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Stereoselective synthesis and antiproliferative activity of *allo*-gibberic acid-based 1,3-aminoalcohol regioisomers†

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A new library of *allo*-gibberic acid-based aminoalcohol regioisomers was synthesised stereoselectively starting from commercially available gibberellic acid, which yields *allo*-gibberic acid under mild acidic conditions. The successful formation of hydroxymethyl ketone derivative **5**, by acid-mediated rearrangement of previously prepared epoxide, paved the way to obtain the desired 1,3-aminoalcohols through Schiff base formation. To obtain the desired regioisomers, the primary alcohol functionality of **5** was subjected to mesylation, then replaced with either primary amine or sodium azide. The formed azide derivative was subjected to either CuAAC reaction to obtain 1,2,3-triazoles or underwent Pd-catalysed hydrogenolysis to obtain primary aminoalcohol, which was further transformed into 1,3-aminoalcohols by reductive alkylation. All prepared aminoalcohols were identified in a satisfactory manner using modern spectroscopic techniques and assessed for their antiproliferative activity against a panel of human cancer cell lines. The antiproliferative effects of the prepared compounds were assayed by *in vitro* MTT method against a panel of human cancer cell lines (HeLa, SiHa, A2780, MCF-7 and MDA-MB-231). A significant difference was observed in the antiproliferative activity between the regioisomers. Some compounds exerted outstanding activities against the malignant cells with limited action on fibroblasts, indicating considerable cancer selectivity.

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1. Introduction

Based on the variety of research that has been carried out in drug discovery and medicinal chemistry, it is a well-known reality that nature, including plants, animals, marine organisms and microorganisms, remains the richest, most varied and sustainable source of structurally diverse compounds with critical biological activity.[1,2] The *ent*-kaurane tetracyclic diterpenes represent a large group of natural products widely found in different plant families and endowed with remarkable biological activities.[3] Structurally, the majority of *ent*-kauranes discovered so far have a tetracyclic core structure formed by combining a perhydrophenanthrene skeleton with a cyclopentane ring.[4,5] Almost 600 of the known *ent*-kaurane diterpenes have been identified and characterised within the *Isodon* (Lamiaceae) plants, which have been employed to treat cancer and other inflammatory diseases for centuries.[6] The antiproliferative activity of different *ent*-kaurane diterpenoids has received considerable attention and has been deeply studied. Fujita *et al.* determined the structure–activity relationship of enmein and oridonin, which suggests the role of α,β-unsaturated ketone as a Michael receptor in easing the addition of nucleophiles such as alkanethiols resulting in inactivation of SH enzymes.[7] However, various pathways can be included in the anticancer activity of *ent*-kaurane diterpenes, such as telomerase activity inhibition (eriocalyxin B),[6,8] p53 activation (oridonin)[9,10] and AKT kinase inhibition (excisanin A).[11] Gibberellins (GAs), a class of *ent*-kaurane diterpenes, are phytohormones responsible for seed germination, plant growth and development. Gibberellic acid (GA_3) **1**, a well-known member of the GA family, attracted the interest of many researchers as a scaffold for antitumor studies because of its diverse functionalities, which are accessible for chemical modifications as well as its commercial availability at tonne quantities by fermentation of *Gibberella fujikuroi*.[12,13] Subsequently, a variety of derivatives with different functionalities has been reported and showed promising antiproliferative activity with different possible mechanisms. Chen *et al.* recorded the complete inhibition of topoisomerase-

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I activity by gibberellic acid methyl ester bearing two α,β-unsaturated ketone moieties.[14] Wu *et al.* reported that S phase arrest in the cell cycle and apoptosis could be induced by *allo*-gibberic-based 1,2,3-triazoles with an α,β-unsaturated ketone moiety.[15] Zhu *et al.* prepared a series of *allo*-gibberic acid benzyl esters endowed with strong antitumor activity. This activity could be linked to inhibiting $FGFR_1$ and KDR activation.[16] Moreover, Goel *et al.* demonstrated that the expression of PARP-1 and caspase 3 can be inhibited by ipomone, a novel gibberic acid-derived diterpene.[17]

On the other hand, 1,3-aminoalcohols and their *N*-substituted analogues have been studied extensively for their application as chiral auxiliaries for different reactions, such as ring opening, aldol condensation and catalytic reduction[18] as well as for their diverse biological activities. A library of isosteviol-based *N*-substituted 1,3-aminoalcohols was recently prepared and showed remarkable antiproliferative activity with a preference for benzyl substituents.[19] Moreover, 1,3-aminoalcohols have proven to be promising building blocks for new biologically active heterocyclic derivatives such as oxazines, thiazines and pyrimidines. 2,4-Diaminopyrimidine derivatives with potent antiproliferative activity were prepared starting from pinane- and (−)-isopulegol-based 1,3-aminoalcohols.[20,21]

In our previous work, we designed and evaluated the antiproliferative activity of a series of *N*-substituted *allo*-gibberic acid-based aminodiols. We found that *N*-naphthylethyl-substituted aminodiol derivatives showed the most promising antiproliferative activity. In particular, compound **A** presented in Fig. 1 exhibited a modest cancer selectivity (IC_{50} = 4.38–7.49 μM) over NIH/3 T3 fibroblast cells (IC_{50} = 10.88 μM).[22] Furthermore, a group of *allo*-gibberic acid-based aminoalcohols **B** shown in Fig. 1 has been recently considered for their antimicrobial activity against a panel of multidrug-resistant Gram-negative bacteria.[23] Combining these results with our continuous effort to obtain promising, more potent and selective anticancer agents has led us to the field of diterpene-based aminoalcohols. Herein, we report the synthesis of new gibberellic acid-based 1,3-aminoalcohol derivatives and their *in vitro* antiproliferative evaluation against different human cancer cell lines.

2. Results and discussion

2.1. Synthetic procedure

2.1.1. Synthesis of *allo*-gibberic acid-based 1,3-aminoalcohols

2.1.1.1. Synthesis of key intermediates (hydroxymethyl ketone 5 and primary aminoalcohol 7). The allylic alcohol derivative, *allo*-gibberic acid **2**, was obtained by HCl-mediated hydrolysis of the commercially available gibberellic acid **1** following literature methods.[12,16] As mentioned in our previous work, *cis*-epoxy alcohol **4** was prepared in a stereospecific manner by *m*-CPBA-mediated epoxidation of *allo*-gibberic acid ethyl ester **3** (Scheme 1).[22]

The key intermediate hydroxymethyl ketone **5** was obtained by HCl-mediated rearrangement of epoxy alcohol **4**. In this process, a six-membered transition state is formed and the carbonium ion is stabilised by Wagner–Meerwein rearrangement with the inversion of ring C/D configuration.[24] Moreover, compound **5** could also be prepared more efficiently on a gram scale, with higher yield and shorter reaction, by $BF_3{\cdot}Et_2O$-catalysed rearrangement, which can be explained by the coordination between the Lewis acid and the epoxide oxygen.[25]

Primary amines have attracted substantial interest as building blocks for the biosynthesis of bioactive molecules and they can be obtained simply by hydrogenation of unsaturated ligands, mainly oximes, containing the C–N bond. However, the heterogeneous catalytic hydrogenation of aldoximes and ketoximes remains the most resourceful selective method to obtain the corresponding amines.[26] Similarly, to obtain primary 1,3-aminoalcohol **7**, hydroxymethyl ketone **5** was first subjected to an oximation reaction by hydroxylamine hydrochloride in the presence of $NaHCO_3$. The formed oxime **6** underwent further RANEY® Ni-catalysed hydrogenation in THF and led to compound **7** with good yield and in a stereospecific manner as shown by NMR experiments (Scheme 2).

2.1.1.2. Synthesis of allo-gibberic acid-based 1,3-aminoalcohols via Schiff base formation. A series of *N*-substituted 1,3-aminoalcohols was prepared by either reductive amination of hydroxymethyl ketone **5** with different primary amines or reductive alkylation of primary aminoalcohol **7** with several aldehydes *via* the formation of Schiff bases followed by $NaBH_4$-mediated reduction. However, the efficiency

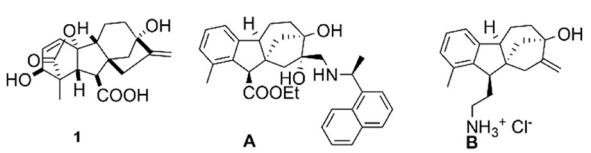
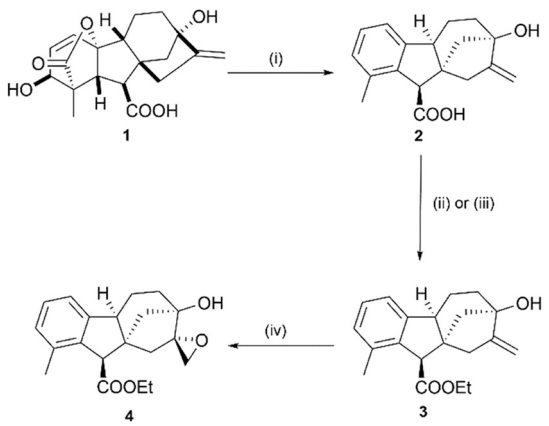
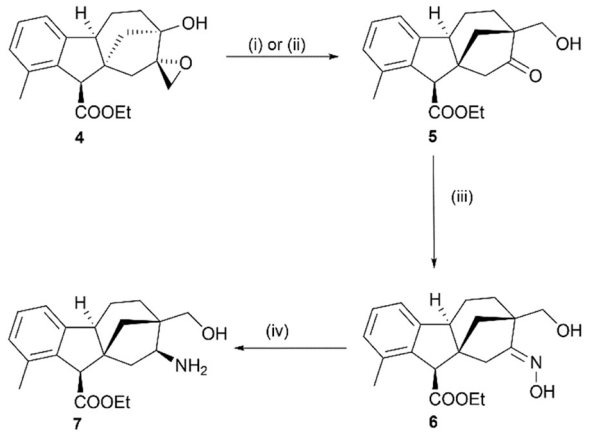


Fig. 1 The structure of gibberellic acid **1** and its bioactive derivatives.



Scheme 1 Synthesis of epoxy alcohol **4**. (i) HCl 1.2 M, 65 °C, 3 h, 70%; (ii) C_2H_5I (2 eq.), TBAF 1 M in THF (2.5 eq.), dry THF, Ar atm., 25 °C, 4 h, 95%; (iii) C_2H_5I (2.5 eq.), Cs_2CO_3 (2 eq.), MeCN, reflux, 1 h, 99%; (iv) *m*-CPBA 75% (2.5 eq.), dry DCM, 25 °C, 2 h, 62%.

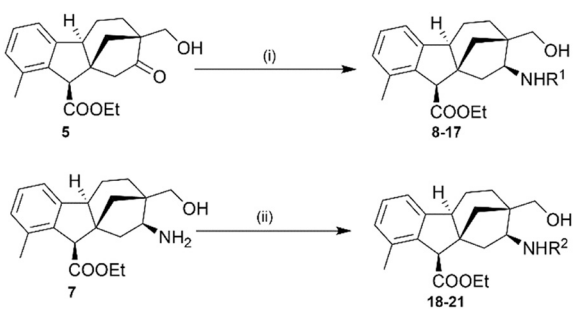


Scheme 2 Synthesis of primary 1,3-aminoalcohol **7**. (i) HCl (3 N), 25 °C, 72 h, 80%; (ii) cat. $BF_3{\cdot}Et_2O$, toluene, 25 °C, 12 h, 95%; (iii) H_2-NOH·HCl (2 eq.), $NaHCO_3$ (1 eq.), EtOH, reflux, 12 h, 93%; (iv) RANEY® Ni, H_2 (10 atm), THF, 25 °C, 24 h, 72%.

of reductive amination of compound **5** was enhanced by using a catalytic amount of $BF_3{\cdot}Et_2O$, as it promotes the nucleophilic attack of the primary amine on the carbonyl carbon.[27] A variety of nitrogen substituents were employed to study the steric and electronic effects on the antiproliferative activity of the designed aminoalcohols (Scheme 3 and Table 1).

