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Synthesis of norbornane bisether antibiotics *via* silver-mediated alkylation†

Shane M. Hickey,[a] Trent D. Ashton,[a] Jonathan M. White,[b] Jian Li,[c] Roger L. Nation,[c] Heidi Y. Yu,[c] Alysha G. Elliott,[d] Mark S. Butler,[d] Johnny X. Huang,[d] Matthew A. Cooper[d] and Frederick M. Pfeffer*[a]

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A small series of norbornane bisether diguanidines have been synthesized and evaluated as antibacterial agents. The key transformation—bisalkylation of norbornane diol **6**—was not successful using Williamson methodology but has been accomplished using Ag_2O mediated alkylation. Further functionalization to incorporate two guanidinium groups gave rise to a series of structurally rigid cationic amphiphiles; several of which (**16d**, **16g** and **16h**) exhibited antibiotic activity. For example, compound **16d** was active against a broad range of bacteria including *Pseudomonas aeruginosa* (MIC = 8 μg mL^{-1}), *Escherichia coli* (MIC = 8 μg mL^{-1}) and methicillin-resistant *Staphylococcus aureus* (MIC = 8 μg mL^{-1}).

Introduction

Antibacterial resistance is now a global medical concern.[1–4] A decline in the number of pharmaceutical companies pursuing new therapeutics, and the continued misuse of antibiotics has only served to exacerbate the problem.[1–5] Many antibacterial agents that target the lipopolysaccharide (LPS) layer of Gram-negative bacteria either possess or adopt an amphiphilic structure.[6–10] It has also been shown that appropriate functionalization of a rigidified core (such as a calixarene) enables facially amphiphilic compounds to be constructed.[7–11] The bicyclo[2.2.1]-heptane (norbornane) scaffold represents one of the most accessible, preorganized frameworks available and has a history of use in many fields of chemistry. Biologically active examples include: naxifylline **1** (an A_1-adenosine receptor antagonist),[12] N^6-(5,6-epoxynorbornyl)adenonsines (A_1-adenosine receptor agonists)[13–15] and diguanidine **3**, (active against Gram-negative bacteria).[16] In supramolecular chemistry norbornanes have found use in organogel formation,[17] whilst fused poly-norbornanes have been successfully employed as scaffolds for both anion recognition,[18–21] and as ligands for the construction of metal–organic cages.[22] In the field of asymmetric synthesis, chiral auxiliaries (such as **2**) based on the norbornane framework have also been successfully employed.[23,24]

It is known that ethers typically demonstrate better *in vivo* stability than acetals,[25] therefore, analogs of antibacterial **3**[16] (Fig. 1) that followed the general structure **4** (Scheme 1) were considered attractive targets. In order to construct this class of compounds it was envisaged that bisether diacids (**5**) would be useful building blocks and these could in turn be synthesized from norbornane diol **6** (Scheme 1).

The direct alkylation of norbornane diol **6** is as yet unreported in the literature, which is presumably because the reaction is troublesome. Indeed, it has been shown that in some cases alkylation of alcohols using typical Williamson protocols gives lower than expected yields, or no desired product.[26,27] Indeed, in circumstances where a stabilized leaving group can be formed the basic conditions employed can lead to an elimination/fragmentation event.[28,29] An example of this competitive elimination was described by Hergueta *et al.* (Scheme 2); alkoxide **7**, derived from a norbornane fused to a quinoxaline, undergoes elimination to give a carbanion (**8**) which is stabilized by the aromatic heterocyclic.[30]

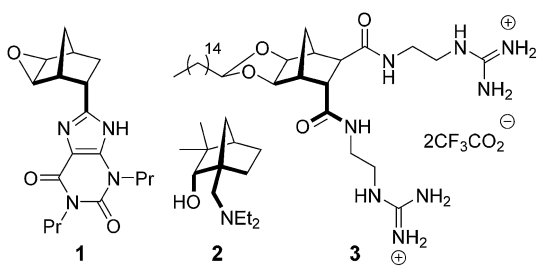


Fig. 1 Examples of functionalized norbornanes.

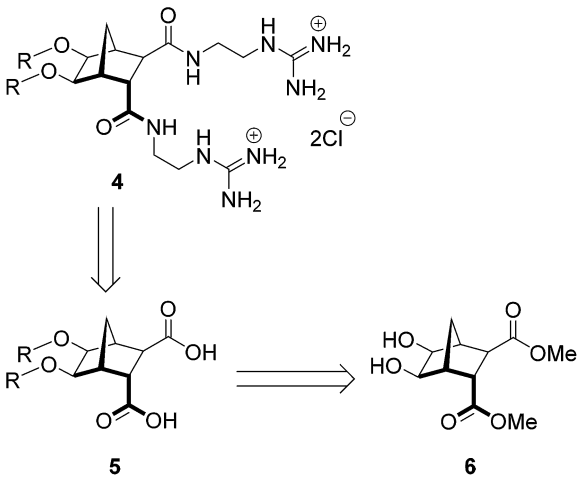
[a]*Research Centre for Chemistry and Biotechnology, School of Life and Environmental Sciences, Deakin University, Waurn Ponds, Victoria, 3216, Australia. E-mail: fred.pfeffer@deakin.edu.au*

[b]*Bio21 Institute, School of Chemistry, University of Melbourne, Parkville, Victoria, 3010, Australia*

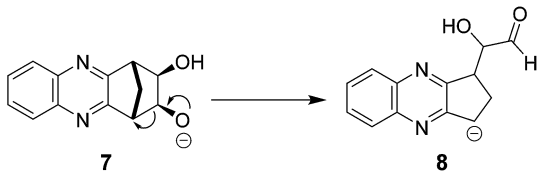
[c]*Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Science, Royal Parade, Parkville, Victoria, 3052, Australia*

[d]*Institute for Molecular Bioscience, The University of Queensland, Brisbane, Queensland, 4072, Australia*

† Electronic supplementary information (ESI) available: Crystal structure of compound **12h** (CIF), synthetic procedures for all previously reported compounds and copies of NMR spectra (^{1}H, ^{13}C, ^{19}F) for all new compounds. CCDC 1050585. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5ra03321g



Scheme 1 Access to bisether diguanidine **4** from diol **6**.



Scheme 2 Ring opening to give stabilized 'benzylic' carbanion as observed by Hergueta *et al*.[30]

The use of silver(I) oxide for the transformation of an alcohol to a methyl ether has been known for well over a century.[31] The Irvine–Purdie method has been used to achieve (i) mono-alkylations;[32–36] (ii) bisalkylation of unhindered diols such as cycohexanediol;[37] and (iii) per-methylation of carbohydrates such as glucose, galactose and fructose.[31,38] Inefficient reaction conditions (*e.g.* multiple additions of the alkylating agent[34] or carrying the reaction out in neat alkylating agent) means the Irvine–Purdie alkylation is often overlooked in favour of Williamson methodology. To the best of our knowledge, the use of silver(I) oxide for the bisalkylation of eclipsed *syn*-1,2-diols has not been previously described.

Herein, we report a protocol for the bisalkylation of the sterically hindered 1,2-diol **6** using silver(I) oxide and a small excess (4.6 equiv.) of suitable alkyl halides. Hydrolysis of the esters gave access to compounds of the general structure **5**, which were shown to exist in a sterically congested environment around the two alkyl groups by X-ray crystallography. Subsequent functionalization afforded a series of diguanidines (**4**, Scheme 1), that were tested against a range of Gram-negative and Gram-positive bacteria (Tables 3 and 4).

Results & discussion

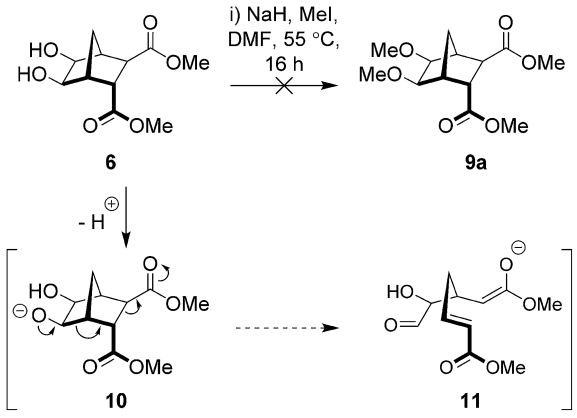
Chemistry

The starting diester diol **6** was synthesized in two steps from dimethyl fumarate.[16,39] The norbornane framework was constructed using either standard Diels–Alder conditions (99%) or by a solvent-free, microwave-assisted approach (2 hours at 150 °C, 98%) similar to that reported by Nencka and co-workers.[39] The *syn*-1,2-diol **6** was synthesized in excellent yields (94%) on multigram scales (up to 4 g), using OsO_4 (0.1 mol%) mediated dihydroxylation of the norbornene using 4-methylmorpholine *N*-oxide (NMO) as a co-oxidant.[16,40] Dihydroxylation using $KMnO_4$, as detailed by Donohoe,[41] was also successful, albeit in lower yield (58%) (see ESI† for full reaction conditions).

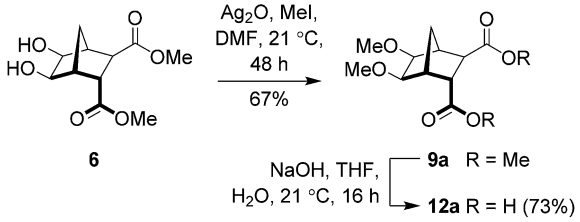
Williamson methodology was initially trialled using **6**, NaH, MeI, at 55 °C (Scheme 2) and after 16 hours the diol had been completely consumed (as determined by TLC analysis). However, examination of the crude product using ^{1}H NMR spectroscopy showed no signs of the desired bisether **9a**. Instead, a complex mixture (inseparable by column chromatography) was produced. Deprotonation with *n*-BuLi in THF at −78 to 0 °C was also trialled but again the reaction was unsuccessful. Given that similar norbornane diols undergo base-induced ring opening to give stabilized anions (Scheme 2),[30] we propose that following deprotonation, a Grob-type fragmentation occurs to give a stabilized enolate (**11**, Scheme 3).[42]

The Sakai group have described the reduction of esters to the corresponding ethers using Et_3SiH in the presence of catalytic $InBr_3$.[43] Unfortunately, in the current work, after acetylation of diol **6** to form diacetate **20** (63%, see Experimental section),[41] reaction with $InBr_3$ failed to produce the bisether product; instead ^{1}H NMR analysis indicated that a complex mixture of products had formed.

In light of these failures, attention turned towards the use of Ag_2O.[32–37,44,45] Indeed, when diol **6** was reacted with Ag_2O (1.6 equiv.) and MeI (4.6 equiv.) in DMF at ambient temperature for 48 hours (Scheme 4), bisether **9a** was isolated in good yield (67%).[33] Saponification of diester **9a** gave the required bisether diacid (**12a**) in 73% yield (Scheme 4). Extended reaction times, adding further portions of MeI throughout the reaction, and heating the reaction (both conventional and microwave irradiation), did not lead to increased yields. Using Ag_2CO_3, $AgNO_3$, $AgBF_4$ or $AgPF_6$ gave none of the desired product with only starting material recovered.



Scheme 3 Failed attempt to access bisether **9a** and the possible pathway leading to enolate **11**.



Scheme 4 Synthesis of diacid **12a**.

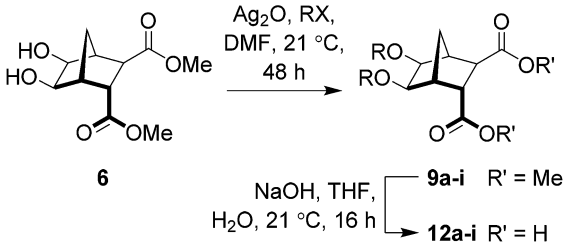
To further test the scope of these reaction conditions a range of benzyl halides were used. Using benzyl bromide (Table 1, entry 2), bisether diacid **12b** was attained over two steps (18% using 300 mg of **6**). Pleasingly, when the reaction was performed on a larger scale (900 mg of **6**), the yield increased to 37%. A Finkelstein approach[46] using NaI did not increase the yield of bisether diacid **12b**. The low yields can be rationalized somewhat by the steric bulk introduced as a result of the first benzylation—the reaction with the second equivalent of benzyl halide is considerably inhibited. Indeed, an appreciable amount of the monoalkylated regioisomer (37%) was isolated along with the desired bisether product **12b**. Similarly, using 2-methylbenzyl bromide, **12c** was accessed in 19% yield (Table 1, entry 3), and a reasonable quantity of a monoalkylated intermediate was also isolated (39%). Despite the modest yields, this protocol provided access to the desired norbornane bisethers—a previously inaccessible family of compounds.

