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Aminodiols, aminotetraols and 1,2,3-triazoles based on *allo*-gibberic acid: stereoselective syntheses and antiproliferative activities†

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A new series of aminodiols, aminotetraols and 1,2,3-triazoles based on *allo*-gibberic acid were synthesized in a stereoselective manner, starting from commercially available gibberellic acid. *allo*-Gibberic acid, prepared from gibberellic acid according to a literature method, was applied to SeO_2/*t*-BuOOH-mediated allylic oxidation, yielding the triol, which is a key intermediate. After protecting the 1,4-diol functionality as acetonide, epoxidation was performed using either *m*-CPBA or *t*-BuOOH/VO(acac)$_2$ to produce the epoxy alcohol. Then, the oxirane ring was opened with either primary amines to provide aminodiols or sodium azide to afford azido diols. The latter was subjected to the CuAAC reaction to obtain dihydroxy 1,2,3-triazoles. HCl-mediated acetonide deprotection of the prepared derivatives furnished aminotetraols and tetrahydroxy 1,2,3-triazoles. The antiproliferative effects of the prepared compounds were studied by the *in vitro* MTT method against a panel of human cancer cell lines (HeLa, SiHa, A2780, MCF-7 and MDA-MB-231) and fibroblasts, and the structure–activity relationships for the prepared compounds were explored.

1 Introduction

In 2022, according to the IARC (International Agency for Research on Cancer) estimates, 20 million new cancer cases and 9.7 million deaths were recorded. Global concerns have been expressed about the escalating burden of cancer as the cases are expected to grow by 77% in 2035.[1] Subsequently, efforts in drug discovery alongside other fields, such as genomics, proteomics, molecular biology and pharmaceutical sciences, have been employed to reach the most effective and selective cancer therapy.[2–6] Nevertheless, existing cancer treatments often result in significant adverse effects with a high possibility of drug resistance.[7] Through the last decades, nature has remained the richest, most sustainable and regenerative source of new promising lead compounds with not only anticancer activity but also a variety of biological properties, for instance, anti-hypertension, antimalarial and antimicrobial properties.[8,9] This was emphasised by Newman and Cragg in their review on drug sources covering the period from 1981 to 2014.[10] The main obstacles faced during the development of leads from natural sources have been the structural complexity of natural products and their production in minor quantities.[11] However, the enormous progress in genomics and biosynthetic methods has overcome these challenges.[12] In the near past, the FDA granted approval for several natural products currently available in the global market, such as doxorubicin[13] and vincristine,[14] to be used for anticancer therapy. Moreover, the discovery of new lead compounds has been highly accelerated by the application of high throughput screening (HTS) that triggered the need to generate extensive compound libraries by utilising pharmaceutical chemistry aspects.[15]

The *ent*-kaurene diterpenoids, containing opposite stereochemistry compared to kaurene diterpenoids,[16] first isolated from New Zealand Kauri (*Agathis australis* Salisb.),[17] form a distinctive group of the diterpenoid family, and they have attracted the attention of researchers owing to their diverse and complex structures as well as their broad range of bioactive properties, in particular, antitumour[18] and antimicrobial activities.[19,20] Gibberellic acid (GA_3) **1**, a famous C_{19} *ent*-kaurene diterpenoid, is known for its agricultural applications as a plant growth hormone responsible for seed germination and stem elongation.[21,22] Over the past decades, it has captured the interest of synthetic scientists due to its commercial availability and extensive possibilities for chemical transformations.[23,24] These efforts brought to light the promising biological applications of **1** and its derivatives, most notably for anticancer activity. The early aspiring report announced in 2009 by Koehler

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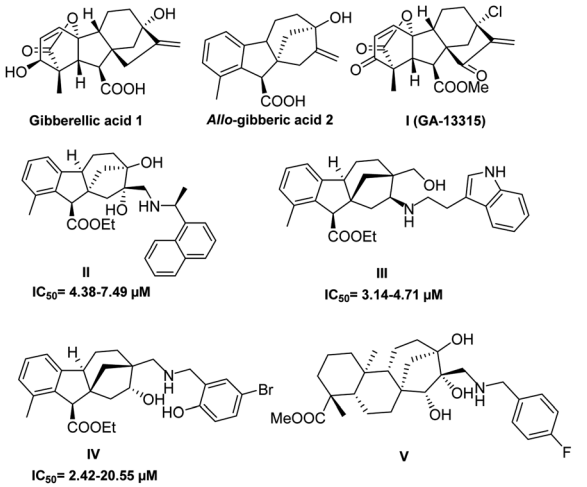


Fig. 1 Structures of bioactive gibberellic acid and steviol derivatives.

showed the ability of gibberellic acid **1** and 9α-H *allo*-gibberic acid **2** to modulate the NF-κB pathway activity.[25] Lately, Y. Zhang *et al.* demonstrated the *in vitro* and *in vivo* antiangiogenic activity of compound **I** (GA-13315),[26] which was prepared using the synthetic pathway of GA_3-based α,β-unsaturated diketone derivatives accomplished by Chen *et al.*[27] This work inspired Jang Wu *et al.* to engage a 1,2,3-triazole functionality with hydroxy-functionalised *epiallo*-gibberic acid with an α,β-unsaturated ketone moiety that expressed the ability to induce cell cycle arrest in the S phase and apoptosis.[28] Furthermore, a potent anticancer activity was also observed with a group of *allo*-gibberic acid *meta*-substituted benzyl esters prepared by Zhu *et al.*[29]

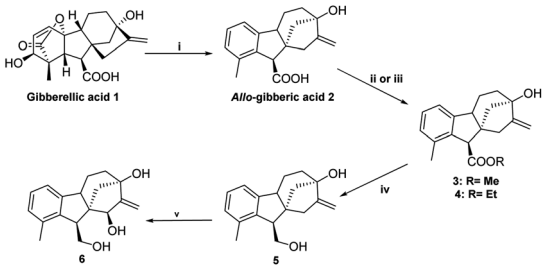
In our previous work, we successfully prepared two libraries of aminodiols and aminoalcohols based on *N*-substituted *allo*-gibberic acid with potent and selective antiproliferative activity (compounds **II**, **III** and **IV** presented in Fig. 1).[30,31] Furthermore, a new series of steviol-based aminotriols (**V** presented in Fig. 1) was prepared by our research group and these were evaluated through an antiproliferative activity assay (MTT) that showed the importance of the *N*-benzyl substituents for potent and selective cytotoxicity.[32] Integrating these results with our ongoing effort to develop more powerful and selective anticancer agents has guided us to prepare a new library of aminodiols, aminotetraols and 1,2,3-triazoles based on *allo*-gibberic acid and evaluate their *in vitro* antiproliferative activity against different human cancer cell lines.

2 Results and discussion

2.1 Synthetic procedure

2.1.1 Synthesis of *allo*-gibberic acid-based aminotetraols

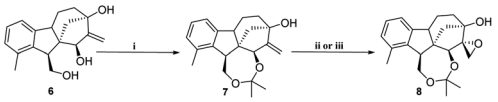
*2.1.1.1 Stereoselective synthesis of key intermediates (triol **6** and epoxyalcohol **8**).* Starting from commercially available gibberellic acid **1**, *allo*-gibberic acid **2** was derived by HCl-mediated hydrolysis, in which lactone opening, decarboxylation and then ring A aromatisation occur gradually.[29,33] Diol **5** was productively prepared by $LiAlH_4$-mediated reduction of the ester group



Scheme 1 Stereoselective synthesis of triol **6**. (i) HCl 1.2 M, 65 °C, 3 h, 70%; (ii) CH_2N_2, Et_2O, 25 °C, 2 min, 85%; (iii) C_2H_5I (2.5 equ.), Cs_2CO_3 (2 equ.), MeCN, reflux, 1 h, 99%; (iv) $LiAlH_4$ (2 equ.), dry THF, 40 °C, 12 h, 80%; (v) SeO_2 (0.5 equ.), *t*-BuOOH (3 equ.), dry THF, 40 °C, 12 h, 60%.

of either ethyl[30] or methyl *allo*-giberate.[28] Allylic diol **5** was oxidised with selenium(IV) dioxide and *tert*-butyl hydroperoxide (*t*-BuOOH), yielding triol **6** in a stereospecific manner (16(*S*)-OH) (de ≥ 95%, NMR determination) (Scheme 1).[34] The first attempt to obtain the spiro-epoxide was performed by the direct epoxidation of **6** with *t*-BuOOH in the presence of vanadyl acetylacetonate ($VO(acac)_2$) as the catalyst. However, it was dismissed considering the low yield and long reaction time, mainly due to the low solubility of triol **6** in organic solvents. To overcome this obstacle, the 1,4-diol functionality was protected as acetonide using dry acetone in the presence of *p*-toluene sulfonic acid (*p*TSA).[35] Subsequently, the synthesized compound **7** was subjected to the epoxidation of the terminal alkene by utilising either *t*-BuOOH/$VO(acac)_2$ in dry toluene or *m*-CPBA in dry DCM. Under the former conditions, the reaction proceeded at a slow rate and heating was needed to obtain the desired product. When using *m*-CPBA, the reaction was endowed with a higher yield and shorter time at room temperature. In both cases, the reaction took place in a stereospecific manner and *cis*-epoxy alcohol **8** was observed as a single product (de ≥ 95%, NMR determination) (Scheme 2). Allylic alcohol **7** played a promoting and directing role in epoxidation through the formation of a hydrogen bond with the peracid oxygen of *m*-CPBA in the transition state.[36]

*2.1.1.2 Synthesis of the desired aminotetraols (aminolysis of epoxyalcohol **8**).* As described earlier by our research group, nucleophilic addition of amines to epoxides is the optimal approach to obtain aminodiols and aminotriols.[37–39] Hence, a library of aminodiols **9–18** based on *N*-substituted *allo*-gibberic acid was effectively prepared by the ring opening of oxirane **8** with a variety of primary amines due to the importance of the secondary amine functionality for antiproliferative activity according to our previous work.[30] This step was preferably catalysed by $LiClO_4$, where Li^+ coordinates with the epoxide oxygen, thereby making the epoxide more prone to nucleophilic attack by amines.[40] Moreover, $LiClO_4$ also improves the stereoselectivity of ring opening.[41] Aminodiols **9–18** were then deprotected in acidic conditions to provide the desired aminotetraols **19–28** as hydrochloride salts. Nevertheless, in the case of compound **28**, a mixture of mono-, di- and trihydrochloride salts was obtained; therefore, in order to access the pure compounds, an alkaline liberation was achieved



Scheme 2 Stereoselective synthesis of the intermediate spiro-epoxide **8**. (i) *p*TSA, dry acetone, 25 °C, 12 h, 80%; (ii) *m*-CPBA (2.5 equ.), dry DCM, 25 °C, 3 h, 65%; (iii) $VO(acac)_2$, *t*-BuOOH (1.5 equ.), dry toluene, 50 °C, 12 h, 55%.

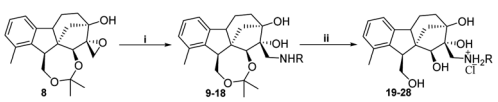
through a chemical extraction applying aqueous Na_2CO_3 (Scheme 3 and Table 1).

2.1.2 Synthesis of *allo*-gibberic acid-based 1,2,3-triazoles. The pyrimidine scaffold generally exists in small bioactive agents, especially in cancer agents.[42,43] In addition, the 1,2,3-triazole motif can not only serve as a pharmacophore with diverse biological properties, but it can also act as a linker to connect different pharmacophores.[44,45] For the exploration of potent and novel anticancer agents, *allo*-gibberic acid analogues were synthesized based on the strategies of *allo*-gibberic acid hybrids with aminopyrimidine scaffolds through the 1,2,3-triazole-bearing linkers. There are several synthetic methodologies for constructing triazoles. However, the CuAAC reaction (copper-catalysed azide–alkyne cycloaddition) has gained significant attention, and it was applied extensively to synthesise a broad range of 1,2,3-triazoles.[46,47]

In order to obtain the desired triazoles, azido diol **29** was first prepared by epoxide ring-opening with sodium azide (NaN_3) in the presence of NH_4Cl. A new series of dihydroxy *allo*-gibberic acid-based 1,2,3-triazoles **30–35** was again generated by the reaction between dihydroxy azide **29** and pyrimidine-type alkynes[48] under Sharpless click chemistry conditions. Acetonide deprotection and subsequent extraction of the resulting hydrochloride salts with aqueous solution of Na_2CO_3 produced the corresponding tetrahydroxy 1,2,3-triazoles **36–41** (Scheme 4 and Table 2).

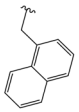
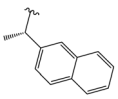
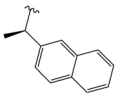
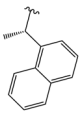
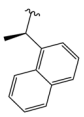
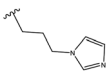
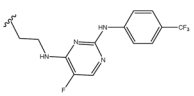
2.1.3 Determination of the relative configuration of synthesized compounds. During the aforementioned synthetic routes, two new chiral centres were formed through the allylic oxidation of diol **5** (new OH group at position 16) and epoxidation of compound **7**. The relative configuration of the new stereocentres was determined by NOESY experiments.

*2.1.3.1 Relative configuration of triol **6**.* As shown in Fig. 2 (compound **6**), two clear NOE signals were observed between H-16 and H-13 as well as between OH-16 and H-15. Moreover, a clear COSY signal was observed between H-16 and H-10. In addition, an extra NOE signal was noticed between H-16 and H-9 in compound **7**, emphasising the suggested configuration.



Scheme 3 Synthesis of aminodiols **9–18** and aminotetraols **19–28**. (i) RNH_2 (2.25 equ.), $LiClO_4$ (2.25 equ.), MeCN, 80–90 °C, 24–48 h, 45–85%; (ii) HCl 10%, EtOH, 25 °C, 3 h, 63–91%, then (compound **28**) Na_2CO_3 10%, EtOAc.

Table 1 Preparation of aminodiols **9–18**

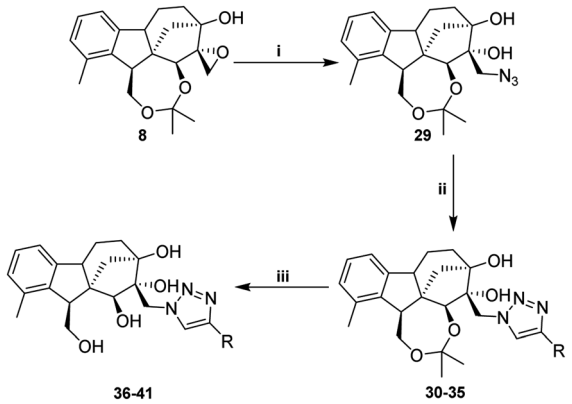
Entry	Compound	R	Yield (%)
1	**9**		85
2	**10**		45
3	**11**		46
4	**12**		62
5	**13**		63
6	**14**		68
7	**15**		59
8	**16**		54
9	**17**		70
10	**18**[a]		47

[a] Preparation of amine **18** is described in the ESI.

*2.1.3.2 Relative configuration of epoxyalcohol **8**.* The configuration of *cis*-epoxide was confirmed by two clear NOE signals recorded between H-25 and H-12, along with H-25 and H-13. Since the aminolysis of spiro-epoxide **8** does not affect the absolute configuration, the relative configuration of the chiral centres of **9–41** is known to be the same as that of epoxide **8** (Fig. 3).

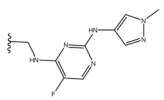
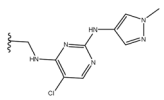
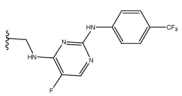
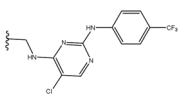
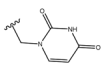
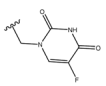
2.2 Antiproliferative activity

The *in vitro* antiproliferative activities of the synthesized aminodiols **9–18**, aminotetraols **19–28**, and dihydroxy and tetrahydroxy substituted 1,2,3-triazoles **30–41** against a panel of different human cancer cell lines, including cervical (SiHa and HeLa), breast (MCF-7 and MDA-MB-231) and ovary (A2780)



Scheme 4 Synthesis of dihydroxy and tetrahydroxy 1,2,3-triazoles. (i) NaN_3 (5 equ.), NH_4Cl (2.5 equ.), EtOH : H_2O = 8 : 2, reflux, 48 h, 71%; (ii) acetylenes (1.1 equ.), $Cu(OAc)_2 \cdot H_2O$ (0.1 equ.), sodium ascorbate (0.3 equ.), *t*-BuOH : H_2O (2 : 1), 40 °C, 12 h, 51–83%; (iii) HCl 10%, EtOH, 25 °C, 3 h, 63–85%.

