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SELENIUM-FUNCTIONALIZED CYCLIC ETHERS DERIVED FROM NATURAL TERPENIC ALCOHOLS – BIOLOGICAL *IN VITRO* PROFILE

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Terpenic alcohols linalool, nerolidol and α-terpineol were subjected to the PhSe-induced cyclization, where corresponding cyclic ethers were obtained. The heterocyclic product derived from α-terpineol is a derivate of the natural product eucalyptol, while linalool cyclization produces precursors of the natural product karahanaenone. All three cyclic ether products have an organoselenium moiety in the side chain, which can represent a significant source of bioactivities. Biological evaluation of obtained products, *in vitro* cytotoxicity and redox status parameters, was performed on two model systems: HCT-116 – immortalized colon cancer cell line, and MRC-5 – healthy fibroblasts isolated from lung pleura. The results indicate a strong prooxidative character of all compounds on colon cancer HCT-116 and healthy MRC-5 cells in the highest applied concentrations. Selectivity towards cancer cells was not observed, except when nerolidol-derived product was used for longer exposure time. A biological evaluation was conducted to establish the quantitative relationship between enhanced radical species formation and cell viability.

Key words: terpenic alcohols; selenium; cyclic ethers; cytotoxicity; redox status

СО СЕЛЕН ФУНКЦИОНАЛИЗИРАНИ ЦИКЛИЧНИ ЕТЕРИ ИЗВЕДЕНИ ОД ПРИРОДНИ ТЕРПЕНСКИ АЛКОХОЛИ – БИОЛОШКИ *IN VITRO* ПРОФИЛ

Терпенските алкохоли линалоол, неролидол и α-терпинеол беа подложени на циклизација со PhSe, при што беа добиени соодветни циклични етери. Хетероцикличниот производ добиен од α-терпинеол е дериват на природниот производ еукалиптол, додека циклизацијата на линалоол дава прекурзори на природниот производ караханаенон. Сите три етерски производи имаат органоселенски дел во страничната низа кој претставува значаен извор на биоактивностите. Биолошката евалуација на добиените производи, *in vitro* цитотоксичноста и параметрите на редокс статусот, беа изведени на два моделни система: HCT-116 – деактивирани клеточни соеви на рак на дебелото црево, и MRC-5 – здрави фибробласти изолирани од белодробната плевра. Резултатите покажуваат моќен прооксидациски карактер на сите соединенија врз клетките на рак HCT-116 и здравите клетки MRC-5 кај највисоко употребените концентрации. Не беше забележана селективност спрема клетките на рак, освен при подолготрајна примена на производот изведен од неродилол. Беше спроведена биолошка евалуација за да се утврди квантитативна зависност меѓу образувањето на засилените радикалски видови и виталноста на клетките.

Клучни зборови: терпенски алкохоли; селен; циклични етери; цитотоксичност; редокс статус

1. INTRODUCTION

Linalool **1**, nerolidol **2** and α-terpineol **3** (Fig. 1) represent members of the terpenic alcohol family – the compounds which are widely spread as constituents of different essential oils in plants and flowers.[1,2] Their pleasant smell is one of the major reasons why these compounds have been explored as perfume ingredients and fragrances. Apart from the extraordinary olfactory properties, these alkenols also possess rich biological potential, which is reflected in wide range of the expressed biological activities, such as antifungal, anticancer, antimalarial, analgesic, anticonvulsant and anti-anxiety activities.[3–7] Terpenes, as one of the largest and most versatile groups of naturally occurring compounds, represent rich reservoirs of structurally diverse multifunctional precursors for many organic syntheses. Due to the presence of the double bonds and hydroxyl functionalities in the structure, these terpenic alkenols are the subject of intensive synthetic studies[8–12] focused on the preparation of different reaction products and useful intermediates. One of the especially important and challenging synthetic transformations of terpenic alcohols is their cyclofunctionalization. The cyclization, promoted by electrophilic selenium reagents (such as phenylselenyl halides), represent the efficient and selective approach for the construction of versatile organoselenium-functionalized five- or six-membered cyclic ethers.[13] The cyclic ethers are particularly interesting molecules due to their occurrence as structural segments of many natural marine products[14] and in a vast number of biologically active natural products and pharmaceutically active compounds.[15] Cyclic ether products obtained by this method have an organoselenium moiety in a side chain which can provide a significant source of bioactivities, including antioxidative and anticancer activities.[16–20]

The product obtained from PhSe-induced cyclization of α-terpineol is a precursor of eucalyptol **4** (1,8-cineol), a naturally occurring bicyclic compound found in many essential oils (Fig. 1), while the cyclization of linalool under similar reaction conditions provides a precursor of karahanaenone **5** (Fig. 1).[21–23] Eucalyptol (1,8-cineol) is a well-known secondary plant metabolite present in many herbal sources, such as *Salvia* and *Eucalyptus* and possesses a wide range of activities. As a plant metabolite, it is used as an allelopathic agent and repellent for leaf-eating animals.[24–26] There are many studies of potential biological activity of eucalyptol and karahanaenone, pure or as a part of various essential oils, which are often used in traditional medicine.[27–29]