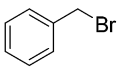
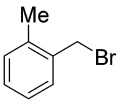
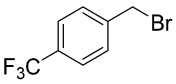
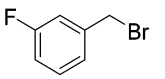
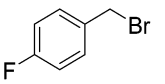
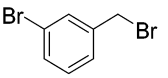
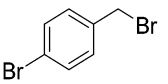
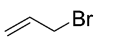
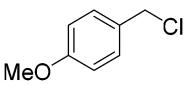
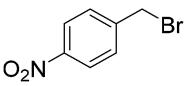
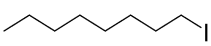
When a range of fluorinated benzyl bromides were used good yields of the desired bisether products were obtained. Following the aforementioned two-step process, **12d** (51%) and **12e** (55%) were accessed using 4-(trifluoromethyl)benzyl bromide and 3-fluorobenzyl bromide respectively (Table 1, entries 4 and 5). Furthermore, when 4-fluorobenzyl bromide was employed to alkylate diol **6**, and following hydrolysis of the ester groups using NaOH/THF (Table 1, entry 6) diacid **12f** was obtained in moderate yield (25%) over the two steps.

Using 3-bromobenzyl bromide and 4-bromobenzyl bromide the synthesis of bisether diacids **12g** and **12h** (24 and 28% over two steps respectively, Table 1, entries 7 and 8) was carried out in the same fashion. Crystals suitable for X-ray diffraction were obtained for bisether diacid **12h** after recrystallization from EtOH/pet. spirits. The resulting structure contained a unit cell comprised of two conformational isomers (as shown in Fig. 2). The O⋯O distance (*ca.* 2.6 Å), clearly illustrates the proximity of the two benzyl groups and their non-symmetric orientation (presumably due to steric constraints).

When allyl bromide was used, stirring for 4 days was required to consume all the starting material; subsequent ester hydrolysis gave diacid **12i** in a 25% yield over the two steps (Table 1, entry 9). Unfortunately, reactions with 4-methoxybenzyl chloride and 4-nitrobenzyl bromide (Table 1, entries 10 and 11) failed to give any of the desired product with only minimal consumption of starting material taking place (as evidenced by ^{1}H NMR analysis of the crude reaction mixture). Also, when 1-iodooctane (Table 1, entry 12) was employed alkylation was unsuccessful.

Table 1 Synthesis of bisether diacids **12a–i**



Entry	RX	Diacid	Yield[c] (%)
1	MeI	**12a**	48
2		**12b**	37
3		**12c**	19
4		**12d**	51
5		**12e**	55
6		**12f**	25
7		**12g**	24
8		**12h**	28
9[a]		**12i**	25
10		N.R[b]	N.R
11		N.R	N.R
12		N.R	N.R

[a] Reaction was stirred for 4 days. [b] N.R = no reaction. [c] Yield calculated over two steps.

In six of the alkylation reactions (**12b**, **12d–h**) transesterification occurred to a small extent (6–12%, as determined using ^{1}H NMR spectroscopy). This mixed-ester side-product (example **13** from synthesis of **9b**, Fig. 3) was difficult to separate from the desired dimethyl ester product using column chromatography. The presumption that the more sterically accessible *exo* methyl ester was replaced is based on a previous report by Niwayama and co-workers that illustrated how the *exo* face is less hindered than the *endo* face of related norbornane diesters.[40] Despite the presence of small amounts of mixed-ester

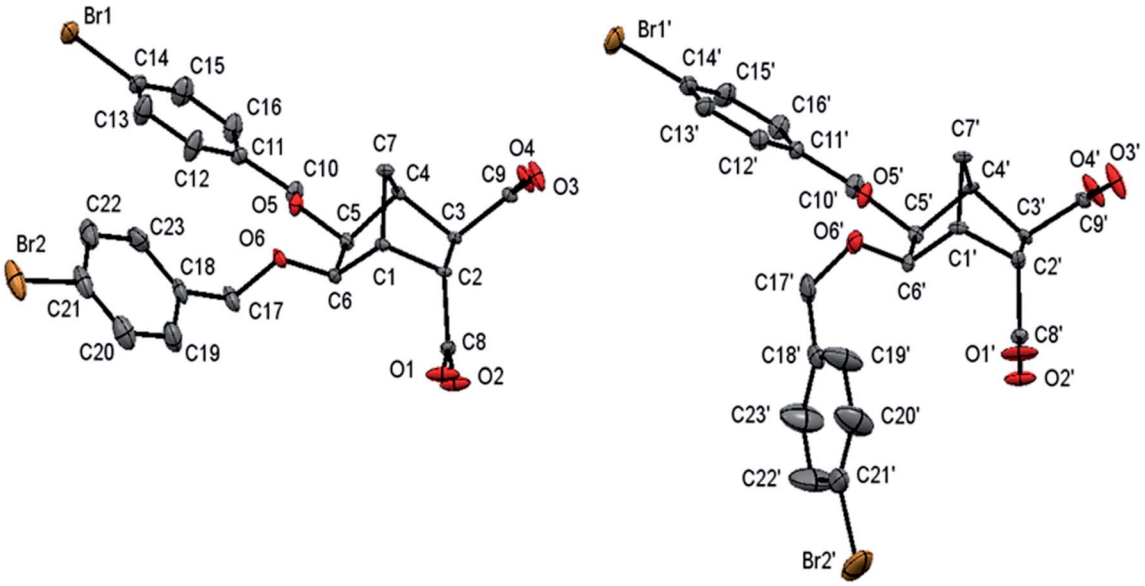
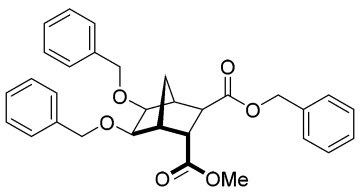


Fig. 2 Thermal ellipsoid plot of the two independent molecular confirmations (ellipsoids at 20% probability level) of compound **12h**.



13

Fig. 3 Representative structure of proposed mixed-ester **13** formed during reaction with BnBr.

by-products, in each case hydrolysis proceeded smoothly and pure diacids were isolated in every instance.

With bisethers diacids (**12a–i**) in hand, functionalization to the required amphiphiles was pursued. Attachment of 2-[2,3-bis(*tert*-butoxycarbonyl)guanidino]ethylamine (**14**)[47,48] to the norbornane scaffold was carried out using EDCI and HOBt in either DMF or $CHCl_3$ using microwave irradiation at 50 °C for 30 minutes to give compounds **15a–i** in moderate to good yields (26–72%, Table 2). Subsequent deprotection was accomplished using HCl (generated *in situ* from AcCl in MeOH) to give the desired guanidines as the guanidinium chloride salts (**16a–i**, Table 2).

A balance of both hydrophobicity and hydrophilicity is essential for the antibacterial activity of structural amphiphiles.[49] In light of this, the calculated log *P* (*c* log *P*) values (the log of the octanol/water partition coefficient) were determined for bisether diguanidines (**16a–i**) using http://www.molinspiration.com software (Table 2) and these will be discussed in relation to activity in the following section.

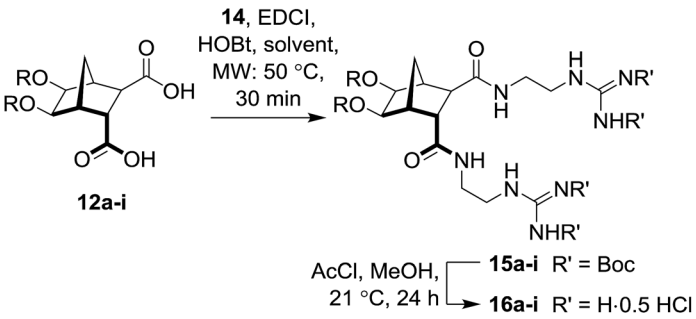
Biological evaluation

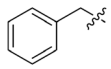
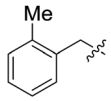
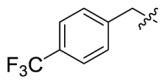
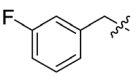
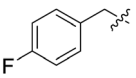
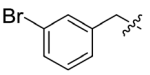
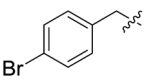
The antibacterial activity of these compounds was evaluated against a range of Gram-negative and Gram-positive bacteria, including members of the ESKAPE pathogens;[1] first using the disk diffusion assay to identify active compounds then micro-broth dilution assays to determine minimum inhibitory concentrations (MICs).

Bis-methyl ether **16a** and allyl ether **16i**, did not show any inhibition in disk diffusion studies at 50 μg per disk (Table 3). For the bis-benzyl ether **16b**, a noticeable zone of inhibition (ZOI) was observed (11 mm) against *Pseudomonas aeruginosa*. The inclusion of small substituents to the phenyl rings, such as 2-methyl (**16c**), 3-fluoro (**16e**) and 4-fluoro (**16f**), led to improved activity as shown by ZOI's of 14–16 mm against *P. aeruginosa* and *Klebsiella pneumoniae* (Table 3). Furthermore, appreciable ZOI's (11–15 mm) were also observed against Gram-positive methicillin-resistant *Staphylococcus aureus* (MRSA). When larger substituents occupied the 4-position of the phenyl ring, inhibition of vancomycin-resistant *Enterococcus faecium* (VRE) was also seen in addition to the aforementioned strains. The 4-(trifluoromethyl)benzyl (**16d**) and 4-bromobenzyl (**16h**) analogs showed ZOI of 18 and 16 mm respectively for VRE (Table 3). The 3-bromobenzyl derivative (**16g**) was active against all pathogens assessed in this study, and was the sole compound to exhibit activity against *Acinetobacter baumannii* (ZOI = 15 mm). Comparison of ZOI between **16g** and **16h** indicates that activity against *A. baumannii*, *K. pneumoniae* and *E. faecium* can be influenced by subtle changes to substituent locations and may have implications in the design of subsequent compounds.

Given the promising results in the disk diffusion screen the substituted benzyl ethers were subjected to a micro-broth dilution assay to quantify MICs (Table 4). When smaller substituents; 2-methyl (**16c**), 3-fluoro (**16e**) and 4-fluoro (**16f**) displaying no MIC $\leq$ 32 μg mL^{-1} against any bacterial strain tested (Table 4). When larger substituents were included on the benzyl rings such as 4-(trifluoromethyl)benzyl (**16d**) MIC values of 32 μg mL^{-1} against *A. baumannii*, and 8 μg mL^{-1} against each of *P. aeruginosa*, *Escherichia coli* and MRSA (Table 4) were

Table 2 Formation of HCl salts **16a–i** and associated *c* log *P* values



Diacid	R	Diamide (yield, %)	Diguanidine[b] (yield, %)	*c* log *P*[c]
12a	Me	**15a** (72)	**16a** (96)	−4.80
12b[a]		**15b** (57)	**16b** (96)	−2.04
12c		**15c** (54)	**16c** (24)	−1.23
12d		**15d** (56)	**16d** (66)	−0.24
12e		**15e** (26)	**16e** (99)	−1.76
12f[a]		**15f** (45)	**16f** (77)	−1.71
12g[a]		**15g** (53)	**16g** (97)	−0.47
12h		**15h** (26)	**16h** (99)	−0.42
12i		**15i** (63)	**16i** (31)	−3.94

[a] Reaction was performed in $CHCl_3$. [b] Product was isolated as an HCl salt. [c] Calculated using http://www.molinspiration.com software.

observed. The 3-bromo benzyl-substituted analog (**16g**) showed a reasonable MIC against both Gram-negative *P. aeruginosa* (32 μg mL^{-1}) and Gram-positive MRSA (16 μg mL^{-1}) bacterial strains. Furthermore, an MIC of 32 μg mL^{-1} was observed for the 4-bromo benzyl-substituted analog (**16h**) against MRSA (Table 4). A correlation between antibacterial activity and *c* log *P* was apparent with compounds with higher *c* log *P* values (Table 2) showing stronger antibacterial activity.

Given the encouraging MIC values for compounds **16d** and **16g** against MRSA (Table 4), both compounds were evaluated

Table 3 Zone of inhibition (ZOI) as measured (in mm) using disk diffusion[a]

	Compound									
	16a	**16b**	**16c**	**16d**	**16e**	**16f**	**16g**	**16h**	**16i**	COL[c]
A. baumannii ATCC 19606	NT[b]	NT	—	—	—	—	15	—	—	
P. aeruginosa ATCC 27853	—	11	16	15	16	15	16[d]	15	—	19
K. pneumoniae ATCC13883	—	—	14	16	14	14	15	8	—	20
S. aureus MRSA ATCC 43300	—	—	15	17	11	11	17[d]	18	—	—
E. faecium VRE ATCC 700221	—	—	—	18	—	—	7	16	—	—

[a] Measured after incubation of disk (6 mm diameter, 50 μg per disk) at 37 °C for 20 hours. [b] NT = not tested. [c] Tested at 10 μg per disk. [d] As seen in Fig. 4.

