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IN SILICO PHARMACOKINETIC AND TOXICOLOGICAL STUDY OF DNASE INHIBITORS

Ana Kolarević[1], Gordana Kocić[2], Denitsa Yancheva[3], Andrija Šmelcerović[1,4]

Deoxyribonucleases (DNases) are the enzymes able to catalyze DNA hydrolysis and they play important roles in cell function, while DNase inhibitors are the compounds able to control or modify their activities. Using admetSAR, Toxtree and OSIRIS Property Explorer, we calculated and compared pharmacokinetic and toxicological properties of some natural and synthetic DNase inhibitors. Finally, we selected among the DNase inhibitors the ones with the most favorable toxicological and pharmacokinetical profiles. *Acta Medica Medianae 2016;55(4):5-13.*

Key words: *DNase inhibitors, in silico study, pharmacokinetic properties, toxicological properties*

University of Niš, Faculty of Medicine, Department of Pharmacy, Serbia[1]
University of Niš, Faculty of Medicine, Institute of Biochemistry, Serbia[2]
Bulgarian Academy of Sciences, Institute of Organic Chemistry with Centre of Phytochemistry, Laboratory of Structural Organic Analysis, Sofia, Bulgaria[3]
University of Niš, Faculty of Medicine, Department of Chemistry, Serbia[4]

Contact: Andrija Šmelcerović
University of Niš, Faculty of Medicine
Bul. dr Zorana Đinđića 81, 18000, Niš, Serbia
E-mail: a.smelcerovic@yahoo.com

Introduction

Deoxyribonucleases (DNases) are the enzymes able to catalyze the hydrolysis of deoxyribonucleic acid (DNA), and they therefore play an important role in programmed cell death (apoptosis) and pathogenesis of various diseases (1). On the other hand, DNase inhibitors are the compounds able to control or modify those activities (2). There are two main types of DNase: DNase I and DNase II. DNase I enzymes are Ca^{2+}/Mg^{2+}-dependent endonucleases which produce 3'-oligonucleotides. DNase I family consists of DNase I, DNase X and DNase γ, as neutral endonu-cleases, and DNAS1L2, as an acidic endonuclease (3). All DNases I are glycoproteins (4) with variable tissue distribution (pancreas, parotid glands, kidney, liver, stomach, small intestine, large intestine, spleen, heart, lung, cerebrum and cerebellum) (5). DNase II enzymes are endonucleases which produce 5'-oligonucleotides and have optimal function at acidic pH values without divalent cations. They are involved in engulfment-mediated DNA degradation which is necessary for proper development and homeostasis (6). DNases and their inhibitors can be of use in diagnosis, monitoring and treatment of various pathological conditions (7-10). Recently, we have reviewed the literature on natural and synthetic DNase inhibitors and calculated their physico-chemical properties (11).

Aim

The aim of this article was to provide an *in silico* study of pharmacokinetic and toxicological properties of some natural and synthetic DNase inhibitors.

DNase inhibitors

Natural DNase inhibitors

Some natural DNase I inhibitors have been isolated from microorganisms, such as actinomycin D (**1**), daunomycin (**2**), nogalamycin (**3**), neomycin B (**4**) and paromomycin (**5**) (12, 13). Natural pigment curcumin (**6**) is able to inhibit DFF40/CAD (DNA fragmentation factor 40/caspase-activated DNase) and thus prevents DNA fragmentation during apoptosis (14). Two forms of vitamin B6, pyridoxal (**7**) and pyridoxal 5'-phosphate (**8**), also have the ability to inhibit DNase activity (Figure 1) (15).