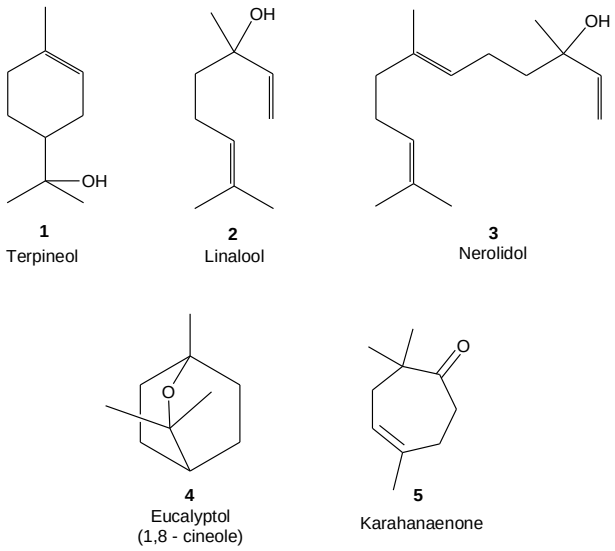


Fig. 1. Chemical structures of terpenic alcohol and its natural derivatives

In previous studies, our group has been included in the systematic synthetic study focused on the development of effective methods for the synthesis of substituted organoselenium-functionalized five- or six-membered cyclic ethers from unsaturated alcohols.[13,30,31] Besides the synthetic part of the investigation, selected examples of the cyclic ethers have been subjected to screening of the biological properties, preferentially antiproliferative and antioxidative activities,[32] as well as to their complexation with transition metal ions (palladium and platinum) and investigation of the medical potential of the obtained complexes.[33,34] The results of these studies have revealed the ability of the organoselenium-functionalized cyclic ethers to serve as reducers of reactive oxygen species (ROS) and anticancer agents.

Taking into consideration that the obtained cyclic ethers originate from terpenic alkenols (linalool, α-terpineol and nerolidol) are precursors of naturally occurring heterocyclic compounds and possess organoselenium-functionality in a side chain which can serve as a potential source of supplemental bioactivity, we have conducted the study to screen their possible cytotoxic and redox activities on the human colorectal carcinoma HCT-116 and human healthy fibroblast MRC-5 cell lines.

2. EXPERIMENTAL

2.1. *Instrumentation*

GC analyses were conducted with an Agilent Technologies instrument (model 6890 N) with HP-5NS columns (5 % phenyl-, 95 % methylpolysiloxane). ^{1}H NMR spectra were measured on a Varian Gemini 200 MHz NMR spectrometer in $CDCl_3$ as a solvent. Terpenic alcohols and PhSeCl are commercially available (Aldrich). Thin-layer chromatography (TLC) was carried out on 0.25 mm E. Merck precoated silica gel plates (60F-254) with the use of UV light for visualization. Column chromatography was performed with E. Merck silica gel (60, particle size 0.063–0.200 mm).

2.2. *General experimental procedure*

All reactions were carried out on a 1 mmol scale. To a stirred solution of terpenic alkenols (0.154 g of α-terpineol and linalool or 0.222 g of nerolidol) and 0.079 g pyridine in 5 cm^3 dry dichloromethane 0.212 g solid PhSeCl (1.1 mmol) was added at room temperature and stirred for 2 h. The resulting pale-yellow solution was washed with 2 M HCl, then with saturated $NaHCO_3$ aqueous solution, and brine. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed. The cyclic ether products were obtained after the elution of the diphenyldiselenide traces on the silica gel column with dichloromethane. The NMR spectra of the synthesized compounds were in accordance with spectra available in literature.[13]

***cis*- and *trans*-5-ethenyl-5-methyl-2-[2-(phenylseleno)-prop-2-yl]tetrahydrofuran** (**1a**, $C_{16}H_{22}OSe$)

^{1}H NMR (200 MHz, $CDCl_3$) δ/ppm: 1.31 (s, 3H, CH_3), 1.33 and 1.36 (2 s, 2 × 3H, $C(CH_3)_2$), 1.55–2.12 (m, 4H, H-3 and H-4), 3.94 (m, 1H, H-2), 4.98 (dd, 1H, $J_{Hz\text{-}8,H\text{-}7}$ = 9 Hz, $J_{HZ\text{-}8,He\text{-}8}$ = 1 Hz), 5.18 (dd, 1H, $J_{He\text{-}8,H\text{-}7}$ = 12.6, Hz, $J_{He\text{-}8,\ Hz\text{-}8}$ = 1 Hz, H_e-8), 5.86 (dd, 1H, $J_{H\text{-}7,\ He\text{-}8}$ = 12.6 Hz, $J_{H\text{-}7,Hz\text{-}8}$ = 9 Hz, H-7), 7.25 (m, 3H, H_{Ph}), 7.67 (m, 2H, H_{Ph}).; MS *m/z*: 310.0 $[C_{16}H_{22}OSe]^+$, 184.0 $[C_6H_5SeCHCH_2]^+$, 157.0 $[C_6H_5Se]^+$, 77.1, 43.1

