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Original article

Virtual screening in drug-likeness and structure/activity relationship of pyridazine derivatives as Anti-Alzheimer drugs

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ABSTRACT

Virtual screening emerged as an important tool in our quest to access successful CNS medicaments for treating Alzheimer's disease. The computational techniques applied in this screening are central nervous system multiparameter optimization (CNS MPO), golden triangle rule, structure activity/property relationships (SAR/SPR), Drug-likeness properties, and lipophilicity indices. These techniques offer the ability to guide drug design and selection to a quickly identify the compounds from a class of acetylcholinesterase inhibitors being pyridazine derivatives, with desirable drug-like attributes.

1. Introduction

In medicinal chemistry, bioisosteric replacement is one of the standard techniques used in drug design (Patani et al., 1996). Bioisosteric transformations are used in the process of optimizing drugs to improve their properties. It can be estimated that about 50% of all the drug molecules used in medicine contain a phenyl ring which can be substituted or not (Wermuth, 2011). The bioisosteric replacement of these phenyl rings by the corresponding pyridazine(1,2-diazines) rings opens an access to several thousands of diazine analogues with more possibilities for interaction.

Recently, pyridazine has been considered by GlaxoSmithKline as one of the 'most developable heterocycles for drug design (Ritchie et al., 2012). The compounds containing pyridazine ring is proved to be useful ligands for different targets. Therefore, the pyridazine derivatives has demonstrated versatile biological activities such as antibacterial (El-Sayed et al., 2009), anti-inflammatory (Refaat et al., 2007), antiproliferative (Elagawanyet al., 2013), anticancer (Rathish et al., 2012), antituberculosis (Moldoveanu et al., 2003), antihypertensive (Siddiqui et al., 2011), and antidepressant activities (Laborit, 1979). Pyridazines derivatives have been proposed as "privileged structure" for drug discovery neurodegenerative. In the present study we will focus primarily upon acetylcholinesterase (AChE) inhibitors, this activity serves for the treatment of neurodegenerative Alzheimer's disease (Gualtieri et al., 1995).

Alzheimer's disease (AD) is manifested by the deterioration of nerve cells releasing a substance called acetylcholine (ACh) in different areas of the central nervous system (CNS), whose role is to transmit messages between brain cells (Francis et al., 1999). Acetylcholine deficiency in patients is aggravated by the action of an enzyme, acetylcholinesterase (AChE), which hydrolyzes ACh. Inhibitors of AChE activity promote an increase in the concentration and duration of action of synaptic ACh. This strategy is one of possible approach to treat AD (Rollinger et al., 2004).

According to the World Alzheimer Report 2016, 'Alzheimer's Disease International 'there were 47 million people living with dementia worldwide in 2016, with a possible increase to 131 million by 2050 (Prince et al., 2016).

Virtual screening (VS) is a new branch of medicinal chemistry that represents a fast and cost-effective tool for computationally screening database in search for the novel drug-like. (Reddy et al., 2007).

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The multi-parameter optimization (MPO) methods used to evaluate drug-likeness and identify compounds with a good balance of the many physicochemical and biological properties necessary to become a successful, efficacious and safe drug (Segall, 2012). In the MPO methods we carried out rules of thumb including Lipinski and Veber rules and calculated metrics (Lipinski et al., 1997; Veber et al., 2002). On the other side, calculated metrics method is the calculation of lipophilicity indices.

The CNS MPO desirability scores enhance the odds of identifying compounds with drug-like ADME and safety, while maintaining good blood-brain barrier (BBB) penetration (Wager et al., 2010b).

The Golden Triangle (Johnson et al., 2009) is a visualization tool to simultaneously optimize drug absorption and clearance. By plotting the molecular weight with respect to the distribution coefficient at pH 7.4 (log D 7.4) for a series of molecules.

In our present research, we calculated CNS MPO desirability score, golden triangle rule and a qualitative prediction of structure activity/property relationships (SAR/SPR), we finished with the calculation of drug likeness properties of a bioactive series of pyridazines derivatives. The focus of these calculations is to identify compounds with drug-like ADME and safety attributes, great ability to penetrate the blood-brain barrier (BBB), for designing a successful CNS drug.

2. Computational details

We used the HyperChem 8.08 (HyperChem, 2008) software to determine the geometric optimization of seventeen pyridazine derivatives by means of the Molecular Mechanics force (MM+), the resulted minimized structures were further refined using the semi-empirical PM3 method. After that, the drug-likeness, CNS MPO, QSAR properties of pyridazine derivatives were calculated by MarvinSketch 17.13.0 (MarvinSketch, 2017) software and module QSAR properties (version 8.0.6) integrated in HyperChem software.

3. Results and discussion

3.1. CNS MPO desirability as a measure of CNS drug-likeness

The diseases of the central nervous system (CNS) represent an unsatisfied medical zone of enormous needs. The discovery of drugs in this therapeutic zone faces particular challenges. For designing a CNS drug, it must have optimal pharmacokinetic and safety properties and have a great chance to penetrate the blood-brain barrier (BBB) (Ghose et al., 2011).

A new tool for optimization of CNS parameters (CNS MPO Desirability score) has been developed to optimize the design of molecules with increased penetration of the brain and drug-like properties (Wager et al., 2010b, a).