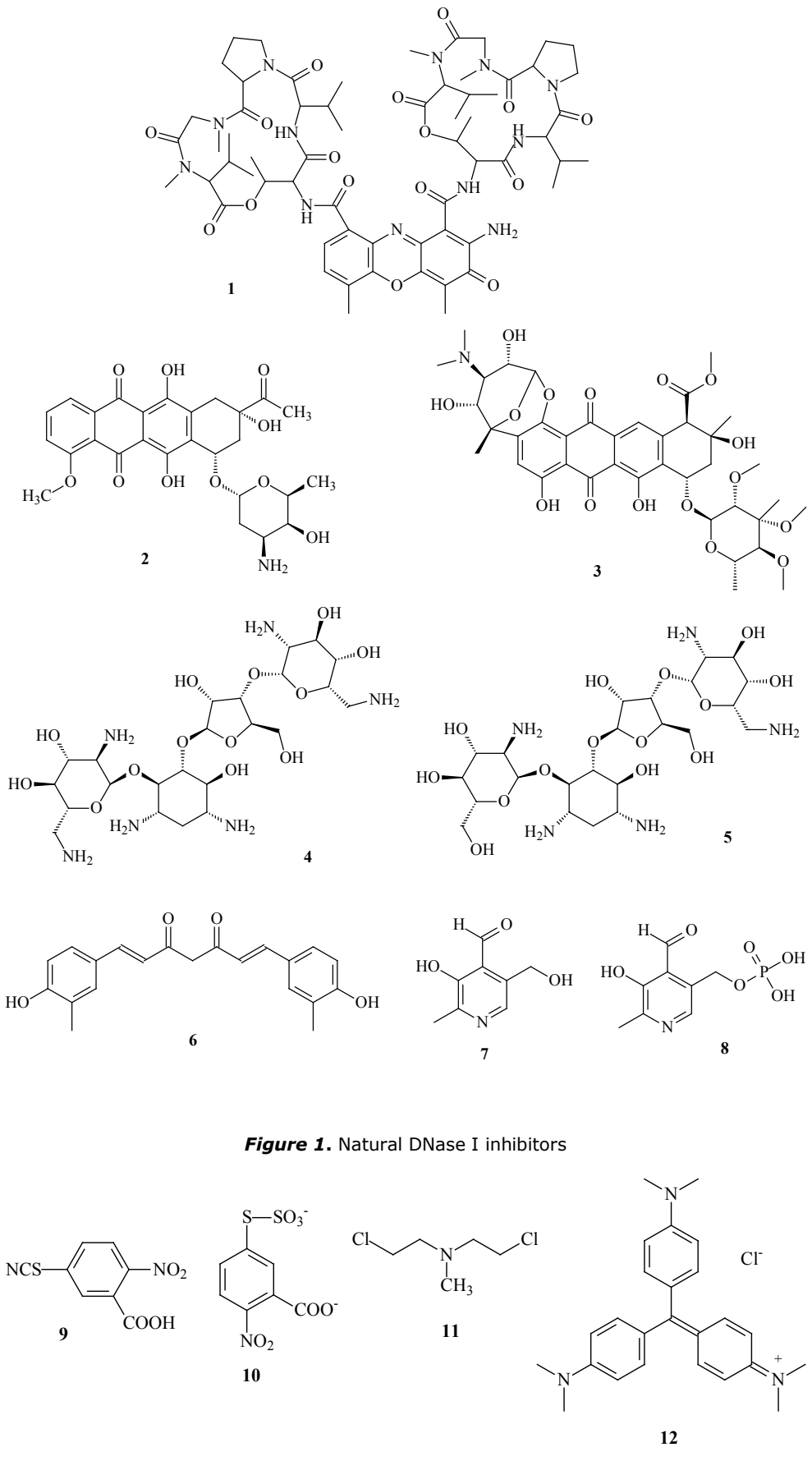

Figure 1. Natural DNase I inhibitors

Figure 2. Synthetic DNase I inhibitors

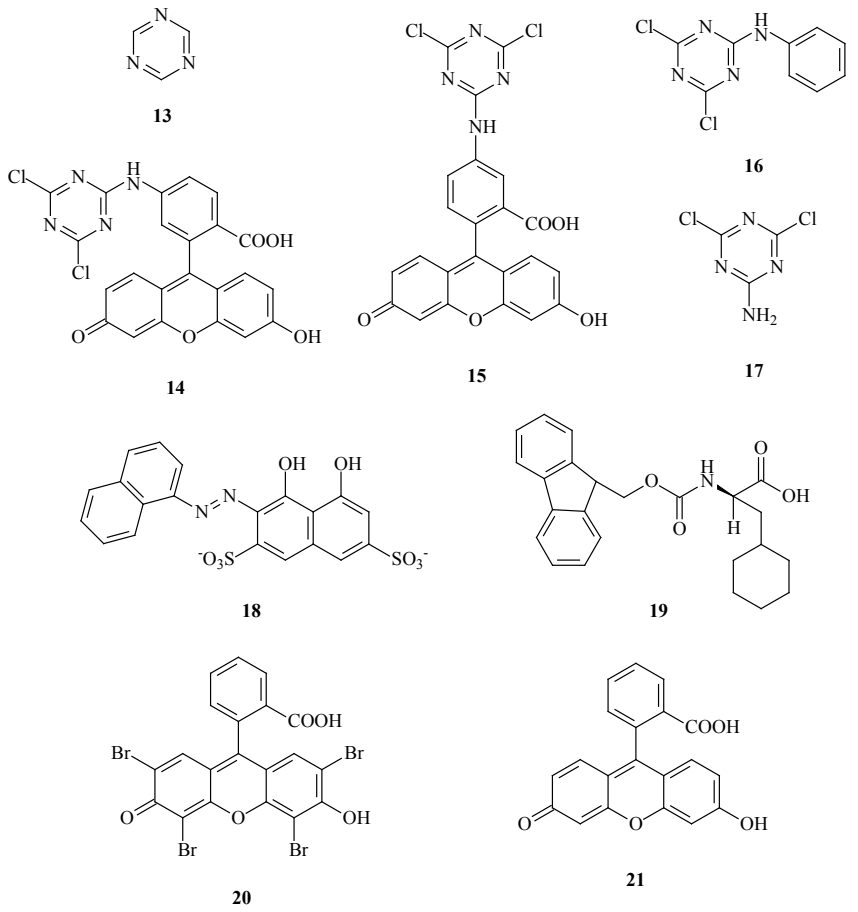

Figure 3. Synthetic DNase γ inhibitors

Synthetic DNase inhibitors

It has been found that some synthetic compounds, such as 2-nitro-5-thiocyanobenzoic acid (**9**) (16), 2-nitro-5-thiosulfobenzoic acid (**10**) (17), chemotherapeutic drug nitrogen mustard (**11**) (18) and triphenylmethane dye crystal violet (**12**) (19), are able to inhibit DNase I activity (Figure 2).

s-Triazine (**13**) and its derivatives, DR396 (4-(4,6-dichloro-[1,3,5]-triazin-2-ylamino)-2-(6-hydroxy-3-oxo-3H-xanthen-9-yl)-benzoic acid) (**14**), DF365 (5-(4,6-dichloro-[1,3,5]-triazine-2-ylamino)-2-(6-hydroxy-3-oxo-3H-xanthen-9-yl)-benzoic acid) (**15**), R282049 ((4,6-dichloro-[1,3,5]-triazine-2-yl)-phenyl amine) (**16**) and 2-amino-4,6-dichloro-*s*-triazine (**17**) show the inhibitory effect towards DNase γ. Pontacyl violet 6R (**18**), Fmoc-D-Cha-OH (**19**), eosin yellowish (**20**) and fluorescein (**21**) are the synthetic compounds capable of inhibiting DNase γ activity (Figure 3) (20, 21).