***cis*- and *trans*-5-ethenyl-5-methyl-2-[6-methyl-2-(phenylseleno)hept-5-en-2-yl]tetrahydrofuran** (**2a**, $C_{21}H_{30}OSe$)

cis-**2a**: ^{1}H NMR (200 MHz, $CDCl_3$) δ/ppm:1.23 (s, CH_3Se), 1.28 (s, CH_3CO), 1.62 and 1.68 (2 s, $(CH_3)_2C$=), 1.65–1.71(m, CH_2CO), 1.71–2.05 (m, CH_2CSe, CH_2CHO), 2.08–2.33 (m, CH_2CH=), 3.99 (t, J = 7.3 Hz, CHO), 4.98 (dd, J = 1.5 Hz, 10.8 Hz, CH=CH), 5.08 (tq, J = 1.4 Hz, 7.1 Hz, $CH=C(CH_3)_2$), 5.22 (dd, J = 1.5 Hz, 17.4 Hz, CH=CH), 6.0 (dd, J = 6.7 Hz, 10.8 Hz, $CH=CH_2$), 7.18–7.32 (*m*, *o*-, *p*-CH), 7.6–7.71 (*m*, m-CH);
trans-**2a**: ^{1}H NMR (200 MHz, $CDCl_3$) δ/ppm:1.21 (s, CH_3Se), 1.33 (s, CH_3CO), 1.62 and 1.68 (2 s $(CH_3)_2C$=), 1.65–1.71 (m, CH_2CO), 1.71–2.05 (m, CH_2CSe, CH_2CHO), 2.08–2.33 (m, CH_2CH=), 3.97 (t, J = 10.9 Hz, CHO), 4.97 (dd, J = 1.5 Hz, 10.8 Hz, CH=CH), 5.08 (tq, J = 1.4 Hz, 7.1 Hz, $CH=C(CH_3)_2$), 5.13 (dd, J = 1.5 Hz, 17.4 Hz, CH=CH), 5.86 (dd, J = 6.7 Hz, 10.8 Hz, $CH=CH_2$), 7.18–7.32 (*m*, *o*-, *p*-CH), 7.6–7.71 (*m*, *m*-CH);
MS *m/z*: 378.1 $[C_{21}H_{30}OSe]^+$, 221.2 $[M\text{-}C_6H_5Se]^+$, 157.0 $[C_6H_5Se]^+$, 109.1, 69.1, 41.1

6-(phenylseleno)-1,3,3-trimethyl-2-oxabicyclo [2.2.2]octane (**3a**, $C_{16}H_{22}OSe$)

^{1}H NMR (200 MHz, $CDCl_3$) δ/ppm: 1.11 (s, 3H, CH_3CO), 1.23 and 1.25 (2 s, 2 9 3H, $(CH_3)_2CO$), 1.42–1.80 (m, 4H, H-5, H-8), 1.90–2.14 (m, H, H-7), 2.62 (tt, 1H, J = 3.3 Hz, 7.7 Hz, H-4), 3.52 (dd, 1H, J = 2.6 Hz, 5.9 Hz, H-6), 7.20–7.29 (m, 3H, H_{Ph}), 7.51–7.59 (m, 2H, H_{Ph}).; MS *m/z*: 310.1 $[C_{16}H_{22}OSe]^+$, 184.0 $[C_6H_5SeCHCH_2]^+$, 153.1 $[C_6H_5Se]^+$, 109.1, 77.1, 43.1

