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Halogenated (F, Cl) 1,3-benzodiazoles, 1,2,3-benzotriazoles, 2,1,3-benzothia(selena)diazoles and 1,4-benzodiazines inducing Hep2 cell apoptosis

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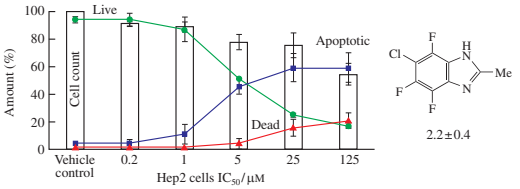
The title compounds synthesized from halogenated arene-1,2-diamines revealed, together with the latter, cytotoxicity towards the Hep2 (laryngeal epidermoid carcinoma) cells. The cytotoxicity was high and was accompanied by pronounced apoptotic activity at low concentrations for fluorinated diazoles, triazoles and selenadiazoles.

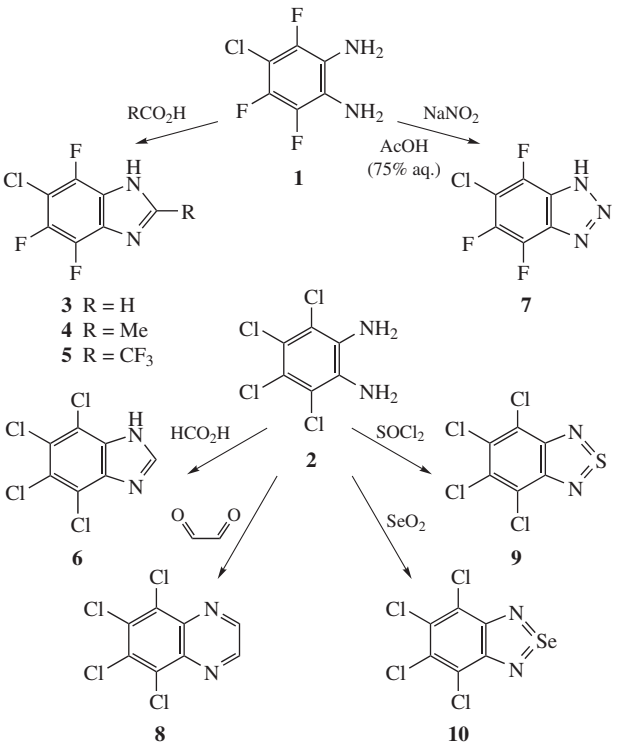


Whilst rare natural organofluorine compounds are poisons to humans and animals,[1] numerous synthetic derivatives are real or potential drugs.[2] Replacement of hydrogen atom in organic compounds with fluorine one frequently produces positive impact on ADME toxicity and metabolic stability of substances, particularly by preventing oxidative attack by cytochrome P450 enzymes, as well as on some other relevant properties.[2,3] Three other halogens, particularly chlorine, are also massively involved into current development of pharmaceuticals.[4] These results stimulate synthesis of new organofluorine compounds, their chlorine congeners and hybrid F/Cl derivatives for biomedical applications.

Various benzo-fused aza-heterocycles of biomedical significance covering 1,3-benzodiazoles (benzimidazoles), 1,2,3-benzotriazoles, 1,4-benzodiazines (quinoxalines),[5] *etc.*, can be synthesized from 1,2-diaminobenzenes. Recently, our group described original synthesis of (poly)fluorinated 1,2-diaminobenzenes and derived 1,4-benzodiazines and 2,1,3-benzothia(selena)diazoles.[6] Here we report on synthesis of halogenated (F, Cl) 1,3-benzodiazoles, 1,2,3-benzotriazoles, 2,1,3-benzothia(selena)diazoles and 1,4-benzodiazines, and studies of cytotoxicity of these and our previous[6] compounds towards the Hep2 (laryngeal epidermoid carcinoma) cells. We have found that for fluorinated diazoles, triazoles and selenadiazoles the cytotoxicity is high and is accompanied by pronounced apoptotic activity at low concentrations. It should be mentioned that for the laryngeal epidermoid carcinoma, a kind of oral cancer, the 5-year survival rate has remained ~50% over the past decades.[7] Its surgical and radiation treatment is seriously complicated thus encouraging medicament one with the targeted elimination of tumor through apoptosis, *i.e.* programmed cell death inherent to all eukaryotic cells.[8]

The parent halogenated 1,2-diaminobenzenes and the archetypal hydrocarbon 1,3-benzodiazole, 1,2,3-benzotriazole and 2,1,3-benzoselenadiazole were also tried to clarify ring-closure and halogenation effects, respectively.