In silico studies of DNase inhibitors

Pharmacokinetic properties of DNase inhibitors

The absorption properties of DNase inhibitors were predicted by admetSAR (22) (Table 1). The results suggested that natural DNase inhibitors, **6**-**8**, as well as synthetic DNase inhibitors, **10**-**17** and **19**-**21**, might be able to cross the blood-brain barrier (BBB) and penetrate into the CNS, while antibiotics (**1**-**5**) and synthetic compounds **9** and **18** might not have this ability. The majority of the investigated compounds (15 out of 21) were predicted to be capable of being absorbed by the intestine. The exceptions were antibiotics (**2**-**5**) and compounds **9** and **10**. Among the natural DNase inhibitors, only compound **6** was supposed to have positive Caco-2 permeability, while synthetic compounds with this property were numerous, including **11**-**13**, **16**, **17** and **20**. In most instances, DNase inhibitors were predicted as non-substrates for P-glycoprotein, except compounds **1**-**3** and **6**, among natural, and compounds **19** and **21**, among synthetic compounds. All synthetic DNase inhibitors were predicted as non-inhibitors of P-glycoprotein, while compound **6** was the only natural DNase inhibitor predicted as P-glycoprotein inhibitor. All of the investigated compounds, except compound **11**, were predicted as non-inhibitors against renal organic cation transporter (ROCT) (Table 1).

The metabolic properties of DNase inhibitors were predicted by admetSAR (22) (Table 2). None of the DNase inhibitors was predicted as CYP450 2C9 and 2D6 substrate. Compounds **1**-**3** among natural, and only compound **12** among synthetic

Table 1. Absorption properties of DNase inhibitors predicted by admetSAR (22)

Compound	BBB	HIA	Caco-2 Permeability	P-gp Substrate	P-gp Inhibitor	ROCT Inhibitor
1	no	yes	no	yes	no	no
2	no	no	no	yes	no	no
3	no	no	no	yes	no	no
4	no	no	no	no	no	no
5	no	no	no	no	no	no
6	yes	yes	yes	yes	yes	no
7	yes	yes	no	no	no	no
8	yes	yes	no	no	no	no
9	no	no	no	no	no	no
10	yes	no	no	no	no	no
11	yes	yes	yes	no	no	yes
12	yes	yes	yes	no	no	no
13	yes	yes	yes	no	no	no
14	yes	yes	no	no	no	no
15	yes	yes	no	no	no	no
16	yes	yes	yes	no	no	no
17	yes	yes	yes	no	no	no
18	no	yes	no	no	no	no
19	yes	yes	no	yes	no	no
20	yes	yes	yes	no	no	no
21	yes	yes	no	yes	no	no

*BBB – blood brain barrier; HIA – human intestinal absorption; P-gp – P-glycoprotein; ROCT – renal organic cation transporter

***Table 2*.** Metabolic properties of DNase inhibitors predicted by admetSAR (22)

	CYP450 Substrate			CYP450 Inhibitor					
Compound	2C9	2D6	3A4	1A2	2C9	2D6	2C19	3A4	CYP450 Inhibitory Promiscuity
1	no	no	yes	no	no	no	no	no	low
2	no	no	yes	yes	no	no	no	no	low
3	no	no	yes	yes	no	yes	no	no	low
4	no	no	no	no	no	no	no	no	low
5	no	no	no	no	no	no	no	no	low
6	no	no	no	yes	yes	yes	yes	no	high
7	no	no	no	no	no	no	no	no	low
8	no	no	no	no	no	no	no	no	low
9	no	no	no	no	no	no	no	no	low
10	no	no	no	no	no	no	no	no	low
11	no	no	no	no	no	no	no	no	low
12	no	no	yes	yes	no	no	no	no	high
13	no	no	no	no	no	no	no	no	low
14	no	no	no	yes	no	no	no	no	low
15	no	no	no	yes	no	no	no	no	low
16	no	no	no	yes	no	no	no	no	high
17	no	no	no	no	no	no	no	no	low
18	no	no	no	yes	no	no	no	no	low
19	no	no	no	yes	no	no	no	no	low
20	no	no	no	no	yes	no	no	no	low
21	no	no	no	no	yes	no	no	yes	low

Table 3. Ability of DNase inhibitors to bind to DNA and proteins predicted by Toxtree (25)