2.1.2. Preparation of 1,3-aminoalcohol regioisomers

*2.1.2.1. Synthesis route of the critical intermediates for regioisomer preparation (mesylated alcohol **23** and the primary aminoalcohol **25**).* Within the framework of our synthetic plan, the next step includes the building of regioisomers of aminoalcohols **8–21**. For this purpose and starting from the considerable application of derivatives bearing mesyl, a good leaving group,[28] the alcoholic function of compound **5** was quantitatively transformed into the mesyl derivative by the reaction with methanesulfonyl chloride in the presence of dry pyridine. Since sodium borohydride is well known as a highly reactive and chemoselective reducing agent under specific conditions,[29] the $NaBH_4$-mediated ketone reduction of compound **22** was accomplished effectively and quantitatively in a mixture of DCM and MeOH (1 : 1). As the stereoselectivity



Scheme 3 Preparation of secondary 1,3-aminoalcohols **8–21**. (i) (1) R^1NH_2 (2 eq.), $BF_3{\cdot}Et_2O$ (5 μL), dry toluene, reflux (Dean–Stark), 24–48 h; (2) $NaBH_4$ (2 eq.), dry EtOH, 25 °C, 3 h, 54–70%; (ii) (1) aldehydes (1.2 eq.), dry EtOH, 25 °C, 3 h; (2) $NaBH_4$ (2 eq.), dry EtOH, 25 °C, 3 h, 46–55%.

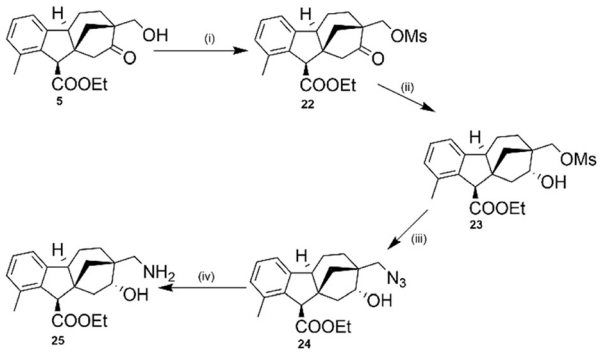
Table 1 1,3-Aminoalcohols **9–23**

Entry	Compound	R^1/R^2	Yield (%)
1	**8**	Benzyl	65
2	**9**	1-Naphthylmethyl	62
3	**10**	(*S*)-(−)-1-(2-Naphthyl)ethyl	60
4	**11**	(*R*)-(−)-1-(2-Naphthyl)ethyl	70
5	**12**	(*S*)-(−)-1-(1-Naphthyl)ethyl	55
6	**13**	(*R*)-(+)-1-(1-Naphthyl)ethyl	58
7	**14**	4-Fluorobenzyl	61
8	**15**	4-Methoxybenzyl	50
9	**16**	2-(1*H*-Indol-3-yl)ethyl	55
10	**17**	3-(1*H*-Imidazol-1-yl)propyl	54
11	**18**	5-Bromo-2-hydroxybenzyl	53
12	**19**	Quinolin-2-ylmethyl	51
13	**20**	Quinolin-4-ylmethyl	55
14	**21**	Pyridin-4-ylmethyl	46

of the reduction of the prochiral ketone can be influenced by the reaction temperature, product **23** was obtained as a single product under ice cooling. Next, the azidation of compound **23** with sodium azide was fully and preferably performed in dry DMF at 90 °C. Then, the favoured primary 1,3-aminoalcohol **25** was efficiently prepared by hydrogenation of 1,3-azido alcohol **24** catalysed by Pd/C and H_2 at 10 bar[30] (Scheme 4).

2.1.2.2. Preparation of 1,3-aminoalcohols via either MsO/primary amine exchange or Schiff base formation. As mesylates are well-known to be excellent leaving groups in nucleophilic substitution reactions, the exchange of the MsO function to form primary amino derivatives was successfully accomplished in the presence of triethylamine, yielding *N*-substituted 1,3-aminoalcohols **26–29** with acceptable yields.[31] Another series of 1,3-aminoalcohols **30–37** was prepared in a similar manner by reductive alkylation of primary aminoalcohol **25** (Scheme 5 and Table 2).

2.1.3. Preparation of hydroxy-1,2,3-triazoles. To expand our library and obtain a better understanding of the structure–activity relationship, two hydroxy triazoles were prepared through the CuAAC reaction (copper-catalysed azide–alkyne cycloaddition).[32,33] In detail, azido alcohol **24** was subjected to a 1,3-dipolar cycloaddition reaction with



Scheme 4 Preparation of primary 1,3-aminoalcohol **25**. (i) MsCl (6 eq.), dry pyridine, 25 °C, 12 h, 76%; (ii) $NaBH_4$ (2 eq.), DCM, MeOH (1 : 1), 0 °C, 3 h, 76%; (iii) NaN_3 (2 eq.), dry DMF, reflux, 12 h, 90%; (iv) Pd/C (10%), H_2 (10 atm), MeOH, 25 °C, 12 h, 75%.

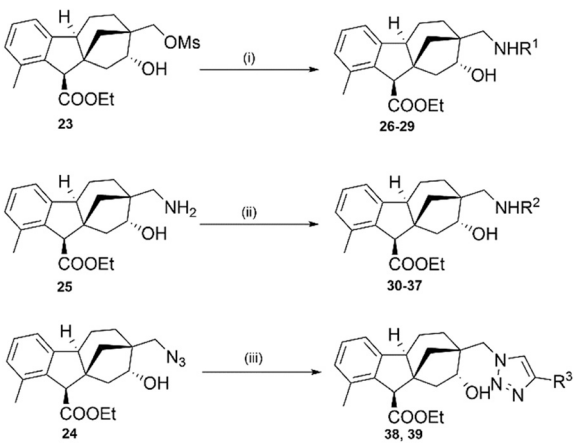
phenylacetylene and 3-phenyl-1-propyne under Sharpless click chemistry conditions [$Cu(OAc)_2{\cdot}H_2O$ and sodium ascorbate in a mixture of *t*-BuOH : H_2O (2 : 1)] to afford 1,4-disubstituted 1,2,3-triazoles **38** and **39** in a regioselective manner (Scheme 4 and Table 3).

2.2. Determination of relative configuration of synthesised 1,3-aminoalcohols

The relative configuration of the new stereocenter of the synthesised 1,3-aminoalcohols at position **16** was determined by means of NOESY experiments.

For aminoalcohols **8–21**, three clear NOE signals were observed between H-15 and H-16, H-15 and H-7, and H-15 and H-19. Therefore, the structure of *N*-substituted 1,3-aminoalcohols was determined as shown in Fig. 2. Besides the NOESY experiments, the relative configuration of primary aminoalcohol **7** was transformed by reductive alkylation with benzaldehyde yielding a compound that was identical to compound **8** obtained by reductive amination of **5**.

In addition, the relative configuration of **26–39** was defined by NOE spectral analysis of compound **23**. Based on the observed signals between H-15 and H-16 and between H-15 and H-10, the structure of **23** was determined, as shown in Fig. 3.



Scheme 5 (i) R^1NH_2 (4 eq.), Et_3N, MeCN (1 : 1), reflux, 72 h, 41–50%; (ii) (1) aldehydes (1.2 eq.), dry EtOH, 25 °C, 3 h; (2) $NaBH_4$ (2 eq.), dry EtOH, 25 °C, 3 h, 43–66%; (iii) acetylenes (1.5 eq.), $Cu(OAc)_2{\cdot}H_2O$ (2 mol%), sodium ascorbate (10 mol%), *t*-BuOH, H_2O (2 : 1), 25 °C, 12 h, 90%.

Table 2 1,3-Aminoalcohols **26–37**

Entry	Compound	R^1/R^2	Yield (%)
1	**26**	(*S*)-(−)-1-(2-Naphthyl)ethyl	50
2	**27**	(*R*)-(−)-1-(2-Naphthyl)ethyl	50
3	**28**	(*S*)-(−)-1-(1-Naphthyl)ethyl	46
4	**29**	(*R*)-(+)-1-(1-Naphthyl)ethyl	41
5	**30**	Benzyl	66
6	**31**	1-Naphthylmethyl	50
7	**32**	4-Fluorobenzyl	55
8	**33**	4-Methoxybenzyl	50
9	**34**	5-Bromo-2-hydroxybenzyl	53
10	**35**	Quinoline-2-ylmethyl	43
11	**36**	Quinoline-4-ylmethyl	55
12	**37**	Pyridine-4-ylmethyl	50

Table 3 Hydroxy triazoles **38–39**

Entry	Compound	R^3	Yield (%)
1	**38**	Phenyl	90
2	**39**	Benzyl	90

3. Antiproliferative activity

The *in vitro* antiproliferative activities of the synthesised 1,3-aminoalcohols **8–21** and **26–37** and hydroxy triazoles **38** and **39** against a panel of different human cancer cell lines, including cervical (SiHA and HeLa), breast (MCF7 and MDA-MB-231) and ovary (A2780) cancers as well as non-cancerous fibroblast cells were assayed by the MTT method.[34] Cisplatin, which is one of the most effective anticancer agents, was used as the reference drug and the results are summarised in Fig. 4 (Table 4).

4. Structure–activity relationship (SAR)

The *in vitro* antiproliferative activities of the prepared *N*-substituted 1,3-aminoalcohols against a group of cancer cell lines, involving cervical (SiHA and HeLa), breast (MCF-7 and MDA-MB 231) and ovary (A2780) cancers were evaluated by the MTT method, and the obtained results are summarised as the following:

Both *N*-benzyl-substituted aminoalcohol **8** and its corresponding regioisomer **30** showed modest suppression against all tested cancer cell lines. As the aromatic ring had the tendency to form hydrophobic and/or π interactions with the potential target, we further explored the activity by introducing either electron-withdrawing groups (F, Br) or electron-donating groups (OH, OCH_3). The results indicated that compounds **14** and **15** with fluoro and methoxy

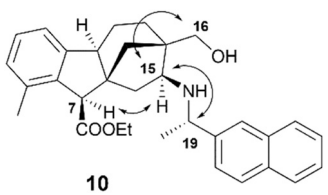


Fig. 2 The relative configuration of compound **10** (1,3-aminoalcohols **8–21**).

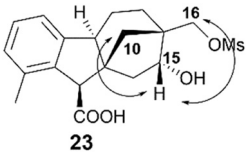


Fig. 3 The relative configuration of compound **23**.

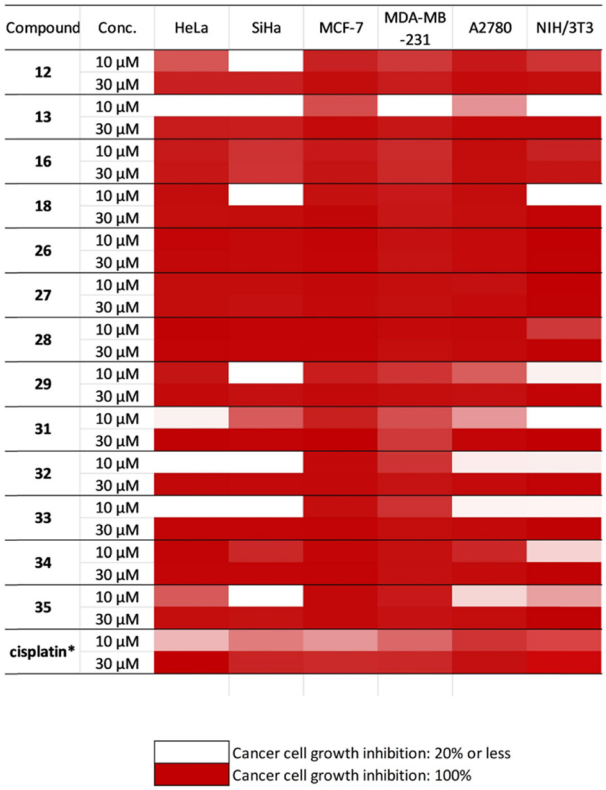


Fig. 4 Antiproliferative properties of the selected *allo*-gibberic acid-based aminoalcohols against cancer cells and NIH/3T3 fibroblasts. *Data from ref. 35.

Table 4 Antiproliferative properties of the selected *allo*-gibberic acid-based aminoalcohols against cancer cells and NIH/3T3 fibroblasts. Cisplatin data from ref. 35

	Calculated IC_{50} (μM)					
Compound	HeLa	SiHa	MCF-7	MDA-MB-231	A2780	NIH/3T3
12	20.70	22.34	3.43	10.38	6.17	6.02
13	18.55	22.73	7.07	19.29	4.57	14.47
16	4.01	4.12	3.14	4.71	4.57	12.95
18	5.06	21.87	3.85	6.48	5.08	19.71
26	5.10	4.36	3.66	4.47	4.57	4.62
32	18.78	8.40	4.40	7.71	15.03	15.17
33	12.91	17.67	4.08	6.50	13.83	14.74
34	4.71	20.55	2.42	4.99	5.39	13.02
Cisplatin	12.14	4.29	8.34	25.56	5.27	5.50

substituents at the *para* position, respectively, displayed a cell line-dependent influence, while their related regioisomers **32** and **33** elicited substantial enhancement in inhibitory activity with high selectivity towards MCF-7 and MDA-MB-231 as well as low cytotoxicity against NIH fibroblast cells. However, the introduction of both *o*-OH and *m*-Br (*para* to each other) in compounds **18** and **34** led to a further rise in activity but with mixed effects on cancer selectivity. Based on their calculated IC_{50} values, the latter molecules (**18**, **32**–**34**) are more potent than or comparable with the reference agent cisplatin (Fig. 5).

