66	67	50	66	69	27
2...(.....	+	+	+	-	-	-	31	30	25	36	35	10
C.....	-	-	-	+	+	+	66	67	50	101	102	42
C3.....0...	-	-	-	+	+	+	66	66	49	99	102	43
C...=.....	-	-	-	+	+	+	26	28	23	80	80	24
pIC50-split2-logBB-split2												
O.....	+	+	+	-	-	-	66	67	50	64	75	28
2...(.....	+	+	+	-	-	-	31	30	25	35	43	8

(Table 5) contd….

	1	1	1	2	2	2	TRN1*	iTRN1	CLB1	TRN2	iTRN2	CLB2
pIC50-split2-logBB-split2												
C7.....0...	+	+	+	-	-	-	27	23	21	90	88	34
C.....	-	-	-	+	+	+	66	67	50	101	106	41
C3.....0...	-	-	-	+	+	+	66	66	49	103	103	41
C...=.....	-	-	-	+	+	+	26	28	23	80	86	24
pIC50-split2-logBB-split3												
O.....	+	+	+	-	-	-	66	67	50	66	69	28
2...(.....	+	+	+	-	-	-	31	30	25	37	36	11
C7.....0...	+	+	+	-	-	-	27	23	21	92	86	35
C.....	-	-	-	+	+	+	66	67	50	103	104	40
C3.....0...	-	-	-	+	+	+	66	66	49	102	104	40
C...=.....	-	-	-	+	+	+	26	28	23	76	87	25
pIC50-split3-logBB-split1												
=...(.....	+	+	+	-	-	-	61	63	53	62	58	23
O...(.....	+	+	+	-	-	-	61	63	55	43	49	19
C.....	-	-	-	+	+	+	61	63	55	101	102	42
C...C.....	-	-	-	+	+	+	48	47	46	90	88	41
C...=.....	-	-	-	+	+	+	28	25	22	80	80	24
pIC50-split3-logBB-split2												
=...(.....	+	+	+	-	-	-	61	63	53	56	71	23
O...(.....	+	+	+	-	-	-	61	63	55	41	54	18
C7.....0...	+	+	+	-	-	-	22	23	24	90	88	34
C.....	-	-	-	+	+	+	61	63	55	101	106	41
C...C.....	-	-	-	+	+	+	48	47	46	89	96	37
C...=.....	-	-	-	+	+	+	28	25	22	80	86	24
pIC50-split3-logBB-split3												
=...(.....	+	+	+	-	-	-	61	63	53	66	63	18
O...(.....	+	+	+	-	-	-	61	63	55	46	48	15
C7.....0...	+	+	+	-	-	-	22	23	24	92	86	35
C.....	-	-	-	+	+	+	61	63	55	103	104	40
C...C.....	-	-	-	+	+	+	48	47	46	92	97	33
C...=.....	-	-	-	+	+	+	28	25	22	76	87	25

*)TRN1, iTRN1 and CLB1 are the numbers of feature in the training, invisible training and calibration sets for endpoint 1; TRN2, iTRN2, and CLB2 mean the same for endpoint 2.

3.5. Molecular Features which Influence the pIC50 and logBB Extracted from Coral-models

Table **3** contains correlation weights of different molecular features obtained in three runs of the Monte Carlo method optimization procedure. These features are extracted according to the principles: (i) these have significant prevalence in training, invisible training and calibration sets; and (ii) these features have stable positive or stable negative correlation weights in all runs.

3.5. Molecular Features, which have Similar Effects for pIC50 and logBB

Table **4** contains lists of molecular features which are promoters of increase for both pIC50 and logBB together with features which are promoters of decrease for both pIC50 and logBB. In the first approximation, oxygen and nitrogen connected in rings and oxygen connected with carbon or nitrogen are promoters of increase for both pIC50 and logBB. Branching and the presence of double bonds as well as nitrogen itself are promoters of decrease for both pIC50 and logBB.