	Alerts for DNA binding					Alerts for Protein binding				
Compound	S_N1[a]	Schiff Base[b]	Michael Acceptor[c]	Acyl Transfer[d]	S_N2[e]	S_NAr[f]	Schiff Base	Michael Acceptor	Acyl Transfer	S_N2
1	yes	no	yes	no	no	no	no	yes	no	no
2	no	no	yes	no	no	no	no	yes	no	yes
3	yes	no	yes	no	no	no	no	yes	no	yes
4	no	no	no	no	no	no	no	no	no	no
5	no	no	no	no	no	no	no	no	no	no
6	no	no	yes	no	no	no	no	yes	no	no
7	no	no	no	no	no	yes	yes	no	no	yes
8	no	no	no	no	no	yes	yes	no	no	yes
9	no	no	yes	no	no	no	no	yes	no	yes
10	yes	no	yes	no	no	no	no	yes	no	no
11	yes	no	no	no	yes	no	no	no	no	yes
12	yes	no	yes	no	no	no	no	yes	no	no
13	no	no	no	no	no	no	no	no	no	no
14	yes	no	yes	no	no	no	no	yes	no	no
15	yes	no	yes	no	no	no	no	yes	no	no
16	yes	no	yes	no	no	no	no	yes	no	no
17	yes	no	no	no	no	no	no	no	no	no
18	yes	no	yes	no	no	no	no	yes	no	no
19	no	no	yes	no	no	no	no	yes	no	yes
20	no	no	yes	no	no	no	no	yes	no	no
21	no	no	yes	no	no	no	no	yes	no	no

[a] ability to undergo nucleophilic aliphatic substitution (S_N1 reactions); [b] ability to form Schiff base; [c] ability to undergo Michael addition; [d] ability to participate in acyl transfer; [e] ability to undergo S_N2 reactions ; [f] ability to undergo nucleophilic aromatic substitution (S_NAr reactions)

***Table 4*.** Toxicological properties of DNase inhibitors predicted by admetSAR (22)

Compound	HERG Inhibitor	AMES Toxic	Carcinogens	Fish Toxicity	*T. Pyriformis* Toxicity	Honey Bee Toxicity	Biodegradation	Acute Oral Toxicity	Carcinogenicity
1	weak	no	no	high	high	low	not ready	I	non-required
2	weak	yes	no	high	high	low	not ready	II	non-required
3	weak	yes	no	high	high	low	not ready	III	non-required
4	weak	no	no	low	low	low	not ready	IV	non-required
5	weak	no	no	low	low	low	not ready	IV	non-required
6	weak	no	no	high	high	high	not ready	III	non-required
7	weak	no	no	low	low	low	ready	III	non-required
8	weak	no	no	high	high	high	ready	IV	non-required
9	weak	yes	no	high	low	low	not ready	III	non-required
10	weak	no	yes	high	low	low	not ready	III	non-required
11	strong	yes	yes	high	high	low	not ready	I	danger
12	weak	no	yes	high	high	low	not ready	III	warning
13	weak	no	no	low	low	low	ready	III	non-required
14	weak	no	no	high	high	low	not ready	III	non-required
15	weak	no	no	high	high	low	not ready	III	non-required
16	weak	no	no	high	high	low	not ready	III	non-required
17	weak	no	no	low	high	low	not ready	II	non-required
18	weak	no	yes	high	high	low	not ready	III	non-required
19	weak	no	no	high	high	low	not ready	III	non-required
20	weak	no	no	high	high	high	not ready	II	non-required
21	weak	no	no	high	high	high	not ready	II	non-required

DNase inhibitors, were predicted as CYP450 3A4 substrates. None of the natural DNase inhibitors was supposed to inhibit CYP450 3A4. Enzymes CYP450 2C9 and 2C19 might be inhibited by compound **6**, CYP450 2D6 by compounds **3** and **6**, and CYP450 1A2 by compounds **2**, **3** and **6**. Among synthetic DNase inhibitors, compounds **12**, **14**-**16**, **18** and **19** were predicted as CYP450 1A2 inhibitors, compound **20** as CYP450 2C9 inhibitor, compound **21** as CYP450 2C9 and CYP450 3A4 inhibitor, while none of the synthetic DNase inhibitors was predicted as CYP450 2C19 and 2D6 inhibitor. In most cases, DNase inhibitors were predicted to have a low CYP inhibitory promiscuity, except for compounds **6**, **12** and **16**.