This new CNS MPO algorithm was based on a set of six fundamental physicochemical parameters: ((1) lipophilicity, partition coefficient logP; (2) distribution coefficient at pH = 7.4 logD; (3) molecular weight MW; (4) topological polar surface area TPSA; (5) number of hydrogen bond donors HBD; (6) most basic center pKa). The desirability score for these physicochemical properties is 0.0 to 1.0 for each property. The most desirable (T0 = 1.0) and least desirable (T0 = 0.0) inflection points are marked with green and red arrows, respectively are given in Fig. 1, the total CNS MPO desirability score ranging from 0.0 to 6.0. Compounds having a CNS MPO ≥ 4 show better drug like (Wager et al., 2010b).

In our study, CNS MPO algorithm was applied to a set for a class of cholinesterase inhibitors (AChE, 17 molecules) being pyridazine derivatives, which are synthesized characterized by Contreras et al. (2001, 1999) (Fig. 2).

Transformed values (T0) of the six properties were determined for each compound, and overall CNS MPO desirability scores for pyridazines derivatives drugs are shown in Table 1. The CNS MPO algorithm shows that 12 compounds (1,5,8,9,10,11,12,13,14, 15,16,17) displayed a high CNS MPO score ≥ 4. The CNS MPO score of these compounds may allow for the prospective design of compounds that occupy diverse property space while maintaining the desirable drug-like attributes including CNS penetration.

The likelihood of a compound with desirable ADME in vitro attributes increases with increased CNS desirability score. The compounds 10,12,13,14 and 16 have the highest CNS MPO desirability score ≥ 5. The 77% of the drugs with CNS MPO desirability scores of ≥ 5 showed full alignment of all three ADME attributes in one molecule (high passive permeability (P_{app}), low P-gp liability, low metabolic clearance ($Cl_{int,u}$)) and safety attributes (high cell viability (THLE Cv) and low risk of interference with the cardiac ion channel hERG) (Wager et al., 2010b,a). So, the five compounds10, 12, 13, 14 and 16 with the highest CNS MPO ≥ 5 leads to desirable ADME and safety attributes with an ability to penetrate the BBB.

3.2. Structure activity/property relationship for pyridazine derivative

In most cases, it is more advantageous to try to improve the pharmacological activity and properties of drug, such as solubility, stability and permeability during drug discovery. This is best achieved by modifying the chemical structure. Medicinal chemists determine the relationship between structure and activity /properties by developing qualitative approach of structure activity/Property relationships (SAR/SPA) (Belaidi et al., 2015; Melkemi and Belaidi, 2014).

The SAR /SPA study is applied on our anti-cholinesterase series (Fig. 2). The physico-chemical parameters involved are: Surface area grid (SAG), Molar volume (MV), Hydration energy (HE), Molecular weight (MW), partition coefficient octanol/water (log*P*), polar surface area (TPSA) and hydrogen bond donors/ acceptors (HBDs, HBAs) (Tables 2, 3).

Molecular weight (MW) is among the factors that determines drug permeability of drug candidates. CNS drugs have significantly reduced molecular weights compared with other therapeutics. An analysis of small drug-like molecules (MW < 450) suggested that for better brain permeation and to have a good oral absorption (Atkinson et al., 2002; Van de Waterbeemd et al., 1998).

The golden triangle and Warring rules (Johnson et al., 2009; Waring, 2009) show that the distribution coefficient at pH 7.4 (log $D_{7.4}$) and the molecular weight (MW) have an important impact on ADME and drug-likeness properties.

Waring suggests that log$D_{7.4}$ and molecular weight are the important factors in determining the permeability of drug candidates. The influences of molecular weight and log$D_{7.4}$ are not independent and the log$D_{7.4}$ threshold for high permeability is a lower value for compounds of lower molecular weight (Martin,2005). According to the Warring rule, there is a 74% chance of achieving high permeability for compounds with MW < 414 and log$D_{7.4}$ > 1.3. most of our compounds are within the limits of Lipinski rules. These results should help design compounds with improved permeability.

The Golden Triangle is a visualization tool developed from in vitro permeability, in vitro clearance and computational data designed to help medicinal chemists obtain metabolically stable, permeable and potent drug candidates. The probability of success in maximizing potency, stability and permeability is realized by moving the design properties into an area with a baseline of log $D_{7.4}$ = −2.0 to log $D_{7.4}$ = 5.0 at MW = 200 and a peak at log $D_{7.4}$ = 1, 0–2,0 and MW = 450, these boundaries give a triangular shape,