For *N*-1-naphthylmethyl-substituted aminoalcohol **9**, the inhibition values were substantial only at higher concentration (30 μM), whereas its related regioisomer **31** showed more pronounced growth in activity with marked selectivity towards SiHa, MCF-7 and MDA-MDB 231. For both regioisomers, the introduction of a methyl group at the *α* position (compounds **12**, **13**, **28** and **29**) resulted in highly active compounds. In particular, the *R*-diastereoisomers **13** and **29** were endowed with marked selectivity indicated by limited cytotoxicity against NIH/3T3. On the other hand, the inhibition activity of *R*- and *S*-α-methyl-2-naphthylmethyl derivatives **10** and **11** has decreased, whilst their regioisomers **26** and **27** were marked with both potent inhibition of cell growth and high cytotoxicity on non-cancerous cells.

Among all prepared aminoalcohols with heterocyclic substituents (quinoline, pyridine and 1,2,3-trizole), compound **35** with a quinolin-2-ylmethyl substituent showed potent inhibition activity against breast cancers (MCF-7 and MDA-MB-231) with much less cytotoxicity against fibroblasts, while compound **16** with the *N*-2-(1*H*-indol-3-yl)ethyl substituent exhibited lower than 5 μM IC_{50} values against all utilized cancerous cell lines but substantially higher value (12.95 μM) against fibroblasts, indicating a cancer-selective antiproliferative property of the molecule. Based on these findings, **16** may be regarded as a lead compound utilizable for the design and synthesis of further anticancerous gibberellic acid analogues.

5. Experimental

Commercially available compounds were used as obtained from suppliers (Molar Chemicals Ltd., Halásztelek, Hungary; Merck Ltd., Budapest, Hungary, and VWR International Ltd., Debrecen, Hungary), while solvents were dried according to standard procedures. Optical rotations were measured in MeOH at 20 °C using a PerkinElmer 341 polarimeter (PerkinElmer Inc., Shelton, CT, USA). Chromatographic separations and monitoring of reactions were carried out on a Merck Kieselgel 60 instrument (Merck Ltd., Budapest, Hungary). HR-MS flow injection analysis was performed using 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™ system (Waters, Manchester, UK). Melting points were determined on a Kofler apparatus (Nagema, Dresden, Germany) and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX 500 spectrometer (Bruker Biospin, Karlsruhe, Baden Württemberg, Germany) [500 MHz

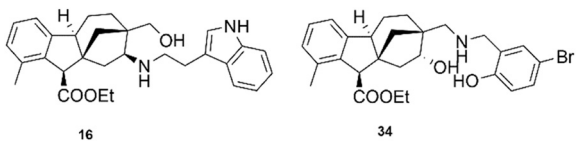


Fig. 5 The structure of the most promising *allo*-gibberic acid derivatives.

(^{1}H) and 125 MHz (^{13}C), δ = 0 (TMS)]. Chemical shifts are expressed in ppm (δ) relative to TMS as the internal reference. *J* values are given in Hz.

Gibberellic acid **1** is commercially available from Merck with ee% = 90% ($[\alpha]_D^{20}$ = +78.0, c 2, MeOH). *Allo*-gibberic acid **2** was prepared from gibberellic acid **1** according to a literature method.[12] Compounds **3** and **4** were prepared as mentioned in our previous work.[22] All spectroscopic data were similar to those described therein.

Preparation of hydroxymethyl ketone derivative 5

Ethyl (4b*S*,7*S*,9a*S*,10*R*)-7-(hydroxymethyl)-1-methyl-8-oxo-4b,6,7,8,9,10-hexahydro-5*H*-7,9a-methanobenzo[*a*]azulene-10-carboxylate 5

Method A. Epoxide **4** (2.00 g, 6.09 mmol) was suspended in 50 mL HCl (3 N) solution. The mixture was stirred for 72 hours at room temperature and then the solvent was evaporated. The residue was diluted with water (30 mL) and extracted with EtOAc (3 × 50 mL). After that, the organic phase was washed with brine solution (3 × 50 mL), dried over Na_2SO_4, filtered and then evaporated. The crude product was purified by column chromatography using *n*-hexane : EtOAc (1 : 1) as eluent.

Method B. To the solution of epoxide **4** (2.00 g, 6.09 mmol) in toluene (50 mL), boron trifluoride diethyl etherate (0.50 mL) was added and the mixture was stirred at room temperature for 12 hours. After that, the organic phase was washed with water (50 mL) and brine solution (3 × 50 mL), dried over Na_2SO_4, filtered and then evaporated. The crude product was purified by column chromatography using *n*-hexane : EtOAc (1 : 1) as eluent.

Yield: (method A: 80%, method B: 95%); white crystals; m.p.: 157–160 °C; $[\alpha]_D^{20}$ = +4.4 (c 0.14, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.20 (t, *J* = 7.5 Hz, 1H), 7.06 (d, *J* = 7.5 Hz, 1H), 6.98 (d, *J* = 7.5 Hz, 1H), 4.27 (m, 2H), 4.17 (s, 1H), 3.70 (dd, *J* = 6.6, 11.2 Hz, 1H), 3.49 (dd, *J* = 5.0, 11.3 Hz, 1H), 3.05 (t, *J* = 8.0 Hz, 1H), 2.71 (d, *J* = 18.0 Hz, 1H), 2.51 (dd, *J* = 3.2, 18.0 Hz, 1H), 2.19 (s, 3H), 2.17–2.10 (m, 1H), 2.08–2.03 (m, 1H), 1.93 (dd, *J* = 3.2, 12.1 Hz, 1H), 1.90–1.65 (m, 3H), 1.58 (s, 1H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 222.0, 171.6, 145.8, 137.5, 136.1, 129.0, 128.2, 120.4, 65.3, 60.8, 56.0, 53.7, 51.9, 51.6, 49.4, 33.2, 29.0, 22.7, 19.4, 14.4; HR-MS (ESI): *m*/*z* calcd for $C_{20}H_{25}O_4$ $[M + H]^+$: 329.1675; found: 329.1744.

Preparation of primary 1,3-aminoalcohol 7

Synthesis of oxime derivative 6. To a solution of hydroxymethyl ketone **5** (2.00 g, 6.09 mmol) in EtOH (50 mL), hydroxylamine hydrochloride (0.84 g, 12.18 mmol, 2 eq.) was added and the mixture was stirred in the presence of $NaHCO_3$ (0.51 g, 6.09 mmol, 1 eq.) under reflux for 12 hours. After that, the mixture was evaporated to dryness, and the residue was diluted with water and extracted with DCM (3 × 50 mL). The organic phase was washed with brine solution (3 × 50 mL), dried over Na_2SO_4, filtered and then evaporated. The crude product was purified by column chromatography using *n*-hexane : EtOAc (1 : 3) as eluent.

Ethyl (4bS,7R,9aS,10R,E)-8-(hydroxyimino)-7-(hydroxymethyl)-1-methyl-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulene-10-carboxylate ***6.*** Yield: 93%; colourless oily compound; $[\alpha]_D^{20}$ = +66.8 (c 0.13, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.48 (s, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.03 (d, *J* = 7.5 Hz, 1H), 6.98 (d, *J* = 7.5 Hz, 1H), 4.30–4.18 (m, 2H), 4.10 (s, 1H), 3.65–3.58 (m, 2H), 3.01–2.98 (m, 1H), 2.87–2.79 (m, 2H), 2.17 (s, 3H), 2.12–2.03 (m, 1H), 1.95–1.73 (m, 3H), 1.65–1.61 (m, 1H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.25 (d, *J* = 12.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.7, 169.6, 146.0, 138.0, 135.0, 128.4, 127.9, 120.1, 67.9, 60.8, 55.8, 51.9, 51.6, 48.5, 40.1, 35.9, 31.9, 21.8, 19.4, 14.4; HR-MS (ESI): *m*/*z* calcd for $C_{20}H_{26}NO_4$ $[M + H]^+$: 344.1784; found: 344.1857.

Hydrogenolysis of oxime 6. A suspension of RANEY® Ni (0.15 g) in THF (10 mL) was placed in a stainless-steel reactor equipped with a rotor stirrer. Then a solution of oxime **6** (0.50 g, 1.45 mmol) in THF (20 mL) was added, and the mixture was stirred under a H_2 atmosphere (10 atm) at room temperature for 24 hours. After that, the mixture was filtered through Celite and evaporated to dryness. The crude product was then purified by crystallisation using *n*-hexane : Et_2O (1 : 1).

Ethyl (4bS,7R,8S,9aS,10R)-8-amino-7-(hydroxymethyl)-1-methyl-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulene-10-carboxylate ***7.*** Yield: 72%; white crystals; m.p.: 129–132 °C; $[\alpha]_D^{20}$ = +14.2 (c 0.14, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.03 (s, 2H), 7.17–7.13 (m, 1H), 6.99 (dd, *J* = 4.0, 7.2 Hz, 2H), 4.18–4.13 (m, 2H), 4.10 (s, 1H), 3.49–3.43 (m, 1H), 3.39 (d, *J* = 11.1 Hz, 1H), 3.28 (d, *J* = 11.0 Hz, 1H), 3.14–3.08 (m, 1H), 2.5–2.45 (m, 1H), 2.15–2.07 (m, 1H), 2.06 (s, 3H),1.88–1.82 (m, 1H), 1.69–1.60 (m, 1H), 1.44–1.30 (m, 3H), 1.22 (t, *J* = 7.0 Hz, 3H), 0.98 (d, *J* = 12.1 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 172.0, 147.4, 138.3, 134.5, 128.5, 128.2, 121.0, 65.5, 60.5, 56.6, 53.4, 52.0, 52.2, 46.5, 42.7, 34.5, 23.6, 22.3, 19.3, 14.7; HR-MS (ESI): *m*/*z* calcd for $C_{20}H_{28}NO_3$ $[M + H]^+$: 330.2063; found: 330.2064.

Preparation of primary 1,3-aminoalcohol 25

Mesylation of primary alcohol 5. To a solution of hydroxymethyl derivative **5** (1.50 g, 4.56 mmol) in dry pyridine (25.0 mL) methanesulfonyl chloride (2.11 mL, 27.36 mmol, 6 eq.) was added, and the mixture was stirred at room temperature for 12 hours. Then, toluene (30 mL) was added, and the mixture was concentrated under vacuum to dryness. The residue was diluted with water (25 mL) and then extracted with DCM (3 × 25 mL). The organic phase was washed with brine solution (3 × 50 mL), dried over Na_2SO_4, filtered and then evaporated. The crude product was purified by column chromatography on silica gel using *n*-hexane : EtOAc (1 : 1) as eluent and then it was crystallised in Et_2O to afford the product as a white solid (1.4 g, 76%).

Ethyl (4bS,7S,9aS,10R)-1-methyl-7-(((methylsulfonyl)oxy)methyl)-8-oxo-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulene-10-carboxylate ***22.*** Yield: 76%;

white crystals; m.p.: 183–185 °C; $[\alpha]_D^{20}$ = +1.7 (c 0.14, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.21 (t, J = 7.6 Hz, 1H), 7.07 (d, J = 7.6 Hz, 1H), 6.97 (d, J = 7.5 Hz, 1H), 4.31–4.26 (m, 3H), 4.18 (s, 1H), 4.05 (d, J = 9.9 Hz, 1H), 3.08–3.03 (m, 1H), 2.97 (s, 3H), 2.72 (d, J = 18.0 Hz, 1H), 2.53 (dd, J = 3.4, 17.9 Hz, 1H), 2.19 (s, 3H), 2.17–2.12 (m, 1H), 2.07 (dd, J = 3.4, 12.7 Hz, 1H), 1.92–1.83 (m, 1H), 1.71–1.65 (m, 3H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 217.3, 171.4, 145.3, 137.4, 135.2, 129.1, 128.3, 120.4, 70.3, 61.0, 55.9, 51.7, 51.5, 51.1, 49.1, 37.0, 33.1, 28.7, 22.4, 19.4, 14.4; HR-MS (ESI): m/z calcd for $C_{21}H_{26}NaO_6S$ $[M + Na]^+$: 429.1348; found: 429.1336.