Toxicological properties of DNase inhibitors

The ability of exogenous chemicals to act as mutagens or genotoxic carcinogens (collectively termed genotoxicity) is connected to their ability to bind covalently to proteins and DNA. The formation of a covalent adduct with DNA or proteins has been defined as the molecular initiating event, the first step in a series that can ultimately lead to toxicity (23, 24). In this context, it is important to assess the structural alerts indicating that a certain chemical is likely to form a covalent bond with a biological macromolecule. For the purpose of this study it was done by the Toxtree prediction tool based on decision tree approach (25). The structural alerts for DNA and protein binding for compounds **1**-**21** are presented in Table 3. The identified alerts refer to the chemical mechanism by which the studied DNase inhibitors can covalently interact with the biological macromolecule, but does not mean that they would be necessarily toxic, because other factors, such as the toxicokinetic or toxicodynamic profile of the chemical or biological repair mechanisms could prevent the completion of the adverse outcome pathway (23, 24). Natural DNase I inhibitors **4** and **5**, along with the synthetic DNase γ inhibitor **13**, did not show any structural alerts either for DNA binding, or for protein binding. Moreover, **7** and **8** were also predicted not to bind to DNA, while **17** would not bind to proteins.

Toxicological properties of DNase inhibitors predicted by admetSAR (22) are shown in Table 4. All DNase inhibitors, except compound **11**, were predicted as weak HERG (human Ether-à-go-go-Related Gene) inhibitors. Natural compounds, **2** and **3**, and synthetic compounds, **9** and **11**, might be AMES toxic. Natural DNase inhibitors were predicted as non-carcinogens, while some synthetic DNase inhibitors (**10**-**12** and **18**) might be carcinogenic. The majority of the investigated compounds were predicted to have high fish toxicity. The exceptions were compounds **4**, **5** and **7**, among the natural, and compounds **13** and **17**, among the synthetic DNase inhibitors. Low *Tetrahymena pyriformis* toxicity was exhibited by compounds **4**, **5** and **7**, among the natural, and compounds **9**, **10** and **13**, among the synthetic DNase inhibitors. Most of DNase inhibitors were predicted as compounds with low honey bee toxicity, except compounds **6**, **8**, **20** and **21**. Compounds **7**, **8** and **13** were supposed to be readily biodegradable. Depending on the risk for acute oral toxicity, compounds **1** and **11** were predicted as Category I, which included the compounds with LD50 values below 50 mg/kg. Compounds **2**, **17**, **20** and **21** were predicted as Category II, or the compounds with LD50 values greater than **50** mg/kg, but less than 500 mg/kg. Compounds **3**, **6**, **7**, **9**, **10**, **12**-**16**, **18** and **19** were predicted as Category III, including the compounds with LD50 values greater than 500 mg/kg, but less than 5000 mg/kg. Compounds **4**, **5** and **8** were predicted as Category IV, or the compounds with LD50 values greater than 5000 mg/kg. According to TD50 values, DNase inhibitors were predicted as "non-required" or non-carcinogenic chemicals. The exceptions were compound **12** assigned as "warning", or compound with TD50 > 10 mg/kg body wt/day, and compound **11** assigned as "danger", or carcinogenic compound with TD50 ≤ 10 mg/kg body wt/day (Table 4).