2.3. *MTT cell viability assay*

Cells were maintained and propagated in controlled incubator conditions at 37 °C in a humified 5 % CO_2 atmosphere in Dulbecco's Modified Eagle Medium (DMEM) (Sigma, D5796) supplemented with 10 % fetal bovine serum (Sigma, F4135-500ML) and 1% penicillin/streptomycin (Sigma, P4333-100ML). At confluency of about 80 %, 10,000 cells per well were seeded in 96-well plates. After 24 h of incubation time, the cells were treated with enriched DMEM containing **1a**, **2a** and **3a** in concentrations ranging from 0.1 to 500 μM. The cells were treated with drugs for 24 and 72 h incubation periods. The cell viability was determined by a standardized MTT test (Laboratory for Bioengineering Protocol CB-005). MTT assay is based on estimation of the reduction of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (Acros Organics, 158990010) to purple yielded formazan crystals dissolved in dimethyl sulfoxide. The cells were treated with drugs for 24 and 72 h. The reduction rate is equivalent to the number of viable cells. The measurement of absorbance on an ELISA reader at 550 nm provided the quantitative outcome of the number of surviving cells [35]. Dividing the absorbance measured in treated cells by the absorbance of negative control (non-treated cells) and multiplying by 100

yielded the percentage of viable cells. Estimation of the half viability inhibitory concentration provided IC_{50} values at 24 and 72 h for better understanding of the extent of cytotoxicity of the applied drugs.

2.4. *Redox equilibrium parameters*

One of the goals of this study was to investigate the influence of **1a**, **2a**, and **3a** on the production of superoxide anion radicals (Laboratory for Bioengineering protocol CB-006), nitrites (Laboratory for Bioengineering protocol CB-007), and reduced glutathione (Laboratory for Bioengineering protocol CB-008) in the investigated cell lines. Every xenobiotic exerts impact on the redox equilibrium of the cell. The action of prooxidants is indicated by an increase in reactive oxygen species (ROS) and reactive nitrogen species (RNS), while antioxidants primarily suppress the production of ROS/RNS.

The superoxide anion radical ($O_2^{\bullet-}$) level was evaluated by standardized NBT protocol based on the estimation of the reduction of nitroblue tetrazolium (Acros Organics, BP108-1) to nitroblue formazan and the measurement of the purple crystals' absorbance intensity at 630 nm. Similar to the MTT assay, 30,000 cells were seeded into 96-well plates and incubated in controlled conditions for 24 hours. After the incubation period, the cells were treated with 100 µl of investigated terpenic alcohols in the same concentration range as in the MTT assay. The treatment periods, 24 and 72 h, were used as cut-off time points for the evaluation of the level of generated $O_2^{\bullet-}$. The procedure was comprised of replacing the DMEM containing investigated cyclic ethers with 100 µl of fresh DMEM and 10 µl of NBT salt solution (2.5 mg/ml in PBS). After 3 h, the cells were washed of the extracellular $O_2^{\bullet-}$ with warm PBS and by methanol followed by adding 100 µl of 2 M KOH for the cell membrane disruption at room temperature. After 15 minutes, 100 µl DMSO was added for formazan crystals dissolution and absorbance measurement.

Nitrites (NO^{2-}) are indicators for NO and other RNS in cells. Nitrites were detected by consulting the Griess method principle. The diazotization reaction of nitrites with sulfanilamide (SA; Karl Roth, 4716-100G) and N-1-naphthylethylenediamine dihydrochloride (NED; Karl Roth, 4342-25G) yielded a stable yellow compound, whose absorbance intensity is measured at 492 nm. Similar to NBT protocol, 30,000 cells were seeded and treated in the same concentration range. After the treatment incubation period, 50 µl of supernatant was transferred to another well plate with a consequent addition of 50 µl of SA and NED. After 15 minutes, the absorbance was measured.

Reduced glutathione (GSH) tripeptide is one of the key factors reacting with every xenobiotic in the first line of the cell reaction to the possible redox distribution. As GSH reacts in redox cascade biochemical reactions, the cell increases its production, so the level of GSH could be a very usable parameter for estimation of the overall redox state of the cell. The GSH assay is based on the oxidation of glutathione by using a sulfide reagent, 5,5′-dithio-bis(2-nitrobenzoic acid) (DTNB; Karl Roth, 6334.3), to form a yellow compound, 5′-thio-2-nitrobenzoic acid (TNB), whose color intensity is measured on an ELISA reader at 405 nm. As in the NBT and NO assays, 30,000 cells were seeded, incubated for 24 h, and treated in the same concentration range. After incubation, the plates were centrifuged for 10 min at 1,000 g/4 °C. The supernatant was changed with 100 µl of cold 2.5 % sulfosalicylic acid (Centrohem, 0213). After 15 minutes of incubation at 4 °C, the plates were centrifuged for 15 min at 1,000 g/4 °C, and 50 µL of supernatant was transferred to another well plate with an addition of 100 µl of 1 mM DTNB solution. After 5 minutes of incubation, the absorbance was measured. To better understand the redox parameters, all absorbances are re-calculated in relation to the number of survived cells.

2.5. *Statistical analysis*

The data were expressed as mean ± standard error (SE). Cell viability and redox parameters are the result of 3 individual experiments, performed in triplicate for each dose. The IC_{50} values were calculated from the dose curves using the CalcuSyn software.