Reduction of the ketone function of compound 22. Compound **22** (2.00 g, 4.92 mmol) was dissolved in a mixture of DCM and MeOH (1 : 1) (200 mL) and $NaBH_4$ (0.37 g, 9.84 mmol) was added to the solution in small portions under ice cooling. Then, the mixture was stirred at 0 °C for 3 hours. After completion of the reaction (as monitored by TLC), the mixture was evaporated to dryness. The residue was diluted with water (50 mL) and then extracted with DCM (3 × 50 mL). The organic phase was washed with brine solution (3 × 50 mL), dried over Na_2SO_4, filtered and then evaporated. The crude product was purified by column chromatography on silica gel using *n*-hexane : EtOAc (1 : 1) as eluent.

Ethyl (4bS,7S,8R,9aS,10R)-8-hydroxy-1-methyl-7-(((methylsulfonyl)oxy)methyl)-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulene-10-carboxylate ***23****.* Yield: 76%; colourless oily compound; $[\alpha]_D^{20}$ = −8.4 (c 0.15, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.13 (t, J = 7.5 Hz, 1H), 6.97 (d, J = 7.5 Hz, 2H), 4.93 (d, J = 3.8 Hz, 1H), 4.21–4.11 (m, 2H), 4.07–3.97 (m, 3H), 3.93–3.87 (m, 1H), 3.12 (s, 3H), 2.95 (t, J = 8.5 Hz, 1H), 2.48–2.44 (m, 1H), 2.20–2.11 (m, 1H), 2.05 (s, 3H), 2.04–1.98 (m, 1H), 1.64–1.58 (m, 1H), 1.45–1.37 (m, 2H), 1.29–1.24 (m, 1H), 1.22 (t, J = 7.1 Hz, 3H), 0.86 (d, J = 11.9 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 172.0, 147.4, 138.5, 134.5, 128.5, 128.0, 120.8, 75.2, 71.6, 60.4, 56.5, 53.8, 52.2, 46.4, 45.9, 36.8, 34.0, 22.33, 22.31, 19.4, 14.7; HR-MS (ESI): m/z calcd for $C_{21}H_{29}O_6S$ $[M + H]^+$: 408.1607; found: 408.1612.

Preparation of 1,3-azido alcohol 24. Compound **23** (0.50 g, 1.22 mmol) was dissolved in dry DMF (25 mL) and then sodium azide (0.158 g, 2.44 mmol, 2 eq.) was added to the solution. The mixture was stirred under reflux for 12 hours. After the completion of the reaction (as monitored by TLC), the product was evaporated to dryness, the residue was diluted with EtOAc (20 mL) and then extracted with brine (3 × 20 mL). The organic phase was dried over Na_2SO_4, filtered and then evaporated. The crude product was purified by column chromatography on silica gel using *n*-hexane : EtOAc (2 : 1) as eluent.

Ethyl (4bS,7S,8R,9aS,10R)-7-(azidomethyl)-8-hydroxy-1-methyl-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulene-10-carboxylate ***24****.* Yield: 90%; colourless oily compound; $[\alpha]_D^{20}$ = −18.7 (c 0.15, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.16 (t, J = 7.5 Hz, 1H), 7.00 (d, J = 7.4 Hz, 1H), 6.97 (d, J = 7.4 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 4.06 (m, 1H), 4.00 (s, 1H), 3.37 (d, J = 11.7 Hz, 1H), 3.28 (d, J = 11.7 Hz, 1H), 3.03 (t, J = 8.2 Hz, 1H), 2.67 (dd, J = 10.5, 14.0 Hz, 1H), 2.25–2.15 (m, 2H), 2.14 (s, 3H), 1.92 (d, J = 3.6 Hz, 1H), 1.70–1.61 (m, 2H), 1.55–1.51 (m, 1H), 1.41–1.35 (m, 1H), 1.29 (t, J = 7.1 Hz, 3H), 0.85 (d, J = 11.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.2, 146.7, 137.9, 134.7, 128.5, 127.8, 120.3, 75.7, 61.0, 60.5, 56.7, 53.9, 52.6, 46.1, 45.6, 35.1, 24.4, 21.8, 19.4, 14.4; HR-MS (ESI): m/z calcd for $C_{20}H_{26}N_3O_3$ $[M + H]^+$: 355.1896; found: 355.1904.

Hydrogenolysis of 1,3-azido alcohol 24. 1,3-Azido alcohol **24** (2.0 g, 5.62 mmol) was dissolved in MeOH (30 mL) and transferred to a stainless-steel reactor. Then, Pd/C (0.15 g, 10% weight) was added to the solution and the mixture was stirred under a H_2 atmosphere (10 atm) at room temperature for 12 hours. After that, the black suspension was filtered through Celite and evaporated to dryness. The crude product was then purified by column chromatography using $CHCl_3$: MeOH (4 : 1) as eluent.

Ethyl (4bS,7S,8R,9aS,10R)-7-(aminomethyl)-8-hydroxy-1-methyl-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulene-10-carboxylate ***25****.* Yield: 75%; colourless oily compound; $[\alpha]_D^{20}$ = −15.3 (c 0.15, MeOH); ^{1}H NMR (500 MHz, CD_3OD): δ = 7.14 (t, J = 7.5 Hz, 1H), 6.98 (d, J = 7.5 Hz, 2H), 4.25 (q, J = 6.9 Hz, 2H), 4.02 (s, 1H), 3.93 (dd, J = 4.8, 10.5 Hz, 1H), 3.01 (t, J = 8.6 Hz, 1H), 2.70–2.58 (m, 3H), 2.28–2.21 (m,1H), 2.13 (s, 4H), 1.72–1.65 (m, 1H), 1.63–1.50 (m, 2H), 1.49–1.41 (m, 1H), 1.33 (t, J = 7.1 Hz, 3H), 0.76 ppm (d, J = 11.9 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD): δ = 173.0, 147.1, 137.8, 134.2, 127.9, 127.5, 120.1, 75.0, 60.4, 56.8, 54.2, 52.2, 50.0, 46.5, 46.2, 34.2, 22.9, 22.2, 18.2, 13.3; HR-MS (ESI): m/z calcd for $C_{20}H_{28}NO_3$ $[M + H]^+$: 330.2063; found: 330.2058.

Preparation of 1,3-aminoalcohol regioisomers

General procedure of reductive amination. To the solution of **5** (0.30 g, 0.91 mmol) in toluene (30 mL), the appropriate primary amines (1.82 mmol, 2 eq.) and a catalytic amount of $BF_3{\cdot}Et_2O$ (5 μL) were added. The reaction mixture was treated under reflux conditions for 24–48 hours at 110 °C using Dean–Stark equipment in the presence of a molecular sieve. Then the mixture was filtered and evaporated to dryness. The residue was dissolved in dry EtOH (30 mL) and $NaBH_4$ (0.069 g, 1.82 mmol) was added under ice cooling. The mixture was stirred at room temperature for 3 hours followed by solvent evaporation. The residue was diluted with water (20 mL) then extracted with DCM (3 × 20 mL). The organic phase was washed with brine solution (3 × 50 mL), dried over Na_2SO_4, filtered and then evaporated. The crude product was purified by column chromatography on silica gel using *n*-hexane : EtOAc (1 : 1 then 1 : 3) as eluent.

Ethyl (4bS,7R,8S,9aS,10R)-8-(benzylamino)-7-(hydroxymethyl)-1-methyl-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulene-10-carboxylate ***8****.* Prepared with benzylamine, yield: 65%; colorless oily compound; $[\alpha]_D^{20}$ = −1.2 (c 0.14, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.31 (m, 4H), 7.29–7.26 (m, 1H), 7.15 (t, J = 7.1 Hz, 1H), 6.99 (d, J = 7.2 Hz, 1H), 6.95 (d, J = 7.3 Hz, 1H), 4.25–4.19 (m, 2H), 4.01 (s, 1H), 3.89 (d, J = 12.8 Hz, 1H), 3.78 (d, J = 12.8 Hz, 1H), 3.55 (s, 2H), 3.05 (dd, J = 6.0, 10.5 Hz, 1H), 2.96 (t, J =

8.3 Hz, 1H), 2.75–2.69 (m, 1H), 2.15 (s, 3H), 2.13–2.10 (m, 1H), 1.98–1.89 (m, 1H), 1.74–1.64 (m, 2H), 1.59–1.54 (m, 1H), 1.41 (dd, J = 1.9, 11.7 Hz, 1H), 1.30–1.24 (m, 4H), 0.74 (d, J = 11.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.2, 146.7, 138.8, 138.1, 134.7, 128.51, 128.50, 128.2, 127.85, 127.83, 127.22, 127.21, 120.3, 73.8, 64.5, 60.4, 57.1, 54.9, 53.5, 52.8, 45.5, 44.9, 34.9, 24.9, 21.9, 19.4, 14.4; HR-MS (ESI): m/z calcd for $C_{27}H_{34}NO_3$ $[M + H]^+$: 420.2533; found: 420.2528.

Ethyl (4bS,7R,8S,9aS,10R)-7-(hydroxymethyl)-1-methyl-8-((naphthalen-1-ylmethyl)amino)-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulene-10-carboxylate ***9***. Prepared with 1-naphthylmethylamine, yield: 62%; white powder; m.p.: 78–81 °C; $[\alpha]_D^{20}$ = −46.2 (c 0.14, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.12 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.1 Hz, 1H), 7.79 (d, J = 7.9 Hz, 1H), 7.57–7.41 (m, 4H), 7.14 (t, J = 7.5 Hz, 1H), 6.97 (t, J = 7.6 Hz, 2H), 4.33 (d, J = 12.7 Hz, 1H), 4.25–4.07 (m, 3H), 3.63 (s, 1H), 3.53–3.43 (m, 3H), 3.30 (dd, J = 5.7, 10.3 Hz, 1H), 2.56 (dd, J = 10.4, 13.6 Hz, 1H), 2.24 (3H, s), 2.10–2.01 (1H, m), 2.00–1.93 (1H, m), 1.89–1.81 (1H, m), 1.63 (1H, m), 1.55–1.48 (1H, m), 1.31 (dd, J = 2.1, 11.5 Hz, 1H), 1.24 (t, J = 7.1 Hz, 3H), 1.05 (d, J = 11.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.6, 147.4, 138.7, 136.5, 134.4, 133.8, 131.8, 128.7, 128.1, 127.8, 127.6, 126.4, 126.3, 125.8, 125.3, 123.6, 120.4, 73.3, 65.1, 60.4, 58.0, 54.1, 52.0, 50.7, 45.5, 41.2, 40.3, 25.9, 21.0, 18.7, 14.4; HR-MS (ESI): m/z calcd for $C_{31}H_{36}NO_3$ $[M + H]^+$: 470.2689; found: 470.2688.

Ethyl (4bS,7R,8S,9aS,10R)-7-(hydroxymethyl)-1-methyl-8-(((S)-1-(naphthalen-2-yl)ethyl)amino)-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulene-10-carboxylate ***10***. Prepared with (*S*)-(−)-1-(2-naphthyl)ethylamine, yield: 60%; white wax; m.p.: 57–61 °C; $[\alpha]_D^{20}$ = −43.6 (c 0.13, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.85 (dd, J = 8.8, 14.0 Hz, 3H), 7.73 (s, 1H), 7.53–7.43 (m, 3H), 7.15 (t, J = 7.5 Hz, 1H), 6.98 (t, J = 8.5 Hz, 2H), 4.07–3.98 (m, 4H), 3.43 (d, J = 10.1 Hz, 1H), 3.30 (d, J = 10.2 Hz, 1H), 3.00 (t, J = 8.2 Hz, 1H), 2.74–2.62 (m, 2H), 2.20–2.13 (m, 1H), 2.12 (s, 3H), 1.97–1.90 (m, 1H), 1.79–1.59 (m, 3H), 1.44 (d, J = 7.0 Hz, 3H), 1.32–1.27 (m, 1H), 1.04 (t, J = 7.2 Hz, 3H), 0.52 (d, J = 11.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.9, 146.7, 141.9, 138.1, 134.7, 133.4, 133.0, 128.6, 128.5, 127.75, 127.74, 127.73, 126.0, 125.9, 125.6, 124.4, 120.2, 73.3, 62.0, 60.3, 57.1, 56.8, 55.1, 53.4, 45.2, 44.6, 34.6, 25.1, 24.8, 21.9, 19.4, 14.2; HR-MS (ESI): m/z calcd for $C_{32}H_{38}NO_3$ $[M + H]^+$: 484.2773; found: 484.2856.