3.6. Molecular Features, which have Opposite Effects for pIC50 and logBB

Table **5** contains lists of molecular features, which have opposite effect on both pIC50 and for logBB. In the first approximation, presence of two rings and presence of carbon with double covalent bond have opposite effects on pIC50 and logBB.

It is to be noted that the number of features which have the same effect for pIC50 and logBB is larger than the number of features which have opposite effects for pIC50 and logBB. Consequently, the consideration of interrelations between these endpoints (maybe not only those) can be a perspective in the aspect of drug discovery.

Supplementary materials section contains SMILES and numerical data on examined endpoints.

CONCLUSION

There are arguments to consider the interrelation between gamma-secretase inhibitors activity (pIC50) and blood brain barrier permeation (logBB). The interrelation is described in the literature and confirmed in this work (Table **4**). The interrelation can be detected and described in terms of molecular features extracted from SMILES and molecular graph which are involved in building up QSAR models for the pIC50 and logBB. The examination of equivalent and opposite effect of the presence of molecular features for other endpoint can be useful for other pairs of endpoints. From practical point of view, these can be (a) water solubility and octanol water partition coefficient; (b) water solubility and toxicity; (c) carcinogenicity and mutagenicity, *etc*.

LIST OF ABBREVIATIONS

QSAR	=	Quantitative structure – activity relationships
CWs	=	Correlation weights
BBB	=	Blood brain barrier
AD	=	Alzheimer's disease
SMILES	=	Simplified molecular input-line entry system

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's web site along with the published article.

REFERENCES

[1] Trifunović, J.; Borčić, V.; Vukmirović, S.; Mikov, M. Assessment of the pharmacokinetic profile of novel s-triazine derivatives and their potential use in treatment of Alzheimer's disease. *Life Sci.,* **2017**, *168*, 1-6. [http://dx.doi.org/10.1016/j.lfs.2016.11.001] [PMID: 27818183]

[2] Querfurth, H.W.; LaFerla, F.M. Alzheimer's disease. *N. Engl. J. Med.,* **2010**, *362*(4), 329-344. [http://dx.doi.org/10.1056/NEJMra0909142] [PMID: 20107219]

[3] Alzheimer's disease facts and figures. *Alzheimers Dement.,* **2015**, *11*(3), 332-384. [http://dx.doi.org/10.1016/j.jalz.2015.02.003] [PMID: 25984581]

[4] Braak, H.; Braak, E. Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol.,* **1991**, *82*(4), 239-259. [http://dx.doi.org/10.1007/BF00308809] [PMID: 1759558]

[5] Felician, O.; Sandson, T.A. The neurobiology and pharmacotherapy of Alzheimer's disease. *J. Neuropsychiatry Clin. Neurosci.,* **1999**, *11*(1), 19-31. [http://dx.doi.org/10.1176/jnp.11.1.19] [PMID: 9990552]

[6] Sanders, S.; Morano, C. Alzheimer's disease and related dementias. *J. Gerontol. Soc. Work,* **2008**, *50*(Suppl. 1), 191-214. [http://dx.doi.org/10.1080/01634370802137900] [PMID: 18924393]

[7] Abbott, N.J.; Patabendige, A.A.K.; Dolman, D.E.M.; Yusof, S.R.; Begley, D.J. Structure and function of the blood-brain barrier. *Neurobiol. Dis.,* **2010**, *37*(1), 13-25. [http://dx.doi.org/10.1016/j.nbd.2009.07.030] [PMID: 19664713]

[8] Pardridge, W.M. The blood-brain barrier: bottleneck in brain drug development. *NeuroRx,* **2005**, *2*(1), 3-14. [http://dx.doi.org/10.1602/neurorx.2.1.3] [PMID: 15717053]

[9] Pan, W.; Banks, W.A.; Fasold, M.B.; Bluth, J.; Kastin, A.J. Transport of brain-derived neurotrophic factor across the blood-brain barrier. *Neuropharmacology,* **1998**, *37*(12), 1553-1561. [http://dx.doi.org/10.1016/S0028-3908(98)00141-5] [PMID: 9886678]