3. RESULTS AND DISCUSSION

3.1. *Chemistry*

The synthesis of three PhSe-functionalized cyclic ethers, **1a**, **2a** and **3a**, has been achieved by the pyridine-promoted cyclofunctionalization of linalool, nerolidol and α-terpineol, by means of PhSeCl as electrophilic reagent[13] as depicted in Figure 2. In the presence of the equimolar amount of pyridine and using PhSeCl as a reagent, the formation of the cyclic ethers is proceeding in a regioselective manner with almost quantitative yields of cyclic products.

Nerolidol and linalool react similarly in the PhSe-induced cyclization and enable the formation of five-membered cyclic ethers, while the cyclization of α-terpineol proceeds via formation of a six-membered cyclic ether.

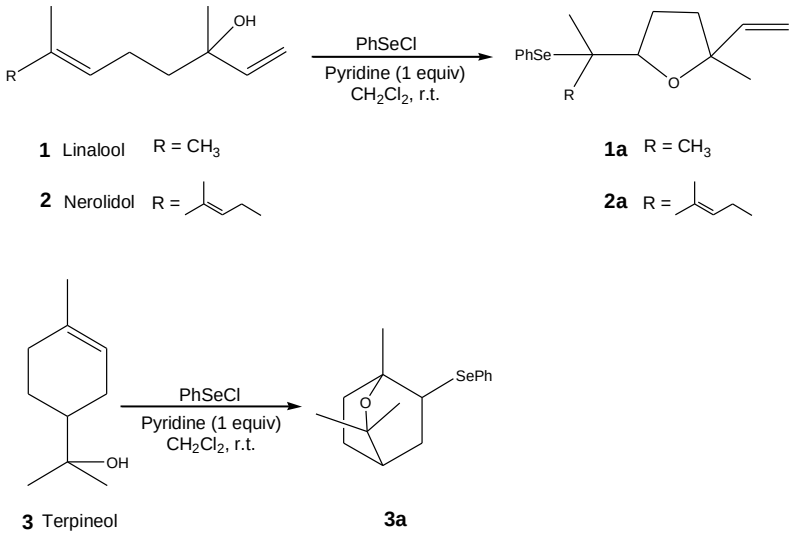
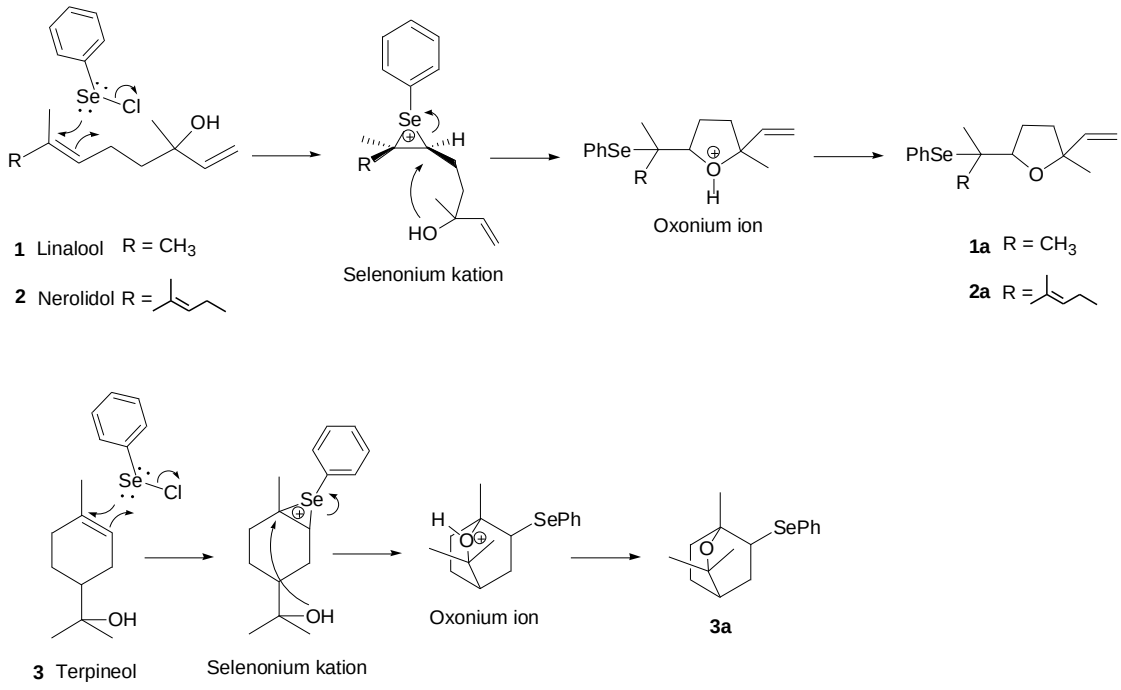


Fig. 2. Cyclofunctionalization of linalool, nerolidol, and α-terpineol with PhSeCl in the presence of pyridine