Table 2 Dihydroxy and tetrahydroxy 1,2,3-triazoles. The preparation of pyrimidine-type alkynes is described in the Experimental section

Entry	Compound	R	Yield (%)
1	**30**		70
2	**31**		83
3	**32**		83
4	**33**		66
5	**34**		51
6	**35**		56

cancers as well as non-cancerous fibroblast cells (NIH/3T3) were assayed by the MTT method.[49] Cisplatin, one of the most widely used anticancer agents, was used as positive control. Results are summarised in Fig. 4.

2.3 Structure–activity relationship (SAR)

Based on the obtained results, the SARs of these novel derivatives were analysed and summarised (detailed data on antiproliferative effects of all investigated compounds are available in Table S1 in the ESI†).

The nitrogen substituent seems to be crucial in determining the cancer-cell-inhibiting properties of the prepared

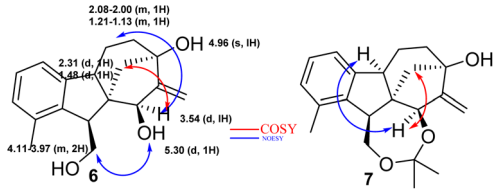


Fig. 2 Relative configuration of compounds **6** and **7**.

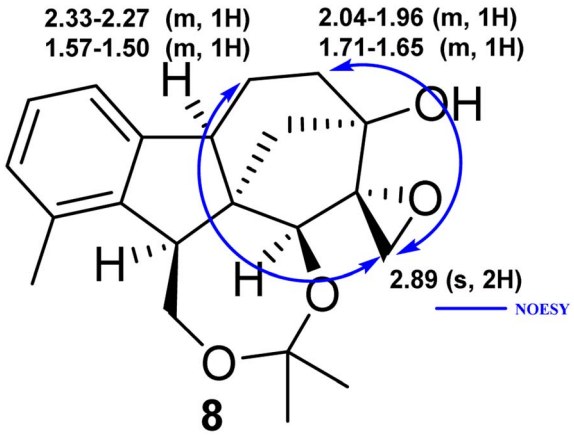


Fig. 3 Relative configuration of epoxyalcohol **8**.

compounds. *N*-Benzyl-substituted aminodiol **9** displayed modest inhibition values against all tested cancer cell lines (less than 50%). Deprotection of the acetonide moiety, forming aminotetraol **19**, led to a moderate increase in the activity. The introduction of either an electron-withdrawing (F) or an electron-donating group (OCH_3) at the *para* position did not show any significant change in the antiproliferative effects of either aminodiols (**10** and **11**) or aminotetraols (**20** and **21**).

In the case of *N*-1-naphthylmethyl-substituted aminodiol **12**, the inhibition values were exceedingly low at a concentration of 10 μM, while its related aminotetraol **22** showed more considerable growth in activity with notable selectivity towards MCF-7 and MDA-MDB 231 cell lines (Table 3).

In the case of naphthyl derivatives, the tetraol skeleton consistently favoured against their diol analogues, indicating a possible interaction of the 1,4-diol scaffold with the molecular target. The introduction of a methyl group at the α position failed to yield any remarkable increase in the activity of aminodiols **15** and **16**. However, *S*-diastereomer **15** showed moderate activity towards MCF-7, A2780 and HeLa cell lines. Interestingly, their relevant aminotetraols **25** and **26** presented a noteworthy incline in cell growth suppression. In turn, they displayed low selectivity and elevated cytotoxicity towards the fibroblast cell line NIH/3T3. Similar situations were observed with *S*- and *R*-α-methyl-2-naphthylmethyl-substituted aminodiols and aminotetraols (**13**, **14**, **23** and **24**).

Furthermore, the importance of the "linker" property between *allo*-gibberic acid and the 2,4-diaminopyrimidine motif was also explored. Based on the results, 2,4-diaminopyrimidine-ethylamine conjugates (compounds **18** and

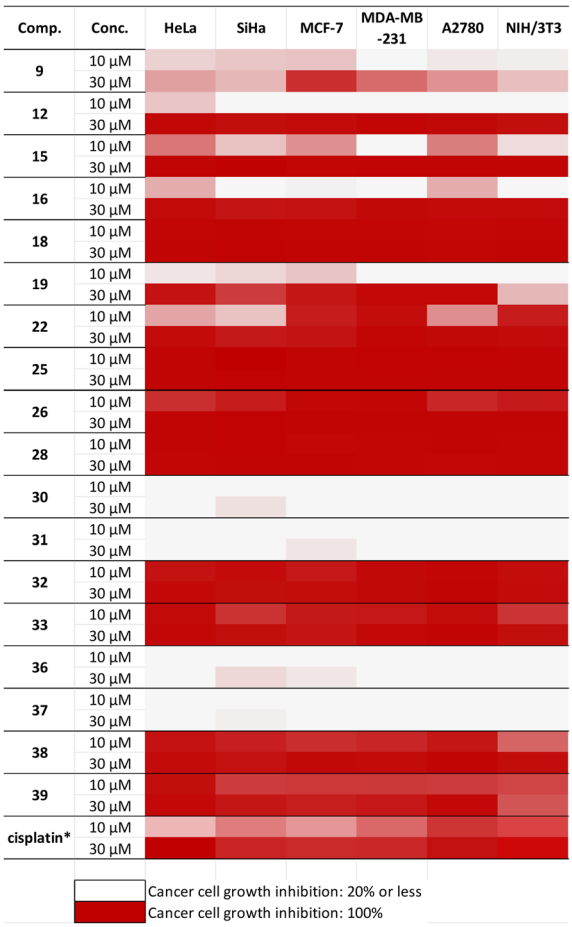


Fig. 4 Antiproliferative activities of selected compounds.

28) exhibited potent antiproliferative activity, whereas they showed low selectivity and high cytotoxicity towards NIH/3T3. This can be justified by the high flexibility of the ethylamine linker, allowing the rise of various conformations that can mimic a higher number of active sites. Replacement of ethylamine by the 1,2,3-triazole linker (compounds **32**, **33**, **38** and **39**) resulted in similar potent compounds with a slight change in the selectivity profile, which is especially true for the aminotetraol analogues (**38**, **39**). The ability of the triazole moiety to create a restricted number of conformations reduced the possibility of fitting several active sites and probably led to enhanced selectivity. On the other hand, the effect of substituents on the 2,4-pyrimidine ring with respect to antiproliferative properties was investigated. When 5-fluoro substitution (**32**) was next compared to the 5-chloro analogue (**33**), the results suggested that 5-chloro-2,4-diaminopyrimidine showed a slightly better selectivity than the 5-fluoro-substituted analogue. Furthermore, the replacement of the N^2-(*p*-trifluoromethyl)phenyl substituent (compound **32** and **33**) by the 1-methyl-1*H*-pyrazol-4-yl group (compound **30** and **31**), as expected, the pyrazole analogue became inactive against the cancer cell lines. Additionally, molecules with pyrimidinedione coupled to a triazole linker (**34**, **35**, **40**, **41**) did not expose any considerable action. The results clearly revealed that the type of substituents at position 4 had a significant effect on the anticancer activity of the 2,4-diaminopyrimidine ring (Table 3).

Table 3 Calculated IC_{50} values of the most promising derivatives (see also Table S1 in ESI)

	Calculated IC_{50} (μM)					
Compounds	HeLa	SiHa	MCF-7	MDA-MB	A2780	NIH/3T3
18	3.08	3.44	2.12	1.98	1.61	4.36
23	3.31	3.52	3.32	5.05	6.26	4.54
24	3.95	3.86	3.94	5.57	6.48	4.92
25	3.44	2.99	3.46	4.45	5.11	4.31
26	3.82	4.64	3.92	5.04	5.99	5.14
28	2.68	3.09	1.49	3.48	3.31	4.16
32	4.10	5.68	3.70	5.51	5.42	4.48
33	4.37	6.04	3.53	6.26	4.90	5.53
38	4.48	6.13	4.65	7.74	5.65	7.00
39	5.31	8.23	5.80	8.05	5.99	8.31
Cisplatin	12.14	4.29	8.34	25.56	5.27	5.50

2.4 Docking study

A docking study was employed to predict the possible target of the most promising compounds (mentioned in Table 1). According to our previous work,[30] a group of protein kinases, such as ALK, Pim-1, AKT, and Pak-1, were used as templates for the docking study using the C-Docker method (Table S2†). The findings suggest that all the tested compounds could have a high affinity towards the ATP-binding site of both ALK and Pim-1 kinases by forming strong bonds with several amino acids, with the exception of compound **18**, which shows higher affinity to Pim-1 kinase (all the 2D interaction diagrams are provided in the ESI, Table S2†). The CDocker interaction energy of the tested compounds varied between −41.1687 and −58.5523 for ALK and between −47.3708 and −77.4483 for Pim-1. The docking results of the studied compounds show the key role of aminodiol, pyrimidine and triazole in forming hydrogen bonding and ionic interactions with the key amino acids.

3 Experimental

Reagents were obtained from commercial suppliers and used without further purification (Molar Chemicals Ltd, Halásztelek, Hungary; Merck Ltd, Budapest, Hungary, and VWR International Ltd, Debrecen, Hungary), while solvents were distilled and dried with several different drying agents following the standard procedures before use (Williams and Lawton 2010). Optical rotations were measured in MeOH at 20 °C with a PerkinElmer 341 polarimeter (PerkinElmer Inc., Shelton, CT, USA). Chromatographic separations and monitoring of reactions were carried out on Merck Kieselgel 60 (Merck Ltd, Budapest, Hungary). The HR-MS flow injection analysis was performed with a Thermo Scientific Q Exactive Plus hybrid quadrupole-Orbitrap (Thermo Fisher Scientific, Waltham, MA, USA) mass spectrometer coupled to a Waters Acquity I-Class UPLC™ (Waters, Manchester, UK). Melting points were determined on a Kofler apparatus (Nagema, Dresden, Germany) and were uncorrected.

^{1}H- and ^{13}C *J*-MOD NMR spectra were recorded on a Brucker Avance DRX 500 spectrometer (Bruker Biospin, Karlsruhe, Baden Württemberg, Germany) [500 MHz (^{1}H) and 125 MHz (^{13}C *J*-MOD), $\delta = 0$ (TMS)]. Chemical shifts are expressed in ppm (δ) relative to TMS as the internal reference. *J* values are given by Hz. The ^{1}H, ^{13}C *J*-MOD, ^{19}F *J*-MOD, COSY, NOESY, HSQC and HMBC NMR spectra of the new compounds are available in the ESI.†

Gibberellic acid **1** is commercially available from Merck Co with ee% > 98%, chemical purity >90% ($[\alpha]_D^{20}$ = +78.0, *c* 2.0, MeOH). Since none of the applied transformations reach all the chiral centers at the same time, we believe that the enantiomer purity of all prepared compounds can be defined as ee ≥ 98%, similar to commercial gibberellic acid.

allo-Gibberic acid **2** was prepared from gibberellic acid **1** according to the literature.[29,33] Compounds **3–5** were prepared as mentioned in the literature. All spectroscopic data were similar to those described therein.

3.1 Preparation of the reagents

3.1.1 The general method for the preparation of reagents R1 and R2

*3.1.1.1 Synthesis of **R1**.* Benzyl (2-aminoethyl)carbamate (1.38 g, 7.11 mmol) was dissolved in EtOH (60 mL), then 2,4-dichloro-5-fluoropyrimidine (1.18 g, 7.11 mmol, 1 equ.) and triethylamine (4.9 mL, 4.9 equ.) were added. After being stirred under reflux for 2 hours, the mixture was evaporated to dryness. The residue was diluted with water (50 mL) and extracted with EtOAc (3 × 50 mL). The organic phase was washed with brine solution (50 mL), dried over Na_2SO_4, filtered and evaporated. The crude product was purified by column chromatography using *n*-hexane : EtOAc (1 : 1) as eluent (Scheme 5).

*3.1.1.2 Benzyl (2-((2-chloro-5-fluoropyrimidin-4-yl)amino) ethyl)carbamate **R1**.* Yield: 54%; white crystals; m.p.: 116–118 °C; ^{1}H NMR (500 MHz, DMSO-d$_6$): δ = 8.13 (s, 1H), 8.05 (d, J = 2.7 Hz, 1H), 7.38–7.28 (m, 6H), 5.02 (s, 2H), 3.42 (q, J = 6.0 Hz, 2H), 3.22 ppm (q, J = 6.1 Hz, 2H); ^{13}C{1H} *J*-MOD NMR (125 MHz, DMSO-d$_6$): δ = 156.7, 154.2 (d, $J_{F,C}$ = 14.9 Hz), 153.9 (d, $J_{F,C}$ = 2.2 Hz), 145.7 (d, $J_{F,C}$ = 255.9 Hz), 139.9 (d, $J_{F,C}$ = 20.1 Hz), 137.6, 128.8 (3C), 128.2 (2C), 65.8, 40.51, 40.31 ppm; ^{19}F *J*-MOD NMR (470 MHz, DMSO-d$_6$): δ = −157.4 (C$_{q\text{-}F}$); HR-MS (ESI): *m*/*z* calcd for $C_{14}H_{15}ClFN_4O_2$ [M + H]$^+$: 325.0867; found: 325.0858.

*3.1.1.3 Synthesis of **R2**.* Compound **R1** (1.00 g, 3.08 mmol) was dissolved in EtOH (20 mL) then 4-trifluoromethylaniline (0.49 g, 3.08 mmol, 1 equ.) was added. The mixture was stirred under reflux for 24 hours. After that, the mixture was evaporated to dryness, and the crude product was purified by column chromatography using *n*-hexane : EtOAc (1 : 1) as eluent.

*3.1.1.4 Benzyl (2-((5-fluoro-2-((4-(trifluoromethyl)phenyl) amino)pyrimidin-4-yl)amino)ethyl)carbamate **R2**.* Yield: 51%; white crystals; m.p.: 160–161 °C; ^{1}H NMR (500 MHz, DMSO-d$_6$): δ = 9.48 (s, 1H), 7.95–7.91 (m, 3H), 7.57 (d, J = 8.4 Hz, 2H), 7.53 (s, 1H), 7.35–7.27 (m, 6H), 5.01 (s, 2H), 3.50 (q, J = 6.0 Hz, 2H), 3.27 ppm (q, J = 5.8 Hz, 2H); ^{13}C{1H} *J*-MOD NMR (125 MHz, DMSO-d$_6$): δ = 156.8, 155.8 (d, $J_{F,C}$ = 2.7 Hz), 152.7 (d, $J_{F,C}$ = 12.4 Hz), 145.3, 141.8 (d, $J_{F,C}$ = 248.1 Hz), 138.0 (d, $J_{F,C}$ = 19.0 Hz), 137.5, 128.8 (3C), 128.2 (2C), 126.4 (q, $J_{F,C}$ = 272.3 Hz), 126.1 (q, $J_{F,C}$ = 4.1 Hz, 2C), 120.6 (q, $J_{F,C}$ = 30.8 Hz), 117.9 (2C), 65.7, 40.6, 40.3 ppm; ^{19}F *J*-MOD NMR (470 MHz, DMSO-d$_6$): δ = −59.7 (C$_{q\text{-}F}$), −165.9 (C$_{q\text{-}F}$); HR-MS (ESI): *m*/*z* calcd for $C_{21}H_{20}F_4N_5O_2$ [M + H]$^+$: 450.1553; found: 450.1540.

3.1.2 The general method for the preparation of reagents R3 and R4

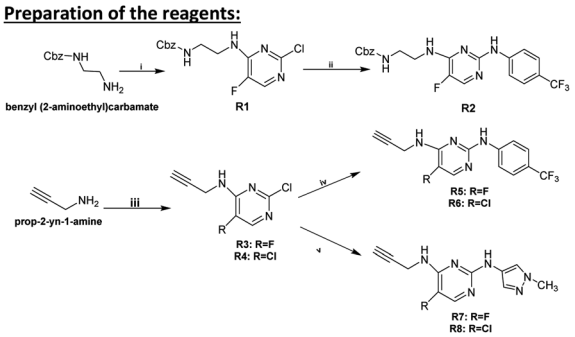
To a solution of substituted pyrimidines (5.92 mmol, Scheme 5) in MeCN (6 mL), propargylamine (1.5 equ.) and triethylamine (1 mL, 4.8 equ.) were added, and the mixture was stirred for 24 hours at room temperature. The mixture was then evaporated to dryness, and the residue was diluted with water (10 mL) and extracted with EtOAc (3 × 10 mL). The organic phase was washed with brine solution (3 × 10 mL), dried over Na_2SO_4, filtered, and evaporated. The crude product was purified by column chromatography using *n*-hexane : EtOAc (4 : 1) as eluent.