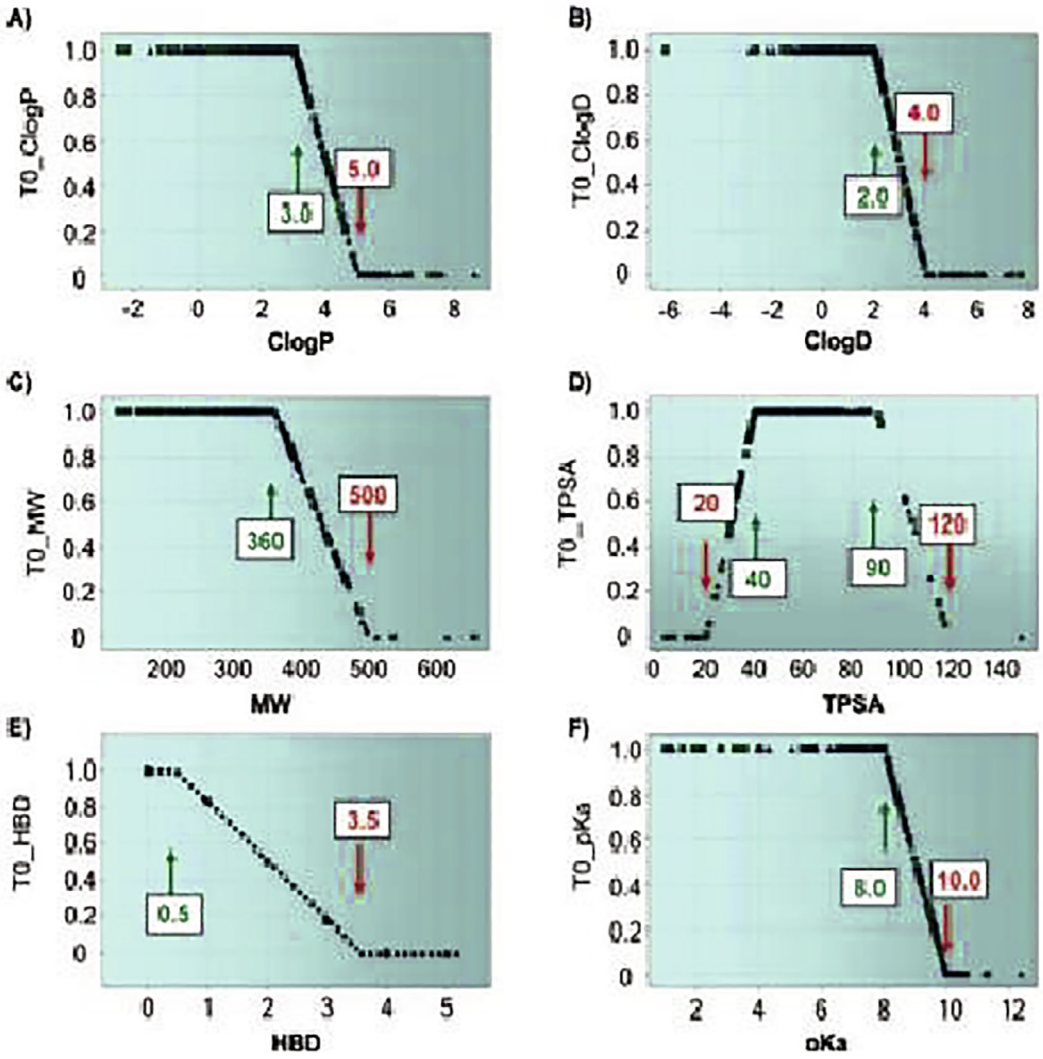

Fig. 1. Each ploy represents one of the six physicochemical property desirability function used to generate the CNS MPO (Wager et al., 2010b). Copyright 2010 ACS.

called golden triangle. For our series of molecules, it is apparent that the compounds 1,9,10,11,12,14 and 16 have good permeability and low clearance because are concentrated within golden triangle area (Fig. 3).

According to the results obtained by these two rules, these compounds (1,9,10,11,12,14,16) have highest probability of success in maximizing potency, stability and permeability.

Pajouhesh et al. (Pajouhesh and Lenz, 2005), showed that two to five nitrogen atoms and zero to two oxygen atoms are the best range for CNS drugs(5 heteroatoms or less). These are applied to our compounds.

The calculation of the hydration energy is based on the exposed surface which depends on the type of atom of the molecular groups which can be donors or acceptor of the hydrogen bonds. The highest HE in absolute value (11.320) was observed for compound 14. The compound 6 have lowest hydration energy value (6.310). The HE increases in the presence of hydrophilic groups in the molecule. The compound 14 (Fig. 4)possesses one hydrogen bond donor HBD (NH) and four hydrogen bond acceptors HBA (three cyclic nitrogen, NH), result the increase in the hydration energy. The HBA are a great number that leads to poor permeability across a membrane bi-layer. The smaller number leads to better permeability (Lipinski et al., 1997).

Lipophilicity (logP) is an important factor in the processes of solubility, ADME properties, as well as pharmacological activity. A general guide for good oral bioavailability (good permeability and solubility) is to have a moderate logP ($0 < \log P < 3$). Indeed, for a log P that is too high, the drug has a low aqueous solubility. In the case of a very low log P, the drug has a difficulty penetrating into the lipid bilayers of cell membranes (Kerns and Li, 2008). For several classes of CNS active substances, Hansch and Leo found that blood-brain barrier penetration is optimal when the logP values are in the range of 1.5–2.7 (Hansch and Leo, 1979).

The compounds 10,12,14 and 16 have logP values (1.68, 2.75, 2.42 and 1.3, respectively). These compounds are considered CNS oral drug, because of their better brain permeation (Bazooyar et al., 2013) and their good intestinal permeability (Fichert et al., 2003).

The polar surface area (TPSA) of a molecule is currently defined as the surface sum over all polar atoms, primarily oxygen and nitrogen. The increasing TPSA is associated with increasing percentages of compound that are not permeable or not bioavailable (Palm et al.,1997). The upper limit of PSA for a molecule to enter the brain is about 90. (Pajouhesh and Lenz, 2005). TPSA was used to calculate the percentage of absorption (%ABS) according to the equation (Zhao et al., 2002): $\%ABS = 109 \pm 0.345 \times TPSA$.