All three compounds were obtained in quantitative yields with pronounced regioselectivity and stereoselectivity, which is reflected in stereospecific anti-addition to the double bond of the alkenol (Scheme 1). The reaction is induced by the electrophilic attack of PhSeCl on the double bond of the alkenol, resulting in the formation of a selenonium cation. In the next step of the reaction, the nucleophilic attack of the OH group through 5-*exo*-trig process (linalool and nerolidol cyclization) or 6-*endo*-trig process (terpineol cyclization) leads to the formation of the corresponding cyclic oxonium ion, which by deprotonation forms the final product of **1a**, **2a** or **3a** (Scheme 1). The presence of pyridine increases the yields and regioselectivity of these reactions.[13, 31]



Scheme 1. Mechanism of cyclization rection of terpenic alcohols induced by PhSeCl

3.2. *Biological evaluation*

For the investigation of the biological effects of synthesized heterocyclic products, **1a**, **2a**, and **3a**, we chose four biological methods that could provide us with information regarding the possible mechanisms of molecular action. Every new substance that entered the cells firstly disrupt the redox equilibrium with subsequent manifestations that lead to various cellular outcomes, e.g., influence on cell viability, introduction of apoptosis, influence on cellular migration, etc. In brief, we noticed a significant increase in ROS/RNS and enhanced cytotoxicity in both cell lines. Unfortunately, we did not observe cancer selectivity, thus we are not discussing the obtained results as anticancer, rather cytotoxic. All three cyclic ethers, **1a**, **2a**, and **3a**, exerted cytotoxic characteristics on both cell lines to a greater or lesser extent (Fig. 3).

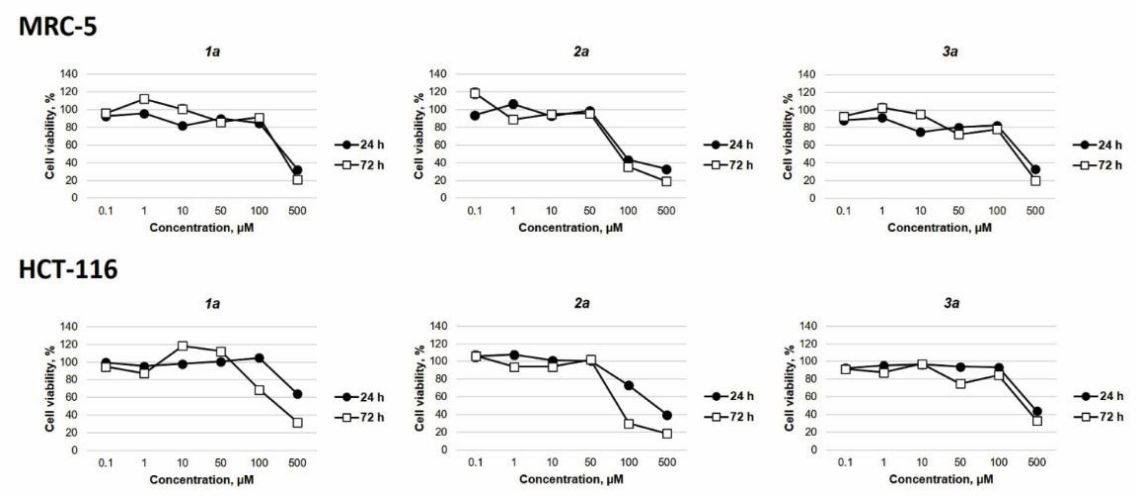


Fig. 3. Cell viability after 24 h and 72 h of exposure, expressed in percentages of viable cells

1a and **3a** showed to possess very weak cytotoxic influence on HCT-116 and MRC-5 cells. Moreover, the effect is more prominent on healthy MRC-5 cells. On the other hand, **2a** was determined to be more toxic to both cell lines in a time- and dose-dependent manner. The acute effect (24 h from treatment) of **2a** is more significant on MRC-5 cells, while the longer exposure (72 h) inhibited HCT-116 growth to a greater extent. It is possible that a longer exposure to **2a** could show an even greater difference and selectivity towards cancer cells, but *in vitro* experiments performed in plastic flasks and plates usually are optimal for 5 days of work without cell passaging and replacing. The evaluation of IC_{50} values provided very useful information in comparing the effects of the investigated drugs (Fig. 4).

As we described above, the investigated ether products possess a potential for interruption of redox equilibrium in the proposed cell model systems. When the number of surviving cells was calculated, the change of $O_2^{\bullet-}$ in the lower concentration range was not significant (Fig. 5).