Compounds **3**–**10** were prepared from diamines **1** and **2** (Scheme 1) using original protocols.† Their authenticity and purity were confirmed by elemental analysis and instrumental



Scheme 1

† 1,3-Benzodiazole, 1,2,3-benzotriazole and 2,1,3-benzoselenadiazole were received from Aldrich, their samples used in the cytotoxicity tests were additionally purified (GC-MS, 99%) by crystallizations. Compounds **1**, **2**, **11**–**14** and more eleven compounds (for their structures, see Online

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methods (see Online Supplementary Materials) including X-ray diffraction (XRD, covering also **2** and **11**; Figure 1);‡ beyond analytical context, XRD molecular and crystal structures of organic compounds are important for drug studies including molecular docking.

High-content screening method was applied to detect cytotoxicity using a vital stain with Hoechst 33342 and propidium iodide (PI).[10] The method allows one to distinguish live, apoptotic and dead cells in accordance with morphological criteria[8] together

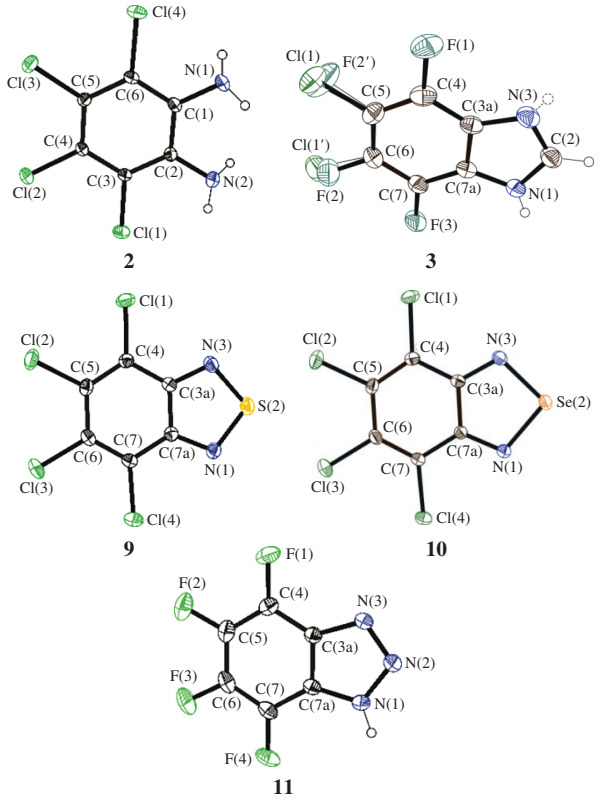


Figure 1 XP Shelx plots of molecules **2**, **3** (average of 1.5 molecule, solvate molecules H_2O omitted; atoms Cl/F and H disordered over two positions, the occupation ratio 0.62 : 0.38) and **9**–**11** (displacement ellipsoids at 30%; for selected bond lengths and angles, see Online Supplementary Materials). In all cases the bond lengths and bond angles correspond to the statistical means.[9]

Supplementary Materials) were prepared by known methods.[6,11–13(a)] In the protocols below, the reaction solutions were stirred, the solvents were distilled off under reduced pressure and the sublimations were performed *in vacuo*.

Compounds **3**–**5**. A mixture of diamine **1**[12] (0.50 g, 2.5 mmol) and formic (*a*), acetic (*b*), or trifluoroacetic (*c*) acid (25 ml) was refluxed for 10 h and cooled to room temperature. The precipitate was filtered off and recrystallized from hexane (*a*); or excess of the acid was removed by co-distillation with CCl_4, the residue refluxed with H_2O (4 ml) for 0.5 h, treated with excess of conc. aqueous ammonia, extracted with Et_2O (4×10 ml), and the extract was dried with $MgSO_4$ and evaporated (*b*, *c*). The residue was recrystallized from toluene–hexane, 2 : 1 (*b*), or benzene–toluene, 3 : 1 (*c*).