Table 5. Toxicological properties of DNase inhibitors predicted by OSIRIS Property Explorer (26)

Compound	Mutagenic risk	Tumorigenic risk	Irritant Effects	Reproductive Effects
1	low	low	low	low
2	low	low	low	low
3	low	low	low	low
4	low	low	low	low
5	low	low	low	low
6	low	low	low	low
7	low	low	medium	low
8	low	low	medium	low
9	low	low	medium	low
10	low	low	low	low
11	high	high	high	high
12	high	high	low	low
13	low	low	low	low
14	medium	medium	high	medium
15	medium	medium	high	medium
16	medium	medium	high	medium
17	medium	medium	high	medium
18	high	high	medium	low
19	low	high	low	low
20	medium	low	low	low
21	low	low	low	low

Toxicological properties of DNase inhibitors predicted by the OSIRIS Property Explorer (26) are presented in Table 5. Natural DNase inhibitors were supposed to have a low risk for mutagenic, tumorigenic and reproductive effects. The majority of natural compounds were supposed to have a low risk for irritant effects, but compounds **7** and **8** were predicted as the ones with a medium risk for irritant effects. Among the synthetic DNase hibitors, compounds **14**-**17** and **20** were supposed to

have medium mutagenic risk, while compounds **11**, **12** and **18** were supposed to have a high mutagenic risk. Compounds **14**-**17** were predicted as compounds with a medium tumorigenic risk, while compounds **11**, **12**, **18** and **19** were predicted as compounds with a high tumorigenic risk. Compounds **9** and **18** might have medium risk, while compounds **11** and **14**-**17** might have a high risk for irritant effects. Further, compounds **14**-**17** were predicted to have a medium risk, while compound **11** was predicted to have a high risk for reproductive effects.

Conclusion

As could be seen from the results obtained by our *in silico* study, DNase inhibitors differ significantly in their pharmacokinetic and toxicological properties. Taken together, natural DNase I inhibitors **4** and **5** and synthetic DNase γ inhibitor **13** had the most favorable toxicological profiles. They were predicted as non-mutagenic, non-tumorigenic, non-irritating, non-AMES toxic and non-carcinogenic compounds, as well as the compounds with low fish, *T. pyriformis* and honey bee toxicity, with no reproductive effects and no structural alerts for DNA or protein binding. However, among those three compounds only compound **13** was likely to have a favorable pharmacokinetic profile. It was predicted as a compound with BBB, Caco-2 and HIA permeability, as well as a P-gp non-substrate, P-gp non-inhibitor, ROCT non-inhibitor, CYP450 non-substrate and CYP450 non-inhibitor.

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IN SILICO FARMAKOKINETIČKA I TOKISKOLOŠKA ISPITIVANJA INHIBITORA DNAZA

Ana Kolarević[1], Gordana Kocić[2], Denitsa Yancheva[3], Andrija Šmelcerović[1,4]

Univerzitet u Nišu, Medicinski fakultet, Odsek za farmaciju, Niš, Srbija[1]
Univerzitet u Nišu, Medicinski fakultet, Institut za biohemiju, Niš, Srbija[2]
Bugarska akademija nauka, Institut za organsku hemiju sa centrom za fitohemiju, Laboratorija za strukturnu organsku analizu, Sofija, Bugarska[3]
Univerzitet u Nišu, Medicinski fakultet, Odsek za hemiju, Niš, Srbija[4]

Kontakt : Andrija Šmelcerović
Univerzitet u Nišu, Medicinski fakultet
Bul. dr Zorana Đinđića 81, 18000, Niš, Srbija
E-mail: a.smelcerovic@yahoo.com

Dezoksiribonukleaze (DNaze) su enzimi koji katalizuju hidrolizu DNK i imaju značajnu ulogu u normalnom ćelijskom funkcionisanju, dok su inhibitori DNaza supstance koje kontrolišu ili modifikuju ove funkcije. Korišćenjem kompjuterskih programa admetSAR, Toxtree i OSIRIS Property Explorer ispitivane su i upoređivane farmakokinetičke i toksikološke osobine nekih prirodnih i sintetskih inhibitora DNaza. Na kraju su selektovani oni inhibitori DNaza koji imaju najpovoljniji toksikološki i farmakokinetički profil. *Acta Medica Medianae 2016;55(4):5-13.*

Ključne reči: *inhibitori DNaza, in silico studija, farmakokinetičke osobine, toksikološke osobine*