[10] Clifford, P.M.; Zarrabi, S.; Siu, G.; Kinsler, K.J.; Kosciuk, M.C.; Venkataraman, V.; D'Andrea, M.R.; Dinsmore, S.; Nagele, R.G. Abeta peptides can enter the brain through a defective blood-brain barrier and bind selectively to neurons. *Brain Res.,* **2007**, *1142*(1), 223-236. [http://dx.doi.org/10.1016/j.brainres.2007.01.070] [PMID: 17306234]

[11] Zlokovic, B.V. New therapeutic targets in the neurovascular pathway in Alzheimer's disease. *Neurotherapeutics,* **2008**, *5*(3), 409-414. [http://dx.doi.org/10.1016/j.nurt.2008.05.011] [PMID: 18625452]

[12] Nagele, R.G.; Clifford, P.M.; Siu, G.; Levin, E.C.; Acharya, N.K.; Han, M.; Kosciuk, M.C.; Venkataraman, V.; Zavareh, S.; Zarrabi, S.; Kinsler, K.; Thaker, N.G.; Nagele, E.P.; Dash, J.; Wang, H.Y.; Levitas, A. Brain-reactive autoantibodies prevalent in human sera increase intraneuronal amyloid-β(1-42) deposition. *J. Alzheimers Dis.,* **2011**, *25*(4), 605-622. [PMID: 21483091]

[13] Bowman, G.L.; Quinn, J.F. Alzheimer's disease and the blood-brain barrier: Past, present and future. *Aging Health,* **2008**, *4*(1), 47-55. [http://dx.doi.org/10.2217/1745509X.4.1.47] [PMID: 19924258]

[14] Heininger, K. A unifying hypothesis of Alzheimer's disease. III. Risk factors. *Hum. Psychopharmacol.,* **2000**, *15*(1), 1-70. [http://dx.doi.org/10.1002/(SICI)1099-1077(200001)15:1<1::AID-HUP153>3.0.CO;2-1] [PMID: 12404343]

[15] Hermens, W.T.J.M.C.; Verhaagen, J. Viral vectors, tools for gene transfer in the nervous system. *Prog. Neurobiol.,* **1998**, *55*(4), 399-

432. [http://dx.doi.org/10.1016/S0301-0082(98)00007-0] [PMID: 9654386]

[16] Campos-Bedolla, P.; Walter, F.R.; Veszelka, S.; Deli, M.A. Role of the blood-brain barrier in the nutrition of the central nervous system. *Arch. Med. Res.,* **2014**, *45*(8), 610-638. [http://dx.doi.org/10.1016/j.arcmed.2014.11.018] [PMID: 25481827]

[17] Shityakov, S.; Förster, C. *In silico* predictive model to determine vector-mediated transport properties for the blood-brain barrier choline transporter. *Adv. Appl. Bioinform. Chem.,* **2014**, *7*, 23-36. [http://dx.doi.org/10.2147/AABC.S63749] [PMID: 25214795]

[18] Bujak, R.; Struck-Lewicka, W.; Kaliszan, M.; Kaliszan, R.; Markuszewski, M.J. Blood-brain barrier permeability mechanisms in view of quantitative structure-activity relationships (QSAR). *J. Pharm. Biomed. Anal.,* **2015**, *108*, 29-37. [http://dx.doi.org/10.1016/j.jpba.2015.01.046] [PMID: 25703237]

[19] Zhang, D.; Xiao, J.; Zhou, N.; Zheng, M.; Luo, X.; Jiang, H.; Chen, K. A genetic algorithm based support vector machine model for blood-brain barrier penetration prediction. *BioMed Res. Int.,* **2015**, *2015*, 292683. [http://dx.doi.org/10.1155/2015/292683] [PMID: 26504797]

[20] Suenderhauf, C.; Hammann, F.; Huwyler, J. Computational prediction of blood-brain barrier permeability using decision tree induction. *Molecules,* **2012**, *17*(9), 10429-10445. [http://dx.doi.org/10.3390/molecules170910429] [PMID: 22941223]

