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 pharmacokinetic profiles.

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

**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 Ca²⁺/Mg²⁺-dependent endonucleases which produce 3'-oligonucleotides. DNase I family consists of DNase I, DNase X and DNase γ, as neutral endonuclease, 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
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                  | yes            | no             | no             |
| 5        | no  | no  | no                  | yes            | 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 | yes                 | no             | no             | no             |
| 15       | yes | yes | yes                 | no             | no             | no             |
| 16       | yes | yes | yes                 | yes            | yes            | yes            |
| 17       | yes | yes | yes                 | no             | no             | no             |
| 18       | no  | no  | no                  | no             | no             | no             |
| 19       | yes | yes | yes                 | no             | yes            | 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)

| Compound | CYP450 Substrate | CYP450 Inhibitor | CYP450 Inhibitory Promiscuity |
|----------|------------------|------------------|------------------------------|
|          | 2C9  | 2D6  | 3A4 | 1A2 | 2C9 | 2D6 | 2C19 | 3A4 |                  |
| 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  | low            |
| 13       | no   | no   | no  | no  | no  | no  | no   | no  | low            |
| 14       | no   | no   | yes | no  | no  | no  | no   | no  | low            |
| 15       | no   | no   | yes | no  | no  | no  | no   | no  | low            |
| 16       | no   | no   | yes | no  | no  | no  | no   | no  | low            |
| 17       | no   | no   | yes | no  | no  | no  | no   | no  | low            |
| 18       | no   | no   | yes | no  | no  | no  | no   | no  | low            |
| 19       | no   | no   | yes | yes | no  | no  | no   | no  | low            |
| 20       | no   | no   | no  | yes | no  | no  | no   | no  | low            |
| 21       | no   | no   | no  | yes | no  | no  | yes  | no  | low            |
### Table 3. Ability of DNase inhibitors to bind to DNA and proteins predicted by Toxtree (25)

| Compound | $S_n1^a$ | Michael Acceptor $^b$ | Acyl Transfer $^c$ | $S_n2^e$ | Schiff Base $^d$ | $S_nAr^f$ | Michael Acceptor | Acyl Transfer | $S_n2^g$ |
|----------|----------|-----------------------|-------------------|---------|-----------------|----------|-----------------|--------------|---------|
| 1        | yes      | no                    | yes               | no       | no              | no       | yes             | no           | no      |
| 2        | no       | no                    | yes               | no       | no              | no       | yes             | no           | yes     |
| 3        | yes      | no                    | yes               | no       | no              | no       | yes             | no           | yes     |
| 4        | no       | no                    | no                | no       | no              | no       | no              | no           | no      |
| 5        | no       | no                    | no                | no       | no              | no       | no              | no           | no      |
| 6        | no       | no                    | yes               | no       | yes             | no       | yes             | no           | yes     |
| 7        | no       | no                    | no                | no       | yes             | no       | yes             | no           | yes     |
| 8        | no       | no                    | no                | no       | yes             | no       | yes             | no           | yes     |
| 9        | no       | no                    | yes               | no       | no              | no       | no              | yes          | yes     |
| 10       | yes      | no                    | no                | yes      | no              | no       | yes             | no           | no      |
| 11       | yes      | no                    | no                | yes      | no              | no       | yes             | no           | yes     |
| 12       | yes      | no                    | yes               | no       | no              | no       | yes             | no           | no      |
| 13       | no       | no                    | yes               | no       | no              | no       | yes             | no           | no      |
| 14       | yes      | no                    | no                | no       | no              | no       | yes             | no           | no      |
| 15       | yes      | no                    | yes               | no       | no              | no       | yes             | no           | no      |
| 16       | yes      | no                    | yes               | no       | no              | no       | yes             | no           | no      |
| 17       | yes      | no                    | yes               | no       | no              | no       | yes             | no           | no      |
| 18       | yes      | no                    | yes               | no       | no              | no       | yes             | no           | no      |
| 19       | no       | no                    | yes               | no       | no              | no       | yes             | no           | yes     |
| 20       | no       | no                    | yes               | no       | no              | no       | yes             | no           | no      |
| 21       | no       | no                    | yes               | 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         | low         | 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          | high                  | 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          | low           | low                   | low               | not ready       | III                 | non-required     |
| 15       | weak           | no         | high        | low           | low                   | low               | not ready       | III                 | non-required     |
| 16       | weak           | no         | no          | high          | low                   | low               | not ready       | III                 | non-required     |
| 17       | weak           | no         | no          | high          | low                   | 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                  | low               | 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            | low             | 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 inhibitors, 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

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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