For **3**: yield 0.46 g (88%), needle-like yellowish crystals, mp 220–222 °C. ^{1}H NMR (DMSO-d_6) δ: 8.87 (s, 1H), 3.88 (s, 1H). ^{13}C NMR (DMSO-d_6) δ: 206.8, 145.2, 142.9, 141.1, 136.1, 126.3, 102.7. ^{19}F NMR (DMSO-d_6) δ: 28.6, 14.8, 6.6. UV-VIS [λ_{max}/nm (logε) (MeOH)]: 244 (3.74), 276 (3.14). FL [λ_{max}(λ_{exc})/nm (MeOH)]: 410 (356). MS, *m*/*z*: 205.9850 (calc. for $C_7H_2{}^{35}ClF_3N_2$, *m*/*z*: 205.9853). Found (%): C, 40.73; H, 0.96; Cl, 17.15; F, 27.58; N, 13.58. Calc. for $C_7H_2ClF_3N_2$ (%): C, 40.70; H, 0.98; Cl, 17.16; F, 27.59; N, 13.56.

For **4**: yield 0.43 g (76%), needle-like grayish crystals, mp 226–228 °C. ^{1}H NMR ($CDCl_3$) δ: 12.47 (s, 1H), 2.59 (s, 3H). ^{19}F NMR ($CDCl_3$) δ: 26.9, 13.8, 5.2. UV-VIS [λ_{max}/nm (logε) ($CHCl_3$)]: 245 (3.79), 277 (3.14). FL [λ_{max}(λ_{exc})/nm ($CHCl_3$)]: 345 (263). MS, *m*/*z*: 220.0013 (calc. for $C_8H_4{}^{35}ClF_3N_2$, *m*/*z*: 220.0010). Found (%): C, 43.53; H, 1.67; Cl, 16.55; F, 25.74; N, 12.51. Calc. for $C_8H_4ClF_3N_2$ (%): C, 43.56; H, 1.83; Cl, 16.07; F, 25.84; N, 12.70.

For **5**: yield 0.43 g (61%), needle-like white crystals, mp 153–155 °C. ^{1}H NMR ($CDCl_3$) δ: 4.54 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 143.6, 142.9, 142.8, 142.5, 136.2, 125.9, 117.9, 105.1. ^{19}F NMR ($CDCl_3$) δ: 97.9, 30.2, 18.2, 7.2. UV-VIS [λ_{max}/nm (logε) ($CHCl_3$)]: 251 (3.77), 281 (3.36). FL [λ_{max}(λ_{exc})/nm ($CHCl_3$)]: 335 (262). MS, *m*/*z*: 273.9728 (calc. for $C_8H^{35}ClF_6N_2$, *m*/*z*: 273.9727). Found (%): C, 35.36; H, 0.53; Cl, 12.96; F, 41.20; N, 9.95. Calc. for $C_8HClF_6N_2$ (%): C, 35.00; H, 0.37; Cl, 12.91; F, 41.52; N, 10.20.

Compound **6**. A mixture of diamine **2**[13(a)] (0.20 g, 0.80 mmol) and 98% formic acid (7 ml) was refluxed for 3 h, cooled to room temperature, poured into excess of 10% aq. NaOH and filtered. The filtrate was acidified with HCl and extracted with $CHCl_3$ (2×15 ml). The extract was dried with $CaCl_2$ and evaporated. The residue was recrystallized from hexane–$CHCl_3$ (10 : 1). Yield 0.13 g (64%), pale yellow crystals, mp 264–266 °C, 330–332 °C (AcOH) [lit.,[13(a)] mp 327–328 °C (AcOH)]. ^{1}H NMR ($CDCl_3$) δ: 8.14 (s, 1H), 4.82 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 142.5, 139.3, 130.7, 120.7. MS, *m*/*z*: 253.8963 (calc. for $C_7H_2{}^{35}Cl_4N_2$, *m*/*z*: 253.8967). Found (%): C, 32.83; H, 0.73; Cl, 55.31; N, 11.13. Calc. for $C_7H_2Cl_4N_2$ (%): C, 32.85; H, 0.79; Cl, 55.41; N, 10.95. The aforementioned difference in the mp values indicates polymorphism of **6** known for its hydrocarbon archetype. For crystals of **6** grown by gas-phase hexane diffusion into EtOH solution XRD is reported (CCDC 955360); mp, however, not indicated.[13(b)]