*3.1.2.1 2-Chloro-5-fluoro-N-(prop-2-yn-1-yl)pyrimidin-4-amine **R3**.* Prepared with 2,4-dichloro-5-fluoropyrimidine, yield: 65%; white crystals; m.p.: 102–104 °C; ^{1}H NMR (500 MHz, DMSO-d$_6$): δ = 8.59 (t, J = 5.0 Hz, 1H), 8.14 (d, J = 3.2 Hz, 1H), 4.14 (dd, J = 2.2, 5.6 Hz, 2H), 3.14 ppm (t, J = 2.3 Hz, 1H); ^{13}C{1H} *J*-MOD NMR (125 MHz, DMSO-d$_6$): δ = 153.8 (d, $J_{F,C}$ = 2.8 Hz), 153.4 (d, $J_{F,C}$ = 13.2 Hz), 145.8 (d, $J_{F,C}$ = 256 Hz), 140.8 (d, $J_{F,C}$ = 20.2 Hz), 80.7, 73.8, 29.9 ppm; ^{19}F *J*-MOD NMR (470 MHz, DMSO-d$_6$): δ = −157.0 (C$_{q\text{-}F}$); HR-MS (ESI): *m*/*z* calcd for $C_7H_6ClFN_3$ [M + H]$^+$: 186.0234; found: 186.0227.

*3.1.2.2 2,5-Dichloro-N-(prop-2-yn-1-yl)pyrimidin-4-amine **R4**.* Prepared with 2,4,5-trichloropyrimidine, yield: 88%; white crystals; m.p.: 100.2–102.9 °C; ^{1}H NMR (500 MHz, DMSO-d$_6$): δ = 8.33 (t, J = 4.8 Hz, 1H), 8.24 (s, 1H), 4.14 (dd, J = 2.7, 2.7 Hz, 2H), 3.11 ppm (t, J = 2.4 Hz, 1H); ^{13}C{1H} *J*-MOD NMR (125 MHz, DMSO-d_6): δ = 158.8, 157.8, 154.7, 113.6, 80.8, 73.5, 30.5 ppm; HR-MS (ESI): *m*/*z* calcd for $C_7H_6Cl_2N_3$ [M + H]$^+$: 201.9938; found: 201.9932.

3.1.3 General procedure for the preparation of N^2-substituted pyrimidines (reagents R5, R6, R7, R8).

To a solution of reagent **R3** or **R4** (0.40 g, Scheme 5) in EtOH (8 mL), either 4-



Scheme 5 Synthesis of reagents **R1–R8**. (i) 2,4-Dichloro-5-fluoropyrimidine (1 equ.), triethylamine (4.9 equ.), EtOH, reflux, 2 h, 54%; (ii) 4-trifluoromethylaniline (1 equ.), EtOH, reflux, 24 h, 51%; (iii) 2,4-dichloro-5-fluoropyrimidine or 2,4,5-trichloropyrimidine (0.6 equ.), triethylamine (4.8 equ.), MeCN, 25 °C, 24 h, **R3** (65%), **R4** (88%); (iv) 4-trifluoromethylaniline (1.1 equ.), EtOH, MW, 150 °C, 200 W, 19 bar, 2 h, **R5** (58%), **R6** (52%); (iv) 1-methyl-1*H*-pyrazol-4-amine (1.1 equ.), EtOH, MW, 150 °C, 200 W, 19 bar, 2 h, **R7** (91%), **R8** (50%).

trifluoromethylaniline or 1-methyl-1*H*-pyrazol-4-amine (1.1 equ.) was added. Then, the mixture was heated in a microwave reactor at 150 °C, 200 W, and 19 bar for 2 hours. After the completion of the reaction, the mixture was evaporated to dryness. The crude product was purified by column chromatography using different eluents: *n*-hexane : EtOAc (4 : 1) for **R5**, *n*-hexane : EtOAc (2 : 1) for **R6**, and $CHCl_3$: MeOH (19 : 1) for **R7** and **R8**.

*3.1.3.1 5-Fluoro-N^4-(prop-2-yn-1-yl)-N^2-(4-(trifluoromethyl) phenyl)pyrimidine-2,4-diamine **R5**.* Prepared with **R3** and 4-trifluoromethylaniline, yield: 58%; white crystals; m.p.: 188–192 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.59 (s, 1H), 8.00–7.96 (m, 4H), 7.55 (d, J = 8.5 Hz, 2H), 4.16 (d, J = 4.0 Hz, 2H), 3.14 ppm (s, 1H); ^{13}C{1H} *J*-MOD NMR (125 MHz, DMSO-d_6): δ = 155.7 (d, $J_{F,C}$ = 3.1 Hz), 152.0 (d, $J_{F,C}$ = 12.4 Hz), 144.0 (d, $J_{F,C}$ = 301.2 Hz), 140.8, 139.7 (d, $J_{F,C}$ = 18.9 Hz), 126.1 (q, $J_{F,C}$ = 6.1 Hz, 2C), 123.3 (q, $J_{F,C}$ = 270.8 Hz), 120.6 (q, $J_{F,C}$ = 33.2 Hz), 118.0 (2C), 81.7, 73.2, 28.9 ppm; ^{19}F *J*-MOD NMR (470 MHz, DMSO-d_6): δ = −59.7 ($C_{q\text{-}F}$), −165.9 ($C_{q\text{-}F}$); HR-MS (ESI): *m*/*z* calcd for $C_{14}H_{11}F_4N_4$ $[M + H]^+$: 311.0919; found: 311.0908.

*3.1.3.2 5-Chloro-N^4-(prop-2-yn-1-yl)-N^2-(4-(trifluoromethyl) phenyl)pyrimidine-2,4-diamine **R6**.* Prepared with **R4** and 4-trifluoromethylaniline, yield: 52%; white crystals; m.p.: 158–160 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.73 (s, 1H), 8.06 (s, 1H), 8.01 (d, J = 8.5 Hz, 2H), 7.71 (t, J = 5.5 Hz, 1H), 7.57 (d, J = 8.5 Hz, 2H), 4.16 (d, J = 4.0 Hz, 2H), 3.12 ppm (s, 1H); ^{13}C{1H} *J*-MOD NMR (125 MHz, DMSO-d_6): δ = 158.0, 157.6, 153.9, 144.8, 126.0 (q, $J_{F,C}$ = 4.1 Hz, 2C), 124.1 (q, $J_{F,C}$ = 276.8 Hz), 121.2 (q, $J_{F,C}$ = 32.2 Hz), 118.6 (2C), 105.2, 81.9, 73.0, 43.4 ppm; ^{19}F *J*-MOD NMR (470 MHz, DMSO-d_6): δ = −59.8 ($C_{q\text{-}F}$); HR-MS (ESI): *m*/*z* calcd for $C_{14}H_{11}ClF_3N_4$ $[M + H]^+$: 327.0624; found: 327.0613.

*3.1.3.3 5-Fluoro-N^2-(1-methyl-1H-pyrazol-4-yl)-N^4-(prop-2-yn-1-yl)pyrimidine-2,4-diamine **R7**.* Prepared with **R3** and 1-methyl-1*H*-pyrazol-4-amine, yield: 91%; white crystals; m.p.: 166–169 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.89 (s, 1H), 7.86 (d, J = 5.0 Hz, 2H), 7.72 (t, J = 5.3 Hz, 1H), 7.45 (s, 1H), 4.15–4.12 (m, 2H), 3.76 (s, 3H), 3.10 ppm (s, 1H); ^{13}C{1H} *J*-MOD NMR (125 MHz, DMSO-d_6): δ = 156.0 (d, $J_{F,C}$ = 1.7 Hz), 152.1 (d, $J_{F,C}$ = 12.4 Hz), 141.8, 139.8 (d, $J_{F,C}$ = 27.1 Hz), 129.9, 124.5, 120.2, 82.1, 73.1, 39.0, 29.7 ppm; ^{19}F *J*-MOD NMR (470 MHz, DMSO-d_6): δ = −169.9 ($C_{q\text{-}F}$); HR-MS (ESI): *m*/*z* calcd for $C_{11}H_{12}FN_6$ $[M + H]^+$: 247.1107; found: 247.1098.

*3.1.3.4 5-Chloro-N^2-(1-methyl-1H-pyrazol-4-yl)-N^4-(prop-2-yn-1-yl)pyrimidine-2,4-diamine **R8**.* Prepared with **R4** and 1-methyl-1*H*-pyrazol-4-amine, yield: 50%; white crystals; m.p.: 194–196 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.07 (s, 1H), 7.93–7.89 (m, 2H), 7.50–7.45 (m, 2H), 4.14 (d, J = 3.8 Hz, 2H), 3.77 (s, 3H), 3.09 ppm (s, 1H); ^{13}C{1H} *J*-MOD NMR (125 MHz, DMSO-d_6): δ = 158.1, 158.0, 157.7, 154.0, 130.2, 124.0, 120.6, 82.2, 72.9, 39.1, 30.3 ppm; HR-MS (ESI): *m*/*z* calcd for $C_{11}H_{12}ClN_6$ $[M + H]^+$: 263.0811; found: 263.0802.

3.1.4 Preparation of triol 6. To a solution of compound **5** (2.00 g, 7.39 mmol) and selenium dioxide (0.40 g, 3.69 mmol, 0.5 equ.) in dry THF (150 mL), 70% *tert*-butyl hydroperoxide aqueous solution (2.84 mL, 1.99 g, 22.17 mmol, 3 equ.) was added. Then, the mixture was stirred at 40 °C overnight. After completion of the reaction (as shown by TLC), the reaction mixture was concentrated. The residue was then purified *via* column chromatography on silica gel using $CHCl_3$: MeOH (9 : 1) as eluent to obtain compound **6** as a white solid (1.40 g, 66%).

*3.1.4.1 (4bR,7S,9S,9aR,10S)-10-(Hydroxymethyl)-1-methyl-8-methylene-4b,5,6,8,9,10-hexahydro-7H-7,9a-methanobenzo[a] azulene-7,9-diol **6**.* Yield: 66%; R_f = 0.4, white crystals; m.p.: 165.6–168.2 °C; $[\alpha]_D^{20}$ = −72.5 (*c* 0.18, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.00 (t, J = 7.1 Hz, 1H), 6.89 (d, J = 7.2 Hz, 1H), 6.84 (d, J = 7.2 Hz, 1H), 5.30 (d, J = 5.2 Hz, 1H), 5.06 (s, 1H), 5.04 (t, J = 4.6 Hz, 1H), 5.00 (s, 1H), 4.96 (s, 1H), 4.11–3.97 (m, 2H), 3.54 (d, J = 4.3 Hz, 1H), 3.04 (t, J = 3.9 Hz, 1H), 2.49–2.46 (m, 1H), 2.45 (s, 3H), 2.31 (d, J = 10.5 Hz, 1H), 2.08–2.00 (m, 1H), 1.81–1.73 (m, 1H), 1.56–1.44 (m, 2H), 1.21–1.13 ppm (m, 1H); ^{13}C{1H} *J*-MOD NMR (125 MHz, DMSO-d_6): δ = 161.4, 145.2, 142.1, 134.3, 129.4, 126.1, 119.4, 106.8, 78.1, 78.7, 58.8, 58.3, 54.4, 51.7, 45.1, 40.09, 21.7, 19.8; HR-MS (ESI): *m*/*z* calcd for $C_{18}H_{21}O_2$ $[M - H_2O]^+$: 269.1541; found: 269.1537.

3.1.5 Preparation of compound 7 (diol protection). Triol **6** (1.00 g, 3.49 mmol) was dissolved in dry acetone (100 mL), then *p*-toluene sulfonic acid (66.00 mg) was added, and the reaction mixture was stirred at room temperature overnight. The mixture was concentrated under a vacuum to dryness. The crude product was purified by column chromatography on silica gel using *n*-hexane : EtOAc (2 : 1) as an eluent to get compound **7** as a white solid (1.00 g, 87.7%).

*3.1.5.1 (4aR,4a1R,6S,12bS)-3,3,12-Trimethyl-5-methylene-4a,5,7,8,8a,12b-hexahydro-4a1,6-methanobenzo[2,3]azuleno[8,1-de][1,3]dioxepin-6(1H)-ol **7**.* Yield: 87.7%; R_f = 0.6, white crystals; m.p.: 188.1–190.9 °C; $[\alpha]_D^{20}$ = −106.0 (*c* 0.18, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.07 (t, J = 7.5 Hz, 1H), 6.95 (d, J = 7.5 Hz, 1H), 6.88 (d, J = 7.5 Hz, 1H), 5.29 (s, 1H), 5.06 (s, 1H), 4.26–4.16 (m, 2H), 4.03 (s, 1H), 3.12 (s, 1H), 2.74 (dd, J = 5.1, 13.2 Hz, 1H), 2.44 (s, 4H), 2.20–2.14 (m, 1H), 1.98–1.91 (m, 1H), 1.79–1.74 (m, 1H), 1.68 (d, J = 10.1 Hz, 1H), 1.45–1.35 (m, 1H), 1.29 (s, 3H), 1.08 ppm (s, 3H); ^{13}C{1H} *J*-MOD NMR (125 MHz, $CDCl_3$): δ = 158.6, 143.9, 140.9, 135.3, 129.2, 126.2, 118.8, 108.7, 101.0, 79.2, 74.9, 56.8, 55.4, 52.5, 50.9, 46.5, 39.1, 26.8, 24.4, 21.7, 20.6; HR-MS (ESI): *m*/*z* calcd for $C_{21}H_{27}O_3$ $[M + H]^+$: 327.1960; found: 327.1956.

3.1.6 Preparation of epoxyalcohol 8

3.1.6.1 Method A. To a solution of **7** (2.00 g, 6.12 mmol) in DCM (100 mL), *m*-CPBA (3.16 g, 18.36 mmol, 3 equ., 70% purity) was added. After stirring for 4 hours at room temperature (indicated by TLC), the mixture was washed with a saturated solution of Na_2SO_3 (3 × 50 mL). The organic phase was then dried over Na_2SO_4, filtered, and evaporated. The crude product was purified by column chromatography using *n*-hexane : EtOAc (1 : 1) as eluent.

3.1.6.2 Method B. To a solution of **7** (2.00 g, 6.12 mmol) in dry toluene (200 mL), $VO(acac)_2$ (20 mg) was added, and the green solution was stirred at 0 °C for 30 minutes. Then, *t*-BuOOH (extracted from its 70% H_2O solution with toluene and dried over Na_2SO_4, 9.18 mmol, 1.5 equ.) was added dropwise to the former solution and the mixture turned to dark red and then faded to orange as the reaction proceeded. The reaction mixture was stirred at 70 °C overnight. A saturated solution of $NaHCO_3$ (30 mL) was added, followed by extraction with toluene (3 × 30

mL). The organic phase was washed with brine (3 × 30 mL), dried over Na_2SO_4 and then evaporated at low pressure. The crude product was purified by column chromatography using *n*-hexane : EtOAc (1 : 1) as eluent.

*3.1.6.3 (2R,4a′S,4a^{1}′R,6′S,12b′S)-3′,3′,12′-Trimethyl-7′,8′,8a′,12b′-tetrahydro-4a′H-spiro[oxirane-2,5′-[4a^{1},6]methanobenzo[2,3]azuleno[8,1-de][1,3]dioxepin]-6′(1′H)-ol **8**.* Yield: A: 65%, B: 55%; R_f = 0.5, white crystals; m.p.: 173.2–175.9 °C; $[\alpha]_D^{20}$ = −90.5 (*c* 0.17, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.08 (t, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 7.4 Hz, 1H), 6.90 (d, *J* = 7.4 Hz, 1H), 4.24–4.22 (m, 2H), 3.75 (s, 1H), 3.18 (s, 1H), 2.89 (s, 2H), 2.77 (dd, *J* = 5.1, 13.2 Hz, 1H), 2.52 (dd, *J* = 2.1, 10.5 Hz, 1H), 2.44 (s, 3H), 2.41 (s, 1H), 2.33–2.26 (m, 1H), 2.04–1.96 (m, 1H), 1.77 (dd, *J* = 1.3, 10.5 Hz, 1H), 1.71–1.65 (m, 1H), 1.57–1.50 (m, 1H), 1.32 (s, 3H), 0.93 ppm (s, 3H); ^{13}C{1H} *J*-MOD NMR (125 MHz, $CDCl_3$): δ = 143.4, 140.8, 135.4, 129.4, 126.3, 118.8, 101.0, 74.0, 73.8, 65.3, 56.8, 56.5, 52.8, 50.5, 48.2, 45.9, 36.1, 26.3, 23.8, 21.1, 20.6; HR-MS (ESI): *m*/*z* calcd for $C_{18}H_{21}O_3$ [M − C_3H_4–H_2O]$^+$: 285.1490; found: 285.1483.