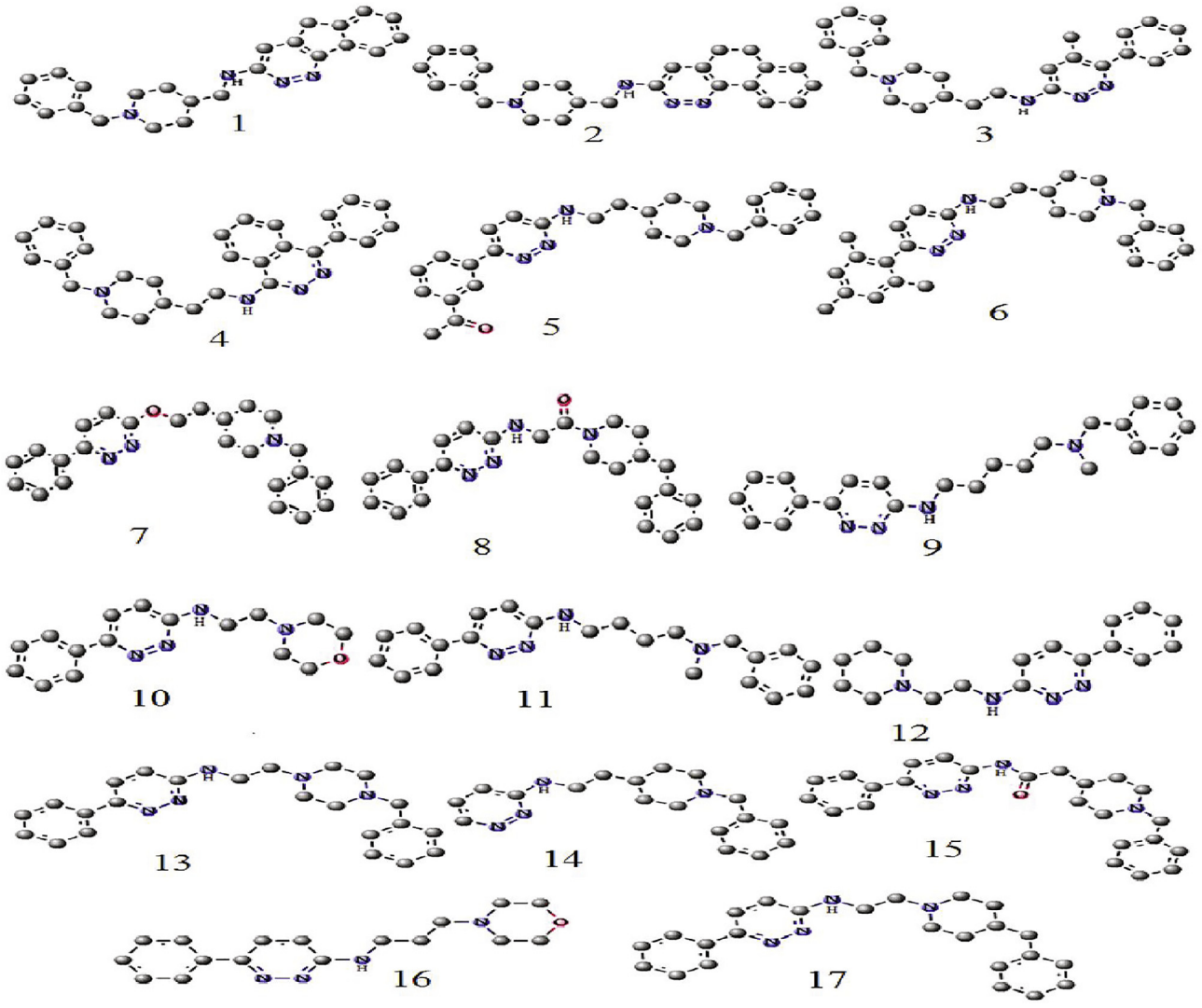

Fig. 2. 3D structures of pyridazines derivatives.

Table 1
CNS MPO Scores and Individual Transformed Scores (T0) of anti-cholinesterase compounds.

Comp.	LogP		LogD		TPSA		MW (u.m.a)		NHD		Pka		CNS MPO
	Value	T0	Value	T0	Value	T0	Value	T0	Value	T0	Value	T0	–
1	4.21	0.39	2.41	0.79	41.05	1.00	370.5	0.99	1	0.83	9.2	0.40	4.4
2	4.65	0.18	2.86	0.57	41.05	1.00	384.52	0.89	1	0.83	9.20	0.40	3.8
3	4.97	0.02	3.09	0.46	41.05	1.00	386.54	0.87	1	0.83	9.28	0.36	3.5
4	5.44	0.00	3.57	0.22	41.05	1.00	422.57	0.62	1	0.83	9.28	0.36	3.0
5	4.01	0.49	2.13	0.94	58.12	1.00	414.55	0.68	1	0.83	9.28	0.36	4.3
6	5.99	0.00	4.12	0.00	41.05	1.00	414.59	0.68	1	0.83	9.28	0.36	2.7
7	4.82	0.09	3.05	0.48	38.25	0.91	373.50	0.97	0	1.00	9.17	0.42	3.9
8	3.71	0.65	3.71	0.15	58.12	1.00	386.50	0.87	1	0.83	3.70	1.00	4.5
9	4.64	0.18	2.62	0.69	41.05	1.00	360.50	1.09	1	0.83	9.43	0.29	4.0
10	1.68	1.00	1.64	1.00	50.28	1.00	284.36	1.00	1	0.83	6.35	1.00	5.8
11	4.20	0.40	2.18	0.91	41.05	1.00	346.48	1.00	1	0.83	9.43	0.28	4.4
12	2.75	1.00	1.58	1.00	41.05	1.00	282.39	1.00	1	0.83	8.54	0.73	5.6
13	3.47	0.77	2.93	0.54	44.29	1.00	373.50	0.97	1	0.83	7.78	1.00	5.1
14	2.42	1.00	0.54	1.00	41.05	1.00	296.42	1.00	1	0.83	9.28	0.36	5.2
15	4.04	0.48	2.67	0.67	58.12	1.00	388.51	0.87	1	0.83	8.75	0.63	4.5
16	1.74	1.00	1.59	1.001	50.28	1.00	298.39	1.00	1	0.83	7.00	1.00	5.8
17	4.61	0.19	3.33	0.34	41.05	1.00	372.51	0.97	1	0.83	8.66	0.67	4.0

TPSA values were found in the range of 58.12–38.25, these compounds have a chance to cross the BBB and have better bioavailability. We can observe obviously that all exhibited a great%ABS ranging from 88.949 to 94.838%, indicating that these compounds should have good cellular plasmatic membrane permeability.