Compound **7**. A solution of $NaNO_2$ (0.36 g, 5.22 mmol) in water (3 ml) was added to an ice bath-cooled solution of diamine **1**[12] (0.45 g, 2.29 mmol) in 75% acetic acid (40 ml). The reaction mixture was heated at 70 °C for 30 min, cooled to room temperature, diluted with water (10 ml) and extracted with CH_2Cl_2 (3×40 ml). The extract was dried with $MgSO_4$, filtered and evaporated. The residue was sublimed and recrystallized from MeOH–toluene (5 : 1). Yield 0.35 g (74%), white crystals, mp 193–194 °C. ^{1}H NMR (DMSO-d_6) δ: 3.39 (s, 1H). ^{13}C NMR (DMSO-d_6) δ: 143.8, 141.9, 135.4, 133.3, 128.6, 106.7. ^{19}F NMR (DMSO-d_6) δ: 34.3, 21.0, 10.5. UV-VIS [λ_{max}/nm (logε) (MeOH)]: 262 (3.60). FL [λ_{max}(λ_{exc})/nm (MeOH)]: 404 (262). MS, *m*/*z*: 206.9890 (calc. for $C_6H^{35}ClF_3N_3$, *m*/*z*: 206.9893). Found (%): C, 34.74; H, 0.51; Cl, 17.05; F, 27.47; N, 20.23. Calc. for $C_6HClF_3N_3$ (%): C, 34.72; H, 0.49; Cl, 17.08; F, 27.46; N, 20.25.

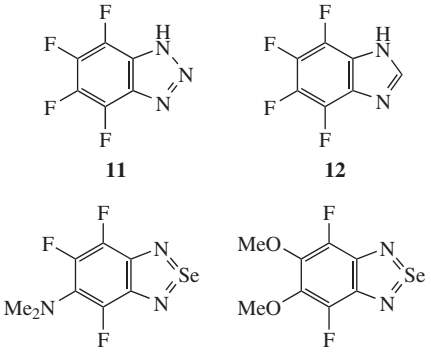
Compound **8**. A solution of diamine **2**[13(a)] (0.50 g, 2.03 mmol) and solid glyoxal (0.16 g, 2.84 mmol) in EtOH (50 ml) was stirred at room temperature for 8 h. The precipitate was filtered off and recrystallized from hexane–Me_2CO (10 : 1). Yield 0.43 g (79%), needle-like yellow crystals, mp 201–202 °C [lit.,[13(a)] mp 195–197 °C (AcOEt)]. ^{1}H NMR ($CDCl_3$) δ: 9.01 (s, 4H). ^{13}C NMR ($CDCl_3$) δ: 146.2, 146.1, 145.3, 139.1, 134.7, 131.9, 131.0. UV-VIS [λ_{max}/nm (logε) ($CHCl_3$)]: 255 (4.58), 330 (3.81). FL [λ_{max}(λ_{exc})/nm ($CHCl_3$)]: 394 (378). MS, *m*/*z*: 265.8972 (calc. for $C_8H_2{}^{35}Cl_4N_2$, *m*/*z*: 265.8967). Found, %: C, 35.74; H, 0.88; Cl, 52.97; N, 10.41. Calc. for $C_8H_2Cl_4N_2$ (%): C, 35.86; H, 0.75; Cl, 52.93; N, 10.46.

Compound **9**. A solution of $SOCl_2$ (0.83 g, 7.00 mmol) in Et_2O (18 ml) was added dropwise to a solution of diamine **2**[13(a)] (0.78 g, 3.21 mmol) and Et_3N (0.72 g, 7.11 mmol) in Et_2O (50 ml) at room temperature. After 20 min, the mixture was neutralized with aq. NaOH and extracted with Et_2O (3×20 ml). The extract was dried with $CaCl_2$, evaporated, the residue was chromatographed on silica column with benzene, the proper fraction was collected and its component was sublimed. Yield 0.66 g (77%), goldish plates, mp 160–162 °C. ^{13}C NMR ($CDCl_3$) δ: 150.5, 134.3, 124.2. UV-VIS [λ_{max}/nm (logε) ($CHCl_3$)]: 243 (4.22), 318 (4.08), 331 (4.15). MS, *m*/*z*: 271.8530 (calc. for $C_6{}^{35}Cl_4N_2{}^{32}S$, *m*/*z*: 271.8531). Found (%): C, 26.52; Cl, 51.54; N, 10.14; S, 11.80. Calc. for $C_6Cl_4N_2S$ (%): C, 26.31; Cl, 51.76; N, 10.23; S, 11.70.