3.1.7 Preparation of azidodiol 29. To a solution of epoxide **8** (0.99 g, 2.92 mmol) in ethanol/water = 8 : 2 (100 mL), NaN_3 (0.95 g, 14.6 mmol, 5 equ.) and NH_4Cl (0.39 g, 7.29 mmol, 2.49 equ.) were added. After treatment under reflux conditions for 48 h, the reaction mixture was cooled to room temperature, and then ethanol was evaporated. The residue was dissolved in water (50 mL) and extracted with Et_2O (3 × 50 mL). The organic phase was washed with a brine solution, dried over Na_2SO_4, and then evaporated. The compound was purified by flash column chromatography on silica gel (eluted with *n*-nexane : EtOAc = 1 : 1) to provide azido diol.

*3.1.7.1 (4aR,4a^{1}R,5R,6S,12bS)-5-(Azidomethyl)-3,3,12-trimethyl-4a,5,7,8,8a,12b-hexahydro-4a^{1},6-methanobenzo[2,3]azuleno[8,1-de][1,3]dioxepine-5,6(1H)-diol **29**.* Yield: 71%; R_f = 0.7, white crystals; m.p.: 175.1–176.9 °C; $[\alpha]_D^{20}$ = +64.5 (*c* 0.15, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.09 (t, *J* = 7.4 Hz, 1H), 6.97 (d, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 7.3 Hz, 1H), 4.61 (s, 1H), 4.24–4.22 (m, 2H), 3.84 (s, 1H), 3.54 (d, *J* = 12.8 Hz, 1H), 3.24–3.17 (m, 2H), 3.15 (d, *J* = 12.8 Hz, 1H), 2.76 (dd, *J* = 5.6, 13.1 Hz, 1H), 2.46 (d, *J* = 11.2 Hz, 1H), 2.41 (s, 3H), 2.34–2.26 (m, 1H), 2.05–1.93 (m, 1H), 1.77 (dd, *J* = 5.3, 13.7 Hz, 1H), 1.51 (dd, *J* = 2.3, 10.9 Hz, 1H), 1.48–1.40 (m, 1H), 1.38 (s, 3H), 0.94 ppm (s, 3H); ^{13}C{1H} *J*-MOD NMR (125 MHz, $CDCl_3$): δ = 143.0, 140.6, 135.6, 129.5, 126.5, 118.8, 101.3, 80.3, 79.0, 75.4, 57.4, 55.3, 52.9, 52.6, 51.3, 46.0, 31.3, 27.5, 23.6, 21.1, 20.6; HR-MS (ESI): *m*/*z* calcd for $C_{21}H_{27}N_3O_4Na$ [M + Na]$^+$: 408.1899; found: 408.1889.

3.1.8 General procedure for aminolysis (preparation of compounds 9–18). To a solution of epoxide **8** (100 mg, 0.29 mmol) in MeCN (15.0 mL), $LiClO_4$ (70 mg, 0.65 mmol, 2.25 equ.) and appropriate amines (0.65 mmol, 2.25 equ.) were added. The reaction mixture was treated under reflux for 48 h at 70–80 °C before the solvent was evaporated. The residue was diluted with water (15 mL) and then extracted with DCM (3 × 15 mL). The organic phase was washed with brine (3 × 30 mL), dried over Na_2SO_4 and then evaporated at low pressure. The crude product was purified by column chromatography on silica gel ($CHCl_3$: MeOH = 19 : 1), followed by the second column chromatography using *n*-hexane : EtOAc = 1 : 2 as eluent.

*3.1.8.1 (4aS,4a^{1}R,5R,6S,12bS)-5-((Benzylamino)methyl)-3,3,12-trimethyl-4a,5,7,8,8a,12b-hexahydro-4a^{1},6-methanobenzo[2,3]azuleno[8,1-de][1,3]dioxepine-5,6(1H)-diol **9**.* Prepared with benzylamine, yield: 85%; R_f = 0.8 ($CHCl_3$: MeOH = 19 : 1), white wax; m.p.: 127–130 °C; $[\alpha]_D^{20}$ = −50.9 (*c* 0.18, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29–7.22 (m, 5H), 7.09 (t, *J* = 7.4 Hz, 1H), 6.97 (d, *J* = 7.4 Hz, 1H), 6.87 (d, *J* = 7.4 Hz, 1H), 4.39 (s, 1H), 4.22 (s, 2H), 3.83 (s, 1H), 3.77 (s, 2H), 3.17 (s, 1H), 2.84 (d, *J* = 11.4 Hz, 1H), 2.75–2.67 (m, 2H), 2.47 (d, *J* = 10.8 Hz, 1H), 2.41 (s, 3H), 2.24–2.15 (m, 1H), 1.94–1.86 (m, 1H), 1.80 (dd, *J* = 5.1, 13.5 Hz, 1H), 1.50–1.37 (m, 2H), 1.31 (s, 3H), 0.92 ppm (s, 3H); ^{13}C{1H} *J*-MOD NMR (125 MHz, $CDCl_3$): δ = 143.6, 140.9, 140.6, 135.5, 129.3, 128.3, 128.2, 128.0, 127.9, 126.8, 126.4, 118.9, 101.0, 79.1, 78.9, 76.1, 57.5, 55.5, 54.3, 53.0, 51.3, 50.6, 45.9, 31.9, 27.9, 24.0, 21.3, 20.7; HR-MS (ESI): *m*/*z* calcd for $C_{28}H_{36}NO_4$ [M + H]$^+$: 450.2644; found: 450.2634.

*3.1.8.2 (4aS,4a^{1}R,5R,6S,12bS)-5-(((4-Fluorobenzyl)amino)methyl)-3,3,12-trimethyl-4a,5,7,8,8a,12b-hexahydro-4a^{1},6-methanobenzo[2,3]azuleno[8,1-de][1,3]dioxepine-5,6(1H)-diol **10**.* Prepared with 4-fluorobenzylamine, yield: 45%; R_f = 0.7 ($CHCl_3$: MeOH = 19 : 1), white wax; m.p.: 58–60 °C; $[\alpha]_D^{20}$ = −55.9 (*c* 0.18, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.23–7.19 (m, 2H), 7.10 (t, *J* = 7.4 Hz, 1H), 6.98–6.92 (m, 3H), 6.86 (d, *J* = 7.3 Hz, 1H), 4.38 (s, 1H), 4.22 (d, *J* = 2.3 Hz, 2H), 3.81 (d, *J* = 1.4 Hz, 3H), 3.73–3.68 (m, 2H), 3.16 (s, 1H), 2.82 (d, *J* = 11.7 Hz, 1H), 2.72 (dd, *J* = 5.6, 12.9 Hz, 1H), 2.66 (d, *J* = 11.7 Hz, 1H), 2.46 (dd, *J* = 1.9, 10.5 Hz, 1H), 2.41 (s, 3H), 2.24–2.17 (m, 1H), 1.94–1.86 (m, 1H), 1.78 (dd, *J* = 5.5, 13.6 Hz, 1H), 1.49–1.36 (m, 2H), 1.31 (s, 3H), 0.91 ppm (s, 3H); ^{13}C{1H} *J*-MOD NMR (125 MHz, $CDCl_3$): δ = 161.8 (d, $J_{F,C}$ = 243.6 Hz), 143.5, 140.8, 136.3 (d, $J_{F,C}$ = 3.6 Hz), 135.5, 129.4, 129.3 (d, $J_{F,C}$ = 4.1 Hz, 2C), 126.4, 118.8, 115.0 (d, $J_{F,C}$ = 20.3 Hz, 2C), 101.0, 79.0, 78.9, 76.2, 57.5, 55.5, 53.8, 53.0, 51.3, 50.5, 45.9, 31.8, 27.8, 23.9, 21.3, 20.6; ^{19}F *J*-MOD NMR (470 MHz, $CDCl_3$): δ = −116.3 ($C_{q\text{-}F}$) ppm; HR-MS (ESI): *m*/*z* calcd for $C_{28}H_{35}FNO_4$ [M + H]$^+$: 468.2550; found: 468.2533.

*3.1.8.3 (4aS,4a^{1}R,5R,6S,12bS)-5-(((4-Methoxybenzyl)amino)methyl)-3,3,12-trimethyl-4a,5,7,8,8a,12b-hexahydro-4a^{1},6-methanobenzo[2,3]azuleno[8,1-de][1,3]dioxepine-5,6(1H)-diol **11**.* Prepared with 4-methoxybenzylamine, yield: 46%; R_f = 0.7 ($CHCl_3$: MeOH = 19 : 1), white wax; m.p.: 133–134 °C; $[\alpha]_D^{20}$ = −57.3 (*c* 0.18, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.18 (d, *J* = 7.8 Hz, 2H), 7.09 (t, *J* = 7.4 Hz, 1H), 6.97 (d, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 7.5 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 2H), 4.22 (s, 2H), 3.80–3.71 (m, 6H), 3.16 (s, 1H), 2.85 (d, *J* = 12.0 Hz, 1H), 2.76–2.67 (m, 2H), 2.47 (d, *J* = 10.1 Hz, 1H), 2.41 (s, 3H), 2.23–2.17 (m, 1H), 1.94–1.85 (m, 1H), 1.82–1.77 (m, 1H), 1.49–1.38 (m, 2H), 1.31 (s, 3H), 0.90 ppm (s, 3H); ^{13}C{1H} *J*-MOD NMR (125 MHz, $CDCl_3$): δ = 158.6, 143.5, 140.9, 135.5, 129.3, 129.2, 129.2 126.4, 118.8, 113.7, 113.7, 101.04, 79.1, 78.8, 76.2, 57.5, 55.5, 55.2, 53.7, 53.0, 51.4, 50.4, 45.9, 31.9, 27.9, 23.9, 21.3, 20.6; HR-MS (ESI): *m*/*z* calcd for $C_{29}H_{38}NO_5$ [M + H]$^+$: 480.2749; found: 480.2735.

*3.1.8.4 (4aS,4a^{1}R,5R,6S,12bS)-3,3,12-Trimethyl-5-(((naphthalen-1-ylmethyl)amino)methyl)-4a,5,7,8,8a,12b-hexahydro-4a^{1},6-methanobenzo[2,3]azuleno[8,1-de][1,3]dioxepine-5,6(1H)-diol **12**.* Prepared with 1-naphthylmethylamine, yield: 62%; R_f = 0.6 ($CHCl_3$: MeOH = 19 : 1), colourless oily compound; $[\alpha]_D^{20}$ =

−31.0 (*c* 0.19, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 8.2 Hz, 1H), 7.82 (d, *J* = 7.9 Hz, 1H), 7.74 (d, *J* = 7.9 Hz, 1H), 7.46–7.35 (m, 4H), 7.10 (t, *J* = 7.4 Hz, 1H), 6.97 (d, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 7.2 Hz, 1H), 4.25–4.17 (m, 4H), 3.84 (s, 1H), 3.15 (s, 1H), 2.96 (d, *J* = 11.7 Hz, 1H), 2.82 (d, *J* = 11.8 Hz, 1H), 2.72 (dd, *J* = 6.3, 13.5 Hz, 1H), 2.47 (d, *J* = 10.1 Hz, 1H), 2.41 (s, 3H), 2.24–2.15 (m, 1H), 1.93–1.84 (m, 1H), 1.78 (dd, *J* = 6.1, 14.2 Hz, 1H), 1.51–1.41 (m, 2H), 1.25 (s, 3H), 0.82 ppm (s, 3H); ^{13}C{1H} *J*-MOD NMR (125 MHz, $CDCl_3$): δ = 143.5, 140.9, 136.0, 135.5, 133.7, 131.8, 129.3, 128.5, 127.6, 126.4, 125.8, 125.6, 125.5, 125.2, 123.9, 118.8, 101.0, 79.1, 79.0, 76.2, 57.5, 55.5, 53.0, 52.3, 51.4, 51.2, 45.9, 31.9, 27.8, 23.8, 21.3, 20.6; HR-MS (ESI): *m*/*z* calcd for $C_{32}H_{38}NO_4$ $[M + H]^+$: 500.2800; found: 500.2789.

*3.1.8.5 (4aS,4a^{1}R,5R,6S,12bS)-3,3,12-Trimethyl-5-((((S)-1-(naphthalen-2-yl)ethyl)amino)methyl)-4a,5,7,8,8a,12b-hexahydro-4a^1,6-methanobenzo[2,3]azuleno[8,1-de][1,3]dioxepine-5,6(1H)-diol **13**.* Prepared with (*S*)-(−)-1-(2-naphthyl)ethylamine, yield: 63%; R_f = 0.5 ($CHCl_3$: MeOH = 19 : 1), white crystals; m.p.: 126–129 °C; $[\alpha]_D^{20}$ = −102.1 (*c* 0.16, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.84–7.76 (m, 3H), 7.68 (s, 1H), 7.47–7.43 (m, 3H), 7.06 (t, *J* = 7.4 Hz, 1H), 6.95 (d, *J* = 7.5 Hz, 1H), 6.82 (d, *J* = 7.2 Hz, 1H), 4.32 (s, 1H), 4.24–4.21 (m, 2H), 3.82 (q, *J* = 6.5 Hz, 1H), 3.75 (s, 1H), 3.16 (s, 1H), 2.73–2.67 (m, 2H), 2.61 (d, *J* = 11.6 Hz, 1H), 2.49 (d, *J* = 10.5 Hz, 1H), 2.41 (s, 3H), 2.16–2.08 (m, 1H), 1.88–1.80 (m, 1H), 1.76 (dd, *J* = 5.4, 13.2 Hz, 1H), 1.44 (d, *J* = 10.8 Hz, 1H), 1.39–1.34 (m, 4H), 1.33 (s, 3H), 0.91 ppm (s, 3H); ^{13}C{1H} *J*-MOD NMR (125 MHz, $CDCl_3$): δ = 143.5, 143.2, 140.9, 135.5, 133.4, 132.8, 129.3, 128.2, 127.69, 127.66, 126.3, 125.9, 125.4, 125.1, 124.7, 118.8, 100.9, 78.2, 78.9, 76.4, 59.0, 57.5, 55.4, 53.0, 51.5, 49.5, 46.0, 32.0, 27.9, 24.1, 23.9, 21.3, 20.6; HR-MS (ESI): *m*/*z* calcd for $C_{33}H_{40}NO_4$ $[M + H]^+$: 514.2957; found: 514.2942.

*3.1.8.6 (4aS,4a^{1}R,5R,6S,12bS)-3,3,12-Trimethyl-5-((((R)-1-(naphthalen-2-yl)ethyl)amino)methyl)-4a,5,7,8,8a,12b-hexahydro-4a^1,6-methanobenzo[2,3]azuleno[8,1-de][1,3]dioxepine-5,6(1H)-diol **14**.* Prepared with (*R*)-(−)-1-(2-naphthyl)ethylamine, yield: 68%; R_f = 0.5 ($CHCl_3$: MeOH = 19 : 1), white crystals; m.p.: 158–160 °C; $[\alpha]_D^{20}$ = −60.8 (*c* 0.16, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.84–7.80 (m, 1H), 7.70 (d, *J* = 8.7 Hz, 1H), 7.66 (s, 1H), 7.63–7.59 (m, 1H), 7.47–7.44 (m, 2H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.01 (d, *J* = 7.5 Hz, 1H), 6.65 (d, *J* = 7.2 Hz, 1H), 4.50 (s, 1H), 4.24 (d, *J* = 2.1 Hz, 2H), 3.95 (s, 1H), 3.87 (q, *J* = 6.7 Hz, 1H), 3.15 (s, 1H), 2.72 (d, *J* = 11.7 Hz, 1H), 2.61 (dd, *J* = 5.9, 13.0 Hz, 1H), 2.54 (d, *J* = 12.8 Hz, 1H), 2.44 (s, 3H), 2.44–2.40 (m, 1H), 1.93–1.85 (m, 1H), 1.81–1.72 (m, 1H), 1.59–1.56 (m, 1H), 1.42 (dd, *J* = 1.8, 10.3 Hz, 1H), 1.38 (s, 3H), 1.32 (d, *J* = 6.6 Hz, 3H), 1.10 (s, 3H), 1.08–0.98 ppm (m, 1H); ^{13}C {1H} *J*-MOD NMR (125 MHz, $CDCl_3$): δ = 143.6, 143.4, 140.8, 135.4, 133.4, 132.7, 129.3, 128.1, 127.9, 127.5, 126.3, 125.8, 125.3, 125.0, 1224.8, 118.9, 101.1, 79.3, 78.8, 76.1, 58.4, 57.5, 55.5, 53.0, 51.0, 48.3, 45.9, 31.6, 27.9, 25.1, 24.2, 21.0, 20.6; HR-MS (ESI): *m*/*z* calcd for $C_{33}H_{40}NO_4$ $[M + H]^+$: 514.2957; found: 514.2941.