Table 2
Physico-chemical parameters of pyridazine derivatives.

Compounds	MV (Å^3)	SAG (Å^2)	HE (kcal/mol)	LogD	ABS%
1	1125.910	654.050	−7.890	2.41	94.838
2	1156.590	668.590	−8.640	2.86	94.838
3	1199.420	699.040	−8.100	3.09	94.838
4	1269.240	730.050	−8.900	3.57	94.838
5	1256.520	733.920	−9.140	2.13	88.949
6	1295.910	752.850	−6.310	4.12	94.838
7	1149.010	673.330	−8.610	3.05	95.804
8	1153.150	679.560	−10.360	3.71	88.946
9	1133.210	645.440	−9.880	2.62	94.838
10	874.10	528.890	−10.930	1.64	91.653
11	1091.770	626.210	−9.680	2.18	94.838
12	897.280	538.840	−8.380	1.58	94.838
13	1147.60	670.790	−10.030	2.93	93.719
14	940.820	557.820	−11.320	0.54	94.838
15	1157.060	644.330	−8.720	2.67	88.949
16	928.170	562.930	−10.600	1.59	91.653
17	1131.680	655.170	−9.820	3.33	94.838

Table 3
Drug-likeness parameters and Lipophilicity Indices of pyridazine derivatives.

Comps	Lipinski rules					Veber rules		Lipophilicity indices				
	MW <500	LogP <5	NHD <5	NHA <10	ROF-score	NBR <10	TPSA <140	LE –	LipE –	LELP	pIC_{50}[a]	N_H
1	370.500	4.210	1	4	4	5	41.050	0.400	3.790	10.525	8	28
2	384.520	4.650	1	4	4	5	41.050	0.358	2.760	12.999	7.41	29
3	386.540	4.970	1	4	4	7	41.050	0.371	2.710	13.405	7.68	29
4	422.570	5.440	1	4	3	7	41.050	0.276	0.870	19.706	6.31	32
5	414.550	4.010	1	5	4	8	58.120	0.328	3.260	12.214	7.27	31
6	414.590	5.990	1	4	3	7	41.050	0.249	-0.470	24.028	5.52	31
7	373.500	4.820	0	4	4	7	38.250	0.343	2.030	14.073	6.85	28
8	386.500	3.710	1	4	4	6	58.120	0.189	0.210	19.605	3.92	29
9	360.500	4.640	1	4	4	10	41.050	0.330	1.490	14.057	6.13	26
10	284.360	1.680	1	5	4	5	50.280	0.207	1.420	8.129	3.1	21
11	346.480	4.200	1	4	4	9	41.050	0.267	0.760	15.726	4.96	26
12	382.390	2.750	1	4	4	5	41.050	0.277	1.400	9.939	4.15	21
13	373.500	3.470	1	5	4	7	44.290	0.291	2.350	11.924	5.82	28
14	296.420	2.420	1	4	4	6	41.050	0.507	4.100	4.772	6.52	18
15	386.500	4.040	1	4	4	6	58.120	0.259	1.340	15.555	5.38	29
16	298.390	1.300	1	5	4	6	50.280	0.216	2.090	6.026	3.39	22
17	372.510	4.610	1	4	4	7	41.050	0.231	0.010	19.957	4.62	28

[a] pIC50 = Log(1/IC50) in μM (Contreras et al., 2001, 1999).

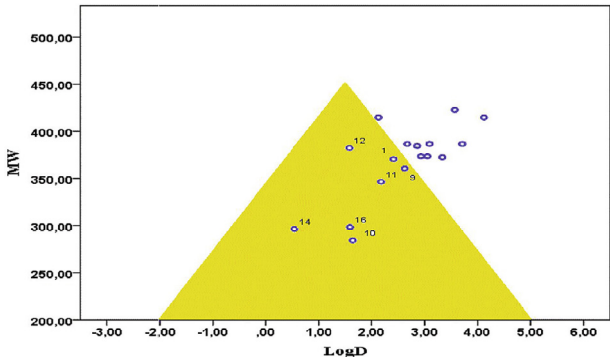

Fig. 3. In vitro permeability and clearance trends across MW and logD.

The number of rotatable bonds (NRB) expresses the flexibility of a molecule. NRB is the number of bonds which allow free rotation around themselves (Veber et al., 2002). Molecular flexibility relates to the ease by which the molecule transverses the membrane. Number of rotatable bonds of a successful CNS drug is < 8 (Pajouhesh and Lenz, 2005).

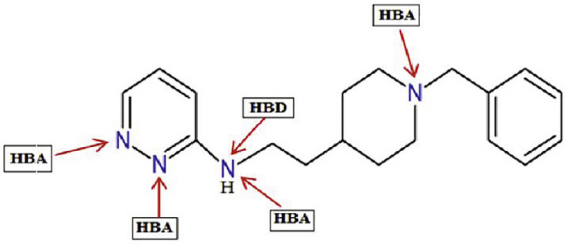

Fig. 4. Donor and acceptor sites of compound 14.