Compound **10**. A solution of diamine **2**[13(a)] (0.32 g, 1.30 mmol) and SeO_2 (0.18 g, 1.30 mmol) in 0.2 M HCl (60 ml) and Et_2O (40 ml) was kept at room temperature for 2 h. The precipitate was filtered and recrystallized from EtOH–Me_2CO (3 : 1). Yield 0.40 g (97%), needle-like goldish crystals, mp 235–236 °C. ^{13}C NMR ($CDCl_3$) δ: 153.8, 131.5, 125.1. ^{77}Se NMR (DMSO-d_6): 1557. UV-VIS [λ_{max}/nm (logε) ($CHCl_3$)]: 339 (4.15), 353 (4.24). MS, *m*/*z*: 317.7987 (calc. for $C_6{}^{35}Cl_4N_2{}^{78}Se$, *m*/*z*: 317.7983). Found (%): C, 22.52; Cl, 44.30; N, 8.53; Se, 24.65. Calc. for $C_6Cl_4N_2Se$ (%): C, 22.46; Cl, 44.20; N, 8.73; Se, 24.61.

with counting their numbers. With fluorescence, it was proved that the compounds got really infiltrated into the cells. The medium inhibitory concentrations were determined with the corresponding curves quantifying the percentage of live cells (Figure S1; see Online Supplementary Materials).§

The cytotoxicity and apoptotic activity of the compounds strongly depended on scaffold structure and its substitution patterns. Some 1,3-benzodiazoles, 1,2,3-benzotriazoles and 2,1,3-benzoselenadiazoles displayed high cytotoxicity combined with high apoptotic activity at low concentrations, especially diazole **4**, triazole **11**, and selenadiazoles **13** and **14** (see Figure S1). With **13**, the cell death dynamics was observed already in the first hours after the treatment; and with diazole **12**, additional evidence of concentration dependence of apoptotic cell amount was obtained together with well-resolved illustration of their typical morphological differences, *i.e.* cell shrinkage and pyknosis.[8] The archetypal hydrocarbon 1,3-benzodiazole, 1.2,3-benzotriazole and 2,1,3-benzoselenadiazole were low toxic and provided significant level of apoptosis only at concentration of 125 μM (see Online Supplementary Materials).



The diamines induced apoptosis of the Hep2 cells but less effective than diazole **4**, triazole **11** and selenadiazoles **13** and **14**. Interplay of the ring-closure and halogenation effects was as follows: diazoles **3** and **12** and triazoles **7** and **11** were more toxic, whereas the corresponding thiadiazole, selenadiazole and diazine were less toxic than the parent diamines (**1**, see Figure S1). With triazole **11** and diazole **12**, it was seen that the diazole ring-closure gave more active compound.

In conclusion, combination of benzo-fused aza-heterocyclic scaffolds and substituents F and Cl brings about compounds possessing high cytotoxicity together with high apoptotic activity at low concentrations. Within 21 compounds studied in detail, those synthesized in this work and containing three fluorine atoms and one chlorine atom in the carbocycles belong to the most promising; this may also cover substituent Me_2N in front of three fluorine atoms. Overall, the apoptosis-inducing diazoles **3**, **4** and **12**, triazole **11**, and selenadiazoles **13** and **14** can be considered as potential lead compounds for development of new anticancer drugs. Polychlorinated derivatives possess strong cytotoxicity and can be used beyond the apoptosis context.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2017.09.002.

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‡ *X-ray structure determination*. Single crystals suitable for XRD were obtained for compounds **2**, **3** (solvate with H_2O), **9** and **11** by slow evaporation of hexane, methanol, toluene and benzene solutions, respectively, and for **10** by slow diffusion of hexane into ethanol solution. XRD data were obtained at 296 K on a Bruker Kappa Apex II CCD diffractometer using φ-, ω-scans of narrow (0.5°) frames with MoKα radiation (λ = 0.71073 Å) and a graphite monochromator. The structure was solved by direct methods and refined by full-matrix least-squares method against all F^2 in anisotropic approximation using the SHELX-97 program set.[15] Absorption corrections were applied empirically using SADABS program package.[16] For compounds **3** and **11**, the H atoms positions were calculated with the riding model, and for compound **2**, located from difference Fourier map and refined by isotropic approximation.