*3.1.8.7 (4aS,4a^{1}R,5R,6S,12bS)-3,3,12-Trimethyl-5-((((S)-1-(naphthalen-1-yl)ethyl)amino)methyl)-4a,5,7,8,8a,12b-hexahydro-4a^1,6-methanobenzo[2,3]azuleno[8,1-de][1,3]dioxepine-5,6(1H)-diol **15**.* Prepared with (*S*)-(−)-1-(1-naphthyl)ethylamine, yield: 59%; R_f = 0.5 ($CHCl_3$: MeOH = 19 : 1), white crystals; m.p.: 177–179 °C; $[\alpha]_D^{20}$ = −68.2 (*c* 0.18, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 8.5 Hz, 1H), 7.87–7.84 (m, 1H), 7.73 (d, *J* = 8.2 Hz, 1H), 7.57 (d, *J* = 7.0 Hz, 1H), 7.48–7.43 (m, 3H), 7.07 (t, *J* = 7.4 Hz, 1H), 6.96 (d, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 7.3 Hz, 1H), 4.53 (q, *J* = 6.6 Hz, 1H), 4.37 (s, 1H), 4.24–4.21 (m, 2H), 3.81 (s, 1H), 3.16 (s, 1H), 2.83 (d, *J* = 11.7 Hz, 1H), 2.71 (dd, *J* = 5.6, 13.5 Hz, 1H), 2.64 (d, *J* = 11.4 Hz, 1H), 2.49 (d, *J* = 10.5 Hz, 1H), 2.41 (s, 3H), 2.21–2.14 (m, 1H), 1.91–1.77 (m, 2H), 1.48–1.43 (m, 2H), 1.42 (d, *J* = 6.5 Hz, 3H), 1.31 (s, 3H), 0.91 ppm (s, 3H); ^{13}C {1H} *J*-MOD NMR (125 MHz, $CDCl_3$): δ = 143.6, 141.4, 140.9, 135.5, 133.9, 131.2, 129.3, 128.9, 127.1, 126.3, 125.69, 125.64, 125.2, 123.0, 122.6, 118.8, 101.0, 79.1, 79.0, 76.4, 57.5, 55.4, 54.3, 53.0, 51.5, 49.6, 46.1, 31.9, 27.9, 23.9, 23.6, 21.3, 20.6; HR-MS (ESI): *m*/*z* calcd for $C_{33}H_{40}NO_4$ $[M + H]^+$: 514.2957; found: 514.2943.

*3.1.8.8 (4aS,4a^{1}R,5R,6S,12bS)-3,3,12-Trimethyl-5-((((R)-1-(naphthalen-1-yl)ethyl)amino)methyl)-4a,5,7,8,8a,12b-hexahydro-4a^1,6-methanobenzo[2,3]azuleno[8,1-de][1,3]dioxepine-5,6(1H)-diol **16**.* Prepared with (*R*)-(+)-1-(1-naphthyl)ethylamine, yield: 54%; R_f = 0.5 ($CHCl_3$: MeOH = 19 : 1), white crystals; m.p.: 83–86 °C; $[\alpha]_D^{20}$ = −49.9 (*c* 0.18, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 8.5 Hz, 1H), 7.86 (d, *J* = 8.2 Hz, 1H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.53 (d, *J* = 7.2 Hz, 1H), 7.44 (t, *J* = 7.1 Hz, 1H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.31 (t, *J* = 7.7 Hz, 1H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.00 (d, *J* = 7.5 Hz, 1H), 6.77 (d, *J* = 7.2 Hz, 1H), 4.57–4.50 (m, 2H), 4.24 (dd, *J* = 11.8, 13.4 Hz, 2H), 4.00 (s, 1H), 3.15 (s, 1H), 2.72 (d, *J* = 11.7 Hz, 1H), 2.64 (dd, *J* = 5.0, 12.9 Hz, 1H), 2.58 (d, *J* = 11.7 Hz, 1H), 2.44 (s, 3H), 2.43–2.41 (m, 1H) 1.98–1.91 (m, 1H), 1.80–1.71 (m, 1H), 1.52–1.52 (m, 1H), 1.44–1.42 (m, 1H), 1.42 (d, *J* = 6.4 Hz, 3H), 1.38 (s, 3H), 1.15–1.07 (m, 1H), 1.05 ppm (s, 3H); ^{13}C{1H} *J*-MOD NMR (125 MHz, $CDCl_3$): δ = 143.7, 141.2, 140.8, 135.4, 134.0, 131.3, 129.3, 128.8, 127.1, 126.3, 125.6, 125.5, 125.2, 123.0, 122.9, 118.8, 101.1, 79.3, 78.8, 76.0, 57.5, 55.6, 54.8, 53.0, 51.1, 48.7, 45.9, 31.7, 27.9, 24.1, 24.0, 21.0, 20.6; HR-MS (ESI): *m*/*z* calcd for $C_{33}H_{40}NO_4$ $[M + H]^+$: 514.2957; found: 514.2943.

*3.1.8.9 (4aS,4a^{1}R,5R,6S,12bS)-5-(((3-(1H-Imidazol-1-yl) propyl)amino)methyl)-3,3,12-trimethyl-4a,5,7,8,8a,12b-hexahydro-4a^1,6-methanobenzo[2,3]azuleno[8,1-de][1,3]dioxepine-5,6(1H)-diol **17**.* Prepared with 1-(3-aminopropyl) imidazole, yield: 70%; R_f = 0.6 ($CHCl_3$: MeOH = 19 : 1), white crystals; m.p.: 68–70 °C; $[\alpha]_D^{20}$ = −56.5 (*c* 0.2, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42 (s, 1H), 7.10 (t, *J* = 7.4 Hz, 1H), 7.04 (s, 1H), 6.97 (d, *J* = 7.5 Hz, 1H), 6.90 (d, *J* = 7.5 Hz, 1H), 6.85 (s, 1H), 4.23 (d, *J* = 1.8 Hz, 2H), 3.97 (t, *J* = 7.0 Hz, 2H), 3.78 (s, 1H), 3.18 (s, 1H), 2.81 (d, *J* = 11.5 Hz, 1H), 2.75 (dd, *J* = 5.7, 13.1 Hz, 1H), 2.67–2.59 (m, 2H), 2.53–2.45 (m, 2H), 2.41 (s, 3H), 2.33–2.26 (m, 1H), 1.98–1.81 (m, 4H), 1.59–1.46 (m, 2H), 1.33 (s, 3H), 0.89 ppm (s, 3H); ^{13}C{1H} *J*-MOD NMR (125 MHz, $CDCl_3$): δ = 143.4, 140.8, 137.0, 135.5, 129.44, 129.45, 126.5, 118.8, 118.9, 101.0, 79.1, 78.7, 76.2, 57.5, 55.5, 53.0, 51.45, 51.40, 46.9, 45.9, 44.7, 31.9, 31.4, 27.8, 23.9, 21.4, 20.6; HR-MS (ESI): *m*/*z* calcd for $C_{27}H_{38}N_3O_4$ $[M + H]^+$: 468.2862; found: 468.2852.

3.1.8.10 (4aS,4a^{1}R,5R,6S,12bS)-5-(((2-((5-Fluoro-2-((4-(trifluoromethyl)phenyl)amino)pyrimidin-4-yl)amino)ethyl)amino) methyl)-3,3,12-trimethyl-4a,5,7,8,8a,12b-hexahydro-4a^1,6-

methanobenzo[2,3]azuleno[8,1-de][1,3]dioxepine-5,6(1H)-diol ***18***. Prior to the aminolysis, the reagent **R2** was subjected to a Cbz-deprotection reaction to obtain the primary amine as follows:

An amount of the reagent **R2** (0.15 g) was dissolved in MeOH (40 mL), then Pd/C (37 mg, 10% weight) was added to the solution and the mixture was stirred under an H_2 atmosphere at room temperature overnight. After that, the mixture was filtered through Celite and evaporated to dryness. The obtained crude product was used for the aminolysis reaction.

Prepared with **R2**, yield: 47%; $R_f = 0.6$ ($CHCl_3$: MeOH = 9 : 1), white wax; m.p.: 90–93 °C; $[\alpha]_D^{20} = -26.0$ (*c* 0.16, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.76$ (d, $J = 3.1$ Hz, 1H), 7.70 (d, $J =$ 8.4 Hz, 2H), 7.53 (d, $J = 8.5$ Hz, 2H), 7.17 (s, 1H), 7.08 (t, $J =$ 7.4 Hz, 1H), 6.97 (d, $J = 7.5$ Hz, 1H), 6.87 (d, $J = 7.2$ Hz, 1H), 5.48 (s, 1H), 4.26–4.18 (m, 2H), 3.79 (s, 1H), 3.65–3.49 (m, 2H), 3.17 (s, 1H), 2.99–2.89 (m, 2H), 2.87–2.80 (m, 1H), 2.78–2.71 (m, 2H), 2.48 (d, $J = 10.7$ Hz, 1H), 2.41 (s, 3H), 2.31–2.24 (m, 1H), 1.99–1.85 (m, 2H), 1.57–1.46 (m, 2H), 1.31 (s, 3H), 0.88 ppm (s, 3H); ^{13}C{1H} *J*-MOD NMR (125 MHz, $CDCl_3$): $\delta = 155.1$ (d, $J_{F,C} = 3.1$ Hz), 152.8 (d, $J_{F,C} = 12.5$ Hz), 143.4, 143.3, 141.8 (d, $J_{F,C} = 246$ Hz), 140.7, 138.5 (d, $J_{F,C} = 20.1$ Hz), 135.5, 129.4, 126.4, 126.0 (q, $J_{F,C} = 3.6$ Hz, 2C), 125.5 (q, $J_{F,C} = 293.2$ Hz), 123.2 (q, $J_{F,C} = 32.1$ Hz), 118.8, 117.5 (2C), 101.06, 79.1, 78.7, 76.1, 57.5, 55.5, 53.0, 51.4, 50.9, 49.1, 46.0, 40.2, 31.7, 27.7, 23.8, 21.4, 20.6; ^{19}F *J*-MOD NMR (470 MHz, $CDCl_3$): $\delta = -62.5$ ($C_{q\text{-}F}$), -165.1 ($C_{q\text{-}F}$) ppm; HR-MS (ESI): *m*/*z* calcd for $C_{34}H_{40}F_4N_5O_4$ $[M + H]^+$: 658.3016; found: 658.3005.

3.1.9 General procedure for the preparation of dihydroxy 1,2,3-triazoles 30–35. To a solution of azido diol **29** (0.10 g, 0.26 mmol) in a mixture of *t*-BuOH, H_2O (2 : 1), $Cu(OAc)_2 \cdot H_2O$ (0.1 equ.), sodium ascorbate (0.3 equ.) and acetylene derivative (0.28 mmol, 1.1 equ.) were added. The mixture was stirred at 40 °C for 48 hours, then *t*-BuOH was evaporated. The residue was dissolved in water (10 mL) and extracted with DCM (3 × 10 mL). The organic phase was washed with brine (3 × 10 mL), dried over Na_2SO_4, and then evaporated at low pressure. The crude product was then purified by column chromatography on silica gel using $CHCl_3$: MeOH (19 : 1) as eluent, followed by recrystallisation using a mixture of *n*-hexane : Et_2O to obtain pure products as white crystals.

3.1.9.1 (4aS,4a^{1}R,5R,6S,12bS)-5-((4-(((5-Fluoro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)methyl)-3,3,12-trimethyl-4a,5,7,8,8a,12b-hexahydro-4a1,6-methanobenzo[2,3]azuleno[8,1-de][1,3]dioxepine-5,6(1H)-diol ***30***. Prepared with **R7**, yield: 70%; $R_f = 0.6$ ($CHCl_3$: MeOH = 9 : 1), white crystals; m.p.: 139–142 °C; $[\alpha]_D^{20} = +8.1$ (*c* 0.18, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.74$ (s, 1H), 7.71 (s, 1H), 7.65 (s, 1H), 7.46 (s, 1H), 7.11 (t, $J = 7.4$ Hz, 1H), 6.97–6.93 (m, 2H), 6.55 (s, 1H), 5.47 (s, 1H), 4.79 (d, $J =$ 14,2 Hz, 1H), 4.76–4.64 (m, 2H), 4.41 (s, 1H), 4.25 (d, $J = 14.0$ Hz, 1H), 4.14 (dd, $J = 4.9$, 13.8 Hz, 1H), 4.05 (d, $J = 13.1$ Hz, 1H), 3.92 (s, 1H), 3.86 (s, 3H), 3.13 (d, $J = 3.5$ Hz, 1H), 2.79 (dd, $J = 5.3$, 13.0 Hz, 1H), 2.47–2.39 (m, 2H), 2.35 (s, 3H), 2.11–2.02 (m, 1H), 1.93 (dd, $J = 5.2$, 13.8 Hz, 1H), 1.82–1.71 (m, 1H), 1.54 (d, $J = 10.7$ Hz, 1H), 1.31–1.24 (m, 1H), 0.90 (s, 3H), 0.34 ppm (s, 3H); ^{13}C{1H} *J*-MOD NMR (125 MHz, $CDCl_3$): $\delta = 155.8$ (d, $J_{F,C} = 3.1$ Hz), 152.3 (d, $J_{F,C} =$ 11.9 Hz), 144.2, 142.7, 141.1 (d, $J_{F,C} = 244.9$ Hz), 140.3, 139.3, 139.1 (d, $J_{F,C} = 19.7$ Hz), 135.5, 131.0, 129.6, 126.7, 124.0, 123.3, 121.2, 119.2, 101.2, 79.0, 78.4, 74.8, 57.4, 55.3, 52.7, 51.6, 51.4, 45.8, 39.2, 35.8, 31.3, 27.4, 23.0, 21.1, 20.4 ppm; ^{19}F *J*-MOD NMR (470 MHz, $CDCl_3$): $\delta = -170.5$ ($C_{q\text{-}F}$) ppm; HR-MS (ESI): *m*/*z* calcd for $C_{32}H_{39}FN_9O_4$ $[M + H]^+$: 632.3109; found: 632.3092.

3.1.9.2 (4aS,4a^{1}R,5R,6S,12bS)-5-((4-(((5-Chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)methyl)-3,3,12-trimethyl-4a,5,7,8,8a,12b-hexahydro-4a1,6-methanobenzo[2,3]azuleno[8,1-de][1,3]dioxepine-5,6(1H)-diol ***31***. Prepared with **R8**, yield: 83%; $R_f = 0.6$ ($CHCl_3$: MeOH = 9 : 1), white crystals; m.p.: 237–239 °C; $[\alpha]_D^{20} = +14.8$ (*c* 0.16, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.86$ (s, 1H), 7.71 (s, 1H), 7.64 (s, 1H), 7.48 (s, 1H), 7.11 (t, $J = 7.4$ Hz, 1H), 6.97–6.93 (m, 2H), 6.71 (s, 1H), 5.75 (t, $J = 5.0$ Hz, 1H), 4.82–4.64 (m, 3H), 4.41 (s, 1H), 4.25 (d, $J = 14.0$ Hz, 1H), 4.14 (dd, $J = 4.1$, 13.3 Hz, 1H), 4.05 (d, $J = 13.3$ Hz, 1H), 3.91 (d, $J = 17.8$ Hz, 1H), 3.88 (s, 3H), 3.13 (d, $J = 3.4$ Hz, 2H), 2.79 (dd, $J = 5.3$, 12.9 Hz, 1H), 2.47–2.39 (m, 2H), 2.35 (s, 3H), 2.06 (dt, $J = 5.8$, 13.5 Hz, 1H), 1.93 (dd, $J =$ 4.3, 13.6 Hz, 1H), 1.84–1.73 (m, 1H), 1.54 (d, $J = 10.8$ Hz, 1H), 0.89 (s, 3H), 0.33 ppm (s, 3H); ^{13}C{1H} *J*-MOD NMR (125 MHz, $CDCl_3$): $\delta = 158.0$, 157.6, 153.2, 144.2, 142.7, 140.3, 135.5, 131.2, 129.6, 126.7, 124.0, 122.8, 121.5, 119.2, 101.2, 79.0, 78.6, 74.8, 57.4, 55.3, 52.7, 51.6, 51.4, 45.8, 39.2, 36.2, 31.3, 27.4, 23.0, 21.1, 20.4 ppm; HR-MS (ESI): *m*/*z* calcd for $C_{32}H_{39}ClN_9O_4$ $[M + H]^+$: 648.2813; found: 648.2800.