All the compounds of our anti-cholinesterase inhibitors series (AChE) have NBR < 8, except the compounds 9 and 11 their NBR is 10, 9 respectively.

3.3. Drug-likeness properties and lipophilicity indices

The main objective of this study is to evaluate oral bioavailability of seventeen pyridazine derivatives (Fig. 2). High oral bioavailability is frequently an important consideration for the development of bioactive molecules as therapeutic agents. (Salah et al., 2015; BenBrahim et al., 2016; Kerassa et al., 2016)

Table 4
The summary of results obtained by the prediction rules.

Comps	CNS MPO	Structure activity/property relationships (SAR/SPR)							Drug-likeness		Lipophilicity indice
	–	Golden triangle	Warring rule	LogP	HBD	Hetero-atom	TPSA	NRB	ROF-score	Veber rules	LELP
	≥5	–	–	1.5–2.7	≤2	≤5	TPSA < 90	<8	4	–	10 < LELP < 10
1		**X**	**X**		**X**	**X**	**X**	**X**	**X**	**X**	
2			**X**		**X**	**X**	**X**	**X**	**X**	**X**	
3			**X**		**X**	**X**	**X**	**X**	**X**	**X**	
4					**X**	**X**	**X**	**X**		**X**	
5					**X**	**X**	**X**	**X**	**X**	**X**	
6			**X**		**X**	**X**	**X**	**X**		**X**	
7			**X**		**X**	**X**	**X**	**X**	**X**	**X**	
8			**X**		**X**	**X**	**X**	**X**	**X**	**X**	
9		**X**	**X**		**X**	**X**	**X**		**X**		
10	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*
11		**X**	**X**		**X**	**X**	**X**		**X**	**X**	
12	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*
13	**X**		**X**		**X**	**X**	**X**	**X**	**X**	**X**	
14	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*
15			**X**		**X**	**X**	**X**	**X**	**X**	**X**	
16	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*
17			**X**		**X**	**X**	**X**	**X**	**X**	**X**	
rivastigmine	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	–

X: Compound satisfies at the rule. ***Italics:*** Successful CNS drug, which may pass at clinic test.
N.B: I can't calculate the LEPE of rivastigmine, since their IC_{50} activity must be measured by one and the same test as the other compounds, with identical experimental conditions.

In vivo pharmacokinetic parameters are strongly influenced by the physicochemical properties of a drug. The earliest thorough analysis of ADME properties was performed by Lipinski (Lipinski et al., 1997), and resulted in the famous "rule of 5", which argues that good absorption or permeation are more likely when: The molecular weight (MW) <500, The number of hydrogen bond donors (HBDs) <5 (counting the sum of all NH and OH groups) partition coefficient octanol/water Log P < 5, The number of hydrogen bond acceptors (HBAs) <10 (counting all N and O atoms). The total number of violation in this ROF-score, which lies between 0 and 4. The results obtained are shown in Table 3.

There are two other descriptors identified by Veber et al. (2002): Number of Rotatable bonds (NBR) <10 and Polar surface area (PSA) <140 Å2.

All compounds meet the Lipinski and Veber rules of the five, suggesting that these compounds theoretically have ideal oral bioavailability. These physicochemical parameters are associated with acceptable aqueous solubility and intestinal permeability that are the first steps in oral bioavailability.

The control of lipophilic efficiency indices such as ligand lipophilic efficiency LipEand ligand-efficiency dependent lipophilicity LELP, which may contribute significantly to the overall quality of drugs at different stages of discovery.

If the lipophilicity is too high, there is an increased likelihood of binding to other targets than those desired and, therefore, there is more potential for toxicity (Leeson and Springthorpe, 2007). To facilitate the optimization of the affinity with respect to lipophilia. Leeson and Springthorpe (2007) defined the efficacy of ligand lipophilicity efficiency LipE (LLE); this parameter tries to improve potency while maintaining low lipophilicity, which makes the interaction with the receptor more specific.

$$\mathrm{LipE} = \mathrm{pIC}_{50} - \mathrm{LogP}$$

The 90% of the drugs have LipE value > 3.3 (Wager et al., 2010a). That compound 1, and 14 have value and were deemed to be the optimal compounds.

To obtain optimal ADMET properties, molecular size and lipophilicity are important factors to consider. Keseru and Makara (2009) propose ligand efficiency-dependent lipophilicity index (LELP) to combine molecular size and lipophilia into a single measure of efficacy. The optimal LELP scores as $-10 < \mathrm{LELP} < 10$.

$$\mathrm{LELP} = \mathrm{LogP}/\mathrm{LE}$$

Where LE is ligand efficiency ($\mathrm{LE} = 1.4\mathrm{p}IC_{50}/N_H$) (Hopkins et al., 2004).The compounds 10,12,14 and 16 reach an LELP of 8.129, 9.939, 4.772 and 6.026, which are situated in the suggested range $-10 < \mathrm{LELP} < 10$. On the other side, all the compounds have LELP less than 16.5, which mean that these compounds are in the Lipinski zone (ROF-score = 4). Except the compounds 4 and 6 their LELP is 19.706 and 24.028respectively are in agreement with their weak ROF-score < 4.