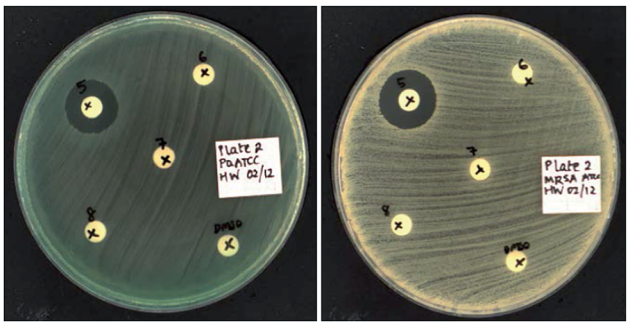


Fig. 4 Antibacterial activity of compound **16g** (50 μg per disk) against *P. aeruginosa* (LHS) and MRSA (RHS) using a disk diffusion assay.

against seven additional Gram-positive bacterial strains including such *S. aureus* bacterial isolates as multi-resistant methicillin resistant (mMRSA), glycopeptide-intermediate (GISA) and vancomycin-intermediate (VISA), as well as *Streptococcus pneumoniae* and *E. faecalis* (Table 5). The 4-(trifluoromethyl)benzyl bisether (**16d**) was again the most active compound; exhibiting antibacterial activity (MIC = 8–16 μg mL^{-1}) against all eight bacterial strains tested. Furthermore, activity was observed by 3-bromobenzyl bisether (**16g**) against all Gram-positive bacterial strains tested which was highlighted by an MIC of 8 μg mL^{-1} against *S. pneumoniae* (Table 4).

The cell viability (% survival) against human embryonic kidney cells (HEK293) and hepatocellular carcinoma (HepG2) was determined after exposure to compounds **16d** or **16g** at 100 μM for 24 hours (Table 5). The 4-(trifluoromethyl)benzyl bisether (**16d**) exhibited moderate cytotoxicity with 43 and 56% cell survival observed against HEK293 and HepG2 respectively (Table 5). In the case of bis-3-bromobenzyl ether (**16g**) the cell viability was determined to be 90% and 96% against HEK293 and HepG2 respectively (IC_{50} < 100 μM). The cytotoxicity profile for these compounds is acceptable when compared to previously reported antibacterial agents.[50]

Table 5 Cytotoxicity values (% of cell survival at 24 h)

	Compound	
	16d	**16g**
ATCC CRL-1573 HEK293	43	90
ATCC HB-8065 HepG2	56	96

Conclusions

The previously inaccessible norbornane bisether diacids **12a–i**, were successfully prepared using Ag_2O and a suitable alkyl or benzyl halide as the key step. An X-ray crystal structure of bisether diacid **12h** highlighted the sterically crowded environment of the ethers; which presumably hindered the second etherification step and resulted in lower yields. Nevertheless, the protocol presented here provides a viable alternative for the alkylation of congested *syn*-diols or base-sensitive alcohols where typical Williamson ether synthesis conditions fail. Further functionalization of bisether diacids (**12a–i**) gave a series of bisguanidines as hydrochloride salts (**16a–i**).

Several of the compounds (**16d**, **16g** and **16h**) displayed antibacterial activity, with MIC values as low as 8 μg mL^{-1}, against a range of problematic bacterial species including *P. aeruginosa*, *E. coli*, *S. pneumonia*, *E. faecalis* and several strains of *S. aureus*. The results presented here reinforce the notion that the activity of cationic antimicrobial peptides can be mimicked by relatively small, structurally rigid amphiphiles. Indeed, when compared to other synthetic scaffolds (such as calixarenes) which are used to generate antibacterial amphiphiles,[9] the low molecular weight of these compounds and their reasonable antibacterial activity make them an attractive class of compounds worthy of further investigation.

Experimental section

The following compounds were prepared using literature methods and full reaction details can be found in the ESI;† dimethyl bicyclo-[2.2.1]hept-5-ene-3-*endo*-2-*exo*-dicarboxylate (**17**),[39,51] **6**[16,41] and **14**.[47]

Table 4 MIC values (μg mL^{-1})

	Compound							
	16c	**16d**	**16e**	**16f**	**16g**	**16h**	COL[b]	VAN[c]
A. baumannii ATCC 19606	>32	32	>32	>32	>32	>32	0.06	NT
P. aeruginosa ATCC 27853	>32	8	>32	>32	32	>32	0.25	NT
K. pneumoniae ATCC 700603	>32	>32	>32	>32	>32	>32	0.03	NT
E. coli ATCC 25922	>32	8	>32	>32	>32	>32	0.06	NT
S. aureus MRSA ATCC 43300	>32	8	>32	>32	16	32	NT	1
S. aureus mMRSA	NT[a]	16	NT	NT	32	NT	NT	1
S. aureus GISA, NRS 17	NT	8	NT	NT	16	NT	NT	4
S. aureus VISA, NRS 1	NT	16	NT	NT	32	NT	NT	8
S. aureus MRSA	NT	16	NT	NT	32	NT	NT	2
S. aureus NARSA VRS 10	NT	8	NT	NT	16	NT	NT	2
S. pneumoniae MDR ATCC 700677	NT	8	NT	NT	8	NT	NT	2
VanA *E. faecalis*	NT	8	NT	NT	32	NT	NT	>32

[a] NT = not tested due to lack of activity against the primary Gram-positive strain (MRSA ATCC 43300). [b] COL = colistin sulphate. [c] VAN = vancomycin.

General information

All microwave reactions were conducted using a CEM Discover S-Class Explorer 48 Microwave Reactor, operating on a frequency of 50/60 Hz and continuous irradiation power from 0–300 W. All reactions were performed in sealed reaction vessels. All melting points are uncorrected. All ^{1}H, ^{13}C and ^{19}F NMR spectra were collected on either a 270 MHz FT-NMR spectrometer, a 400 MHz FT-NMR spectrometer, or a 500 MHz FT-NMR spectrometer where indicated. All 2D NMR experiments were performed on a 500 MHz FT-NMR spectrometer. Variable temperature (VT) NMR experiments were performed on a 270 MHz FT-NMR spectrometer. Samples were dissolved in $CDCl_3$, DMSO-d_6 or CD_3OD where specified with the residual solvent peak used as the internal reference – $CDCl_3$; 7.26 (^{1}H) and 77.0 (^{13}C), DMSO-d_6; 2.50 (^{1}H) and 39.52 (^{13}C), CD_3OD; 3.31 (^{1}H) and 49.0 (^{13}C).[52] Proton spectra are reported as chemical shift δ (ppm) (integral, multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, quin = quintet and m = multiplet), coupling constant (Hz), assignment). Carbon spectra are reported as chemical shift δ (ppm) (integral, multiplicity (d = doublet and q = quartet), coupling constant (Hz)) were appropriate. Fluorine spectra are reported as chemical shift δ (ppm) and were externally referenced using 0.05% α,α,α-trifluorotoluene in $CDCl_3$; −63.72 (^{19}F).

High resolution mass spectral data was collected on using a QTOF mass spectrometer (LC-1200 series) under the following conditions: gas temperature (300 °C), nitrogen drying gas (10.0 L min^{-1}), capillary voltage (3500 V), fragmentor (140 V), and nebuliser (45 psi) in a 80% MeCN in H_2O solvent system. Analyte solutions were prepared in HPLC grade methanol (conc. ~1 mg mL^{-1}).

All chemicals and solvents were used as received without further purification unless otherwise stated. Column chromatography was performed on silica gel (230–400 mesh).

Dimethyl 5,6-diacetate bicyclo[2.2.1]heptane-3-*endo*-2-*exo*-dicarboxylate (20). The stirring solution of diol **6** (130 mg, 0.532 mmol), DMAP (13 mg, 0.11 mmol), pyridine (171 μL, 2.13 mmol) and CH_2Cl_2 (1.1 mL) was treated with AcCl (130 μL, 1.81 mmol) slowly and the reaction was stirred at ambient temperature for 16 h. The resulting bright orange solution was quenched with sat. $NaHCO_3$ (6 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was washed with 1 M HCl (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a clear oil that was purified by column chromatography (35–50% EtOAc in pet. spirits). The title compound (110 mg, 63%) was isolated as a clear oil; $R_f = 0.68$ (50% EtOAc in pet. spirits). ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.53 (1H, dt, $J = 11.0$, 1.4 Hz, H7s), 1.94 (1H, dd, $J = 11.0$, 1.6 Hz, H7a), 2.01 (6H, s, 2 × Me), 2.61 (1H, br s, H1), 2.64–2.66 (1H, m, H4), 2.87 (1H, dd, $J = 5.6$, 1.2 Hz, H2), 3.23 (1H, app. t, $J = 5.6$ Hz, H3), 3.69 (3H, s, Me), 3.73 (3H, s, Me), 4.75 (1H, dd, $J = 6.0$, 1.6 Hz, H6), 4.87 (1H, dd, $J = 6.0$, 1.4 Hz, H5). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 20.6, 20.7, 33.7, 44.6, 44.7, 46.1, 46.2, 52.4, 52.5, 72.4, 74.8, 169.7, 169.9, 172.2, 173.7. HRMS (ESI, *m*/*z*) for $C_{15}H_{20}O_8$ $[M + H]^+$ calc. 329.1231 found 329.1233.

General procedure A for the bis-alkylation of diol 6

Anhydrous DMF (2.4 mL) was added to a pre-dried round-bottom flask protected from light, containing diol **6** (3.7 mmol) and Ag_2O (1.6 equiv.) at ambient temperature. To the stirring solution was added the appropriate alkylating agent (4.6 equiv.) and the reaction was stirred for 48 h before the reaction vessel was cooled to 4 °C (refrigerator) for a further 16 h without agitation. The resulting precipitate was removed by vacuum filtration and washed with EtOAc (15 mL). The filtrate was washed with H_2O (3 × 10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product which was purified by column chromatography to give the desired bisether.

Dimethyl 5,6-bis(methoxy) bicyclo[2.2.1]heptane-3-*endo*-2-*exo*-dicarboxylate (9a). Compound **9a** was prepared from diol **6** (915 mg, 3.74 mmol) and iodomethane (1.1 mL, 17.7 mmol) according to general procedure A and was purified by column chromatography (20% EtOAc in pet. spirits) to give the title compound (682 mg, 67%) as a clear viscous oil; $R_f = 0.17$ (20% EtOAc in pet. spirits). ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.39 (1H, dquin, $J = 10.7$, 1.6 Hz, H7s), 1.89 (1H, ddd, $J = 10.7$, 1.6, 1.5 Hz, H7a), 2.64–2.69 (3H, m, H1, H2, H4), 3.20 (1H, dd, $J = 5.5$, 0.8 Hz, H3), 3.29 (1H, dd, $J = 6.0$, 1.7 Hz, H5), 3.37 (3H, s, Me), 3.42 (3H, s, Me), 3.46 (1H, dd, $J = 6.1$, 1.8 Hz, H6), 3.70 (3H, s, Me), 3.72 (3H, s, Me). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 32.9, 43.3, 44.8, 45.0, 46.4, 52.2, 52.4, 58.7, 58.8, 81.0, 84.1, 173.2, 174.2. HRMS (ESI, *m*/*z*) for $C_{13}H_{20}O_6$ $[M + H]^+$ calc. 273.1333; found 273.1328.

Dimethyl 5,6-bis(benzyloxy) bicyclo[2.2.1]heptane-3-*endo*-2-*exo*-dicarboxylate (9b). Compound **9b** was prepared from diol **6** (917 mg, 3.75 mmol) and benzyl bromide (2.1 mL, 17.3 mmol) according to general procedure A and was purified by column chromatography (10% EtOAc in pet. spirits) to give the title compound (743 mg, 47%) as a clear oil; $R_f = 0.43$ (20% EtOAc in pet. spirits). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45 (1H, dt, $J = 10.7$, 1.5 Hz, H7s), 2.10 (1H, dd, $J = 10.7$, 1.6 Hz, H7a), 2.64–2.65 (2H, m, H1, H2), 2.70–2.71 (1H, m, H4), 3.19 (1H, app. t, $J = 5.3$ Hz, H3), 3.46 (1H, dd, $J = 5.8$, 1.6 Hz, H5), 3.60 (3H, s, Me), 3.62 (1H, dd, $J = 5.9$, 1.4 Hz, H6), 3.69 (3H, s, Me), 4.53–4.62 (4H, m, 2 × $ArCH_2$), 7.25–7.38 (10H, m, ArH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.4, 44.2, 45.1, 45.9, 46.4, 52.2, 52.4, 72.5, 72.7, 77.9, 81.7, 127.7 (2 × C), 127.9 (2 × C), 128.0 (2 × C), 128.4 (2 × C), 128.5 (2 × C), 138.4, 138.5, 173.1, 174.3. HRMS (ESI, *m*/*z*) for $C_{25}H_{28}O_6$ $[M + Na]^+$ calc. 447.1778; found 447.1754.

