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Assessment of the pharmacokinetic profile of novel s-triazine derivatives and their potential use in treatment of Alzheimer's disease

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ABSTRACT

Aims: The current treatment of Alzheimer's disease is purely symptomatic. Scientists are looking for new treatment options which could alter the course of the disease and improve the quality of life in patients with Alzheimer's disease. In this paper 14 novel s-triazine molecules have been evaluated for their lipophilicity. In addition docking study was carried out to evaluate acetylcholinesterase activity of these compounds.
Main methods: Lipophilicity was evaluated by RP HPTLC using 5 different mobile phases and obtained results were used in calculations of pharmacokinetic parameters - logBB, Ka and Pej. Multiple linear regression analysis was refined, taking account of molecular polarity (total polar surface area, TPSA) and molecular weight (Mw) descriptors. Appropriate QSAR models were developed. Docking studies were carried out using the Vina docking.
Key findings: Five out of fourteen compounds evaluated [5-10] are selected as the most promising compounds with satisfactory pharmacokinetic properties and good docking scores.
Significance: Compound 10 possesses the best combination of favourable pharmacokinetic characteristics (brain penetration, intestinal absorption) and capacity for acetylcholinesterase inhibition. Consequently this molecule should be further evaluated for potential therapeutic use in Alzheimer's disease.

1. Introduction

Alzheimer's disease is a chronic neurodegenerative disorder caused by overproduction and accumulation of abnormally folded amyloid beta (Aβ) peptide [1]. Currently there is no cure for Alzheimer's disease (AD), but several medications are used to treat the symptoms of this disease [2]. Since reduction of the activity of the cholinergic neurons is a well-known feature of AD, acetylcholinesterase inhibitors (AChIs) (e.g. donepezil, galantamine, rivastigimine) are used in symptomatic treatment. AChIs reduce the rate at which acetylcholine is broken down, thereby increasing the concentration of acetylcholine in the brain. In that manner these drugs antagonize the loss of acetylcholine caused by the death of cholinergic neurons [3].

Due to their strong binding affinity towards many receptors, s-triazines have drawn attention of scientists. This fact is related to their rapid synthesis and interesting pharmacological potential. Both plant-derived and synthetic s-triazines show different biological effects like antimicrobial, antituberculotic, antiviral and antimalarial [4]. 1,3,5-Triazines are a class of very effective anticancer agents used in treatment of breast, lung and ovarian cancers [5].

As heterocyclic molecules s-triazines represent group of chemical compounds widely used as pharmaceuticals, herbicides and pesticides [4,5]. Since they are widely used for agricultural purposes, their potential contact with human cells should not be underestimated. Several important toxicities in humans have been reported so far [6].

Different triazine substituted compounds demonstrate numerous biological properties, and are being tested for possible cardioactive, anti-HIV and anticancer effect [7,8,9,10,11]. There are some indications that these molecules could also speed up the discovery of new potent drugs in treatment of AD, which has been pretty slow due to the complex etiopathology of this disease. One of the novel approaches implies use of multitarget-directed ligands which are helpful in modulation of different neurodegenerative pathways [12]. Recent studies have shown that s-triazines might have significant neuroprotective role in patients with AD and different effects were verified in rats [13].

Studied 1,3,5-triazines substituted at positions 4 and 6 are shown in Fig. 1.

2. Methods

All of the studied s-triazine derivatives were synthesized from cyanuric chloride and corresponding amines according to the adapted method of Thurston et al. [14]. RP HPTLC analysis was performed at Faculty of Technology, University of Novi Sad, Serbia. RP-HPTLC experiments were carried out using CRP-18W/UV254 plates (Macherey-