4. Conclusion

In our study, we have made virtual screening applied to a set for a class of anti-cholinesterase inhibitors (AChE, 17 molecules) being pyridazine derivatives and the rivastigmine drug (Jann, 2000), which is one of the marketed cholinergic drugs primarily AChE inhibitors indicated for the treatment of mild to moderate AD. To identify compounds that have high potency, were assayed in comparison with rivastigmine as reference compounds. The use of CNS MPO desirability score, Lipinski, Veber, golden triangle rules, lipophilicity indices and SAR/SPR approaches (Table 4) showed that the compounds 10,12,14,16 have a better BBB permeation, good intestinal permeability and oral bioavailability, they have a desired in vitro ADME and safety attributes. The rivastigmine drug also meet these rules, so these compounds (10,12,14,16) are likely to achieve outcome in the clinic. These results help us to design a successful CNS drug, with better anti-cholinesterase activity.

References

Atkinson, F., Cole, S., Green, C., Van de Waterbeemd, H., 2002. Lipophilicity and other parameters affecting brain penetration. Cent. Nerv. Syst. Agents. Med. Chem. 2, 229–240.

Bazooyar, F., Taherzadeh, M., Niklasson, C., Bolton, K., 2013. Molecular modelling of cellulose dissolution. J. Comput. Theor. Nanosci. 10, 2639–2646.
Belaidi, S., Youcef, O., Salah, T., Lanez, T., 2015. In Silico Approach for Conformational Analysis, Drug-Likeness Properties and Structure Activity Relationships of 12-Membered Macrolides. J. Comput. Theor. Nanosci. 12, 4855–4861.
BenBrahim, I., Belaidi, S., Alafeefy, L., 2016. In Silico Modeling of Substitution-Induced Effect and Structure Property/Activity Relationship Profile of 1, 3, 4-Oxadiazole Derivatives. Rev. Theor. Sci.
Contreras, J.M., Parrot, I., Sippl, W., Rival, Y.M., Wermuth, C.G., 2001. Design, synthesis, and structure− activity relationships of a series of 3-[2-(1-benzylpiperidin-4-yl) ethylamino] pyridazine derivatives as acetylcholinesterase inhibitors. J. Med. Chem. 44, 2707–2718.
Contreras, J.M., Rival, Y.M., Chayer, S., Bourguignon, C.G., 1999. Aminopyridazines as acetylcholinesterase inhibitors. J. Med. Chem. 42, 730–741.
Elagawany, M., Schmitt, M., Ghiaty, A., Ibrahim, M., Bihel, F., Borba Sbardelotto, A., Jacques, J., 2013. Synthesis and antiproliferative effects of 5, 6-disubstituted pyridazin-3 (2H)-ones designed as conformationally constrained combretastatin A-4 analogues. Anticancer Agents Med. Chem. 13, 1133–1140.
El-Sayed, H.A., Moustafa, A.H., Haikal, A.Z., El-Ashry, E.S.H., 2009. Synthesis and antibacterial activity of some glucosyl-and ribosyl-pyridazin-3-ones. Nucleos. Nucleo. Nucl. 28, 184–192.
Fichert, T., Yazdanian, M., Proudfoot, J.R., 2003. A structure–permeability study of small drug-like molecules. Bioorg. Med. Chem. Lett. 13, 719–722.
Francis, P.T., Palmer, A.M., Snape, M., Wilcock, G.K., 1999. The cholinergic hypothesis of Alzheimer's disease. J. Neurol. Neurosurg. Psychiatry 66, 137–147.
Ghose, A.K., Herbertz, T., Hudkins, R.L., Dorsey, B.D., Mallamo, J.P., 2011. Knowledge-based, central nervous system (CNS) lead selection and lead optimization for CNS drug discovery. ACS Chem. Neurosci. 3, 50–68.
Gualtieri, F., Dei, S., Manetti, D., Romanelli, M.N., Scapecchi, S., Teodori, E., 1995. The medicinal chemistry of Alzheimer's and Alzheimer-like diseases with emphasis on the cholinergic hypothesis. Farmaco 50, 489–503.
Hansch, C., Leo, A., 1979. Substituent constants for correlation analysis in chemistry and biology. Wiley, New York.
Hopkins, A.L., Groom, C.R., Alex, A., 2004. Ligand efficiency: a useful metric for lead selection. Drug Discov. Today 9, 430–431.
Hyperchem (Molecular Modeling System) Hypercube, 2008. Gainesville, FL 32601, USA.
Jann, M.W., 2000. Rivastigmine, a new-generation cholinesterase inhibitor for the treatment of Alzheimer's disease. Pharmacother. J. Hum. Pharmacol. Drug Ther. 20 (1), 1–12.
Johnson, T.W., Dress, K.R., Edwards, M., 2009. Using the Golden Triangle to optimize clearance and oral absorption. Bioorg. Med. Chem. Lett. 19, 5560–5564.
Kerassa, A., Belaidi, S., Harkati, D., Lanez, T., Prasad, O., Sinha, L., 2016. Investigations on Molecular Structure, Electronic Properties, NLO Properties and Comparison of Drug-Likeness of Triazolothiadiazole Derivatives by Quantum Methods and QSAR Analysis. Reviews. Theor. Sci. 4, 85–96.
Kerns, E.H., Li, Di, 2008. Drug-Like Properties: Concepts, Structure Design and Methods from ADME to Toxicity Optimization. Elsevier, United States.
Keserü, G.M., Makara, G.M., 2009. The influence of lead discovery strategies on the properties of drug candidates. Nat. Rev. Drug Discov. 8, 203–212.