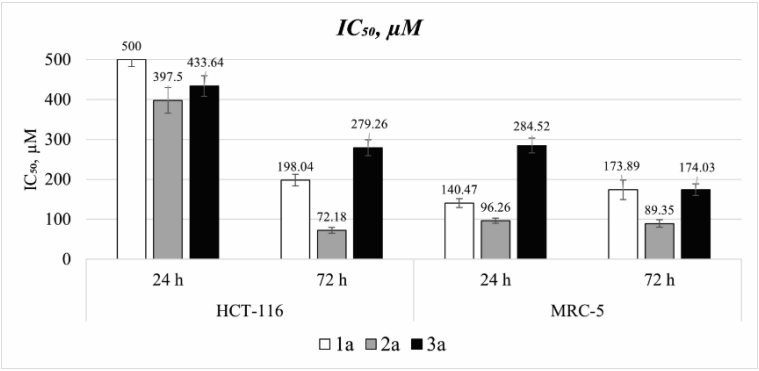


Fig. 4. The cytotoxic effects (IC_{50} values) of **1a**, **2a**, and **3a** after 24 h and 72 h exposure

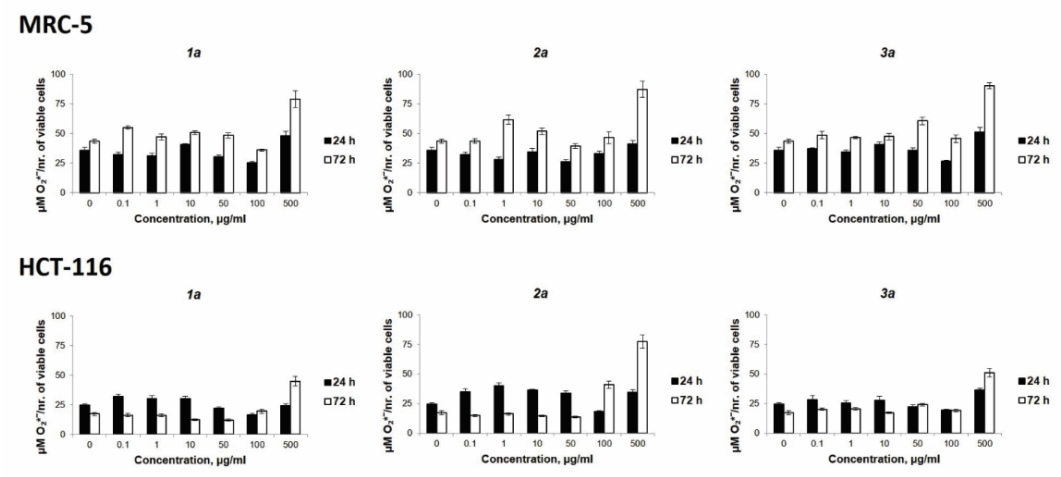


Fig. 5. Effects of **1a**, **2a**, and **3a** on HCT-116 and MRC-5 cell lines, expressed as the $O_2^{\bullet-}$ concentration after 24 h and 72 h of exposure

The highest applied concentration induced significant $O_2^{\bullet-}$ increase, thus leading to a decrease in cell viability. We note the greater increase in $O_2^{\bullet-}$ on MRC-5 cells in comparison to HCT-116 cells, which is in accordance with cell viability effects. A similar effect is observed with NO_2^- concentrations (Fig. 6).

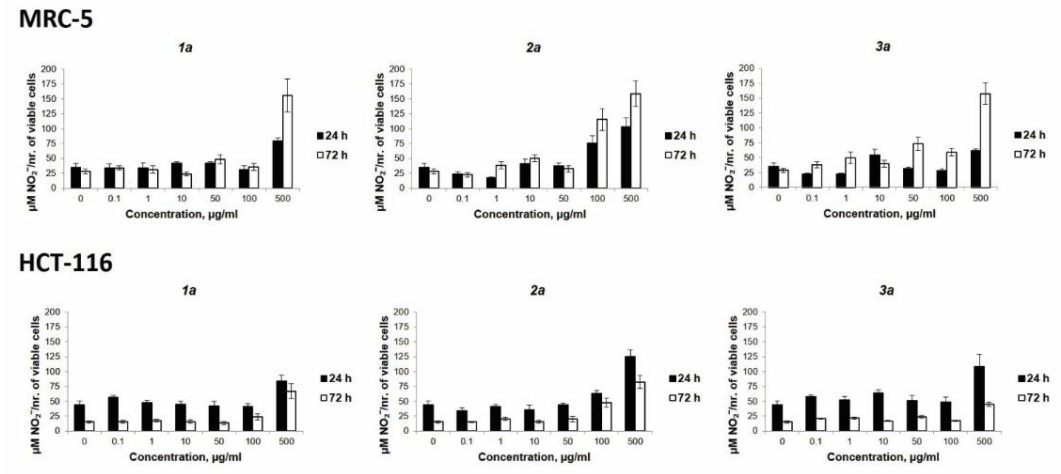


Fig. 6. Effects of **1a**, **2a**, and **3a** on HCT-116 and MRC-5 cell lines, expressed as the NO_2^- concentration after 24 h and 72 h of exposure

The influence of $O_2^{\bullet-}$ and NO_2^- in such studies is commonly used for the overall evaluation of ROS/RNS as a wide group of species involved in the cellular answer to xenobiotics, even though their molecular pathways are separated to a great extent. To evaluate exact molecular mechanisms, it is necessary to perform a whole series of other biological assays, which is not the focus of this study. Also, the choice of these two parameters is based on the high possibility of synergistic effect because NO has a great affinity towards $O_2^{\bullet-}$, forming very aggressive peroxynitrite species. The results of GSH determination are represented in Figure 7.