3.1.9.3 (4aS,4a^{1}R,5R,6S,12bS)-5-((4-(((5-Fluoro-2-((4-(trifluoromethyl)phenyl)amino)pyrimidin-4-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)methyl)-3,3,12-trimethyl-4a,5,7,8,8a,12b-hexahydro-4a1,6-methanobenzo[2,3]azuleno[8,1-de][1,3]dioxepine-5,6(1H)-diol ***32***. Prepared with **R5**, yield: 83%; $R_f = 0.5$ ($CHCl_3$: MeOH = 19 : 1), white crystals; m.p.: 134–136 °C; $[\alpha]_D^{20} = +7.4$ (*c* 0.16, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.81$ (d, $J = 2.3$ Hz, 1H), 7.69 (d, $J = 8.4$ Hz, 2H), 7.67 (s, 1H), 7.54 (d, $J = 8.4$ Hz, 2H), 7.20 (s, 1H), 7.10 (t, $J = 7.4$ Hz, 1H), 6.97–6.92 (m, 2H), 5.65 (s, 1H), 4.80–4.71 (m, 3H), 4.35 (s, 1H), 4.24 (d, $J = 14.0$ Hz, 1H), 4.14 (dd, $J = 4.1$, 13.3 Hz, 1H), 4.05 (d, $J = 13.3$ Hz, 1H), 3.92 (s, 1H), 3.14 (d, $J = 3.4$ Hz, 1H), 3.08 (s, 1H), 2.78 (dd, $J = 5.3$, 13.0 Hz, 1H), 2.45–2.38 (m, 2H), 2.35 (s, 3H), 2.08–2.00 (m, 1H), 1.92 (dd, $J = 4.2$, 13.7 Hz, 1H), 1.82–1.70 (m, 1H), 1.53 (d, $J =$ 10.8 Hz, 1H), 0.90 (s, 3H), 0.35 ppm (s, 3H); ^{13}C{1H} *J*-MOD NMR (125 MHz, $CDCl_3$): $\delta = 155.1$ (d, $J_{F,C} = 3.1$ Hz), 152.2 (d, $J_{F,C} =$ 12.3 Hz), 143.8, 143.1, 142.7, 140.7, 140.3, 139.0 (d, $J_{F,C} = 21.2$ Hz), 135.5, 129.6, 126.7, 126.1 (q, $J_{F,C} = 3.9$ Hz, 2C), 124.0, 125.5 (q, $J_{F,C} = 243.6$ Hz), 123.3 (q, $J_{F,C} = 16.3$ Hz), 119.2, 117.92 (2C), 101.23, 79.0, 78.4, 74.8, 57.4, 55.3, 52.7, 51.6, 51.4, 45.8, 35.8, 31.3, 27.4, 23.0, 23.1, 20.4 ppm; ^{19}FNMR (470 MHz, $CDCl_3$): $\delta =$ -61.6 ($C_{q\text{-}F}$), -167.3 ($C_{q\text{-}F}$) ppm; HR-MS (ESI): *m*/*z* calcd for $C_{35}H_{38}F_4N_7O_4$ $[M + H]^+$: 696.2921; found: 696.2899.

3.1.9.4 (4aS,4a^{1}R,5R,6S,12bS)-5-((4-(((5-Chloro-2-((4-(trifluoromethyl)phenyl)amino)pyrimidin-4-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)methyl)-3,3,12-trimethyl-4a,5,7,8,8a,12b-hexahydro-4a^1,6-methanobenzo[2,3]azuleno[8,1-de][1,3]dioxepine-5,6(1H)-diol ***33***. Prepared with **R6**, yield: 66%; $R_f = 0.5$ ($CHCl_3$: MeOH = 19 : 1), white crystals; m.p.: 132–134 °C; $[\alpha]_D^{20} = +5.1$ (*c* 0.18, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.93$ (s, 1H), 7.70 (d, $J = 8.4$ Hz, 2H), 7.65 (s, 1H), 7.56 (d, $J = 8.4$ Hz, 2H), 7.23 (s,

1H), 7.11 (t, J = 7.4 Hz, 1H), 6.97–6.92 (m, 2H), 5.87 (t, J = 5.3 Hz, 1H), 4.81–4.69 (m, 3H), 4.35 (s, 1H), 4.23 (d, J = 14.0 Hz, 1H), 4.14 (dd, J = 4.1, 13.3 Hz, 1H), 4.05 (d, J = 13.4 Hz, 1H), 3.92 (s, 1H), 3.14 (d, J = 3.4 Hz, 1H), 3.10 (s, 1H), 2.79 (dd, J = 5.3, 12.9 Hz, 1H), 2.47–2.40 (m, 2H), 2.35 (s, 3H), 2.10–2.01 (m, 1H), 1.92 (dd, J = 4.2, 13.7 Hz, 1H), 1.83–1.71 (m, 1H), 1.53 (d, J = 10.7 Hz, 1H), 0.90 (s, 3H), 0.35 ppm (s, 3H); ^{13}C{1H} J-MOD NMR (125 MHz, $CDCl_3$): δ = 157.5, 157.4, 153.2, 143.8, 142.8, 142.7, 140.2, 135.5, 129.6, 126.7, 126.1 (q, $J_{F,C}$ = 3.5 Hz, 2C), 125.4 (q, $J_{F,C}$ = 161.9 Hz), 124.0, 123.6 (q, $J_{F,C}$ = 25.4 Hz), 119.2, 118.4 (2C), 106.0, 101.2, 79.0, 78.4, 74.8, 57.4, 55.3, 52.7, 51.6, 51.4, 45.8, 36.3, 31.3, 27.5, 23.0, 21.1, 20.4 ppm; ^{19}F J-MOD NMR (470 MHz, $CDCl_3$): δ = −61.7 ($C_{q\text{-}F}$) ppm; HR-MS (ESI): m/z calcd for $C_{35}H_{38}ClF_3N_7O_4$ $[M + H]^+$: 712.2625; found: 712.2610.

*3.1.9.5 1-((1-(((4aS,4a^{1}R,5R,6S,12bS)-5,6-Dihydroxy-3,3,12-trimethyl-1,4a,5,6,7,8,8a,12b-octahydro-4a^1,6-methanobenzo[2,3]azuleno[8,1-de][1,3]dioxepin-5-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)pyrimidine-2,4(1H,3H)-dione **34**.* Prepared with *N*-1-propargyluracil, yield: 51%; white crystals; m.p.: 260–264 °C; $[\alpha]_D^{20}$ = +13.1 (c 0.16, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.69 (s, 1H), 7.91 (s, 1H), 7.47 (d, J = 7.9 Hz, 1H), 7.10 (t, J = 7.4 Hz, 1H), 6.97–6.93 (m, 2H), 5.65 (d, J = 7.9 Hz, 1H), 5.00 (d, J = 15.1 Hz, 1H), 4.88 (d, J = 15.4 Hz, 1H), 4.81 (d, J = 13.8 Hz, 1H), 4.49 (s, 1H), 4.29 (d, J = 14.0 Hz, 1H), 4.15 (dd, J = 4.1, 13.3 Hz, 1H), 4.06 (d, J = 13.3 Hz, 1H), 3.91 (s, 1H), 3.29 (s, 1H), 3.15 (d, J = 3.5 Hz, 1H), 2.80 (dd, J = 5.3, 13.0 Hz, 1H), 2.47–2.40 (m, 2H), 2.35 (s, 3H), 2.11–2.02 (m, 1H), 1.94 (dd, J = 4.6, 13.9 Hz, 1H), 1.82–1.70 (m, 1H), 1.55 (d, J = 10.8 Hz, 1H), 0.95 (s, 3H), 0.29 ppm (s, 3H); ^{13}C{1H} J-MOD NMR (125 MHz, $CDCl_3$): δ = 163.1, 150.4, 144.1, 142.7, 141.3, 140.2, 135.5, 129.6, 126.7, 125.6, 119.1, 102.5, 101.1, 79.0, 78.5, 74.8, 57.4, 55.3, 52.7, 51.8, 51.4, 45.7, 42.9, 31.4, 27.4, 23.0, 21.1, 20.4 ppm; HR-MS (ESI): m/z calcd for $C_{28}H_{34}N_5O_6$ $[M + H]^+$: 536.2509; found: 536.2501.

*3.1.9.6 1-((1-(((4aS,4a^{1}R,5R,6S,12bS)-5,6-Dihydroxy-3,3,12-trimethyl-1,4a,5,6,7,8,8a,12b-octahydro-4a^1,6-methanobenzo[2,3]azuleno[8,1-de][1,3]dioxepin-5-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)-5-fluoropyrimidine-2,4(1H,3H)-dione **35**.* Prepared with *N*-1-propargyl-5-fluorouracil, yield: 56%; white crystals; m.p.: 141–144 °C; $[\alpha]_D^{20}$ = +16.4 (c 0.16, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.61 (s, 1H), 7.88 (s, 1H), 7.57 (d, J = 5.3 Hz, 1H), 7.13–7.09 (m, 1H), 6.98–6.93 (m, 2H), 4.99–4.95 (m, 1H), 4.87 (d, J = 15.1 Hz, 1H), 4.81 (d, J = 14.0 Hz, 1H), 4.46 (s, 1H), 4.30 (d, J = 14.0 Hz, 1H), 4.16 (dd, J = 4.1, 13.3 Hz, 1H), 4.06 (d, J = 13.3 Hz, 1H), 3.92 (s, 1H), 3.20 (s, 1H), 3.16 (d, J = 3.8 Hz, 1H), 2.80 (dd, J = 5.3, 13.0 Hz, 1H), 2.48–2.40 (m, 2H), 2.36 (s, 3H), 2.07 (td, J = 6.8, 19.3 Hz, 1H), 1.94 (dd, J = 4.1, 13.9 Hz, 1H), 1.76 (dq, J = 5.3, 13.4 Hz, 1H), 1.54 (d, J = 5.8 Hz, 1H), 0.96 (s, 3H), 0.32 ppm (s, 3H); ^{13}C{1H} J-MOD NMR (125 MHz, $CDCl_3$): δ = 156.5, 148.9, 142.7, 141.3–139.4 (d, $J_{F,C}$ = 242.1 Hz), 140.8, 140.2, 135.6, 129.6, 128.3 (d, $J_{F,C}$ = 32.6 Hz), 126.7, 125.5, 119.1, 101.18, 79.0, 78.4, 74.8, 57.4, 55.4, 52.7, 51.8, 51.4, 45.7, 42.8, 31.3, 27.4, 23.0, 21.1, 20.4 ppm; ^{19}F J-MOD NMR (470 MHz, $CDCl_3$): δ = −164.9 ($C_{q\text{-}F}$) ppm; HR-MS (ESI): m/z calcd for $C_{28}H_{33}FN_5O_6$ $[M + H]^+$: 554.2414; found: 554.2401.

3.1.10 The general method of acetonide deprotection (preparation of aminotetraols and tetrahydroxy 1,2,3-triazoles). An amount of aminodiols **9–18** or dihydroxy triazoles **30–35** (50.0 mg) was dissolved in 10% HCl solution in EtOH (5 mL), then stirred at room temperature for 3 h. After that, the mixture was evaporated to dryness, and the pure compounds were obtained by crystallisation in Et_2O : n-hexane. In the case of compounds (**28**, **36–40**), the crude product was dissolved in 10% Na_2CO_3 solution (5 mL) and then the free base was extracted with EtOAc (3 × 5 mL). The organic phase was dried over Na_2SO_4, filtered and then evaporated at low pressure. The crude product was purified by short column chromatography on silica gel using $CHCl_3$: MeOH (9 : 1) as eluent.

*3.1.10.1 N-Benzyl-1-((7S,8R,9S,9aR,10S)-7,8,9-trihydroxy-10-(hydroxymethyl)-1-methyl-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulen-8-yl)methanaminium chloride **19**.* Yield: 88%; white crystals; m.p.: 245–246 °C; $[\alpha]_D^{20}$ = −10.6 (c 0.18, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.71 (s, 1H), 8.46 (s, 1H), 7.55–7.52 (m, 2H), 7.41–7.38 (m, 3H), 7.02 (t, J = 7.5 Hz, 1H), 6.91 (d, J = 7.4 Hz, 1H), 6.88 (d, J = 7.4 Hz, 1H), 5.33 (d, J = 6.1 Hz, 1H), 4.81 (s, 1H), 4.66 (s, 1H), 4.20–4.08 (m, 3H), 3.92 (dd, J = 2.4, 11.5 Hz, 1H), 3.40 (d, J = 5.0 Hz, 1H), 3.01–2.86 (m, 3H), 2.56–2.51 (m, 2H), 2.44 (s, 3H), 2.16–2.08 (m, 1H), 1.79–1.69 (m, 1H), 1.59–1.54 (m, 1H), 1.36–1.29 ppm (m, 2H); ^{13}C{1H} J-MOD NMR (125 MHz, DMSO-d_6): δ = 144.6, 143.0, 133.8, 132.0, 130.86, 130.84, 129.7, 129.4, 129.01, 129.01, 126.2, 120.0, 78.8, 76.9, 73.0, 59.3, 58.9, 55.0, 51.8, 51.2, 48.6, 43.6, 33.2, 21.3, 19.5; HR-MS (ESI): m/z calcd for $C_{25}H_{32}NO_4$ $[M + H]^+$: 410.2331; found: 410.2318.

*3.1.10.2 N-(4-Fluorobenzyl)-1-((7S,8R,9S,9aR,10S)-7,8,9-trihydroxy-10-(hydroxymethyl)-1-methyl-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulen-8-yl)methanaminium **20**.* Yield: 81%; white crystals; m.p.: 236–238 °C; $[\alpha]_D^{20}$ = −2.8 (c 0.17, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.72 (s, 1H), 8.46 (s, 1H), 7.61–7.56 (m, 2H), 7.23 (t, J = 8.6 Hz, 2H), 7.02 (t, J = 7.5 Hz, 1H), 6.92–6.87 (m, 2H), 4.17–4.07 (m, 3H), 3.92 (dd, J = 2.6, 11.5 Hz, 1H), 3.40 (s, 1H) 3.01–2.86 (m, 3H), 2.56–2.50 (m, 2H), 2.44 (s, 3H), 2.16–2.9 (m, 1H), 1.78–1.70 (m, 1H), 1.59 (dd, J = 4.7, 13.7 Hz, 1H), 1.38–1.29 ppm (m, 2H); ^{13}C{1H} J-MOD NMR (125 MHz, DMSO-d_6): δ = 162.8 (d, $J_{F,C}$ = 246.6 Hz), 144.6, 143.0, 133.8, 133.3 (d, $J_{F,C}$ = 8.2 Hz, 2C), 129.7, 128.3 (d, $J_{F,C}$ = 3.4 Hz), 126.2, 120.0, 115.8 (d, $J_{F,C}$ = 21.2 Hz, 2C), 78.8, 76.9, 73.1, 59.3, 58.9, 55.0, 51.8, 50.4, 48.5, 43.6, 33.2, 21.3, 19.5; ^{19}F J-MOD NMR (470 MHz, DMSO-d_6): δ = −112.7 ($C_{q\text{-}F}$) ppm; HR-MS (ESI): m/z calcd for $C_{25}H_{31}FNO_4$ $[M + H]^+$: 428.2237; found: 428.2224.

*3.1.10.3 N-(4-Methoxybenzyl)-1-((7S,8R,9S,9aR,10S)-7,8,9-trihydroxy-10-(hydroxymethyl)-1-methyl-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulen-8-yl)methanaminium chloride **21**.* Yield: 71%; white crystals; m.p.: 163–165 °C; $[\alpha]_D^{20}$ = −18.7 (c 0.18, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.58 (s, 1H), 8.47 (s, 1H), 7.42 (d, J = 8.4 Hz, 2H), 7.14 (t, J = 7.5 Hz, 1H), 7.01 (d, J = 7.9 Hz, 1H), 6.99 (d, J = 7.5 Hz, 1H), 6.94 (d, J = 8.4 Hz, 2H), 4.39 (dd, J = 5.9, 8.8 Hz, 1H), 4.32 (d, J = 8.7 Hz, 1H), 4.12–4.00 (m, 2H), 3.76 (s, 3H), 3.73 (s, 1H), 3.55 (d, J = 5.6 Hz, 1H), 3.00–2.82 (m, 3H), 2.37 (d, J = 11.3 Hz, 1H), 2.30–2.25 (m, 1H), 2.24 (s, 3H), 1.79 (dt, J = 6.1, 13.5 Hz, 1H), 1.61 (dd, J = 4.7, 13.8 Hz, 1H), 1.47 (d, J = 10.5 Hz, 1H), 1.42–1.31 ppm (m, 1H); ^{13}C{1H} J-MOD NMR (125 MHz, DMSO-d_6): δ = 160.2, 164.6, 143.1, 134.7, 132.4, 132.3, 129.0, 127.9, 123.8, 121.3, 114.4, 114.3, 84.6, 82.8, 76.2, 74.3, 59.8, 55.9, 50.5, 49.0, 48.2, 48.1, 41.9, 33.6, 23.8, 19.1; HR-MS (ESI): m/z calcd for $C_{26}H_{34}NO_5$ $[M + H]^+$: 440.2436; found: 440.2422.