Laborit, H., 1979. Pyridazine derivatives in alleviating depressive. USPTO 4, 169.
Leeson, P.D., Springthorpe, B., 2007. The influence of drug-like concepts on decision-making in medicinal chemistry. Nat. Rev. Drug Discov. 6, 881–890.
Lipinski, C.A., Lombardo, F., Dominy, B.W., Feeney, P.J., 1997. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv. Drug Deliv. Rev. 23, 3–25.
Martin, Y.C., 2005. A bioavailability score. J. Med. Chem. 48 (9), 3164–3170.
MarvinSketch 17.1.2, 2017. ChemAxon (http://www.chemaxon.com).
Melkemi, N., Belaidi, S., 2014. Structure-property relationships and quantitative structure-activity relationship modeling of detoxication properties of some 1, 2-dithiole-3-thione derivatives. J. Comput. Theor. Nanosci. 11, 801–806.
Moldoveanu, C., Mangalagiu, G., Drochioiu, G., Caprosu, M., Petrovanu, M., Mangalagiu, I.I., 2003. New antituberculosis compounds derived from diazine. I. An. Stiint. Univ. Al. I. Cuza Iasi. 11, 367–374.
Pajouhesh, H., Lenz, G.R., 2005. Medicinal chemical properties of successful central nervous system drugs. Neuro Rx. 2, 541–553.
Palm, K., Stenberg, P., Luthman, K., Artursson, P., 1997. Polar molecular surface properties predict the intestinal absorption of drugs in humans. Pharmacol. Res. 14, 568–571.
Patani, G.A., Lavoie, E.J., Isosteres, B.D., Equivalents, D.R., Equivalents, T.R., Bioisosteres, I.I., 1996. Bioisosterism: A Rational Approach in Drug Design. Chem. Rev. 96, 3147.
Prince, M., Comas-Herrera, A., Knapp, M., Guerchet, M., Karagiannidou, M., 2016. World Alzheimer report: The Global Economic Impact of Dementia. Alzheimer's Disease International.
Rathish, I.G., Javed, K., Ahmad, S., Bano, S., Alam, M.S., Akhter, M., Samim, M., 2012. Synthesis and evaluation of anticancer activity of some novel 6-aryl-2-(p-sulfamylphenyl)-pyridazin-3 (2H)-ones. Eur. J. Med. Chem. 49, 304–309.
Reddy, A.S., Pati, S.P., Kumar, P.P., Pradeep, H.N., Sastry, G.N., 2007. Virtual screening in drug discovery-a computational perspective. Curr. Protein Pept. Sci. 8, 329–351.
Refaat, H.M., Khalil, O.M., Kadry, H.H., 2007. Synthesis and anti-inflammatory activity of certain piperazinylthienylpyridazine derivatives. Arch. Pharmacol. Res. 30, 803–811.
Ritchie, T.J., Macdonald, S.J., Peace, S., Pickett, S.D., Luscombe, C.N., 2012. The developability of heteroaromatic and heteroaliphatic rings–do some have a better pedigree as potential drug. Med. Chem. Comm. 3, 1062.
Rollinger, J.M., Hornick, A., Langer, T., Stuppner, H., Prast, H., 2004. Acetylcholinesterase inhibitory activity of scopolin and scopoletin discovered by virtual screening of natural products. J. Med. Chem. 47, 6248–6254.
Salah, T., Belaidi, S., Melkemi, N., Tchouar, N., 2015. Molecular Geometry, Electronic Properties, MPO Methods and Structure Activity/Property Relationship Studies of 1, 3, 4-Thiadiazole Derivatives by Theoretical Calculations. Rev. Theor. Sci. 3, 355–364.
Segall, M., 2012. Multi-parameter optimization: identifying high quality compounds with a balance of properties. Curr. Pharm. Des. 18, 1292.
Siddiqui, A.A., Mishra, R., Shaharyar, M., Husain, A., Rashid, M., Pal, P., 2011. Triazole incorporated pyridazinones as a new class of antihypertensive agents: design, synthesis and in vivo screening. Bioorg. Med. Chem. Lett. 21, 1023–1026.
Van de Waterbeemd, H., Camenisch, G., Folkers, G., Chretien, J.R., Raevsky, O.A., 1998. Estimation of blood-brain barrier crossing of drugs using molecular size and shape, and H-bonding descriptors. J. Drug Target. 6, 151–165.
Veber, D.F., Johnson, S.R., Cheng, H.Y., Smith, B.R., Ward, K.W., Kopple, K.D., 2002. Molecular properties that influence the oral bioavailability of drug candidates. J. Med. Chem. 45, 2615–2623.
Wager, T.T., Chandrasekaran, R.Y., Hou, X., Troutman, M.D., Verhoest, P.R., Villalobos, A., Will, Y., 2010a. Defining desirable central nervous system drug space through the alignment of molecular properties, in vitro ADME, and safety attributes. ACS Chem. Neurosci. 1, 420–434.
Wager, T.T., Hou, X., Verhoest, P.R., Villalobos, A., 2010b. Moving beyond rules: the development of a central nervous system multiparameter optimization(CNS MPO) approach to enable alignment of druglike properties. ACS Chem. Neurosci. 1, 435–449.
Waring, M.J., 2009. Defining optimum lipophilicity and molecular weight ranges for drug candidates molecular weight dependent lower logD limits based on permeability. Bioorg. Med. Chem. Lett. 19, 2844–2851.
Wermuth, C.G., 2011. Are pyridazines privileged structures? Med. Chem. Comm. 2, 935–941.
Zhao, Y.H., Abraham, M.H., Le, J., Hersey, A., Luscombe, C.N., Beck, G., Cooper, I., 2002. Rate-limited steps of human oral absorption and QSAR studies. Pharmacol. Res. 19, 1446–1457.