Dimethyl 5,6-bis[(2-methylbenzyl)oxy] bicyclo[2.2.1]heptane-3-*endo*-2-*exo*-dicarboxylate (9c). Compound **9c** was prepared from diol **6** (321 mg, 1.31 mmol) and 2-methylbenzyl bromide (810 μL, 6.03 mmol) according to general procedure A and was purified by column chromatography (10–20% EtOAc in pet. spirits) to give the title compound (115 mg, 19%) as a clear oil; $R_f = 0.50$ (20% EtOAc in pet. spirits). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45 (1H, d, $J = 10.6$ Hz, H7s), 2.10 (1H, dd, $J = 10.6$, 1.4 Hz, H7a), 2.27 (3H, s, ArMe), 2.30 (3H, s, ArMe), 2.67–2.68 (2H, m, H1, H2), 2.70–2.71 (1H, m, H4), 3.19 (1H, app. t, $J = 5.3$ Hz, H3), 3.49 (1H, dd, $J = 5.8$, 1.4 Hz, H5), 3.62 (3H, s, Me), 3.64 (1H, dd, $J = 5.7$, 1.2 Hz, H6), 3.70 (3H, s, Me), 4.49–4.61 (4H, m, 2 × $ArCH_2$), 7.10–7.20 (6H, m, ArH), 7.24–7.25 (1H, m, ArH), 7.31–

7.33 (1H, m, ArH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.9, 19.0, 33.4, 44.4, 45.1, 45.7, 46.5, 52.2, 52.4, 70.9, 71.0, 78.3, 82.0, 125.8, 125.9, 127.8 (2 × C), 128.8, 128.9, 130.2, 130.3, 136.3, 136.4, 136.7, 136.9, 173.2, 174.3. HRMS (ESI, *m*/*z*) for $C_{27}H_{32}O_6$ [M + Na]$^+$ calc. 475.2091; found 475.2073.

Dimethyl 5,6-bis[(4-trifluoromethyl)benzyloxy] bicyclo[2.2.1]-heptane-3-*endo*-2-*exo*-dicarboxylate (9d). Compound **9d** was prepared from diol **6** (315 mg, 1.29 mmol) and 4-(trifluoromethyl)benzyl bromide (910 μL, 5.93 mmol) according to general A procedure and was purified by column chromatography (10–20% EtOAc in pet. spirits) to give the title compound (461 mg, 64%) as a clear oil; R_f = 0.26 (20% EtOAc in pet. spirits). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.49 (1H, dt, J = 10.7, 1.4 Hz, H7s), 2.10 (1H, dd, J = 10.7, 1.6 Hz, H7a), 2.66–2.68 (2H, m, H1, H2), 2.72–2.75 (1H, m, H4), 3.22 (1H, app. t, J = 5.2 Hz, H3), 3.52 (1H, dd, J = 5.8, 1.6 Hz, H5), 3.63 (3H, s, Me), 3.67 (1H, dd, J = 5.8, 1.4 Hz, H6), 3.71 (3H, s, Me), 4.57–4.68 (4H, m, 2 × $ArCH_2$), 7.38–7.42 (4H, m, ArH), 7.54–7.57 (4H, m, ArH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.3, 44.2, 45.0, 45.8, 46.3, 52.3, 52.5, 71.8, 71.9, 78.6, 82.2, 124.2 (q, J_{CF} = 270.6 Hz, 2 × CF_3), 125.3 (q, $^3J_{CF}$ = 3.6 Hz, 2 × CH), 125.4 (q, $^3J_{CF}$ = 3.6 Hz, 2 × CH), 127.7 (2 × C), 127.8 (2 × C), 129.9 (q, $^2J_{CF}$ = 32.3 Hz), 130.0 (q, $^2J_{CF}$ = 32.3 Hz), 142.4 (2 × C), 173.1, 174.0. ^{19}F NMR (470 MHz, $CDCl_3$) δ −63.02, −63.00. HRMS (ESI, *m*/*z*) for $C_{27}H_{26}F_6O_6$ [M + H]$^+$ calc. 561.1706; found 561.1718.

Dimethyl 5,6-bis[(3-fluorobenzyl)oxy] bicyclo[2.2.1]heptane-3-*endo*-2-*exo*-dicarboxylate (9e). Compound **9e** was prepared from diol **6** (333 mg, 1.36 mmol) and 3-fluorobenzyl bromide (770 μL, 6.26 mmol) according to general procedure A and was purified by column chromatography (10–20% EtOAc in pet. spirits) to give the title compound (326 mg, 52%) as a clear oil; R_f = 0.31 (20% EtOAc in pet. spirits). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.47 (1H, dt, J = 10.7, 1.5 Hz, H7s), 2.09 (1H, dd, J = 10.7, 1.6 Hz, H7a), 2.65–2.67 (2H, m, H1, H2), 2.73 (1H, m, H4), 3.21 (1H, app. t, J = 5.3 Hz, H3), 3.47 (1H, dd, J = 5.9, 1.6 Hz, H5), 3.62–3.64 (4H, m, Me, H6), 3.70 (3H, s, Me), 4.52–4.62 (4H, m, 2 × $ArCH_2$), 6.94–7.13 (6H, m, ArH), 7.25–7.30 (2H, m, ArH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.3, 44.1, 45.0, 45.8, 46.3, 52.2, 52.5, 71.7, 71.9, 78.2, 81.9, 114.52 (d, $^2J_{CF}$ = 21.6 Hz, 2 × CH), 114.59 (d, $^2J_{CF}$ = 21.1 Hz), 114.62 (d, $^2J_{CF}$ = 21.6 Hz), 123.07 (d, $^3J_{CF}$ = 2.8 Hz), 123.23 (d, $^3J_{CF}$ = 2.8 Hz), 129.94 (d, $^4J_{CF}$ = 1.6 Hz), 130.00 (d, $^4J_{CF}$ = 1.7 Hz), 140.98 (d, $^3J_{CF}$ = 2.4 Hz), 141.04 (d, $^3J_{CF}$ = 2.3 Hz), 163.00 (d, $^1J_{CF}$ = 244.6 Hz), 163.05 (d, J_{CF} = 244.4 Hz), 173.1, 174.1. ^{19}F NMR (470 MHz, $CDCl_3$) δ −113.77. HRMS (ESI, *m*/*z*) for $C_{25}H_{26}F_2O_6$ [M + H]$^+$ calc. 461.1770; found 461.1784.

Dimethyl 5,6-bis[(4-fluorobenzyl)oxy] bicyclo[2.2.1]heptane-3-*endo*-2-*exo*-dicarboxylate (9f). Compound **9f** was prepared from diol **6** (308 mg, 1.26 mmol) and 4-fluorobenzyl bromide (720 μL, 5.80 mmol) according to general procedure A and was purified by column chromatography (10–20% EtOAc in pet. spirits) to give the title compound (157 mg, 27%) as a clear oil; R_f = 0.30 (20% EtOAc in pet. spirits). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45 (1H, dt, J = 10.7, 1.5 Hz, H7s), 2.07 (1H, dd, J = 10.7, 1.6 Hz, H7a), 2.64–2.65 (1H, m, H2), 2.66 (1H, m, H1), 2.69 (1H, dd, J = 4.6, 1.4 Hz, H4), 3.20 (1H, app. t, J = 5.1 Hz, H3), 3.47 (1H, dd, J = 5.8, 1.6 Hz, H5), 3.62 (1H, dd, J = 5.8, 1.5 Hz, H6), 3.64 (3H, s, Me), 3.70 (3H, s, Me), 4.47–4.53 (2H, m, $ArCH_2$), 4.54 (2H, m, $ArCH_2$), 6.96–7.01 (4H, m, ArH), 7.23–7.30 (4H, m, ArH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.3, 44.2, 45.1, 45.9, 46.3, 52.2, 52.4, 71.8, 72.0, 78.1, 81.8, 115.2 (d, $^2J_{CF}$ = 21.2 Hz, 2 × CH), 115.3 (d, $^2J_{CF}$ = 21.1 Hz, 2 × CH), 129.6 (d, $^3J_{CF}$ = 9.2 Hz, 2 × CH), 129.7 (d, $^3J_{CF}$ = 8.4 Hz, 2 × CH), 134.1 (d, $^4J_{CF}$ = 3.4 Hz), 134.2 (d, $^4J_{CF}$ = 2.9 Hz), 162.4 (d, $^1J_{CF}$ = 244.0 Hz), 162.5 (d, $^1J_{CF}$ = 244.3 Hz), 173.1, 174.1. ^{19}F NMR (470 MHz, $CDCl_3$) δ −115.36, −115.30. HRMS (ESI, *m*/*z*) for $C_{25}H_{26}F_2O_6$ [M + Na]$^+$ calc. 483.1590; found 483.1594.

Dimethyl 5,6-bis[(3-bromobenzyl)oxy] bicyclo[2.2.1]heptane-3-*endo*-2-*exo*-dicarboxylate (9g). Compound **9g** was prepared from diol **6** (315 mg, 1.29 mmol) and 3-bromobenzyl bromide (1.48 g, 5.93 mmol) according to general procedure A and was purified by column chromatography (10–20% EtOAc in pet. spirits) to give the title compound (266 mg, 35%) as a clear oil; R_f = 0.27 (20% EtOAc in pet. spirits). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.47 (1H, dt, J = 10.7, 1.4 Hz, H7s), 2.09 (1H, dd, J = 10.7, 1.5 Hz, H7a), 2.66–2.67 (2H, m, H1, H2), 2.72 (1H, dd, J = 4.6, 1.3 Hz, H4), 3.21 (1H, app. t, J = 4.9 Hz, H3), 3.48 (1H, dd, J = 6.0, 1.7 Hz, H5), 3.63 (1H, dd, J = 5.7, 1.4 Hz, H6), 3.66 (3H, s, Me), 3.71 (3H, s, Me), 4.49–4.59 (4H, m, 2 × $ArCH_2$), 7.15–7.29 (4H, m, ArH), 7.39–7.53 (4H, m, ArH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.3, 44.2, 45.1, 45.9, 46.3, 52.3, 52.5, 71.7, 71.9, 78.3, 82.0, 122.6, 122.7, 126.2, 126.3, 130.1 (2 × C), 130.7, 130.8 (3 × C), 140.7, 140.8, 173.1, 174.1. HRMS (ESI, *m*/*z*) for $C_{25}H_{26}Br_2O_6$ [M + H]$^+$ calc. 581.0169; found 581.0181.

Dimethyl 5,6-bis[(4-bromobenzyl)oxy] bicyclo[2.2.1]heptane-3-*endo*-2-*exo*-dicarboxylate (9h). Compound **9h** was prepared from diol **6** (333 mg, 1.36 mmol) and 4-bromobenzyl bromide (1.57 g, 6.26 mmol) according to general procedure A and was purified by column chromatography (10–20% EtOAc in pet. spirits) to give the title compound (279 mg, 35%) as a clear oil. R_f = 0.36 (20% EtOAc in pet. spirits). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45 (1H, d, J = 10.7 Hz, H7s), 2.06 (1H, d, J = 10.6 Hz, H7a), 2.64–2.65 (2H, m, H1, H2), 2.68–2.69 (1H, m, H4), 3.20 (1H, app. t, J = 5.0 Hz, H3), 3.46 (1H, dd, J = 5.8, 1.6 Hz, H5), 3.61 (1H, dd, J = 5.8, 1.3 Hz, H6), 3.64 (3H, s, Me), 3.70 (3H, s, Me), 4.45–4.53 (4H, m, 2 × $ArCH_2$), 7.14–7.19 (4H, m, ArH), 7.42–7.45 (4H, m, ArH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.3, 41.2, 45.1, 45.9, 46.3, 52.3, 52.5, 71.8, 72.0, 78.3, 81.9, 121.6 (2 × C), 129.4 (2 × C), 129.6 (2 × C), 131.5 (2 × C), 131.6 (2 × C), 137.4, 137.5, 173.1, 174.1. HRMS (ESI, *m*/*z*) for $C_{25}H_{26}Br_2O_6$ [M + H]$^+$ calc. 581.0169; found 581.0182.

Dimethyl 5,6-bis(allyloxy) bicyclo[2.2.1]heptane-3-*endo*-2-*exo*-dicarboxylate (9i). Compound **9i** was prepared from diol **6** (302 mg, 1.24 mmol) and allyl bromide (530 μL, 5.70 mmol) according to general procedure A (but was stirred for 4 days) and was purified by column chromatography (20% EtOAc in pet. spirits) to give the title compound (107 mg, 29%) as a clear oil; R_f = 0.44 (20% EtOAc in pet. spirits). ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.41 (1H, dt, J = 10.6, 1.5 Hz, H7s), 1.99 (1H, dd, J = 10.7, 1.6 Hz, H7a), 2.58–2.59 (1H, m, H1), 2.64–2.68 (2H, m, H2, H4), 3.18 (1H, dd, J = 5.3, 4.8 Hz, H3), 3.43 (1H, dd, J = 5.9, 1.7 Hz, H5), 3.56 (1H, dd, J = 5.9, 1.6 Hz, H6), 3.69 (3H, s, Me), 3.70 (3H, s, Me), 4.01 (2H, dt, J = 5.6, 1.4 Hz, OCH_2), 4.06 (2H, dt, J = 5.6, 1.4 Hz, OCH_2), 5.13–5.31 (4H, m, 2 × CH_2CH), 5.81–5.98 (2H, m, 2 × CH_2C*H*). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 33.3, 44.2, 45.1, 46.0,

46.4, 52.2, 52.4, 71.8, 71.9, 78.3, 81.8, 117.1 (2 × C), 135.0 (2 × C), 173.2, 174.3. HRMS (ESI, *m*/*z*) for $C_{17}H_{24}O_6$ $[M + Na]^+$ calc. 347.1465; found 347.1479.