Ethyl (4bS,7R,8S,9aS,10R)-7-(hydroxymethyl)-1-methyl-8-(((R)-1-(naphthalen-2-yl)ethyl)amino)-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulene-10-carboxylate ***11***. Prepared with (*R*)-(−)-1-(2-naphthyl)ethylamine, yield: 70%; oily compound; $[\alpha]_D^{20}$ = −63.1 (c 0.14, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.82 (d, J = 8.2 Hz, 3H), 7.73 (s, 1H), 7.50–7.44 (m, 3H), 7.13 (t, J = 7.5 Hz, 1H), 6.95 (d, J = 7.5 Hz, 1H), 6.92 (d, J = 7.5 Hz, 1H), 4.24–4.15 (m, 2H), 4.01 (q, J = 6.5 Hz, 1H), 3.89 (s, 1H), 3.63 (dd, J = 10.1, 25.4 Hz, 2H), 3.18 (dd, J = 6.1, 10.2 Hz, 1H), 2.86 (t, J = 8.3 Hz, 1H), 2.53 (dd, J = 10.4, 13.6 Hz, 1H), 2.10 (s, 3H), 2.09–2.03 (m, 1H), 1.98–1.86 (m, 1H), 1.81–1.72 (m, 1H), 1.68–1.52 (m, 1H), 1.47 (d, J = 6.6 Hz, 3H), 1.42–1.31 (m, 2H), 1.25 (t, J = 7.2 Hz, 3H), 0.71 (d, J = 11.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.2, 146.7, 143.4, 138.1, 134.6, 133.4, 132.9, 128.5, 128.4, 127.78, 127.77, 127.70, 126.1, 125.7, 125.0, 124.7, 120.3, 74.1, 63.2, 60.4, 57.3, 57.0, 55.0, 53.4, 45.6, 45.4, 34.7, 24.8, 23.0, 22.0, 19.4, 14.4; HR-MS (ESI): m/z calcd for $C_{32}H_{38}NO_3$ $[M + H]^+$: 484.2846; found: 484.2837.

Ethyl (4bS,7R,8S,9aS,10R)-7-(hydroxymethyl)-1-methyl-8-(((S)-1-(naphthalen-1-yl)ethyl)amino)-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulene-10-carboxylate ***12***. Prepared with (*S*)-(−)-1-(1-naphthyl)ethylamine, yield: 55%; colorless oily compound; $[\alpha]_D^{20}$ = +27.5 (c 0.12, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.22 (d, J = 8.4 Hz, 1H), 7.89 (d, J = 7.9 Hz, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.67 (d, J = 7.0 Hz, 1H), 7.56–7.45 (m, 3H), 7.15 (t, J = 7.6 Hz, 1H), 6.98 (t, J = 7.0 Hz, 2H), 4.76 (q, J = 6.5 Hz, 1H), 4.05–3.98 (m, 2H), 3.95 (s, 1H), 3.45 (d, J = 10.2 Hz, 1H), 3.35 (d, J = 10.4 Hz, 1H), 3.03–2.97 (m, 1H), 2.78 (dd, J = 6.0, 10.1 Hz, 1H), 2.60 (dd, J = 10.1, 13.2 Hz, 1H), 2.22–2.14 (m, 1H), 2.11 (s, 3H), 1.99–1.92 (m, 1H), 1.74–1.62 (m, 3H), 1.53 (d, J = 6.5 Hz, 3H), 1.33–1.29 (m, 1H), 0.98 (t, J = 7.2 Hz, 3H), 0.56 (d, J = 11.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.9, 146.7, 140.3, 138.2, 134.7, 134.0, 131.5, 129.1, 128.5, 127.7, 127.4, 125.9, 125.8, 125.4, 123.4, 122.6, 120.2, 72.7, 61.8, 60.3, 57.0, 55.1, 53.3, 51.9, 45.5, 45.2, 34.6, 24.8, 24.6, 22.0, 19.4, 14.1; HR-MS (ESI): m/z calcd for $C_{32}H_{38}NO_3$ $[M + H]^+$: 484.2773; found: 484.2853.

Ethyl (4bS,7R,8S,9aS,10R)-7-(hydroxymethyl)-1-methyl-8-(((R)-1-(naphthalen-1-yl)ethyl)amino)-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulene-10-carboxylate ***13***. Prepared with (*R*)-(+)-1-(1-naphthyl)ethylamine, yield: 58%; white powder; m.p.: 50–53 °C; $[\alpha]_D^{20}$ = −7.6 (c 0.13, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.16 (d, J = 8.4 Hz, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.77 (d, J = 8.2 Hz, 1H), 7.61 (d, J = 7.2 Hz, 1H), 7.56–7.45 (m, 3H), 7.13 (t, J = 7.5 Hz, 1H), 6.97 (d, J = 7.5 Hz, 1H), 6.93 (d, J = 7.5 Hz, 1H), 4.72 (q, J = 6.4 Hz, 1H), 4.28–4.16 (m, 2H), 3.95 (s, 1H), 3.65 (d, J = 9.9 Hz, 1H), 3.59 (d, J = 9.9 Hz, 1H), 3.29–3.29 (m, 1H), 2.89–2.83 (m, 1H), 2.70–2.63 (m, 1H), 2.13 (s, 3H), 2.10–1.99 (m, 1H), 1.95–1.86 (m, 1H), 1.81–1.72 (m, 1H), 1.69–1.59 (m, 1H), 1.55 (d, J = 6.5 Hz, 3H), 1.50–1.39 (m, 2H), 1.27 (t, J = 7.1 Hz, 3H), 0.75 (d, J = 11.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.2, 146.7, 141.7, 138.1, 134.6, 133.9, 130.6, 129.1, 128.5, 127.8, 127.6, 126.1, 125.7, 125.5, 123.1, 122.6, 120.3, 74.0, 62.8, 60.4, 57.1, 55.0, 53.4, 51.6, 45.5, 45.1, 34.8, 24.8, 22.3, 21.9, 19.4, 14.4; HR-MS (ESI): m/z calcd for $C_{32}H_{38}NO_3$ $[M + H]^+$: 484.2773; found: 484.2858.

Ethyl (4bS,7R,8S,9aS,10R)-8-((4-fluorobenzyl)amino)-7-(hydroxymethyl)-1-methyl-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulene-10-carboxylate ***14***. Prepared with 4-fluorobenzylamine, yield: 61%; oily compound; $[\alpha]_D^{20}$ = +1.5 (c 0.13, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32–7.26 (m, 2H), 7.16 (t, J = 7.5 Hz, 1H), 7.05–6.94 (m, 4H), 4.25–4.18 (m, 2H), 4.01 (s, 1H), 3.86 (d, J = 12.8 Hz, 1H), 3.73 (d, J = 13.0 Hz, 1H), 3.54 (dd, J = 9.9, 15.0 Hz, 2H), 3.06–2.94 (m, 2H), 2.71 (dd, J = 10.5, 13.4 Hz, 1H), 2.15 (s, 3H), 2.13–2.09 (m, 1H), 1.97–1.89 (m, 1H), 1.74–1.64 (m, 2H), 1.59–1.53 (m, 1H), 1.41 (d, J = 11.4 Hz, 1H), 1.28 (t, J = 7.1 Hz, 3H), 0.75 (d, J = 11.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.2, 163.0, 146.7, 138.1, 135.5, 134.7, 129.7, 129.7, 128.5, 127.8, 120.3,

115.4, 115.2, 73.6, 64.4, 60.5, 57.1, 54.9, 53.5, 52.0, 45.5, 44.9, 34.9, 24.8, 21.9, 19.4, 14.4; ^{19}F NMR (470 MHz, $CDCl_3$): δ = −115.4 ($C_{q\text{-}F}$); HR-MS (ESI): *m*/*z* calcd for $C_{27}H_{33}FNO_3$ $[M + H]^+$: 438.2366; found: 438.2445.

Ethyl (4bS,7R,8S,9aS,10R)-7-(hydroxymethyl)-8-((4-methoxybenzyl)amino)-1-methyl-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulene-10-carboxylate ***15***. Prepared with 4-methoxybenzylamine, yield: 50%; oily compound; $[\alpha]_D^{20}$ = −7.2 (c 0.13, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25–7.22 (m, 2H), 7.15 (t, *J* = 7.5 Hz, 1H), 6.98 (d, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 7.4 Hz, 1H), 6.89–6.85 (m, 2H), 4.28–4.17 (m, 2H), 4.01 (s, 1H), 3.85–3.78 (m, 4H), 3.71 (d, *J* = 12.5 Hz, 1H), 3.55 (s, 2H), 3.06–2.93 (m, 2H), 2.73 (dd, *J* = 10.4, 13.4 Hz, 1H), 2.15 (s, 3H), 2.13–2.08 (m, 1H), 1.97–1.88 (m, 1H), 1.74–1.63 (m, 2H), 1.58–1.52 (m, 1H), 1.41 (dd, *J* = 1.8, 11.7 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.73 (d, *J* = 12.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.2, 158.8, 146.7, 138.2, 134.7, 131.9, 129.4, 129.3, 128.5, 127.7, 120.2, 113.94, 113.91, 73.9, 64.5, 60.4, 57.1, 55.2, 54.9, 53.6, 52.2, 45.4, 45.0, 34.9, 24.9, 21.9, 19.4, 14.4; HR-MS (ESI): *m*/*z* calcd for $C_{28}H_{36}NO_4$ $[M + H]^+$: 450.2638; found: 450.2631.

Ethyl (4bS,7R,8S,9aS,10R)-8-((2-(1H-indol-3-yl)ethyl)amino)-7-(hydroxymethyl)-1-methyl-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulene-10-carboxylate ***16***. Prepared with tryptamine, yield: 55%; white powder; m.p.: 61–65 °C; $[\alpha]_D^{20}$ = −1.3 (c 0.13, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.05 (s, 1H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.19 (t, *J* = 7.24 Hz, 1H), 7.15–7.10 (m, 2H), 7.05 (d, *J* = 2.0 Hz, 1H), 6.98 (d, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 4.25–4.19 (m, 2H), 3.96 (s, 1H), 3.54 (s, 2H), 3.10–2.80 (m, 6H), 2.68 (dd, *J* = 10.5, 13.4 Hz, 1H), 2.13 (s, 3H), 2.02–1.92 (m, 1H), 1.87–1.77 (m, 1H), 1.70–1.56 (m, 2H), 1.45–1.35 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 3H), 0.72 (d, *J* = 11.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.2, 146.7, 138.1, 136.4, 134.7, 128.5, 127.7, 127.3, 122.1, 121.9, 120.2, 119.3, 118.7, 113.8, 111.2, 73.9, 65.3, 60.4, 57.1, 54.8, 53.5, 48.8, 45.3, 44.7, 34.8, 26.1, 24.9, 21.8, 19.4, 14.5; HR-MS (ESI): *m*/*z* calcd for $C_{30}H_{37}N_2O_3$ $[M + H]^+$: 473.2726; found: 473.2804.

Ethyl (4bS,7R,8S,9aS,10R)-8-((3-(1H-imidazol-1-yl)propyl)amino)-7-(hydroxymethyl)-1-methyl-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulene-10-carboxylate ***17***. Prepared with 1-(3-aminopropyl)imidazole, yield: 54%; colorless oily compound; $[\alpha]_D^{20}$ = +30.2 (c 0.11, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.51 (s, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 7.07 (s, 1H), 7.02 (d, *J* = 7.4 Hz, 1H), 6.96 (d, *J* = 7.7 Hz, 1H), 6.93 (s, 1H), 4.22 (q, *J* = 7.3 Hz, 2H), 4.04 (t, *J* = 6.7 Hz, 2H), 3.95 (s, 1H), 3.58–3.53 (m, 2H), 2.98–2.91 (m, 2H), 2.76–2.62 (m, 2H), 2.55–2.49 (m, 1H), 2.14 (s, 3H), 2.12–2.09 (m, 1H), 2.01–1.84 (m, 3H), 1.73–1.63 (m, 2H), 1.51–1.40 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.76 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.2, 146.6, 138.1, 137.2, 134.7, 129.6, 128.5, 127.8, 120.3, 118.8, 73.4, 65.0, 60.5, 57.1, 54.9, 53.4, 45.5, 45.2, 44.9, 44.6, 34.9, 31.5, 24.8, 21.9, 19.4, 14.5; HR-MS (ESI): *m*/*z* calcd for $C_{26}H_{36}N_3O_3$ $[M + H]^+$: 438.2678; found: 438.2767.