*3.1.10.4 1-(Naphthalen-1-yl)-N-(((7S,8R,9S,9aR,10S)-7,8,9-trihydroxy-10-(hydroxymethyl)-1-methyl-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulen-8-yl)methyl)methanaminium chloride **22**.* Yield: 71%; white crystals; m.p.: 215–217 °C; $[\alpha]_D^{20} = -17.7$ (*c* 0.21, MeOH); ^{1}H NMR (500 MHz, DMSO-d$_6$): $\delta = 8.73$ (s, 2H), 8.23 (d, $J = 8.2$ Hz, 1H), 7.99 (d, $J = 7.9$ Hz, 2H), 7.72 (d, $J = 7.4$ Hz, 1H), 7.65–7.53 (m, 3H), 7.14 (t, $J = 7.5$ Hz, 1H), 7.01 (d, $J = 7.5$ Hz, 2H), 4.71–4.61 (m, 2H), 4.41 (dd, $J = 6.0$, 8.7 Hz, 1H), 4.33 (d, $J = 8.5$ Hz, 1H), 3.81 (s, 1H), 3.56 (d, $J = 5.6$ Hz, 1H), 3.24–3.17 (m, 1H), 3.12–3.04 (m, 1H), 2.98 (dd, $J = 5.7$, 11.7 Hz, 1H), 2.41 (d, $J = 10.4$ Hz, 1H), 2.31–2.24 (m, 1H), 2.23 (s, 3H), 1.81–1.74 (m, 1H), 1.66–1.59 (m, 1H), 1.52–1.40 (m, 2H), 1.24 ppm (s, 2H); ^{13}C{1H} *J*-MOD NMR (125 MHz, DMSO-d$_6$): $\delta = 144.6$, 143.1, 134.8, 133.7, 131.7, 130.1, 129.8, 129.1, 129.0, 128.4, 127.9, 127.2, 126.6, 125.7, 124.1, 121.3, 84.9, 82.9, 76.2, 74.2, 59.8, 49.1, 49.0, 48.3, 47.5, 41.8, 33.5, 23.7, 19.1; HR-MS (ESI): *m*/*z* calcd for $C_{29}H_{32}NO_3$ $[M - H_2O]^+$: 442.2382; found: 442.2367.

*3.1.10.5 (1S)-1-(Naphthalen-2-yl)-N-(((7S,8R,9S,9aR,10S)-7,8,9-trihydroxy-10-(hydroxymethyl)-1-methyl-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulen-8-yl)methyl)ethan-1-aminium chloride **23**.* Yield: 91%; white crystals; m.p.: 219–222 °C; $[\alpha]_D^{20} = -56.8$ (*c* 0.18, MeOH); ^{1}H NMR (500 MHz, DMSO-d$_6$): $\delta =$ 8.93 (s, 1H), 8.59 (s, 1H), 8.01–7.92 (m, 3H), 7.87–7.83 (m, 1H), 7.73 (d, $J = 8.5$ Hz, 1H), 7.59–7.55 (m, 2H), 7.14 (t, $J = 7.4$ Hz, 1H), 7.03 (d, $J = 7.5$ Hz, 1H), 6.96 (d, $J = 7.3$ Hz, 1H), 4.54 (t, $J = 6.2$ Hz, 1H), 4.44–4.34 (m, 3H), 3.83 (s, 1H), 3.55 (d, $J = 5.7$ Hz, 1H), 3.00–2.90 (m, 2H), 2.64–2.58 (m, 1H), 2.32 (d, $J = 11.0$ Hz, 1H), 2.26 (s, 3H), 2.24–2.17 (m, 1H), 1.74–1.67 (m, 1H), 1.66 (d, $J = 6.9$ Hz, 3H), 1.54–1.47 (m, 1H), 1.41 (d, $J = 10.4$ Hz, 1H), 1.36–1.22 ppm (m, 1H); ^{13}C{1H} *J*-MOD NMR (125 MHz, DMSO-d$_6$): $\delta = 144.6$, 143.0, 134.79, 134.73, 133.3, 133.0, 129.2, 129.0, 128.4, 128.15, 128.12, 127.9, 127.2, 127.1, 125.2, 121.3, 84.2, 82.7, 76.3, 74.3, 59.7, 58.7, 49.0, 48.1, 47.9, 41.8, 33.5, 23.8, 20.1, 19.1; HR-MS (ESI): *m*/*z* calcd for $C_{30}H_{36}NO_4$ $[M + H]^+$: 474.2644; found: 474.2632.

*3.1.10.6 (1R)-1-(Naphthalen-2-yl)-N-(((7S,8R,9S,9aR,10S)-7,8,9-trihydroxy-10-(hydroxymethyl)-1-methyl-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulen-8-yl)methyl)ethan-1-aminium chloride **24**.* Yield: 82%; white crystals; m.p.: 159–161 °C; $[\alpha]_D^{20} = -30.5$ (*c* 0.14, MeOH); ^{1}H NMR (500 MHz, DMSO-d$_6$): $\delta = 8.82$ (s, 1H), 8.72 (s, 1H), 8.05 (s, 1H), 7.96–7.87 (m, 3H), 7.72 (d, $J = 8.5$ Hz, 1H), 7.59–7.55 (m, 2H), 7.12 (t, $J = 7.4$ Hz, 1H), 6.99 (d, $J = 7.5$ Hz, 1H), 6.90 (d, $J = 7.3$ Hz, 1H), 4.58 (q, $J = 6.05$ Hz, 1H), 4.37 (dd, $J = 5.6$, 8.7 Hz, 1H), 4.29 (d, $J = 8.6$ Hz, 1H), 3.61 (s, 1H), 3.53 (d, $J = 5.6$ Hz, 1H), 3.03–2.88 (m, 2H), 2.73–2.62 (m, 1H), 2.36 (d, $J = 9.5$ Hz, 1H), 2.22 (s, 3H), 2.18–2.10 (m, 1H), 1.76–1.69 (m, 1H), 1.68 (d, $J = 6.7$ Hz, 3H), 1.58–1.51 (m, 1H), 1.44 (d, $J = 10.5$ Hz, 1H), 1.16–1.08 ppm (m, 1H); ^{13}C {1H} *J*-MOD NMR (125 MHz, DMSO-d$_6$): $\delta = 144.5$, 142.9, 134.8, 134.7, 133.3, 132.9, 129.0, 128.9, 128.4, 128.2, 128.1, 127.9, 127.2, 127.1, 125.5, 121.2, 84.3, 82.8, 76.3, 74.2, 59.7, 58.8, 48.9, 48.0, 47.9, 41.8, 33.6, 33.7, 19.0, 18.6; HR-MS (ESI): *m*/*z* calcd for $C_{30}H_{36}NO_4$ $[M + H]^+$: 474.2644; found: 474.2631.

*3.1.10.7 (1S)-1-(Naphthalen-1-yl)-N-(((7S,8R,9S,9aR,10S)-7,8,9-trihydroxy-10-(hydroxymethyl)-1-methyl-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulen-8-yl)methyl)ethan-1-aminium chloride **25**.* Yield: 80%; white crystals; m.p.: 160–163 °C; $[\alpha]_D^{20} = -5.3$ (*c* 0.18, MeOH); ^{1}H NMR (500 MHz, DMSO-d$_6$): $\delta = 9.14$ (s, 1H), 8.61 (s, 1H), 8.13 (d, $J = 8.9$ Hz, 1H), 7.98–7.91 (m, 3H), 7.61–7.54 (m, 3H), 7.13 (t, $J = 7.5$ Hz, 1H), 7.02 (d, $J = 7.5$ Hz, 1H), 6.93 (d, $J = 7.3$ Hz, 1H), 5.34 (s, 1H), 4.78 (s, 1H), 4.43–4.39 (m, 2H), 4.34 (d, $J = 8.7$ Hz, 1H), 3.77 (s, 1H), 3.55 (d, $J = 5.6$ Hz, 1H), 3.08 (t, $J = 8.1$ Hz, 1H), 2.91 (dd, $J = 5.6$, 11.8 Hz, 1H), 2.74–2.67 (m, 1H), 2.33 (d, $J = 10.1$ Hz, 1H), 2.24 (s, 3H), 2.22–2.15 (m, 1H), 1.72–1.66 (m, 1H), 1.66 (d, $J = 6.7$ Hz, 3H), 1.47–1.39 (m, 2H), 1.32–1.20 ppm (m, 1H); ^{13}C{1H} *J*-MOD NMR (125 MHz, DMSO-d$_6$): $\delta = 144.5$, 143.0, 134.7, 133.8, 130.8, 129.4, 129.3, 129.0, 127.9, 127.3, 126.6, 126.1, 125.9, 124.4, 122.9, 121.2, 84.1, 82.7, 76.2, 74.2, 59.9, 53.5, 48.9, 48.1, 47.9, 41.8, 33.4, 23.7, 20.6, 19.12; HR-MS (ESI): *m*/*z* calcd for $C_{30}H_{36}NO_4$ $[M + H]^+$: 474.2644; found: 474.2629.

*3.1.10.8 (1R)-1-(Naphthalen-1-yl)-N-(((7S,8R,9S,9aR,10S)-7,8,9-trihydroxy-10-(hydroxymethyl)-1-methyl-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulen-8-yl)methyl)ethan-1-aminium chloride **26**.* Yield: 79%; white crystals; m.p.: 161–163 °C; $[\alpha]_D^{20} = -53.2$ (*c* 0.20, MeOH); ^{1}H NMR (500 MHz, DMSO-d$_6$): $\delta = 9.21$ (s, 1H), 8.52 (s, 1H), 8.22 (d, $J = 8.5$ Hz, 1H), 7.98 (d, $J = 7.9$ Hz, 1H), 7.95–7.91 (m, 2H), 7.64–7.52 (m, 3H), 7.12 (t, $J = 7.4$ Hz, 1H), 6.99 (d, $J = 7.5$ Hz, 1H), 6.93 (d, $J = 7.3$ Hz, 1H), 5.30 (s, 1H), 5.04 (s, 1H), 4.59 (s, 1H), 4.37 (dd, $J = 7.2$, 7.2 Hz, 1H), 4.32 (d, $J = 8.5$ Hz, 1H), 3.61 (s, 1H), 3.52 (d, $J = 5.3$ Hz, 1H), 3.17 (dd, $J = 9.5$, 9.5 Hz, 1H), 2.98–2.90 (m, 2H), 2.39 (d, $J = 10.5$ Hz, 1H), 2.22 (s, 3H), 2.21–2.13 (m, 1H), 1.75 (td, $J = 6.7$, 20.6 Hz, 1H), 1.68 (d, $J = 6.6$ Hz, 3H), 1.62 (dd, $J = 5.1$, 14.9 Hz, 1H), 1.45 (d, $J = 10.5$ Hz, 1H), 1.26–1.15 ppm (m, 1H); ^{13}C{1H} *J*-MOD NMR (125 MHz, DMSO-d$_6$): $\delta = 144.6$, 143.0, 134.8, 134.7, 133.7, 130.7, 129.4, 128.3, 129.0, 127.9, 127.4, 126.6, 125.9, 124.9, 123.2, 121.3, 84.4, 82.9, 76.3, 74.2, 59.8, 53.8, 49.0, 48.7, 48.2, 41.9, 33.7, 23.7, 19.2, 19.0; HR-MS (ESI): *m*/*z* calcd for $C_{30}H_{36}NO_4$ $[M + H]^+$: 474.2644; found: 474.2632.

*3.1.10.9 3-(1H-Imidazol-1-yl)-N-(((7S,8R,9S,9aR,10S)-7,8,9-trihydroxy-10-(hydroxymethyl)-1-methyl-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulen-8-yl)methyl)propan-1-aminium chloride **27**.* Yield: 80%; white crystals; m.p.: 207–208 °C; $[\alpha]_D^{20} = -29.1$ (*c* 0.18, MeOH); ^{1}H NMR (500 MHz, DMSO-d$_6$): $\delta = 9.19$ (s, 1H), 8.74 (s, 1H), 8.41 (s, 1H), 7.76 (s, 1H), 7.67 (s, 1H), 7.13 (t, $J = 7.4$ Hz, 1H), 7.02–6.96 (m, 2H), 4.50–4.36 (m, 2H), 4.33–4.28 (m, 3H), 3.69 (s, 1H), 3.55 (d, $J = 5.6$ Hz, 1H), 3.17 (s, 1H), 3.00–2.93 (m, 3H), 2.89 (s, 2H), 2.38 (d, $J = 10.6$ Hz, 1H), 2.29–2.24 (m, 1H), 2.23 (s, 3H), 2.22–2.16 (m, 2H), 1.86–1.76 (m, 1H), 1.74–1.66 (m, 1H), 1.50–1.39 ppm (m, 2H); ^{13}C{1H} *J*-MOD NMR (125 MHz, DMSO-d$_6$): $\delta = 144.5$, 143.1, 135.51, 134.7, 129.0, 127.7, 122.3, 121.3, 120.4, 84.9, 82.7, 76.3, 74.3, 59.8, 49.2, 49.0, 48.3, 46.2, 44.7, 41.9, 33.5, 26.2, 23.8, 19.1; HR-MS (ESI): *m*/*z* calcd for $C_{24}H_{32}N_3O_3$ $[M - H_2O]^+$: 410.2443; found: 410.2432.

*3.1.10.10 (7S,8R,9S,9aR,10S)-8-(((2-((5-Fluoro-2-((4-(trifluoromethyl)phenyl)amino)pyrimidin-4-yl)amino)ethyl)amino)methyl)-10-(hydroxymethyl)-1-methyl-4b,5,6,8,9,10-hexahydro-7H-7,9a-methanobenzo[a]azulene-7,8,9-triol **28**.* Yield: 63%; white crystals; m.p.: 92–94 °C; $[\alpha]_D^{20} = -11.6$ (*c* 0.11, MeOH); ^{1}H NMR (500 MHz, DMSO-d$_6$): $\delta = 9.41$ (s, 1H), 7.91 (d, $J = 8.4$ Hz, 2H), 7.88 (d, $J = 3.4$ Hz, 1H), 7.55 (d, $J = 8.5$ Hz, 2H), 7.41 (t, $J = 4.8$ Hz, 1H), 7.09 (t, $J = 7.4$ Hz, 1H), 6.99 (d, $J = 7.5$ Hz, 1H), 6.90 (d, $J = 7.3$ Hz, 1H), 4.30 (dd, $J = 7.2$, 7.2 Hz, 1H), 4.26 (d, $J =$

8.5 Hz, 1H), 2.91 (dd, J = 5.8, 11.7 Hz, 1H), 2.78 (t, J = 6.2 Hz, 2H), 2.64 (d, J = 11.4 Hz, 1H), 2.56 (t, J = 6.2 Hz, 1H), 2.38–2.32 (m, 1H), 2.21 (s, 3H), 2.20–2.16 (m, 1H), 1.73 (td, J = 6.6, 19.2 Hz, 1H), 1.64 (dd, J = 4.1, 13.1 Hz, 1H), 1.41 (d, J = 10.2 Hz, 1H), 1.38–1.30 ppm (m, 1H); ^{13}C{1H} *J*-MOD NMR (125 MHz, DMSO-d_6): δ = 155.7 (d, $J_{F,C}$ = 3.1 Hz), 152.8 (d, $J_{F,C}$ = 12.2 Hz), 145.3, 144.8, 143.3, 142.7–140.7 (d, $J_{F,C}$ = 246.4 Hz), 138.7 (d, $J_{F,C}$ = 18.4 Hz), 134.6, 128.9, 127.7, 126.1 (q, $J_{F,C}$ = 3.5 Hz, 2C), 124.2 (q, $J_{F,C}$ = 274.5 Hz), 120.6 (q, $J_{F,C}$ = 31.2 Hz), 121.14, 117.9 (2C), 85.9, 82.6, 78.0, 73.9, 59.5, 57.5, 50.7, 49.1, 48.9, 48.3, 42.7, 33.6, 24.0, 19.0 ppm; ^{19}F NMR (470 MHz, MeOD): δ = −59.7 ($C_{q\text{-}F}$), −165.8 ($C_{q\text{-}F}$); HR-MS (ESI): *m*/*z* calcd for $C_{31}H_{36}F_4N_5O_4$ $[M + H]^+$: 618.2703; found: 618.2685.