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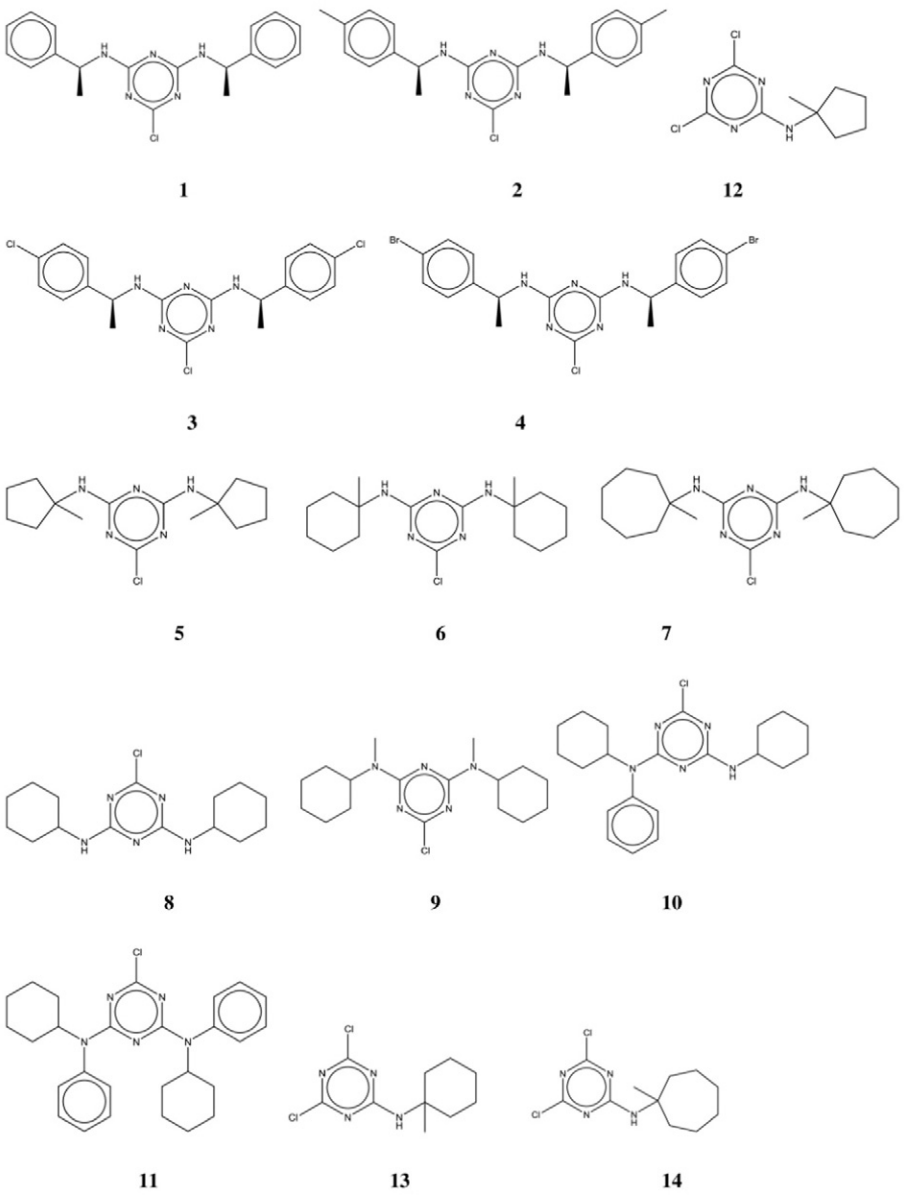

Fig. 1. Structure of the 14 investigated s-triazines.

Nagel GmbH and Co., Düren, Germany). Different combinations of organic solvent and water: acetone-water ($\varphi = 0.5–0.8$; v/v), acetonitrile-water ($\varphi = 0.5–0.9$; v/v), methanol-water ($\varphi = 0.65–0.95$; v/v), 2-propanol-water ($\varphi = 0.4–0.7$; v/v), tetrahydrofuran-water ($\varphi = 0.5–0.75$; v/v) were used as mobile phases. [15].

Docking studies were carried out using the docking Vina. This workflow step utilizes the Vina docking algorithm [16]. For this purpose, the structure of 1dx4 was taken from the sc-PDB database. Furthermore, the water molecules and the original inhibitors were removed from the protein structure. The structures of the compounds 1–14 were provided using ChemDraw Professional 15.1 and converted to SMILES. AutoDockTools was utilized to add hydrogen atoms to the targets, add Gasteiger charges, merge charges and remove non-polar hydrogen atoms, ion-pairs, water molecules and non-standard residues. Binding size was given in Angstroms, default value 22, which typically covers a sufficiently large space for the small molecule docking. The centre of the grid box was set at the centre of tacrine derivatives with co-ordinates $x = 32.222$, $y = 67.7532$, and $z = 9.472$ provided also by sc-PDB database. Flexible ligand docking was performed for the compounds 1–14 series. Default values were accepted for other parameters. The lowest energy conformation of ligand–enzyme complex has been discussed in analysis of interactions between AChE and the inhibitor. The results were visualized using WebGL/Javascript based molecule viewer.

3. Results

Most important principles of thin layer chromatography are based on capillary action. This basic mechanism and its universality are responsible for wide use of thin layer chromatography in QSAR research, where the results of chromatography analysis can be used to predict other characteristics of investigated compounds [17]. R_M^0 values obtained from 5 different solvent systems were used in correlation of chromatography parameters and lipophilicity of novel s-triazines. Afterwards, several pharmacokinetic parameters of investigated compounds were calculated using different software: P_{ej}- Pe jejunum pH = 6,5 (cm/s), K_a- absorption rate constant (min^{-1}), logBB- logarithm of the blood-brain barrier partition coefficient, M_w- molecular weight TPSA- total polar surface area, n(C)- number of C atoms of the molecule and $E_{docking}$- free energy of binding [18,19]. Permeability in human jejunum