General procedure B for the hydrolysis of diesters 9a–i

A biphasic solution of the appropriate diester (0.71 mmol), 2 M NaOH (1.5 mL) and THF (3.0 mL) was stirred at ambient temperature for 16 h. All organic impurities were extracted with CH_2Cl_2 (2 × 5 mL) and the remaining aqueous phase was acidified using 4 M HCl (pH = 1) and extracted with EtOAc (3 × 10 mL). The combined organic phase was washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the required diacid.

5,6-Bis(methoxy) bicyclo[2.2.1]heptane-3-*endo*-2-*exo*-dicarboxylic acid (12a). The title compound **12a** was prepared from diester **9a** (194 mg, 0.71 mmol) according to general procedure B and isolated as a white waxy solid (127 mg, 73%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.43 (1H, d, J = 10.7 Hz, H7s), 1.96 (1H, d, J = 10.0 Hz, H7a), 2.67–2.76 (3H, m, H1, H2, H4), 3.25 (1H, app. t, J = 5.4 Hz, H3), 3.41 (3H, s, Me), 3.44 (3H, s, Me), 3.45–3.50 (2H, m, H5, H6). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 33.1, 43.1, 44.8, 44.9, 46.3, 58.8, 58.9, 80.8, 84.1, 178.0, 179.2. HRMS (ESI, *m*/*z*) for $C_{11}H_{16}O_6$ $[M + Cl]^-$ calc. 279.0641; found 279.0652.

5,6-Bis(benzyloxy) bicyclo[2.2.1]heptane-3-*endo*-2-*exo*-dicarboxylic acid (12b). The title compound **12b** was prepared from diester **9b** (717 mg, 1.69 mmol) according to general procedure B and isolated as a white powder (525 mg, 78%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.48 (1H, d, J = 10.9 Hz, H7s), 2.17 (1H, d, J = 10.5 Hz, H7a), 2.63 (1H, d, J = 5.6 Hz, H1), 2.73 (1H, br s, H2), 2.79 (1H, d, J = 4.0 Hz, H4), 3.23 (1H, app. t, J = 5.4 Hz, H3), 3.63 (2H, t, J = 6.4 Hz, H5, H6), 4.57–4.67 (4H, m, 2 × $ArCH_2$), 7.23–7.35 (10H, m, Ar*H*). ^{13}C NMR (67.5 MHz, DMSO-d_6) δ 32.9, 43.6, 44.7, 45.3, 46.1, 71.6, 71.7, 78.1, 81.5, 127.4 (2 × C), 127.7 (4 × C), 128.1 (2 × C), 128.1 (2 × C), 138.5, 138.7, 173.6, 174.8. HRMS (ESI, *m*/*z*) for $C_{23}H_{24}O_6$ $[M - H]^-$ calc. 395.1501; found 395.1504.

5,6-Bis(2-methylbenzyloxy) bicyclo[2.2.1]heptane-2-*endo*-2-*exo*-dicarboxylic acid (12c). The title compound **12c** was prepared from diester **9c** (121 mg, 0.27 mmol) according to general procedure B and isolated as a clear oil (113 mg, 99%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.31 (1H, d, J = 10.1 Hz, H7s), 1.85 (1H, d, J = 9.4 Hz, H7a), 2.19 (3H, s, Me), 2.21 (3H, s, Me), 2.47 (1H, d, J = 5.5 Hz, H4), 2.55 (1H, br s, H1), 2.61 (1H, d, J = 3.3 Hz, H2), 2.99 (1H, app. t, J = 5.0 Hz, H3), 3.59 (1H, d, J = 5.7 Hz, H5), 3.64 (1H, d, J = 5.6 Hz, H6), 4.44–4.49 (2H, m, $ArCH_2$), 4.53 (2H, br s, $ArCH_2$), 7.08–7.18 (6H, m, ArH), 7.22–7.27 (2H, m, ArH), 12.54 (2H, br s, 2 × COOH). ^{13}C NMR (125 MHz, DMSO-d_6) δ 18.3 (2 × C), 33.0, 43.6, 44.7, 45.2, 46.1, 70.0, 70.1, 78.5, 81.8, 125.5 (2 × C), 127.5 (2 × C), 128.3 (2 × C), 129.8 (2 × C), 136.1 (2 × C), 136.5, 136.6, 173.6, 174.8. HRMS (ESI, *m*/*z*) for $C_{25}H_{28}O_6$ $[M + Na]^+$ calc. 447.1778; found 447.1787.

5,6-Bis[(4-trifluoromethyl)benzyloxy] bicyclo[2.2.1]heptane-3-*endo*-2-*exo*-dicarboxylic acid (12d). The title compound **12d** was prepared from diester **9d** (423 mg, 0.755 mmol) according to general procedure B and isolated as a white powder (316 mg, 79%); m.p: 114.8–143.7 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.34 (1H, d, J = 10.1 Hz, H7s), 1.90 (1H, d, J = 9.7 Hz, H7a), 2.48 (1H, m, H2), 2.58 (1H, br s, H1), 2.62–2.63 (1H, m, H4), 3.01 (1H, dd, J = 5.4, 4.8 Hz, H3), 3.62 (1H, d, J = 5.6 Hz, H6), 3.72 (1H, d, J = 5.5 Hz, H5), 4.57–4.69 (4H, m, 2 × $ArCH_2$), 7.46–7.50 (4H, m, ArH), 7.60–7.63 (4H, m, ArH), 12.58 (2H, br s, 2 × COOH). ^{13}C NMR (125 MHz, DMSO-d_6) δ 33.0, 43.6, 44.6, 45.3, 46.0, 70.7, 70.8, 78.4, 81.7, 124.4 (q, $^1J_{CF}$ = 270 Hz, 2 × CF_3), 124.9 (q, $^3J_{CF}$ = 3.3 Hz, 2 × CH), 125.0 (q, $^3J_{CF}$ = 3.3 Hz, 2 × CH), 127.83 (2 × C), 127.84 (q, $^2J_{CF}$ = 31.6 Hz, 2 × C), 127.9 (2 × C), 143.5, 143.6, 173.6, 174.8. ^{19}F NMR (470 MHz, DMSO-d_6) δ −61.43. HRMS (ESI, *m*/*z*) for $C_{25}H_{22}F_6O_6$ $[M + Na]^+$ calc. 555.1213; found 555.1211.

5,6-Bis(3-fluorobenzyloxy) bicyclo[2.2.1]heptane-3-*endo*-2-*exo*-dicarboxylic acid (12e). The title compound **12e** was prepared from diester **9e** (292 mg, 0.635 mmol) according to general procedure B and isolated as a clear waxy solid (206 mg, 75%). ^{1}H NMR (500 MHz, CD_3OD) δ 1.45 (1H, d, J = 10.5 Hz, H7s), 2.04 (1H, dd, J = 10.5, 1.5 Hz, H7a), 2.61 (1H, dd, J = 5.6, 0.9 Hz, H2), 2.65 (1H, br s, H1), 2.70 (1H, dd, J = 4.5, 1.4 Hz, H4), 3.16 (1H, dd, J = 5.5, 4.8 Hz, H3), 3.67–3.71 (2H, m, H5, H6), 4.56 (2H, s, $ArCH_2$), 4.61 (2H, s, $ArCH_2$), 6.96–7.00 (2H, m, ArH), 7.04–7.14 (4H, m, ArH), 7.27–7.33 (2H, m, ArH). ^{13}C NMR (125 MHz, CD_3OD) δ 33.9, 45.2, 46.2, 47.2, 47.6, 73.7 (d, $^4J_{CF}$ = 1.3 Hz), 72.8 (d, $^4J_{CF}$ = 1.5 Hz), 80.0, 83.4, 115.2 (d, $^2J_{CF}$ = 21.1 Hz), 115.3 (d, $^2J_{CF}$ = 21.6 Hz), 115.4 (d, $^2J_{CF}$ = 22.3 Hz), 115.5 (d, $^2J_{CF}$ = 21.7 Hz), 124.4 (d, $^3J_{CF}$ = 2.7 Hz), 124.5 (d, $^3J_{CF}$ = 2.7 Hz), 130.98, 131.04, 142.6 (d, $^3J_{CF}$ = 7.2 Hz), 142.7 (d, $^3J_{CF}$ = 7.2 Hz), 164.26 (d, $^1J_{CF}$ = 242.9 Hz), 164.28 (d, $^1J_{CF}$ = 242.8 Hz), 175.7, 176.9. ^{19}F NMR (470 MHz, CD_3OD) δ −116.06, −116.03. HRMS (ESI, *m*/*z*) for $C_{23}H_{22}F_2O_6$ $[M + Na]^+$ calc. 455.1277; found 455.1264.

5,6-Bis(4-fluorobenzyloxy) bicyclo[2.2.1]heptane-3-*endo*-2-*exo*-dicarboxylic acid (12f). The title compound **12f** was prepared from diester **9f** (115 mg, 0.25 mmol) according to general procedure B and isolated as a white powder (103 mg, 94%); m.p: 198.1–199.5 °C. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.48 (1H, d, J = 10.6 Hz, H7s), 2.13 (1H, d, J = 10.8 Hz, H7a), 2.64 (1H, d, J = 5.8 Hz, H2), 2.72 (1H, br s, H1), 2.76–2.78 (1H, m, H4), 3.24 (1H, dd, J = 5.7, 4.8 Hz, H3), 3.56–3.64 (2H, m, H5, H6), 4.53 (2H, br s, $ArCH_2$), 4.56 (2H, br s, $ArCH_2$), 6.93–7.02 (4H, m, ArH), 7.23–7.31 (4H, m, ArH). ^{13}C NMR (67.5 MHz, DMSO-d_6) δ 32.9, 43.6, 44.6, 45.3, 46.0, 70.8, 70.9, 78.0, 81.4, 114.8 (d, $^2J_{CF}$ = 21.1 Hz, 2 × CH), 114.9 (d, $^2J_{CF}$ = 21.0 Hz, 2 × CH), 129.6 (d, $^3J_{CF}$ = 8.0 Hz, 2 × CH), 129.7 (d, $^3J_{CF}$ = 8.1 Hz, 2 × CH), 134.7 (d, $^4J_{CF}$ = 3.0 Hz), 134.9 (d, $^4J_{CF}$ = 3.0 Hz), 161.5 (d, $^1J_{CF}$ = 241.3 Hz, 2 × CF), 173.5, 174.7. ^{19}F NMR (470 MHz, DMSO-d_6) δ −116.68. HRMS (ESI, *m*/*z*) for $C_{23}H_{22}F_2O_6$ $[M + Na]^+$ calc. 455.1277; found 455.1270.

5,6-Bis(3-bromobenzyloxy) bicyclo[2.2.1]heptane-3-*endo*-2-*exo*-dicarboxylic acid (12g). The title compound **12g** was prepared from diester **9g** (265 mg, 0.455 mmol) according to general procedure B and isolated as a white powder (171 mg, 68%); m.p: 76.0–78.1 °C. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.50 (1H, d, J = 11.3 Hz, H7s), 2.16 (1H, d, J = 11.1 Hz, H7a), 2.67 (1H, d, J = 4.9 Hz, H2), 2.75 (1H, br s, H1), 2.79 (1H, d, J = 4.3 Hz, H4), 3.27 (1H, app. t, J = 5.6 Hz, H3), 3.62–3.67 (2H, m, H5, H6), 4.55 (2H, s, $ArCH_2$), 4.58 (2H, s, $ArCH_2$), 7.14–7.24 (4H, m, Ar*H*), 7.36–

7.49 (4H, m, Ar*H*). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 33.5, 43.9, 44.9, 45.9, 46.2, 71.9, 72.0, 78.5, 81.9, 122.6, 122.7, 126.2, 126.4, 130.1, 130.2, 130.7, 130.8, 130.9 (2 × C), 140.5, 140.6, 177.5, 178.6. HRMS (ESI, *m*/*z*) for $C_{23}H_{22}Br_2O_6$ $[M - H]^-$ calc. 550.9710; found 550.9729.

5,6-Bis(4-bromobenzyloxy) bicyclo[2.2.1]heptane-3-*endo*-2-*exo*-dicarboxylic acid (12h). The title compound **12h** was prepared from diester **9h** (159 mg, 0.273 mmol) according to general procedure B and isolated as a white powder (119 mg, 79%); m.p: 119.7–124.9 °C. ^{1}H NMR (500 MHz, CD_3OD) δ 1.43 (1H, d, J = 10.4 Hz, H7s), 2.02 (1H, dd, J = 10.4, 1.1 Hz, H7a), 2.60 (1H, d, J = 5.4 Hz, H2), 2.63 (1H, br s, H1), 2.68 (1H, dd, J = 4.5, 1.3 Hz, H4), 3.15 (1H, app. t, J = 5.4 Hz, H3), 3.65–3.68 (2H, m, H5, H6), 4.50 (2H, m, $ArCH_2$), 4.54–4.56 (2H, m, $ArCH_2$), 7.19–7.24 (4H, m, ArH), 7.42–7.44 (4H, m, ArH). ^{13}C NMR (125 MHz, CD_3OD) δ 33.9, 45.2, 46.2, 47.2, 47.6, 72.7, 72.8, 79.8, 83.3, 122.3, 122.4, 130.8 (2 × C), 130.9 (2 × C), 132.4 (4 × C), 138.9, 139.1, 173.6, 174.8. HRMS (ESI, *m*/*z*) for $C_{23}H_{22}Br_2O_6$ $[M - H]^-$ calc. 550.9710; found 550.9723.