3.1.10.11 (7S,8R,9S,9aR,10S)-8-((4-(((5-Fluoro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)methyl)-10-(hydroxymethyl)-1-methyl-4b,5,6,8,9,10-hexahydro-7H-7,9a-methanobenzo[a]azulene-7,8,9-triol ***36***. Yield: 63%; colourless oily compound; $[\alpha]_D^{20}$ = +8.2 (*c* 0.16, MeOH); ^{1}H NMR (500 MHz, MeOD): δ = 7.81 (s, 1H), 7.68 (d, J = 2.7 Hz, 1H), 7.48 (s, 1H), 7.34 (s, 1H), 7.14 (t, J = 7.9 Hz, 1H), 7.02–6.98 (m, 2H), 4.71 (d, J = 15.6 Hz, 1H), 4.63–4.52 (m, 2H), 4.36 (d, J = 14.2 Hz, 1H), 4.21 (dd, J = 6.6, 8.3 Hz, 1H), 4.02 (d, J = 8.7 Hz, 1H), 3.74 (s, 1H), 3.61 (s, 3H), 3.48 (d, J = 5.6 Hz, 1H), 3.03 (dd, J = 5.4, 11.8 Hz, 1H), 2.49–2.39 (m, 2H), 2.15 (s, 3H), 2.05–1.98 (m, 1H), 1.56 (d, J = 10.4 Hz, 1H), 1.42–1.33 (m, 1H), 0.97–0.89 ppm (m, 1H); ^{13}C{1H} *J*-MOD NMR (125 MHz, MeOD): δ = 159.8, 156.7 (d, $J_{F,C}$ = 12.2 Hz), 149.4, 147.5, 146.4, 145.7–143.8 (d, $J_{F,C}$ = 242.5 Hz), 142.1 (d, $J_{F,C}$ = 18.8 Hz), 138.3, 133.7, 132.5, 131.3, 128.0, 127.8, 125.4, 124.4, 87.9, 86.5, 81.2, 78.1, 63.6, 55.4, 52.7, 52.0, 45.9, 41.3, 38.6, 36.5, 27.4, 21.5; ^{19}F *J*-MOD NMR (470 MHz, MeOD): δ = −168.3 ($C_{q\text{-}F}$); HR-MS (ESI): *m*/*z* calcd for $C_{29}H_{33}FN_9O_3$ $[M - H_2O]^+$: 574.2690; found: 574.2676.

3.1.10.12 (7S,8R,9S,9aR,10S)-8-((4-(((5-Chloro-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)methyl)-10-(hydroxymethyl)-1-methyl-4b,5,6,8,9,10-hexahydro-7H-7,9a-methanobenzo[a]azulene-7,8,9-triol ***37***. Yield: 64%; white crystals; m.p.: 251–253 °C; $[\alpha]_D^{20}$ = +15.7 (*c* 0.18, MeOH); ^{1}H NMR (500 MHz, MeOD): δ = 7.81 (s, 1H), 7.79 (s, 1H), 7.46 (s, 1H), 7.36 (s, 1H), 7.16 (t, J = 7.4 Hz, 1H), 7.02 (d, J = 7.3 Hz, 2H), 4.75 (d, J = 17.2 Hz, 1H), 4.63 (d, J = 15.2 Hz, 1H), 4.58 (d, J = 14.4 Hz, 1H), 4.38 (d, J = 14.2 Hz, 1H), 4.25–4.19 (m, 1H), 4.01 (d, J = 8.4 Hz, 1H), 3.75 (s, 1H), 3.60 (s, 3H), 3.50 (d, J = 5.8 Hz, 1H), 3.06 (dd, J = 5.6, 11.7 Hz, 1H), 2.50–2.44 (m, 1H), 2.42 (d, J = 10.4 Hz, 1H), 2.17 (s, 3H), 2.04–1.97 (m, 2H), 1.75–1.68 (m, 1H), 1.58 ppm (d, J = 10.7 Hz, 1H); ^{13}C{1H} *J*-MOD NMR (125 MHz, MeOD): δ = 167.14, 158.2, 157.9, 152.5, 145.4, 142.6, 142.4, 134.3, 129.8, 128.6, 127.4, 123.9, 121.8, 120.5, 84.0, 82.6, 77.3, 74.1, 59.7, 51.5, 48.8, 48.1, 42.0, 37.3, 36.2, 32.8, 23.4, 17.6; HR-MS (ESI): *m*/*z* calcd for $C_{29}H_{33}ClN_9O_3$ $[M - H_2O]^+$: 590.2394; found: 590.2379.

3.1.10.13 (7S,8R,9S,9aR,10S)-8-((4-(((5-Fluoro-2-((4-(trifluoromethyl)phenyl)amino)pyrimidin-4-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)methyl)-10-(hydroxymethyl)-1-methyl-4b,5,6,8,9,10-hexahydro-7H-7,9a-methanobenzo[a]azulene-7,8,9-triol ***38***. Yield: 85%; colourless oily compound; $[\alpha]_D^{20}$ = +9.8 (*c* 0.14, MeOH); ^{1}H NMR (500 MHz, MeOD): δ = 7.77 (s, 1H), 7.68 (d, J = 3.5 Hz, 1H), 7.57 (d, J = 8.5 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H), 7.01 (t, J = 7.5 Hz, 1H), 6.90–6.85 (m, 2H), 4.58 (dd, J = 15.6, 27.2 Hz, 2H), 4.44 (d, J = 14.2 Hz, 1H), 4.27 (d, J = 14.2 Hz, 1H), 4.15 (dd, J = 6.3, 8.8 Hz, 1H), 4.03 (d, J = 8.9 Hz, 1H), 3.65 (s, 1H), 3.39 (d, J = 6.3 Hz, 1H), 2.93 (dd, J = 5.6, 12.1 Hz, 1H), 2.36–2.30 (m, 2H), 2.05 (s, 3H), 1.91–1.85 (m, 2H), 1.63–1.52 (m, 1H), 1.45 ppm (d, J = 10.7 Hz, 2H); ^{13}C{1H} *J*-MOD NMR (125 MHz, MeOD): δ = 155.5 (d, $J_{F,C}$ = 3.1 Hz), 152.5 (d, $J_{F,C}$ = 10.5 Hz), 145.1, 144.2, 143.5, 142.7–140.7 (d, $J_{F,C}$ = 246.7 Hz), 142.4, 137.9 (d, $J_{F,C}$ = 20.2 Hz), 134.2, 130.0 (q, $J_{F,C}$ = 196.7 Hz), 128.5, 127.4, 125.3 (d, $J_{F,C}$ = 3.7 Hz, 2C), 124.2, 122.1 (q, $J_{F,C}$ = 33.1 Hz), 120.5, 117.6 (2C), 84.1, 82.6, 77.3, 74.3, 59.7, 51.5, 48.8, 48.1, 42.0, 35.4, 32.6, 23.4, 17.5 ppm; ^{19}F *J*-MOD NMR (470 MHz, MeOD): δ = −62.9 ($C_{q\text{-}F}$), −169.0 ($C_{q\text{-}F}$); HR-MS (ESI): *m*/*z* calcd for $C_{32}H_{33}F_4N_7O_3$ $[M - H_2O]^+$: 638.2581; found: 638.2485.

3.1.10.14 (7S,8R,9S,9aR,10S)-8-((4-(((5-chloro-2-((4-(trifluoromethyl)phenyl)amino)pyrimidin-4-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)methyl)-10-(hydroxymethyl)-1-methyl-4b,5,6,8,9,10-hexahydro-7H-7,9a-methanobenzo[a]azulene-7,8,9-triol ***39***. Yield: 85%; white crystals; m.p.: 216–219 °C; $[\alpha]_D^{20}$ = +30.5 (*c* 0.17, MeCN); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.94 (s, 1H), 7.69–7.64 (m, 3H), 7.54 (d, J = 8.5 Hz, 2H), 7.18 (dd, J = 7.2, 14.7 Hz, 2H), 7.03 (d, J = 7.6 Hz, 1H), 6.99 (d, J = 7.5 Hz, 1H), 5.89 (t, J = 5.1 Hz, 1H), 4.82–4.69 (m, 2H), 4.54 (d, J = 14.2 Hz, 1H), 4.37–4.31 (m, 2H), 4.20 (d, J = 8.9 Hz, 1H), 3.84 (s, 1H), 3.73 (s, 1H), 3.55 (d, J = 6.4 Hz, 1H), 3.04 (dd, J = 5.6, 12.2 Hz, 1H), 2.93 (s, 1H), 2.52–2.44 (m, 1H), 2.30 (d, J = 10.5 Hz, 1H), 2.18 (s, 3H), 2.12–2.03 (m, 1H), 1.97 (dd, J = 4.7, 14.0 Hz, 1H), 1.74–1.65 (m, 1H), 1.62 ppm (d, J = 10.9 Hz, 1H); ^{13}C{1H} *J*-MOD NMR (125 MHz, $CDCl_3$): δ = 157.7, 157.4, 153.1, 143.9, 143.0, 142.8, 142.4, 134.5, 129.2, 128.0, 126.1 (q, $J_{F,C}$ = 4.1 Hz, 2C), 124.8 (q, $J_{F,C}$ = 163.8 Hz), 123.8, 121.5 (q, $J_{F,C}$ = 32.8 Hz), 120.9, 118.2 (2C), 106.0, 83.7, 83.2, 74.8, 59.9, 51.2, 48.8, 48.3, 43.2, 36.9, 31.8, 29.6, 23.5, 18.9 ppm; ^{19}F *J*-MOD NMR (470 MHz, $CDCl_3$): δ = −61.7 ($C_{q\text{-}F}$); HR-MS (ESI): *m*/*z* calcd for $C_{32}H_{32}ClF_3N_7O_3$ $[M - H_2O]^+$: 654.2207; found: 654.2194.

3.1.10.15 1-((1-(((7S,8R,9S,9aR,10S)-7,8,9-Trihydroxy-10-(hydroxymethyl)-1-methyl-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulen-8-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl) pyrimidine-2,4(1H,3H)-dione ***40***. Yield: 63%; colourless oily compound; $[\alpha]_D^{20}$ = +11.6 (*c* 0.16, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.2 (s, 1H), 7.92 (s, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.14 (t, J = 7.5 Hz, 1H), 7.03–6.99 (m, 2H), 5.53 (d, J = 7.9 Hz, 1H), 4.87 (d, J = 3.5 Hz, 2H), 4.69 (s, 1H), 4.40 (d, J = 14.0 Hz, 1H), 4.30 (d, J = 14.2 Hz, 1H), 4.24 (dd, J = 7.3, 7.3 Hz, 1H), 4.18 (d, J = 8.7 Hz, 1H), 4.08 (s, 1H), 3.70 (s, 1H), 3.52–3.47 (m, 1H), 2.99 (dd, J = 5.7, 11.8 Hz, 1H), 2.35 (d, J = 10.7 Hz, 2H), 2.20 (s, 3H), 1.86 (d, J = 6.3 Hz, 2H), 1.63–1.52 (m, 1H), 1.47 ppm (d, J = 10.5 Hz, 1H); ^{13}C{1H} *J*-MOD NMR (125 MHz, DMSO-d_6): δ = 164.0, 151.2, 145.7, 144.6, 143.1, 141.8, 134.8, 129.0, 127.9, 125.5, 121.3, 101.6, 84.7, 82.7, 77.9, 74.2, 59.7, 52.1, 48.9, 48.3, 42.6, 42.5, 33.5, 24.0, 19.1 ppm; HR-MS (ESI): *m*/*z* calcd for $C_{25}H_{28}N_5O_5$ $[M - H_2O]^+$: 478.2090; found: 478.2077.

3.1.10.16 5-Fluoro-1-((1-(((7S,8R,9S,9aR,10S)-7,8,9-trihydroxy-10-(hydroxymethyl)-1-methyl-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulen-8-yl)methyl)-1H-1,2,3-triazol-4-yl) methyl)pyrimidine-2,4(1H,3H)-dione ***41***. Yield: 65%; white

crystals; m.p.: 156–158 °C; $[\alpha]_D^{20} = +32.1$ (c 0.13, MeOH); ^{1}H NMR (500 MHz, MeOD): $\delta = 8.01$ (s, 1H), 7.79 (d, $J = 6.3$ Hz, 1H), 7.16 (t, $J = 7.5$ Hz, 1H), 7.04 (d, $J = 2.1$ Hz, 1H), 7.02 (d, $J = 2.4$ Hz, 1H), 4.95 (dd, $J = 15.7$, 19.1 Hz, 2H), 4.59 (d, $J = 14.0$ Hz, 1H), 4.52 (s, 1H), 4.45 (d, $J = 14.2$ Hz, 1H), 4.36 (dd, $J = 6.3$, 8.7 Hz, 1H), 4.28 (d, $J = 8.7$ Hz, 1H), 3.81 (s, 1H), 3.57 (d, $J = 6.0$ Hz, 1H), 3.09 (dd, $J = 5.7$, 12.0 Hz, 1H), 2.52–2.45 (m, 2H), 2.24 (s, 3H), 2.06–2.00 (m, 2H), 1.78–1.67 (m, 1H), 1.61 ppm (d, $J = 10.5$ Hz, 1H); ^{13}C{1H}J-MOD NMR (125 MHz, MeOD): $\delta = 158.2$, 149.9 (d, $J_{F,C} = 12.9$ Hz), 143.6, 142.4, 141.3, 141.2–139.4 (d, $J_{F,C} = 233.9$ Hz), 134.3, 129.1 (d, $J_{F,C} = 33.4$ Hz), 128.6, 127.4, 125.5, 120.6, 84.2, 82.6, 77.3, 74.4, 58.7, 51.8, 48.9, 48.1, 42.4, 42.0, 32.6, 23.4, 17.6 ppm; ^{19}FNMR (470 MHz, MeOD): $\delta = -169.8$ ($C_{q\text{-}F}$); HR-MS (ESI): m/z calcd for $C_{25}H_{27}FN_5O_5$ $[M - H_2O]^+$: 496.1996; found: 496.1985.

3.2 Determination of the antiproliferative properties

A panel of human adherent cancer cell lines and fibroblast cells were utilised to determine the antiproliferative action of the prepared compounds by the MTT assay.[49] The applied cell lines and conditions were the same as published earlier.[31]

3.3 Docking study

The protein crystal structures were obtained from PDB (protein data bank). ChemBioDraw Ultra 11.0 was used to draw the tested structures for the docking study. The docking study was performed using Accelrys Discovery Studio 2.5 software.

3.4 Preparation of the crystal structures

Since the extracted crystal structure from PDB does not have hydrogen atoms, hydrogen atoms must be added first by applying several force fields (CHARMm). The addition of hydrogen atoms leads to steric hindrance, and subsequently, to a high-energy and unstable molecule, which should be minimized. Energy minimization of the complex was performed in 2000 steps of the adopted basis minimization method at finding the most stable and less energy structure and reducing H–H interactions without affecting the basic protein skeleton atoms. Then, the active site was determined by a 10 Å radius sphere.[50]

3.5 Docking study (CDocker)

By using the CDocker method, all possible conformations of the compound in the protein active site could be generated. Then, the results can be evaluated by both the CDocker energy and the number of interactions between the ligand and active site. This method requires preparing the crystal structure (as mentioned before) and the designed compounds using the Accelrys Discovery Studio protocol and applying a force field.

Before starting this study, it is important to emphasize that the method used is valid by comparing the conformation of the reference compound with its conformations generated by the applied docking method, where RMSD (Root Mean Square Deviation) should not exceed 2 Å.

4 Conclusions

A new series of *allo*-gibberic acid-based aminodiols, aminotetraols and 1,2,3-triazoles were synthesized in a stereoselective manner starting from commercially available gibberellic acid. The SeO_2/*t*-BuOOH-mediated allylic oxidation yielded a key intermediate triol, which, after the protection of the 1,4-diol functionality and epoxidation, was transformed into epoxide alcohol. The oxirane ring was then opened with either primary amines to provide aminodiols or sodium azide to afford an azido diol. The azido diol was then subjected to the CuAAC reaction to obtain dihydroxy 1,2,3-triazoles. The HCl-mediated acetonide deprotection of the prepared derivatives furnished aminotetraols and tetrahydroxy 1,2,3-triazoles. The antiproliferative effects of the prepared compounds were studied by the *in vitro* MTT method against a panel of human cancer cell lines (HeLa, SiHa, A2780, MCF-7 and MDA-MB-231) and fibroblasts, and the structure–activity relationship for the prepared compounds was explored. A significant difference was observed in the antiproliferative activity between *N*-substituted aminotriols. The importance of the "linker" property between *allo*-gibberic acid and 2,4-diaminopyrimidine motif was also explored. Based on the results, 2,4-diaminopyrimidine-ethylamine conjugates exhibited potent antiproliferative activity; conversely, they were endowed with low selectivity and high cytotoxicity towards the NIH/3T3 regioisomers. These agents seem to be superior to clinically utilised cisplatin. Consequently, some selected compounds could be regarded as potential hit compounds and they may be subjected to further investigation.

Data availability

I declare that the data supporting this article have been included as part of the ESI.†

Author contributions

Z. S. (Zsolt Szakonyi) and I. Z. conceived and designed the experiments; Z. A. K. and Z. S. (Zsuzsanna Schelz) performed the experiments, analysed the data and wrote the experimental part; Z. S. (Zsolt Szakonyi), T. M. L. and I. Z. discussed the results and contributed to writing the paper. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare no conflict of interest. The funders had no role in the design of the study, in the collection, analyses, or interpretation of data in the writing of the manuscript, or in the decision to publish the results.

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