The change in the concentration of GSH is an indicator of the level of redox status in the cells. The overall increased ROS/RNS production, in most cases, leads to enhanced GSH production. As we observed almost no significant change in $O_2^{\bullet-}$ and NO_2^-, the GSH level in all treatments was smooth in general with no high changes; however, higher concentrations of **1a**, **2a**, and **3a** induced greater oxidative stress, so the GSH level significantly increased.

When comparing our results with previous research on substrates with similar structures, 2-(phenylselenomethyl)tetrahydrofuran and 2-(phe-

nylselenomethyl)tetrahydropyran,[32] the major difference in their redox properties can be noticed. 2-(phenylselenomethyl)tetrahydrofuran and 2-(phenylselenomethyl)tetrahydropyran manifested antioxidant properties and no cytotoxic effect on HCT-116 and MDA-MB-231 cells lines after 24 h and 72 h exposure with IC_{50} values >500 μM, while compounds **1a**, **2a**, and **3a** have shown strong prooxidative character on colon cancer HCT-116 cells and healthy MRC-5 cells. It is likely that the main reason for this different behavior could be found in the structural properties of compounds **1a**, **2a**, and **3a**, as they represent highly substituted THF and THP rings with distinct steric hindrances.

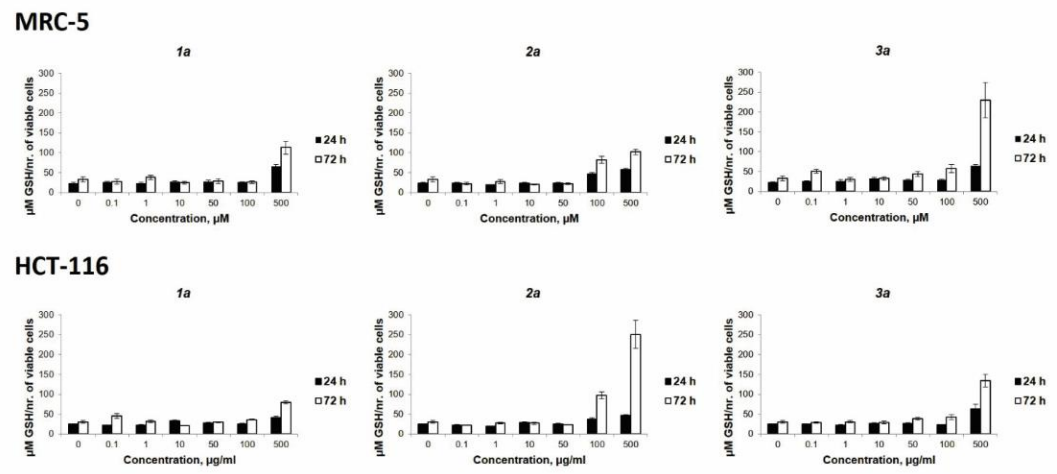


Fig. 7. Effects of **1a**, **2a**, and **3a** on HCT-116 and MRC-5 cell lines, expressed as the GSH concentration after 24 h and 72 h of exposure

4. CONCLUSION

Our results indicate a strong prooxidative character of **1a**, **2a**, and **3a** on colon cancer HCT-116 cells and healthy MRC-5 cells in the highest applied concentrations. Selectivity towards cancer cells was not observed, except when using **2a** for a longer exposure time. The study shows that there is a relationship between the influence on the redox status of the cells and their viability. Investigated substances induced enhanced production of radical species, which consequently affected the cells, resulting in decreased cell viability.

From our previous research, we could see that coordination of organoselenium compounds to some transition metal ions, such as Pd(II) and Pt(II), could lead to the emergence of some prominent biological activities, such as microbiological and cytotoxic activities, as well as interactions with DNA, albumin, and small biomolecules, so the continuation of this research would lead toward the coordination of these compounds to metal ions followed by evaluation of their biological properties.

These results have shown that the modification of some naturally occurring compounds and the introduction of selenium in molecules may lead to the occurrence of new properties, which by further tuning through coordination to various metal ions, can lead to distinguished selectivity towards cancer cells.

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