5,6-Bis(allyloxy) bicyclo[2.2.1]heptane-3-*endo*-2-*exo*-dicarboxylic acid (12i). The title compound **12i** was prepared from diester **9i** (41 mg, 0.127 mmol) according to general procedure B and isolated as a viscous yellow oil (127 mg, 73%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.41–1.45 (1H, m, H7s), 2.04 (1H, d, J = 10.4 Hz, H7a), 2.64–2.72 (3H, m, H1, H2, H4), 3.22 (1H, dd, J = 5.5, 4.7 Hz, H3), 3.56–3.61 (2H, m, H5, H6), 4.03–4.10 (4H, m, 2 × OCH_2), 5.12–5.32 (4H, m, 2 × CH_2CH), 5.82–5.99 (2H, m, CH_2CH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.2, 43.9, 44.9, 45.8, 46.2, 71.7, 71.8, 78.2, 81.6, 117.2, 117.3, 134.6, 134.7, 178.1, 179.2. HRMS (ESI, *m*/*z*) for $C_{15}H_{20}O_6$ $[M + Na]^+$ calc. 319.1152; found 319.1152.

General procedure C for the amidation of diacids 12a–i

A microwave vial was charged with the appropriate carboxylic acid, EDCI (3.0 equiv.), HOBt (0.1 equiv.) and dry DMF and was stirred at ambient temperature for 30 min. Aminoethylguanidine **14** (3.0 equiv.) was then added and the reaction was irradiated to 50 °C for 30 min. The resulting homogenous clear mixture was diluted with EtOAc (15 mL), washed with H_2O (3 × 8 mL), brine (8 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford a solid that was purified by column chromatography (as specified below) to give the title compound.

3-*endo*-2-*exo*-Di[2′-(2″,3″-di-*tert*-butoxycarbonylguanidino)-ethylcarbamoyl]-5,6-bis(methoxy)bicyclo[2.2.1]heptane (15a). Compound **15a** was prepared from diacid **12a** (96 mg, 0.39 mmol) and amine **14** (357 mg, 1.18 mmol) according to general procedure C and after purification by column chromatography (EtOAc) was isolated as a clear oil (230 mg, 72%); R_f = 0.25 (EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45–1.47 (36H, m, 4 × *t*-Bu), 1.56 (1H, d, J = 10.2 Hz, H7a), 1.89 (1H, d, J = 10.2 Hz, H7s), 2.45 (1H, d, J = 6.3 Hz, H2), 2.56 (1H, br s, H1), 2.68 (1H, br s, H4), 2.82 (1H, app. t, J = 5.3 Hz, H3), 3.34 (3H, s, OMe), 3.36 (3H, s, OMe), 3.38–3.60 (10H, m, 4 × CH_2, H5, H6), 6.69 (1H, t, J = 5.4 Hz, NH), 8.02 (1H, t, J = 3.4 Hz, NH), 8.45 (1H, t, J = 5.5 Hz, NH), 8.65 (1H, t, J = 5.6 Hz, NH), 11.44 (1H, s, NH), 11.48 (1H, s, NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 28.2, 28.3, 28.4, 33.8, 39.4, 39.8, 40.1, 40.3, 42.4, 42.9, 43.7, 45.0, 49.3, 58.4, 58.6, 79.5, 80.0, 81.1, 83.3, 83.8, 84.2, 153.1, 153.2, 156.8, 157.9, 163.0, 163.5, 172.3, 174.4. HRMS (ESI, *m*/*z*) for $C_{37}H_{64}N_8O_{12}$ $[M + H]^+$ calc. 813.4717; found 813.4733.

3-*endo*-2-*exo*-Di[2′-(2″,3″-di-*tert*-butoxycarbonylguanidino)-ethylcarbamoyl]-5,6-bis(2-methylbenzyloxy)bicyclo[2.2.1]heptane (15c). Compound **15c** was prepared from diacid **12c** (62 mg, 0.15 mmol) and amine **14** (140 mg, 0.45 mmol) according to general procedure C and after purification by column chromatography (50–70% EtOAc in pet. spirits) was isolated as a white solid (36 mg, 54%); R_f = 0.71 (70% EtOAc in pet. spirits); m.p: 117.7–120.7 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46–1.48 (36H, m, 4 × *t*-Bu), 1.63 (1H, d, J = 10.2 Hz, H7s), 2.12 (1H, d, J = 9.3, Hz, H7a), 2.25 (3H, s, ArMe), 2.27 (3H, s, ArMe), 2.48 (1H, d, J = 6.2 Hz, H2), 2.60 (1H, br s, H1), 2.73 (1H, d, J = 3.1 Hz, H4), 2.82 (1H, app. t, J = 4.7 Hz, H3), 3.23–3.55 (8H, m, 4 × CH_2), 3.58 (1H, d, J = 5.5 Hz, H5), 3.61 (1H, d, J = 5.8 Hz, H9), 4.50–4.58 (4H, m, 2 × CH_2Ar), 6.52 (1H, br s, NH), 7.08–7.19 (6H, m, ArH), 7.27–7.31 (2H, m, ArH), 8.00 (1H, t, J = 4.1 Hz, NH), 8.48 (1H, br s, NH), 8.67 (1H, t, J = 5.6 Hz, NH), 11.45 (1H, s, NH), 11.50 (1H, s, NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.9, 19.0, 28.1, 28.2, 28.40, 28.42, 34.4, 39.2, 40.3, 40.5, 42.3, 44.1, 44.7, 45.2, 49.5, 70.8, 70.9, 78.7, 79.6, 80.2, 82.1, 83.4, 83.8, 125.7, 125.8, 127.6, 127.8, 128.7, 128.9, 130.1, 130.2, 136.6, 136.67, 136.69, 136.8, 153.19, 153.23, 156.7, 157.9, 172.3, 174.6. HRMS (ESI, *m*/*z*) for $C_{51}H_{76}N_8O_{12}$ $[M + H]^+$ calc. 993.5655; found 993.5654.

3-*endo*-2-*exo*-Di[2′-(2″,3″-di-*tert*-butoxycarbonylguanidino)-ethylcarbamoyl]-5,6-bis[(4-trifluoromethyl)benzyloxy]bicyclo-[2.2.1]heptane (15d). Compound **15d** was prepared from diacid **12d** (151 mg, 0.28 mmol) and amine **14** (260 mg, 0.85 mmol) according to general procedure C and after purification by flash column chromatography (EtOAc) was isolated as a clear oil (174 mg, 56%); R_f = 0.45 (EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44–1.52 (36H, m, 4 × *t*-Bu), 1.68 (1H, d, J = 10.3 Hz, H7s), 2.13 (1H, d, J = 9.3 Hz, H7a), 2.48 (1H, d, J = 6.0 Hz, H2), 2.65 (1H, br s, H1), 2.79–2.80 (1H, m, H4), 2.85 (1H, dd, J = 5.7, 4.5 Hz, H3), 3.23–3.56 (8H, m, 4 × CH_2), 3.58 (1H, d, J = 6.1 Hz, H5), 3.62 (1H, dd, J = 5.8, 1.2 Hz, H9), 4.55–4.67 (4H, m, 2 × CH_2Ar), 6.68 (1H, m, NH), 7.38–7.40 (4H, m, ArH), 7.51–7.54 (4H, m, ArH), 8.16 (1H, t, J = 4.0 Hz, NH), 8.49 (1H, m, NH), 8.72 (1H, t, J = 6.0 Hz, NH), 11.48 (1H, s, NH), 11.53 (1H, s, NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 28.2, 28.4, 34.3, 39.4, 40.1, 40.4, 42.5, 43.8, 44.6, 45.1, 49.4, 71.5, 71.6, 78.9, 79.7, 80.3, 82.1, 83.5, 84.0, 125.3 (q, $^3J_{CF}$ = 3.5 Hz, 4 × CH), 126.4 (q, $^1J_{CF}$ = 270 Hz, 2 × CF_3), 127.66 (2 × C), 127.72 (2 × C), 129.7 (q, $^2J_{CF}$ = 32.6 Hz), 129.8 (q, $^2J_{CF}$ = 32.6 Hz), 142.7, 142.8, 153.2 (2 × C), 156.7, 158.1, 163.0, 163.4, 172.2, 174.3. ^{19}F NMR (470 MHz, $CDCl_3$) δ −62.97. HRMS (ESI, *m*/*z*) for $C_{51}H_{70}F_6N_8O_{12}$ $[M + H]^+$ calc. 1101.5090; found 1101.5110.

3-*endo*-2-*exo*-Di[2′-(2″,3″-di-*tert*-butoxycarbonylguanidino)-ethylcarbamoyl]-5,6-bis(3-fluorobenzyloxy)bicyclo[2.2.1]heptane (15e). Compound **15e** was prepared from diacid **12e** (184 mg, 0.43 mmol) and amine **14** (290 mg, 1.28 mmol) according to general procedure C and after purification by column chromatography (50–70% EtOAc in pet. spirits) was isolated as a white solid (111 mg, 26%); R_f = 0.58 (70% EtOAc in pet. spirits); m.p: 214.5–258.2 °C (slow decomposition). ^{1}H NMR (500 MHz, $CDCl_3$)

δ 1.46–1.49 (36H, m, 4 × *t*-Bu), 1.66 (1H, d, J = 10.3 Hz, H7s), 2.12 (1H, d, J = 9.3 Hz, H7a), 2.47 (1H, d, J = 6.1 Hz, H1), 2.63 (1H, br s, H4), 2.78–2.79 (1H, m, H1), 2.84 (1H, app. t, J = 6.0 Hz, H3), 3.25–3.60 (10H, m, 4 × CH_2, H5, H6), 4.51–4.61 (4H, m, 2 × CH_2Ar), 6.62 (1H, br s, NH), 6.91–7.07 (6H, m, ArH), 7.22–7.28 (2H, m, ArH), 8.15 (1H, t, J = 4.0 Hz, NH), 8.50 (1H, br s, NH), 8.72 (1H, br s, NH), 11.47 (1H, s, NH), 11.53 (1H, s, NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 28.2, 28.4, 34.3, 39.3, 40.2, 40.6, 42.4, 43.7, 44.7, 45.1, 49.4, 71.5, 71.6, 78.5, 80.0, 80.4, 81.9, 83.6, 84.0, 114.3 (d, $^2J_{CF}$ = 21.4 Hz), 114.4 (d, $^2J_{CF}$ = 21.1 Hz), 114.5 (d, $^2J_{CF}$ = 21.2 Hz), 114.6 (d, $^2J_{CF}$ = 21.4 Hz), 123.07 (d, $^3J_{CF}$ = 2.8 Hz), 123.16 (d, $^3J_{CF}$ = 2.9 Hz), 129.8, 129.9, 141.3 (d, $^3J_{CF}$ = 7.0 Hz), 141.4 (d, $^3J_{CF}$ = 7.1 Hz), 153.1, 153.2, 156.6, 158.0, 162.71, 162.73, 162.96 (d, $^1J_{CF}$ = 244.0 Hz), 163.02 (d, $^1J_{CF}$ = 244.0 Hz), 172.3, 174.5. ^{19}F NMR (470 MHz, $CDCl_3$) δ −113.92, −113.86. HRMS (ESI, *m*/*z*) for $C_{49}H_{70}F_2N_8O_{12}$ $[M + H]^+$ calc. 1001.5154; found 1001.5165.