General procedure of reductive alkylation. To a solution of the primary aminoalcohol (**7** or **25**) (0.10 g, 0.30 mmol) in dry EtOH (10 mL), different aldehydes (0.36 mmol, 1.2 eq.) were added, and the formed solution was stirred at room temperature for 3 hours. Then, the mixture was evaporated to dryness, redissolved in dry EtOH (10 mL), stirred for a further 1 hour and evaporated again to dryness. The crude product was dissolved in dry EtOH (20 mL) and then $NaBH_4$ (0.023 g, 0.60 mmol) was added to the solution in small portions under ice cooling. The reaction was completed after 3 hours of stirring at room temperature (as monitored by TLC). The mixture was evaporated to dryness. The residue was diluted with water (10 mL) and then extracted with DCM (3 × 10 mL). The organic phase was washed with brine solution (3 × 30 mL), dried over Na_2SO_4, filtered and evaporated. The crude product was purified by column chromatography on silica gel using $CHCl_3$: MeOH 19 : 1 then *n*-hexane : EtOAc 1 : 2 as eluent.

Ethyl (4bS,7R,8S,9aS,10R)-8-((5-bromo-2-hydroxybenzyl)amino)-7-(hydroxymethyl)-1-methyl-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulene-10-carboxylate ***18***. Prepared with 5-bromosalicylaldehyde (5-bromo-2-hydroxybenzaldehyde), yield: 53%; white powder; m.p.: 82–85 °C; $[\alpha]_D^{20}$ = +4.2 (c 0.14, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25–7.23 (m, 1H), 7.18–7.12 (m, 2H), 7.00 (d, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 7.5 Hz, 1H), 6.71 (d, *J* = 8.7 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 4.01 (t, *J* = 6.9 Hz, 2H), 3.88 (d, *J* = 13.9 Hz, 1H), 3.52 (d, *J* = 10.3 Hz, 1H), 3.47 (d, *J* = 10.3 Hz, 1H), 3.10 (dd, *J* = 5.3, 10.3 Hz, 1H), 3.00 (t, *J* = 8.0 Hz, 1H), 2.65–2.58 (m, 1H), 2.18–2.15 (m, 1H), 2.14 (s, 3H), 1.96–1.87 (m, 1H), 1.74–1.65 (m, 2H), 1.56–1.44 (m, 2H), 1.29 (t, *J* = 7.2 Hz, 3H), 0.93 (d, *J* = 11.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.2, 157.3, 146.5, 138.0, 134.7, 131.5, 130.7, 128.6, 127.8, 124.9, 120.3, 118.1, 110.8, 70.7, 62.1, 60.5, 56.8, 54.3, 53.1, 51.4, 46.5, 44.0, 36.1, 24.7, 21.7, 19.4, 14.4; HR-MS (ESI): *m*/*z* calcd for $C_{27}H_{33}BrNO_4$ $[M + H]^+$: 516.1494; found: 516.1558.

Ethyl (4bS,7R,8S,9aS,10R)-7-(hydroxymethyl)-1-methyl-8-((quinolin-2-ylmethyl)amino)-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulene-10-carboxylate ***19***. Prepared with 2-quinoline carboxaldehyde, yield: 51%; oily compound; $[\alpha]_D^{20}$ = +17.2 (c 0.13, MeOH); ^{1}H NMR (500 MHz, CDCl3): δ = 8.16 (t, *J* = 8.5 Hz, 2H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.75–7.70 (m, 1H), 7.56–7.52 (m, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.16 (t, *J* = 7.6 Hz,1H), 7.01–6.97 (m, 2H), 4.30 (d, *J* = 16.4 Hz, 1H), 4.20–4.09 (m, 3H), 3.98 (s, 1H), 3.60 (dd, *J* = 11.2, 13.3 Hz, 2H), 3.16–3.04 (m, 2H), 2.59–2.54 (m. 1H), 2.31–2.24 (m, 2H), 2.13 (s, 3H), 1.78–1.64 (m, 3H), 1.43–1.39 (m, 1H), 1.21 (t, *J* = 7.1 Hz, 3H), 0.75 ppm (d, *J* = 11.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.3, 160.2, 147.3, 147.1, 138.3, 137.0, 134.6, 129.9, 128.38, 128.30, 127.7, 127.6, 127.3, 126.3, 120.7, 120.3, 73.4, 62.6, 60.4, 57.0, 54.4, 53.7, 53.5, 46.4, 45.5, 35.7, 25.2, 21.9, 19.3, 14.4; HR-MS (ESI): *m*/*z* calcd for $C_{30}H_{35}N_2O_3$ $[M + H]^+$: 471.2642; found: 471.2647.

Ethyl (4bS,7R,8S,9aS,10R)-7-(hydroxymethyl)-1-methyl-8-((quinolin-4-ylmethyl)amino)-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulene-10-carboxylate ***20***. Prepared with

4-quinoline carboxaldehyde, yield: 55%; oily compound; $[\alpha]_D^{20}$ = +4.1 (c 0.15, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.89 (d, J = 4.3 Hz, 1H), 8.15 (d, J = 8.2 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.72 (t, J = 7.0 Hz, 1H), 7.59 (t, J = 7.7 Hz, 1H), 7.47 (d, J = 4.3 Hz, 1H), 7.17 (t, J = 7.5 Hz, 1H), 7.00 (d, J = 7.4 Hz, 1H), 6.97 (d, J = 7.4 Hz, 1H), 4.37 (d, J = 14.2 Hz, 1H), 4.28–4.21 (m, 3H), 4.04 (s, 1H), 3.60–3.52 (m, 2H), 3.18 (dd, J = 5.6, 10.2 Hz, 1H), 3.05–2.98 (m, 1H), 2.78 (dd, J = 10.5, 13.2 Hz, 1H), 2.20–2.16 (m, 1H), 2.15 (s, 3H), 2.04–1.98 (m, 1H), 1.74–1.64 (m, 3H), 1.49–1.43 (m, 1H), 1.29 (t, J = 7.1 Hz, 3H), 0.81 (d, J = 12.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.2, 150.3, 148.2, 146.6, 145.2, 138.1, 134.7, 130.2, 129.2, 128.6, 127.8, 126.9, 126.7, 123.1, 120.3, 120.1, 73.0, 64.6, 60.5, 57.0, 54.8, 53.5, 49.2, 46.0, 44.8, 35.0, 24.8, 21.8, 19.4, 14.5; HR-MS (ESI): m/z calcd for $C_{30}H_{35}N_2O_3$ $[M + H]^+$: 471.2642; found: 471.2633.

Ethyl (4bS,7R,8S,9aS,10R)-7-(hydroxymethyl)-1-methyl-8-((pyridin-4-ylmethyl)amino)-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulene-10-carboxylate ***21***. Prepared with 4-pyridine carboxaldehyde, yield: 46%; oily compound; $[\alpha]_D^{20}$ = −13.9 (c 0.13, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.56 (d, J = 5.8 Hz, 2H), 7.29–7.26 (m, 2H), 7.16 (t, J = 7.5 Hz, 1H), 7.00 (d, J = 7.5 Hz, 1H), 6.97 (d, J = 7.5 Hz, 1H), 4.27–4.19 (m, 2H), 4.01 (s, 1H), 3.90 (d, J = 14.7 Hz, 1H), 3.78 (d, J = 14.3 Hz, 1H), 3.59–3.52 (m, 2H), 3.06–2.95 (m, 2H), 2.68 (dd, J = 10.3, 13.4 Hz, 1H), 2.20–2.16 (m, 1H), 2.15 (s, 3H), 2.01–1.95 (m, 1H), 1.74–1.65 (m, 2H), 1.61–1.55 (m, 1H), 1.45–1.41 (m, 1H), 1.28 (t, J = 7.2 Hz, 3H), 0.78 (d, J = 11.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.2, 149.92, 149.93, 149.0, 146.6, 138.1, 134.7, 128.5, 127.8, 122.91, 122.90, 120.3, 73.1, 64.2, 60.5, 57.0, 54.8, 53.4, 51.6, 45.8, 44.8, 35.0, 24.7, 21.9, 19.4, 14.4; HR-MS (ESI): m/z calcd for $C_{26}H_{33}N_2O_3$ $[M + H]^+$: 421.2485; found: 421.2464.

Ethyl (4bS,7S,8R,9aS,10R)-7-((benzylamino)methyl)-8-hydroxy-1-methyl-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulene-10-carboxylate ***30***. Prepared with benzaldehyde, yield: 66%; oily colorless compound; $[\alpha]_D^{20}$ = −2.7 (c 0.14, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.23 (m, 5H), 7.14 (t, J = 7.5 Hz, 1H), 6.98 (d, J = 7.5 Hz, 1H), 6.94 (d, J = 7.5 Hz, 1H), 4.21 (m, 2H), 4.03–3.98 (m, 2H), 3.81–3.72 (m, 2H), 3.04–2.95 (m, 1H), 2.85 (d, J = 11.1 Hz, 1H), 2.66 (dd, J = 10.6, 13.8 Hz, 1H), 2.38 (d, J = 11.1 Hz, 1H), 2.26–2.16 (m, 2H), 2.13 (s, 3H), 1.68–1.62 (m, 1H), 1.60–1.46 (m, 2H), 1.41–1.34 (m, 1H), 1.28 (t, J = 7.2 Hz, 3H), 0.65 ppm (d, J = 11.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.4, 147.2, 138.7, 138.1, 134.6, 128.53, 128.52, 128.4, 128.14, 128.13, 127.8, 127.1, 120.4, 78.7, 60.5, 60.4, 57.1, 54.8, 54.7, 52.6, 45.2, 44.8, 35.0, 23.9, 22.2, 19.4, 14.4; HR-MS (ESI): m/z calcd for $C_{27}H_{34}NO_3$ $[M + H]^+$: 420.2533; found: 420.2525.

Ethyl (4bS,7S,8R,9aS,10R)-8-hydroxy-1-methyl-7-(((naphthalen-1-ylmethyl)amino)methyl)-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulene-10-carboxylate ***31***. Prepared with 1-naphthaldehyde, yield: 50%; colorless oily compound; $[\alpha]_D^{20}$ = −18.4 (c 0.12, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.10 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 7.6 Hz, 1H), 7.80–7.76 (m, 1H), 7.55–7.40 (m, 4H), 7.14 (t, J = 7.5 Hz, 1H), 6.98 (d, J = 7.4 Hz, 1H), 6.93 (d, J = 7.4 Hz, 1H), 4.25–4.14 (m, 4H), 4.04–3.99 (m, 2H), 3.02–2.95 (m, 2H), 2.66 (dd, J = 10.6, 13.8 Hz, 1H), 2.51 (d, J = 11.6 Hz, 1H), 2.23–2.14 (m, 2H), 2.13 (s, 3H), 1.65–1.49 (m, 3H), 1.39–1.31 (m, 1H), 1.29 (t, J = 7.1 Hz, 3H), 0.68 (d, J = 11.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.4, 147.2, 138.1, 135.3, 134.6, 133.9, 131.8, 128.7, 128.4, 128.1, 127.8, 126.34, 126.31, 125.7, 125.3, 123.5, 120.4, 78.8, 61.2, 60.4, 57.1, 54.8, 52.8, 52.6, 45.3, 44.8, 35.1, 23.9, 22.2, 19.4, 14.5; HR-MS (ESI): m/z calcd for $C_{31}H_{36}NO_3$ $[M + H]^+$: 470.2689; found: 470.2681.