Crystal data for **2**. Triclinic, space group $P\bar{1}$, a = 7.0967(3), b = 8.3807(4) and c = 8.6846(4) Å, α = 61.739(2), β = 71.755(2) and γ = 78.034(2)°, V = 431.00(3) Å^3, Z = 2, d_{calc} = 1.895 g cm^{-3}, μ = 1.310 mm^{-1}, $F(000)$ = = 244, crystal size 0.90×0.70×0.40 mm, 2508 independent reflections (R_{int} = 0.026), wR_2 = 0.0736, S = 1.04 for all reflections (R = 0.0268 for 2318 reflections with $F > 4\sigma$).

Crystal data for **3**. $1.5C_7H_2ClF_3N_2 \cdot 2H_2O$, trigonal, space group $R\bar{3}c$, a = 30.189(1), b = 30.189(1) and c = 13.3840(6) Å, V = 10563.8(8) Å^3, Z = 36, d_{calc} = 1.784 g cm^{-3}, μ = 0.491 mm^{-1}, $F(000)$ = 5604, crystal size 0.90×0.20×0.10 mm, 2361 independent reflections (R_{int} = 0.055), wR_2 = = 0.2640, S = 1.21 for all reflections (R = 0.0697 for 1642 reflections with $F > 4\sigma$).

Crystal data for **9**. Monoclinic, space group $P2_1/c$, a = 14.016(1), b = = 3.8751(3) and c = 16.677(1) Å, β = 94.062(4)°, V = 903.5(1) Å^3, Z = 4, d_{calc} = 2.014 g cm^{-3}, μ = 1.484 mm^{-1}, $F(000)$ = 536, crystal size 0.90×0.04×0.04 mm, 1783 independent reflections (R_{int} = 0.036), wR_2 = = 0.0823, S = 1.03 for all reflections (R = 0.0294 for 1443 reflections with $F > 4\sigma$).

Crystal data for **10**. Monoclinic, space group $P2_1/c$, a = 13.8685(7), b = 3.9183(2) and c = 16.6628(8) Å, β = 94.245(2)°, V = 902.99(8) Å^3, Z = 4, d_{calc} = 2.360 g cm^{-3}, μ = 5.285 mm^{-1}, $F(000)$ = 608, crystal size 0.90×0.08×0.03 mm, 2054 independent reflections (R_{int} = 0.036), wR_2 = = 0.2594, S = 1.18 for all reflections (R = 0.0681 for 1642 reflections with $F > 4\sigma$).

Crystal data for **11**. Monoclinic with two crystallographycally independent molecules in the unit cell, space group $P2_1/c$, a = 9.8831(6), b = = 15.2150(7) and c = 9.7079(5) Å, β = 110.182(2)°, V = 1370.2(1) Å^3, Z = 8, d_{calc} = 1.853 g cm^{-3}, μ = 0.195 mm^{-1}, $F(000)$ = 752, crystal size 0.80×0.60×0.12 mm, 3099 independent reflections (R_{int} = 0.030), wR_2 = = 0.1370, S = 1.06 for all reflections (R = 0.0443 for 2297 reflections with $F > 4\sigma$).

CCDC 1524477, 1510245, 1524234, 1487294 and 1524233 contain the supplementary crystallographic data for compounds **2**, **3**, **9**, **10** and **11**, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

§ *Cytotoxicity assessment and statistical analysis.* All reagents for cell cultures were purchased from Thermo Scientific. The Hep2 cell line was received from the State Research Center of Virology and Biotechnology VECTOR (Koltsovo, Russia). The Hep2 cells were cultured in 96 well plate at densities of 5000 cells per well in a final volume of 100 μl per well. The plates were pre-incubated in a 5% CO_2/95% air-humidified atmosphere at 37 °C for 24 h to allow adaptation of cells prior to the addition of the test compounds. All substances were dissolved in DMSO prior to dilution. Cells were treated with increasing concentrations of the studied compounds from 0.2 to 125 μM for 48 h, stained with Hoechst 33342 (Sigma-Aldrich) and PI (Invitrogen) for 10 min at 37 °C. Hoechst staining was used to evaluate the condensation and fragmentation of DNA of the apoptotic cells, PI only stains cells that have lost membranes. In Cell Analyzer 2200 (GE Healthcare, UK) was used to perform six fields per well automatic imaging under 200× magnification in bright-field and fluorescence channels. Images produced were used to analyze live, apoptotic and dead cells among the whole population using the In Cell Investigator software (GE Healthcare, UK). One-way ANOVA was performed using GraphPad Prism version 7.00 for Windows 7[14] with consideration of $p < 0.05$ as statistically representative.

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