3-*endo*-2-*exo*-Di[2′-(2″,3″-di-*tert*-butoxycarbonylguanidino)-ethylcarbamoyl]-5,6-bis(4-bromobenzyloxy)bicyclo[2.2.1]heptane (15h). Compound **15h** was prepared from diacid **12h** (171 mg, 0.31 mmol) and amine **14** (281 mg, 0.93 mmol) according to general procedure C and after purification by column chromatography (50–70% EtOAc in pet. spirits) was isolated as a clear oil (91 mg, 26%); R_f = 0.48 (70% EtOAc in pet. spirits). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46–1.48 (36H, m, 4 × *t*-Bu), 1.64 (1H, d, J = 10.3 Hz, H7s), 2.09 (1H, d, J = 9.4 Hz, H7a), 2.46 (1H, d, J = 6.1 Hz, H1), 2.60 (1H, br s, H4), 2.74 (1H, m, H2), 2.83 (1H, app. t, J = 4.6 Hz, H3), 3.22–3.46 (4H, m, 2 × CH_2), 3.52–3.58 (6H, m, 2 × CH_2, H5, H6), 4.46–4.55 (4H, m, 2 × CH_2Ar), 6.69 (1H, m, NH), 7.14–7.17 (4H, m, ArH), 7.39–7.42 (4H, m, ArH), 8.09 (1H, t, J = 4.0 Hz, NH), 8.54 (1H, m, NH), 8.73 (1H, t, J = 5.1 Hz, NH), 11.47 (1H, s, NH), 11.51 (1H, s, NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 28.2, 28.4, 34.3, 39.3, 40.2, 40.5, 42.4, 43.8, 44.6, 45.1, 49.4, 71.56, 71.61, 78.6, 80.0, 80.4, 81.8, 83.6, 84.0, 121.4, 121.5, 129.5 (2 × C), 129.6 (2 × C), 131.4 (2 × C), 131.5 (2 × C), 137.6, 137.7, 153.1, 153.2, 156.7, 158.0, 162.8, 163.2, 172.2, 174.4. HRMS (ESI, *m*/*z*) for $C_{49}H_{70}Br_2N_8O_{12}$ $[M + H]^+$ calc. 1121.3553; found 1121.3550.

3-*endo*-2-*exo*-Di[2′-(2″,3″-di-*tert*-butoxycarbonylguanidino)-ethylcarbamoyl]-5,6-bis(allyloxy)bicyclo[2.2.1]heptane (15i). Compound **15i** was prepared from diacid **12i** (70 mg, 0.24 mmol) and amine **14** (214 mg, 0.71 mmol) according to general procedure C and after purification by column chromatography (50–70% EtOAc in pet. spirits) was isolated as a clear oil (128 mg, 63%); R_f = 0.34 (70% EtOAc in pet. spirits). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.49–1.50 (36H, m, 4 × *t*-Bu), 1.60 (1H, d, J = 10.3 Hz, H7s), 2.02 (1H, d, J = 10.0 Hz, H7a), 2.48 (1H, d, J = 6.2 Hz, H4), 2.54 (1H, br s, H1), 2.66 (1H, d, J = 2.9 Hz, H2), 2.82 (1H, dd, J = 6.0, 4.6 Hz, H3), 3.33–3.60 (10H, m, 4 × CH_2, H5, H6), 3.98–4.04 (4H, m, 2 × OCH_2), 5.10–5.14 (2H, m, CH_2CH), 5.20–5.27 (2H, m, CH_2CH), 5.84–5.94 (2H, m, 2 × CH_2C*H*), 6.58 (1H, t, J = 5.1 Hz, NH), 8.03 (1H, t, J = 3.9 Hz, NH), 8.48 (1H, br s, NH), 8.68 (1H, t, J = 5.8 Hz, NH), 11.46 (1H, s, NH), 11.50 (1H, s, NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.17, 28.21, 28.41, 28.44, 34.2, 39.3, 40.2, 40.5, 42.5, 43.9, 44.9, 45.2, 49.4, 71.6, 71.7, 78.6, 80.2, 81.9, 83.4, 83.9 (2 × C), 116.6, 116.9, 135.2, 135.3, 153.23, 153.34, 156.7, 158.0, 172.4, 174.6. HRMS (ESI, *m*/*z*) for $C_{41}H_{68}N_8O_{12}$ $[M + H]^+$ calc. 865.5030; found 865.5027.

General procedure D for the amidation of diacids 12a–i

A microwave vial was charged with the appropriate carboxylic acid, EDCI (3.0 equiv.), HOBt (0.1 equiv.) and dry $CHCl_3$ and was stirred at ambient temperature for 30 min. Amino-ethylguanidine **14** (3.0 equiv.) was then added and the reaction was irradiated to 50 °C for 30 min. The resulting homogenous clear mixture was diluted with $CHCl_3$ (20 mL), washed with H_2O (2 × 10 mL), brine (8 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford the crude material that was purified by column chromatography (as specified below) to give the title compound.

3-*endo*-2-*exo*-Di[2′-(2″,3″-di-*tert*-butoxycarbonylguanidino)-ethylcarbamoyl]-5,6-bis(benzyloxy)bicyclo[2.2.1]heptane (15b). Compound **15b** was prepared from diacid **12b** (343 mg, 0.87 mmol) and amine **14** (786 mg, 2.60 mmol) according to general procedure D and after purification by column chromatography (70% EtOAc in pet. spirits) was isolated as a clear oil (563 mg, 57%); R_f = 0.43 (70% EtOAc in pet. spirits). ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.45–1.49 (36H, m, 4 × *t*-Bu), 1.63 (1H, d, J = 10.8 Hz, H7s), 2.12 (1H, d, J = 10.4 Hz, H7a), 2.43 (1H, d, J = 6.2 Hz, H2), 2.60 (1H, s, H1), 2.74–2.76 (1H, m, H4), 2.79–2.83 (1H, m, H3), 3.16–3.57 (10H, m, 4 × CH_2, H5, H6), 4.55 (2H, s, CH_2Ar), 4.59 (2H, s, CH_2Ar), 6.56 (1H, t, J = 5.8 Hz, NH), 7.22–7.33 (10H, m, ArH), 7.99 (1H, t, J = 4.0 Hz, NH), 8.45 (1H, t, J = 5.6 Hz, NH), 8.69 (1H, t, J = 4.0 Hz, NH), 11.45 (1H, s, NH), 11.53 (1H, s, NH). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 28.1, 28.2, 28.4, 34.4, 39.2, 40.1, 40.4, 42.5, 43.8, 44.6, 45.1, 49.5, 72.2, 72.3, 78.3, 79.5, 80.1, 81.6, 83.3, 83.8, 127.5, 127.6, 127.8, 128.1, 128.3, 128.4, 138.6, 138.7, 153.2, 156.7, 158.0, 163.1, 163.6, 172.3, 174.5. HRMS (ESI, *m*/*z*) for $C_{49}H_{72}N_8O_{12}$ $[M + H]^+$ calc. 965.5343; found 965.5371.

3-*endo*-2-*exo*-Di[2′-(2″,3″-di-*tert*-butoxycarbonylguanidino)-ethylcarbamoyl]-5,6-bis(4-fluorobenzyloxy)bicyclo[2.2.1]heptane (15f). Compound **15f** was prepared from diacid **12f** (86 mg, 0.20 mmol) and amine **14** (181 mg, 0.60 mmol) according to general procedure D and after purification by column chromatography (50–70% EtOAc in pet. spirits) was isolated as a clear oil (90 mg, 45%); R_f = 0.13 (50% EtOAc in pet. spirits). ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.46–1.48 (36H, m, 4 × *t*-Bu), 1.62–1.66 (1H, m, H7s), 2.12 (1H, d, J = 10.7 Hz, H7a), 2.46 (1H, d, J = 7.3 Hz, H2), 2.60 (1H, br s, H1), 2.72–2.75 (1H, m, H4), 2.83 (1H, app. t, J = 5.2 Hz, H3), 3.28–3.60 (10H, m, 4 × CH_2, H5, H6), 4.48–4.53 (4H, m, 2 × CH_2Ar), 6.58 (1H, t, J = 5.3 Hz, NH), 6.92–7.00 (4H, m, ArH), 7.22–7.29 (4H, m, ArH), 8.07 (1H, t, J = 4.1 Hz, NH), 8.47 (1H, t, J = 5.7 Hz, NH), 8.70 (1H, t, J = 5.9 Hz, NH), 11.48 (1H, s, NH), 11.52 (1H, s, NH). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 28.1, 28.2, 28.4, 34.3, 39.4, 40.2, 40.4, 42.6, 43.8, 44.7, 45.2, 49.5, 71.6, 71.7, 78.6, 79.6, 80.2, 81.8, 83.4, 83.9, 115.0 (d, $^2J_{CF}$ = 18.4 Hz, 2 × CH), 115.3 (d, $^2J_{CF}$ = 18.5 Hz, 2 × CH), 129.5 (d, $^3J_{CF}$ = 9.8 Hz, 2 × CH), 129.7 (d, $^3J_{CF}$ = 9.9 Hz, 2 × CH), 134.4 (d, $^4J_{CF}$ = 3.2 Hz), 134.5 (d, $^4J_{CF}$ = 3.2 Hz), 162.3 (d, $^1J_{CF}$ = 243.7 Hz), 162.4 (d, $^1J_{CF}$ = 243.7 Hz), 153.2 (2 × C), 156.8, 158.1, 163.1, 163.6, 172.3, 174.4. ^{19}F NMR (470 MHz, $CDCl_3$) δ −115.17, −115.10. HRMS (ESI, *m*/*z*) for $C_{49}H_{70}F_2N_8O_{12}$ $[M + H]^+$ calc. 1001.5154; found 1001.5157.

3-*endo*-2-*exo*-Di[2′-(2″,3″-di-*tert*-butoxycarbonylguanidino)-ethylcarbamoyl]-5,6-bis(3-bromobenzyloxy)bicyclo[2.2.1]heptane (15g). Compound **15g** was prepared from diacid **12g** (170 mg, 0.31 mmol) and amine **14** (280 mg, 0.93 mmol) according to general procedure D and after purification by column chromatography (70% EtOAc in pet. spirits) was isolated as a clear oil (185 mg, 53%); R_f = 0.32 (70% EtOAc in pet. spirits). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46–1.49 (36H, m, 4 × *t*-Bu), 1.66 (1H, d, J = 10.4 Hz, H7s), 2.12 (1H, dd, J = 10.4, 1.2 Hz, H7a), 2.47 (1H, d, J = 5.9 Hz, H2), 2.61 (1H, br s, H1), 2.78–2.79 (1H, m, H4), 2.85 (1H, dd, J = 6.0, 4.5 Hz, H3), 3.30–3.61 (10H, m, 4 × CH_2, H5, H6), 4.47–4.57 (4H, m, 2 × CH_2Ar), 6.59 (1H, t, J = 5.6 Hz, NH), 7.15–7.18 (2H, m, ArH), 7.22–7.24 (2H, m, ArH), 7.37–7.39 (2H, m, ArH), 7.44–7.47 (2H, m, ArH), 8.11 (1H, t, J = 4.0 Hz, NH), 8.47 (1H, t, J = 5.5 Hz, NH), 8.71 (1H, t, J = 6.1 Hz, NH), 11.47 (1H, s, NH), 11.53 (1H, s, NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 28.2, 28.4, 34.3, 39.4, 40.3, 40.4, 42.5, 43.6, 44.8, 45.2, 49.4, 71.5, 71.7, 78.7, 79.6, 80.2, 82.1, 83.4, 83.9, 122.5, 122.6, 126.2, 126.3, 130.0, 130.1, 130.66, 130.68, 130.72, 130.75, 141.0, 141.1, 153.2 (2 × C), 156.9, 158.1, 163.1, 163.6, 172.2, 174.4. HRMS (ESI, *m*/*z*) for $C_{49}H_{70}Br_2N_8O_{12}$ $[M + H]^+$ calc. 1121.3553; found 1121.3541.

General procedure E for Boc-removal of Boc-protected guanidines 15a–i

To the stirring solution of Boc-protected guanidine (0.05 mmol) and MeOH (520 μL), was added dropwise AcCl (20 equiv.) and the reaction was stirred for 24 h at ambient temperature. The reaction mixture was concentrated under vacuum and the product was co-evaporated with MeOH (2 × 0.5 mL) to give the desired guanidinium HCl salt.

5,6-Bis(methoxy)bicyclo[2.2.1]heptane-3-*endo*-2-*exo*-dicarboxamidoethylguanidine hydrogen chloride (16a). Compound **16a** was prepared from Boc-protected diguanidine **15a** (42 mg, 0.05 mmol) according to general procedure E as a white solid (24 mg, 96%); m.p: 161.5–195.0 °C (slow decomposition). ^{1}H NMR (270 MHz, CD_3OD) δ 1.50 (1H, d, J = 10.8 Hz, H7a), 1.80 (1H, d, J = 11.0 Hz, H7s), 2.46 (1H, br s, H2), 2.58–2.59 (1H, m, H1), 2.65 (1H, d, J = 5.3 Hz, H4), 3.17 (1H, app. t, J = 4.5 Hz, H3), 3.33 (3H, s, OMe), 3.41 (3H, s, OMe), 3.35–3.43 (9H, m, 4 × CH_2, H5), 3.51 (1H, d, J = 6.3 Hz, H6), 8.22 (1H, t, J = 4.5 Hz, NH), 8.32 (1H, t, J = 4.6, NH). ^{13}C NMR (67.5 MHz, CD_3OD) δ 33.9, 39.5, 39.7, 42.0, 42.2, 45.4, 46.1, 47.6, 47.8, 58.8, 58.9, 81.8, 85.4, 158.9, 175.0, 176.7. HRMS (ESI, *m*/*z*) for $C_{17}H_{32}N_8O_4$ $[M + 2H]^{2+}$ calc. 207.1346; found 207.1341.