[21] Geldenhuys, W.J.; Manda, V.K.; Mittapalli, R.K.; Van der Schyf, C.J.; Crooks, P.A.; Dwoskin, L.P.; Allen, D.D.; Lockman, P.R. Predictive screening model for potential vector-mediated transport of cationic substrates at the blood-brain barrier choline transporter. *Bioorg. Med. Chem. Lett.,* **2010**, *20*(3), 870-877. [http://dx.doi.org/10.1016/j.bmcl.2009.12.079] [PMID: 20053562]

[22] Trifunović, J.; Borčić, V.; Vukmirović, S.; Mikov, M. Assessment of the pharmacokinetic profile of novel s-triazine derivatives and their potential use in treatment of Alzheimer's disease. *Life Sci.,* **2017**, *168*, 1-6. [http://dx.doi.org/10.1016/j.lfs.2016.11.001] [PMID: 27818183]

[23] Nikolic, K.; Mavridis, L.; Djikic, T.; Vucicevic, J.; Agbaba, D.; Yelekci, K.; Mitchell, J.B.O. Drug design for CNS diseases: Polypharmacological profiling of compounds using cheminformatic, 3D-QSAR and virtual screening methodologies. *Front. Neurosci.,* **2016**, *10*(JUN), 265. [PMID: 27375423]

[24] Tian, Y.L.; Lv, M.; Li, J.J.; Xu, T.; Zhai, H.L.; Zhang, X.Y. Study on the active mechanism of β-secretase inhibitors by molecular simulations. *Eur. J. Pharm. Sci.,* **2015**, *76*, 138-148. [http://dx.doi.org/10.1016/j.ejps.2015.05.007] [PMID: 25965961]

[25] Ajmani, S.; Janardhan, S.; Viswanadhan, V.N. Toward a general predictive QSAR model for gamma-secretase inhibitors. *Mol. Divers.,* **2013**, *17*(3), 421-434. [http://dx.doi.org/10.1007/s11030-013-9441-2] [PMID: 23612850]

[26] Toropova, M.A.; Toropov, A.A.; Raška, I., Jr; Rašková, M. Searching therapeutic agents for treatment of Alzheimer disease using the Monte Carlo method. *Comput. Biol. Med.,* **2015**, *64*, 148-154. [http://dx.doi.org/10.1016/j.compbiomed.2015.06.019] [PMID: 26164035]

[27] Hou, T.; Xu, X. ADME evaluation in drug discovery. 1. Applications of genetic algorithms to the prediction of blood-brain partitioning of a large set of drugs. *J. Mol. Model.,* **2002**, *8*(12), 337-349. [http://dx.doi.org/10.1007/s00894-002-0101-1] [PMID: 12541001]

[28] Weininger, D. SMILES, a chemical language and information system. 1. Introduction to methodology and encoding rules. *J. Chem. Inf. Comput. Sci.,* **1988**, *28*, 31-36. [http://dx.doi.org/10.1021/ci00057a005]

[29] Toropova, A.P.; Toropov, A.A.; Martyanov, S.E.; Benfenati, E.; Gini, G.; Leszczynska, D.; Leszczynski, J. CORAL: Monte Carlo method as a tool for the prediction of the bioconcentration factor of industrial pollutants. *Mol. Inform.,* **2013**, *32*(2), 145-154. [http://dx.doi.org/10.1002/minf.201200069] [PMID: 27481276]

[30] Begum, S.; Achary, P.G.R. Simplified molecular input line entry system-based: QSAR modelling for MAP kinase-interacting protein kinase (MNK1). *SAR QSAR Environ. Res.,* **2015**, *26*(5), 343-361. [http://dx.doi.org/10.1080/1062936X.2015.1039577] [PMID: 25967103]

[31] Achary, P.G.R. QSPR modelling of dielectric constants of π-conjugated organic compounds by means of the CORAL software. *SAR QSAR Environ. Res.,* **2014**, *25*(6), 507-526. [http://dx.doi.org/10.1080/1062936X.2014.899267] [PMID: 24716837]