Ethyl (4bS,7S,8R,9aS,10R)-7-(((4-fluorobenzyl)amino)methyl)-8-hydroxy-1-methyl-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulene-10-carboxylate ***32***. Prepared with 4-fluorobenzaldehyde, yield: 55%; oily compound; $[\alpha]_D^{20}$ = −22.5 (c 0.15, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25–7.21 (m, 2H), 7.14 (t, J = 7.5 Hz, 1H), 7.03–6.93 (m, 4H), 4.24–4.17 (m, 2H), 4.02 (s, 1H), 3.96 (dd, J = 5.8, 8.7 Hz, 1H), 3.76 (d, J = 13.3 Hz, 1H), 3.68 (d, J = 13.1 Hz, 1H), 3.03–2.98 (m, 1H), 2.81 (d, J = 11.3 Hz, 1H), 2.69–2.63 (m, 1H), 2.35 (d, J = 11.3 Hz, 1H), 2.25–2.15 (m, 2H), 2.13 (s, 3H), 1.67–1.47 (m, 3H), 1.41–1.35 (m, 1H), 1.28 (t, J = 7.1 Hz, 3H), 0.64 ppm (d, J = 11.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.4, 147.1, 138.1, 135.67, 135.65, 134.6, 129.6, 129.5, 128.4, 127.8, 120.4, 115.3, 115.2, 78.7, 60.4, 60.3, 57.1, 54.8, 53.9, 52.6, 45.3, 44.8, 35.0, 23.9, 22.2, 19.4, 14.4; ^{19}F NMR (470 MHz, $CDCl_3$): δ = −115.6 ($C_{q\text{-}F}$); HR-MS (ESI): m/z calcd for $C_{27}H_{33}FNO_3$ $[M + H]^+$: 438.2438; found: 438.2429.

Ethyl (4bS,7S,8R,9aS,10R)-8-hydroxy-7-(((4-methoxybenzyl)amino)methyl)-1-methyl-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulene-10-carboxylate ***33***. Prepared with 4-methoxybenzaldehyde, yield: 50%; oily compound; $[\alpha]_D^{20}$ = −7.1 (c 0.13, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.22–7.18 (m, 2H), 7.14 (t, J = 7.4 Hz, 1H), 6.98 (d, J = 7.5 Hz, 1H), 6.94 (d, J = 7.5 Hz, 1H), 6.86 (d, J = 8.7 Hz, 2H), 4.25–4.17 (m, 2H), 4.02 (s, 1H), 3.97 (dd, J = 5.6, 10.7 Hz, 1H), 3.80 (s, 3H), 3.72 (d, J = 13.0 Hz, 1H), 3.67 (d, J = 13.0 Hz, 1H), 3.00 (t, J = 8.5 Hz, 1H), 2.82 (d, J = 11.2 Hz, 1H), 2.69–2.62 (m, 1H), 2.36 (d, J = 11.2 Hz, 1H), 2.24–2.17 (m, 2H), 2.13 (s, 3H), 1.68–1.46 (m, 3H), 1.38–1.33 (m, 1H), 1.28 (t, J = 7.1 Hz, 3H), 0.64 ppm (d, J = 11.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.4, 158.8, 147.2, 138.1, 134.63, 131.97, 129.33, 129.32, 128.4, 127.8, 120.4, 113.91, 113.90, 78.7, 60.4, 60.3, 57.1, 55.2, 54.8, 54.1, 52.6, 45.2, 44.8, 35.0, 24.0, 22.2, 19.4, 14.4; HR-MS (ESI): m/z calcd for $C_{28}H_{36}NO_4$ $[M + H]^+$: 450.2638; found: 450.2631.

Ethyl (4bS,7S,8R,9aS,10R)-7-(((5-bromo-2-hydroxybenzyl)amino)methyl)-8-hydroxy-1-methyl-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulene-10-carboxylate ***34***. Prepared with 5-bromosalicylaldehyde (5-bromo-2-hydroxybenzaldehyde), yield: 53%; colourless oily compound; $[\alpha]_D^{20}$ = −5.2 (c 0.15, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.23 (dd, J = 2.3, 8.7 Hz, 1H), 7.15 (t, J = 7.3 Hz, 1H), 7.07 (d, J = 2.2 Hz, 1H), 6.99 (d, J = 7.5 Hz, 1H), 6.96 (d, J = 7.5 Hz, 1H), 6.69 (d, J = 8.5 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 4.05–4.00 (m, 1H), 3.99 (s, 1H), 3.95–3.88 (m, 2H), 3.02 (t, J = 8.3 Hz, 1H), 2.73–2.62 (m, 2H), 2.55 (d, J = 11.1 Hz, 1H), 2.25–2.15 (m, 2H), 2.13 (s, 3H), 1.67–1.53 (m, 3H), 1.50–1.44 (m, 1H), 1.29

(t, J = 7.1 Hz, 3H), 0.77 ppm (d, J = 11.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.2, 157.3, 146.8, 137.9, 134.6, 131.4, 130.9, 128.5, 127.9, 124.2, 120.4, 118.1, 110.7, 76.8, 60.5, 59.1, 56.8, 54.1, 52.9, 52.5, 47.0, 45.5, 35.8, 24.2, 22.1, 19.3, 14.4; HR-MS (ESI): m/z calcd for $C_{27}H_{33}BrNO_4$ $[M + H]^+$: 516.1494; found: 516.1561.

Ethyl (4bS,7S,8R,9aS,10R)-8-hydroxy-1-methyl-7-(((quinolin-2-ylmethyl)amino)methyl)-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulene-10-carboxylate ***35***. Prepared with 2-quinoline carboxaldehyde, yield: 43%; oily compound; $[\alpha]_D^{20}$ = −15.4 (c 0.13, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.13 (d, J = 8.4 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 7.9 Hz, 1H), 7.74–7.69 (m, 1H), 7.53 (t, J = 7.1 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.14 (t, J = 7.5 Hz, 1H), 6.99–6.94 (m, 2H), 4.22–4.16 (m, 2H), 4.12–4.01 (m, 4H), 3.06–3.00 (m, 1H), 2.94 (d, J = 11.1 Hz, 1H), 2.68 (dd, J = 10.6, 13.8 Hz, 1H), 2.46 (d, J = 11.1 Hz, 1H), 2.36–2.28 (m, 1H), 2.25–2.18 (m, 1H), 2.13 (s, 3H), 1.71–1.65 (m, 1H), 1.62–1.48 (m, 3H), 1.27 (t, J = 7.2 Hz, 3H), 0.68 ppm (d, J = 11.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.4, 158.5, 147.6, 147.2, 138.1, 136.7, 134.6, 129.6, 128.9, 128.4, 127.8, 127.6, 127.3, 126.2, 120.5, 120.3, 78.4, 60.7, 60.4, 57.1, 56.1, 54.8, 52.6, 45.4, 45.0, 35.1, 23.9, 22.2, 19.4, 14.4; HR-MS (ESI): m/z calcd for $C_{30}H_{35}N_2O_3$ $[M + H]^+$: 471.2642; found: 471.2636.

Ethyl (4bS,7S,8R,9aS,10R)-8-hydroxy-1-methyl-7-(((quinolin-4-ylmethyl)amino)methyl)-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulene-10-carboxylate ***36***. Prepared with 4-quinoline carboxaldehyde, yield: 55%; oily compound; $[\alpha]_D^{20}$ = −2.78 (c 0.13, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.87 (d, J = 4.3 Hz, 1H), 8.13 (d, J = 8.2 Hz, 1H), 8.06 (d, J = 8.2 Hz, 1H), 7.75–7.70 (m, 1H), 7.61–7.57 (m, 1H), 7.37 (d, J = 4.4 Hz, 1H), 7.15 (t, J = 7.5 Hz, 1H), 6.99 (d, J = 7.5 Hz, 1H), 6.95 (d, J = 7.5 Hz, 1H), 4.25–4.18 (m, 4H), 4.05–4.00 (m, 2H), 3.05–2.98 (m, 1H), 2.95–2.87 (m, 1H), 2.67 (dd, J = 10.6, 13.8 Hz, 1H), 2.51 (d, J = 11.1 Hz, 1H), 2.25–2.17 (m, 2H), 2.14 (s, 3H), 1.67–1.52 (m, 3H), 1.44–1.39 (m, 1H), 1.28 (t, J = 7.2 Hz, 3H), 0.70 ppm (d, J = 11.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.2, 150.2, 148.3, 147.1, 145.0, 138.0, 134.6, 130.3, 129.2, 128.5, 127.8, 127.0, 126.7, 123.1, 120.4, 120.0, 78.5, 61.0, 60.4, 57.0, 54.7, 52.6, 51.2, 45.5, 45.0, 35.1, 24.0, 22.2, 19.4, 14.5; HR-MS (ESI): m/z calcd for $C_{30}H_{35}N_2O_3$ $[M + H]^+$: 471.2642; found: 471.2631.

Ethyl (4bS,7S,8R,9aS,10R)-8-hydroxy-1-methyl-7-(((pyridin-4-ylmethyl)amino)methyl)-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulene-10-carboxylate ***37***. Prepared with 4-pyridine carboxaldehyde, yield: 50%; oily colorless compound; $[\alpha]_D^{20}$ = −17.5 (c 0.12, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.56 (d, J = 5.5 Hz, 2H), 7.22 (d, J = 4.8 Hz, 2H), 7.15 (t, J = 7.5 Hz, 1H), 6.98 (d, J = 7.5 Hz, 1H), 6.95 (d, J = 7.5 Hz, 1H), 4.20 (q, J = 7.0 Hz, 2H), 4.04–3.98 (m, 2H), 3.85 (d, J = 14.3 Hz, 1H), 3.71 (d, J = 14.1 Hz, 1H), 3.05–2.99 (m, 1H), 2.80 (d, J = 11.1 Hz, 1H), 2.67 (dd, J = 10.5, 13.7 Hz, 1H), 2.36 (d, J = 11.2 Hz, 1H), 2.27–2.16 (m, 2H), 2.13 (s, 3H), 1.69–1.49 (m, 3H), 1.45–1.37 (m, 1H), 1.28 (t, J = 7.1 Hz, 3H), 0.66 ppm (d, J = 12.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.3, 150.0, 149.9, 148.9, 147.1, 138.0, 134.6, 128.5, 127.8, 123.0, 122.9, 120.4, 78.5, 60.44, 60.43, 57.0, 54.7, 53.4, 52.6, 45.4, 45.0, 35.1, 23.9, 22.2, 19.4, 14.4; HR-MS (ESI): m/z calcd for $C_{26}H_{33}N_2O_3$ $[M + H]^+$: 421.2485; found: 421.2482.

General procedure of *O*-mesyl exchange with primary amines. Compound **23** (0.10 g, 0.24 mmol) was dissolved in a mixture of Et_3N : MeCN (1 : 1) (2 mL), then a primary amine (0.96 mmol, 4 eq.) was added to the solution. The mixture was stirred under reflux for 72 hours. After the completion of the reaction (as monitored by TLC), the mixture was evaporated to dryness, the residue was diluted with H_2O (5 mL) and then extracted with DCM (3 × 10 mL). The organic phase was washed with brine solution (3 × 25 mL), dried over Na_2SO_4, filtered and then evaporated. The crude product was purified by column chromatography on silica gel using *n*-hexane : EtOAc (1 : 2) as eluent.

Ethyl (4bS,7S,8R,9aS,10R)-8-hydroxy-1-methyl-7-((((S)-1-(naphthalen-2-yl)ethyl)amino)methyl)-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulene-10-carboxylate ***26***. Prepared with (*S*)-(−)-1-(2-naphthyl)ethylamine, yield: 50%; oily compound; $[\alpha]_D^{20}$ = −24.8 (c 0.14, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.84–7.79 (m, 3H), 7.64 (s, 1H), 7.50–7.42 (m, 2H), 7.39–7.36 (m, 1H), 7.13 (t, J = 7.6 Hz, 1H), 6.97 (d, J = 7.4 Hz, 1H), 6.92 (d, J = 7.4 Hz, 1H), 4.25–4.16 (m, 2H), 4.09–4.03 (m, 1H), 4.02 (s, 1H), 3.84 (q, J = 6.6 Hz, 1H), 3.03–2.97 (m, 1H), 2.72–2.63 (m, 2H), 2.34 (d, J = 11.4 Hz, 1H), 2.25–2.13 (m, 2H), 2.12 (s, 3H), 1.69–1.62 (m, 1H), 1.51–1.40 (m, 5H), 1.33–1.29 (m, 1H), 1.28 (t, J = 7.1 Hz, 3H), 0.63 (d, J = 11.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.4, 147.2, 142.6, 138.1, 134.6, 133.4, 132.7, 128.5, 128.4, 127.8, 127.7, 127.6, 126.1, 125.6, 125.0, 124.2, 120.4, 78.7, 60.3, 59.1, 58.9, 57.1, 54.9, 52.6, 45.2, 44.9, 34.8, 23.9, 23.7, 22.2, 19.4, 14.4; HR-MS (ESI): m/z calcd for $C_{32}H_{38}NO_3$ $[M + H]^+$: 484.2846; found: 484.2838.

Ethyl (4bS,7S,8R,9aS,10R)-8-hydroxy-1-methyl-7-((((R)-1-(naphthalen-2-yl)ethyl)amino)methyl)-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulene-10-carboxylate ***27***. Prepared with (*R*)-(−)-1-(2-naphthyl)ethylamine, yield: 50%; oily compound; $[\alpha]_D^{20}$ = +1.3 (c 0.16, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.86–7.80 (m, 3H), 7.70 (s, 1H), 7.51–7.45 (m, 3H), 7.13 (t, J = 7.5 Hz, 1H), 6.96 (m, 2H), 4.12–4.05 (m, 2H), 3.97 (s, 1H), 3.85–3.77 (m, 2H), 3.03–2.97 (m, 1H), 2.75 (d, J = 11.1 Hz, 1H), 2.57 (dd, J = 10.6, 13.8 Hz, 1H), 2.31–2.24 (m, 1H), 2.22–2.17 (m, 2H), 2.10 (s, 3H), 1.65–1.51 (m, 2H), 1.47–1.39 (m, 5H), 1.16 (t, J = 7.2 Hz, 3H), 0.48 (d, J = 12.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.3, 147.2, 142.4, 138.2, 134.6, 133.4, 132.9, 128.5, 128.4, 127.78, 127.75, 127.70, 126.0, 125.64, 125.61, 124.5, 120.4, 78.6, 60.3, 59.2, 58.9, 57.1, 54.8, 52.6, 45.1, 44.7, 34.9, 24.8, 24.0, 22.2, 19.3, 14.3; HR-MS (ESI): m/z calcd for $C_{32}H_{38}NO_3$ $[M + H]^+$: 484.2846; found: 484.2834.

Ethyl (4bS,7S,8R,9aS,10R)-8-hydroxy-1-methyl-7-((((S)-1-(naphthalen-1-yl)ethyl)amino)methyl)-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulene-10-carboxylate ***28***. Prepared with (*S*)-(−)-1-(1-naphthyl)ethylamine, yield: 46%; oily compound; $[\alpha]_D^{20}$ = +8.3 (c 0.13, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.10 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 7.9 Hz, 1H), 7.76 (dd, J = 2.6, 6.7 Hz, 1H), 7.53–7.46 (m, 4H), 7.14 (t, J = 7.5 Hz, 1H), 6.97 (d, J = 7.4 Hz, 1H), 6.93 (d, J = 7.5 Hz, 1H),

4.55 (q, J = 6.6 Hz, 1H), 4.23–4.16 (m, 2H), 4.07 (dd, J = 6.5, 10.7 Hz, 1H), 4.02 (s, 1H), 3.05–2.98 (m, 1H), 2.80 (d, J = 11.3 Hz, 1H), 2.71–2.65 (m, 1H), 2.42 (d, J = 11.4 Hz, 1H), 2.28–2.14 (m, 2H), 2.13 (s, 3H), 1.69–1.63 (m, 1H), 1.57–1.52 (m, 1H), 1.51 (d, J = 6.5 Hz, 3H), 1.48–1.44 (m, 1H), 1.38–1.32 (m, 1H), 1.28 (t, J = 7.1 Hz, 3H), 0.65 (d, J = 12.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.4, 147.2, 140.7, 138.1, 134.6, 133.9, 131.1, 129.0, 128.4, 127.8, 127.4, 126.0, 125.58, 125.56, 122.6, 122.2, 120.4, 78.7, 60.4, 59.1, 57.1, 54.8, 54.0, 52.6, 45.2, 44.9, 34.9, 24.0, 23.0, 22.2, 19.4, 14.4; HR-MS (ESI): m/z calcd for $C_{32}H_{38}NO_3$ $[M + H]^+$: 484.2846; found: 484.2837.

Ethyl (4bS,7S,8R,9aS,10R)-8-hydroxy-1-methyl-7-((((R)-1-(naphthalen-1-yl)ethyl)amino)methyl)-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulene-10-carboxylate ***29***. Prepared with (*R*)-(+)-1-(1-naphthyl)ethylamine, yield: 41%; oily compound; $[\alpha]_D^{20}$ = −19.3 (c 0.14, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.14 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 7.6 Hz, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.66 (d, J = 7.0 Hz, 1H), 7.53–7.45 (m, 3H), 7.14 (t, J = 7.5 Hz, 1H), 6.99–6.94 (m, 2H), 4.55 (q, J = 6.5 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.99 (s, 1H), 3.95 (dd, J = 5.6, 10.6 Hz, 1H), 3.01 (t, J = 8.7 Hz, 1H), 2.77 (d, J = 11.0 Hz, 1H), 2.63 (dd, J = 10.6, 13.8 Hz, 1H), 2.33–2.25 (m, 2H), 2.23–2.16 (m, 1H), 2.11 (s, 3H), 1.67–1.63 (m, 1H), 1.59–1.54 (m, 1H), 1.49–1.43 (m, 5H), 1.20 (t, J = 7.1 Hz, 3H), 0.54 ppm (d, J = 11.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.3, 147.2, 140.4, 138.1, 134.6, 134.0, 131.4, 129.0, 128.4, 127.8, 127.3, 125.87, 125.80, 125.4, 122.6, 120.4, 78.6, 60.4, 59.2, 57.1, 54.8, 54.3, 52.6, 45.2, 44.8, 35.0, 24.0, 23.8, 22.2, 19.3, 14.3; HR-MS (ESI): m/z calcd for $C_{32}H_{38}NO_3$ $[M + H]^+$: 484.2846; found: 484.2838.

Click reaction (general procedure for the preparation of hydroxy-1,2,3-triazoles). $Cu(OAc)_2{\cdot}H_2O$ (2 mol%, 1.11 mg), sodium ascorbate (10 mol%, 5.54 mg) and acetylene derivative (0.42 mmol, 1.5 eq.) were added to a solution of azido alcohol **24** (0.10 g, 0.28 mmol) in a mixture of *t*-BuOH and H_2O (2 : 1). The mixture was stirred at room temperature for 12 hours, then *t*-BuOH was evaporated. The residue was dissolved in water (10 mL) and extracted with EtOAc (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 purified by column chromatography on silica gel using *n*-hexane : EtOAc (1 : 1) as eluent.

Ethyl (4bS,7S,8R,9aS,10R)-8-hydroxy-1-methyl-7-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulene-10-carboxylate ***38***. Prepared with phenylacetylene, yield: 90%; white crystals; m.p.: 172–174 °C; $[\alpha]_D^{20}$ = −18.5 (c 0.15, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.80 (d, J = 7.3 Hz, 2H), 7.71 (s, 1H), 7.45–7.40 (m, 2H), 7.34 (t, J = 7.4 Hz, 1H), 7.16 (t, J = 7.5 Hz, 1H), 7.00 (d, J = 7.5 Hz, 1H), 6.95 (d, J = 7.5 Hz, 1H), 4.33–4.18 (m, 5H), 4.02 (s, 1H), 3.25 (d, J = 2.9 Hz, 1H), 3.06 (t, J = 8.2 Hz, 1H), 2.73 (dd, J = 10.5, 13.9 Hz, 1H), 2.25–2.17 (m, 1H), 2.14 (s, 3H), 2.07–1.99 (m, 1H), 1.81–1.75 (m, 1H), 1.68–1.61 (m, 2H), 1.33–1.28 (m, 1H), 1.27 (t, J = 7.1 Hz, 3H), 1.01 (d, J = 11.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.2, 147.4, 146.6, 137.9, 134.7, 130.2, 128.91, 128.90, 128.6, 128.3, 127.9, 125.72, 125.71, 121.6, 120.3, 75.9, 60.6, 58.3, 56.5, 53.6, 52.3, 45.9, 45.1, 36.4, 23.7, 21.5, 19.4, 14.5; HR-MS (ESI): m/z calcd for $C_{28}H_{32}N_3O_3$ $[M + H]^+$: 458.2438; found: 458.2429.

Ethyl (4bS,7S,8R,9aS,10R)-7-((4-benzyl-1H-1,2,3-triazol-1-yl)methyl)-8-hydroxy-1-methyl-4b,6,7,8,9,10-hexahydro-5H-7,9a-methanobenzo[a]azulene-10-carboxylate ***39***. Prepared with 3-phenyl-1-propyne, yield: 90%; white crystals; m.p.: 139–140 °C; $[\alpha]_D^{20}$ = −38.6 (c 0.13, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32–7.20 (m, 5H), 7.17–7.11 (m, 2H), 6.99 (d, J = 7.5 Hz, 1H), 6.94 (d, J = 7.5 Hz, 1H), 4.33–4.28 (m, 1H), 4.24–4.06 (m, 6H), 4.01 (s, 1H), 3.38 (d, J = 3.1 Hz, 1H), 3.04 (t, J = 8.2 Hz, 1H), 2.71 (dd, J = 10.6, 13.8 Hz, 1H), 2.21–2.16 (m, 1H), 2.14 (s, 3H), 2.01–1.93 (m, 1H), 1.79–1.73 (m, 1H), 1.63–1.53 (m, 2H), 1.28 (t, J = 7.2 Hz, 3H), 1.23–1.16 (m, 1H), 0.95 (d, J = 11.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.2, 147.3, 146.7, 138.8, 138.0, 134.7, 128.69, 128.68, 128.67, 128.66, 128.65, 127.8, 126.5, 123.6, 120.3, 76.1, 60.5, 58.4, 56.5, 53.6, 52.3, 45.8, 45.1, 36.4, 32.1, 23.6, 21.4, 19.4, 14.5; HR-MS (ESI): m/z calcd for $C_{29}H_{34}N_3O_3$ $[M + H]^+$: 472.2594; found: 472.2584.

Determination of the antiproliferative activities. The growth-inhibitory effects of the presented compounds were determined by a standard MTT [3-(4,5-dimethylthiazol2-yl)-2,5-diphenyltetrazolium bromide] assay against five human cancer cell lines (cervical cancer HeLa and SiHa cell lines, breast cancer MCF-7 and MDA-MB-231 and ovarian cancer A2780). Murine embryonal fibroblast cells (NIH/3T3) were used to characterise selectivity. All cell lines were purchased from the European Collection of Cell Cultures (Salisbury, UK), except for SiHa, which was acquired from the American Tissue Culture Collection (Manassas, VA, USA). The cells were cultivated in Eagle's minimal essential medium supplemented with 10% fetal bovine serum, 1% non-essential amino acids, and 1% antibiotic–antimycotic complex (penicillin, streptomycin, amphotericin B) at 37 °C in a humidified atmosphere containing 5% CO_2. All cell culture media and supplements were purchased from Lonza Group Ltd. (Basel, Switzerland). Cells were seeded into 96-well plates (5000 cells per well) after overnight incubation, and the test compounds were added at two different concentrations (10 and 30 μM) to determine the growth-inhibitory effects and four concentrations (1.0, 3.0, 10.0, and 30.0 μM) for the assessment of IC_{50} values. The treated cells were incubated for another 72 hours under cell-culturing conditions. Untreated cells were used as a control. Finally, 20 μL of 5 mg mL^{-1} MTT solution was added to each well, and the contents were incubated for 4 hours. The medium was removed, and the precipitated formazan crystals were dissolved in DMSO by shaking at 37 °C for 60 minutes. The absorbance was measured at 545 nm using a microplate reader (SPECTROStar Nano, BMG Labtech, Germany). Two separate measurements were carried out with five parallel wells.

Conclusions

A new library of *allo*-gibberic acid-based aminoalcohol regioisomers was synthesised stereoselectively starting from

commercially available gibberellic acid. The successful formation of hydroxymethyl ketone derivative **5** by acid-mediated rearrangement of previously prepared epoxide provided the desired 1,3-aminoalcohols through Schiff base formation. To obtain the desired regioisomers, the primary alcohol functionality of **5** was subjected to mesylation, then replaced with either primary amine or azide function. The formed azide derivative was subjected to either CuAAC reaction to obtain 1,2,3-triazoles or to Pd-catalysed hydrogenolysis to obtain primary aminoalcohol, which was further transformed into 1,3-aminoalcohols by reductive alkylation. The antiproliferative effects were assayed by the MTT method with several *N*-substituted derivatives showing remarkable inhibition of cell growth on human cancer cell lines (HeLa, SiHa, A2780, MCF-7 and MDA-MB-231). A significant difference was observed in the antiproliferative activity between the regioisomers. Some compounds exerted outstanding activities against the malignant cells with limited action on fibroblasts, indicating considerable cancer selectivity. These agents seem to be superior to the clinically utilised cisplatin. Consequently, some selected compounds could be regarded as potential hit compounds and may be subjected to further investigations.

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 the writing of 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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