5,6-Bis(benzyloxy)bicyclo[2.2.1]heptane-3-*endo*-2-*exo*-dicarboxamidoethylguanidine hydrogen chloride (16). Compound **16b** was prepared from Boc-protected diguanidine **15b** (76 mg, 0.08 mmol) according to general procedure E as a white residue (47 mg, 96%). ^{1}H NMR (500 MHz, CD_3OD) δ 1.56 (1H, d, J = 10.0 Hz, H7a), 2.02 (1H, d, J = 10.0 Hz, H7s), 2.53 (1H, br s, H2), 2.66–2.67 (2H, m, H1, H4), 3.18 (1H, app. t, J = 5.7 Hz, H3), 3.21–3.39 (8H, m, 4 × CH_2), 3.62 (1H, d, J = 5.3 Hz, H5), 3.73 (1H, d, J = 5.5 Hz, H6), 4.50–4.65 (4H, m, 2 × $ArCH_2$), 7.26–7.39 (10H, m, ArH). ^{13}C NMR (125 MHz, CD_3OD) δ 34.3, 39.6, 39.7, 41.97, 42.01, 46.4 (2 × C), 47.8, 48.4, 73.4, 73.7, 78.9, 83.2, 128.70, 128.72, 129.2 (2 × C), 129.32 (3 × C), 129.33 (3 × C), 139.6, 139.7, 158.8, 158.9, 175.0, 176.7. HRMS (ESI, *m*/*z*) for $C_{29}H_{40}N_8O_4$ $[M + 2H]^{2+}$ calc. 283.1659; found 283.1667.

5,6-Bis[(2-methylbenzyl)oxy] bicyclo[2.2.1]heptane-3-*endo*-2-*exo*-dicarboxamidoethylguanidine hydrogen chloride (16c). Compound **16c** was prepared from Boc-protected diguanidine **15c** (54 mg, 0.05 mmol) according to general procedure E as a clear oil (8 mg, 24%). ^{1}H NMR (500 MHz, CD_3OD) δ 1.56 (1H, d, J = 10.3 Hz, H7a), 2.01 (1H, d, J = 9.5 Hz, H7s), 2.26 (3H, s, ArMe), 2.30 (3H, s, ArMe), 2.53 (1H, br s, H2), 2.63–2.69 (2H, m, H1, H4), 3.14–3.38 (9H, m, 4 × CH_2, H3), 3.64 (1H, d, J = 5.1 Hz, H5), 3.76 (1H, d, J = 5.5 Hz, H6), 4.49–4.67 (4H, m, 2 × $ArCH_2$), 7.08–7.20 (7H, m, ArH), 7.29 (1H, d, J = 7.3 Hz, ArH). ^{13}C NMR (125 MHz, CD_3OD) δ 19.07, 19.09, 34.4, 39.6, 39.7, 41.98, 42.04, 46.2, 46.3, 47.8, 48.4, 72.0, 72.1, 79.2, 83.6, 126.68, 126.73, 128.96, 128.99, 130.2, 130.3, 131.1, 131.2, 137.4, 137.6, 138.1, 138.2, 158.86, 158.89, 175.1, 176.8. HRMS (ESI, *m*/*z*) for $C_{31}H_{44}N_8O_4$ calc. $[M + 2H]^{2+}$ 297.1816; found 297.1820.

5,6-Bis[(4-trifluoromethylbenzyl)oxy] bicyclo[2.2.1]heptane-3-*endo*-2-*exo*-dicarboxamidoethylguanidine hydrogen chloride (16d). Compound **16d** was prepared from Boc-protected diguanidine **15d** (87 mg, 0.08 mmol) according to general procedure E as a colourless sticky residue (40 mg, 66%). ^{1}H NMR (500 MHz, CD_3OD) δ 1.60 (1H, d, J = 10.2 Hz, H7s), 2.06 (1H, d, J = 9.9 Hz, H7a), 2.59 (1H, br s, H2), 2.70–2.72 (2H, m, H1, H4), 3.21–3.38 (9H, m, 4 × CH_2, H3), 3.69 (1H, d, J = 5.2 Hz, H5), 3.80 (1H, d, J = 5.5 Hz, H6), 4.63 (2H, s, $ArCH_2$), 4.69–4.76 (2H, m, $ArCH_2$), 7.46–7.48 (2H, m, ArH), 7.51–7.52 (2H, m, ArH), 7.55–7.58 (4H, m, ArH). ^{13}C NMR (125 MHz, CD_3OD) δ 34.3, 39.6, 39.7, 41.9, 42.0, 46.1, 46.2, 47.8, 48.4, 72.6, 72.7, 79.6, 83.6, 125.69 (q, $^1J_{CF}$ = 269.7 Hz), 125.71 (q, $^1J_{CF}$ = 269.7 Hz), 126.1 (q, $^3J_{CF}$ = 3.4 Hz, 4 × CH), 129.2 (4 × C), 130.58 (q, $^2J_{CF}$ = 31.8 Hz), 130.60 (q, $^2J_{CF}$ = 31.7 Hz), 144.46, 144.54, 158.83, 158.85, 174.9, 176.6. ^{19}F NMR (470 MHz, CD_3OD) δ −65.41, −65.38. HRMS (ESI, *m*/*z*) for $C_{31}H_{38}F_6N_8O_4$ $[M + 2H]^{2+}$ calc. 351.1533; found 351.1532.

5,6-Bis[(3-fluorobenzyl)oxy] bicyclo[2.2.1]heptane-3-*endo*-2-*exo*-dicarboxamidoethylguanidine hydrogen chloride (16e). Compound **16e** was prepared from Boc-protected diguanidine **15e** (72 mg, 0.07 mmol) according to general procedure E as a yellow solid (46 mg, 99%); m.p: 77.4–82.4 °C (slow decomposition). ^{1}H NMR (500 MHz, CD_3OD) δ 1.58 (1H, d, J = 10.2 Hz, H7s), 2.02 (1H, d, J = 10.0 Hz, H7a), 2.57 (1H, br s, H2), 2.68–2.69 (2H, m, H1, H4), 3.19–3.38 (9H, m, 4 × CH_2, H3), 3.65 (1H, d, J = 5.2 Hz, H5), 3.76 (1H, d, J = 5.6 Hz, H6), 4.53–4.58 (2H, m, $ArCH_2$), 4.62–4.68 (2H, m, $ArCH_2$), 6.97–7.00 (2H, m, ArH), 7.05 (1H, d, J = 9.8 Hz, ArH), 7.10–7.11 (2H, m, ArH), 7.16 (1H, d, J = 7.6 Hz, ArH), 7.28–7.34 (2H, m, ArH). ^{13}C NMR (125 MHz, CD_3OD) δ 34.3, 39.6, 39.7, 41.9, 42.0, 46.1 (2 × C), 47.8, 48.3, 72.6, 72.7, 79.2, 83.4, 115.33 (d, $^2J_{CF}$ = 33.7 Hz), 115.26 (d, $^2J_{CF}$ = 26.6 Hz), 115.40 (d, $^2J_{CF}$ = 34.0 Hz), 115.43 (d, $^2J_{CF}$ = 27.0 Hz), 124.50 (d, $^4J_{CF}$ = 2.7 Hz), 124.52 (d, $^4J_{CF}$ = 2.6 Hz), 131.02 (d, $^3J_{CF}$ = 7.8 Hz), 131.08 (d, $^3J_{CF}$ = 6.6 Hz), 142.6 (d, $^3J_{CF}$ = 7.2 Hz), 142.8 (d, $^3J_{CF}$ = 7.1 Hz), 158.79, 158.81, 164.22 (d, $^1J_{CF}$ = 244.2 Hz), 164.23 (d, $^1J_{CF}$ = 242.8 Hz), 174.9, 176.6. ^{19}F NMR (470 MHz, $CDCl_3$) δ −116.03, −115.86. HRMS (ESI, *m*/*z*) for $C_{29}H_{38}F_2N_8O_4$ $[M + 2H]^{2+}$ calc. 301.1565; found 301.1576.

5,6-Bis[(4-fluorobenzyl)oxy] bicyclo[2.2.1]heptane-3-*endo*-2-*exo*-dicarboxamidoethylguanidine hydrogen chloride (16f). Compound (**16f**) was prepared from Boc-protected diguanidine **15f** (90 mg, 0.09 mmol) according to general procedure E as a white solid (46 mg, 77%); m.p: 94.0–110.0 °C (slow decomposition). ^{1}H NMR (500 MHz, CD_3OD) δ 1.55 (1H, d, J = 10.1 Hz, H7a), 2.01 (1H, d, J = 9.0 Hz, H7s), 2.51 (1H, br s, H2), 2.62 (1H, m, H1), 2.67 (1H, d, J = 5.3 Hz, H4), 3.18–3.41 (9H, m, 4 × CH_2, H3), 3.63 (1H, d, J = 5.8 Hz, H5), 3.73 (1H, d, J = 5.5 Hz, H6), 4.47–4.53 (2H, m, $ArCH_2$), 4.59 (2H, s, $ArCH_2$), 7.00–7.05 (4H, m, ArH), 7.29–7.31 (2H, m, ArH), 7.34–7.37 (2H, m, ArH). ^{13}C NMR (125 MHz, CD_3OD) δ 34.3, 39.6, 39.7, 41.98, 42.04, 46.16, 46.20, 47.7, 48.6, 72.7, 72.9, 79.0, 83.2, 115.96 (d, $^2J_{CF}$ = 21.0 Hz), 115.97 (d, $^2J_{CF}$ = 21.6 Hz), 131.1 (d, $^3J_{CF}$ = 8.1 Hz, 4 × CH), 135.76 (d, $^2J_{CF}$ = 15.4 Hz), 135.78 (d, $^2J_{CF}$ = 15.6 Hz), 163.79 (d, $^1J_{CF}$ = 243.2 Hz), 163.81 (d, $^1J_{CF}$ = 242.9 Hz), 158.9 (2 × C), 175.0, 176.7. ^{19}F NMR (470 MHz, $CDCl_3$) δ −118.04, −117.89. HRMS (ESI, m/z) for $C_{29}H_{38}F_2N_8O_4$ $[M + 2H]^{2+}$ calc. 301.1565; found 301.1567.

5,6-Bis[(3-bromobenzyl)oxy] bicyclo[2.2.1]heptane-3-*endo*-2-*exo*-dicarboxamidoethylguanidine hydrogen chloride (16g). Compound **16g** was prepared from Boc-protected diguanidine **15g** (169 mg, 0.15 mmol) according to general procedure E as a white solid (115 mg, 97%); m.p: 99.9–132.8 °C (slow decomposition). ^{1}H NMR (500 MHz, CD_3OD) δ 1.57 (1H, d, J = 10.5 Hz, H7a), 2.01–2.04 (1H, m, H7s), 2.55 (1H, br s, H2), 2.66–2.69 (2H, m, H1, H4), 3.19–3.40 (9H, m, 4 × CH_2, H3), 3.64 (1H, d, J = 5.6 Hz, H5), 3.75 (1H, d, J = 5.3 Hz, H6), 4.50–4.56 (2H, m, $ArCH_2$), 4.59–4.65 (2H, m, $ArCH_2$), 7.21–7.27 (3H, m, ArH), 7.32 (1H, d, J = 7.7 Hz, ArH), 7.40–7.43 (3H, m, ArH), 7.48 (1H, m, ArH), 7.53 (1H, m, ArH). ^{13}C NMR (125 MHz, CD_3OD) δ 34.3, 39.6, 39.7, 41.96, 42.0, 46.13, 46.15, 47.7, 48.4, 72.6, 72.7, 79.3, 83.5, 123.32, 123.35, 127.59, 127.62, 131.16, 131.21, 131.66, 131.70, 131.8 (2 × C), 142.4, 142.5, 158.86, 158.87, 175.0, 176.7. HRMS (ESI, m/z) for $C_{29}H_{38}Br_2N_8O_4$ $[M + 2H]^{2+}$ calc. 361.0764; found 361.0774.

5,6-Bis[(4-bromobenzyl)oxy] bicyclo[2.2.1]heptane-3-*endo*-2-*exo*-dicarboxamidoethylguanidine hydrogen chloride (16h). Compound **16h** was prepared from Boc-protected diguanidine **15h** (57 mg, 0.05 mmol) according to general procedure E as a clear oil (40 mg, 99%). ^{1}H NMR (500 MHz, CD_3OD) δ 1.56 (1H, d, J = 10.2 Hz, H7s), 2.00 (1H, d, J = 9.9 Hz, H7a), 2.53 (1H, br s, H2), 2.64–2.67 (2H, m, H1, H4), 3.17–3.40 (9H, m, 4 × CH_2, H3), 3.61 (1H, d, J = 5.6 Hz, H5), 3.73 (1H, d, J = 5.6 Hz, H6), 4.46–4.52 (2H, m, $ArCH_2$), 4.56–4.62 (2H, m, $ArCH_2$), 7.20–7.22 (2H, m, ArH), 7.26–7.28 (2H, m, ArH), 7.43–7.46 (4H, m, ArH). ^{13}C NMR (125 MHz, CD_3OD) δ 34.3, 39.6, 39.7, 41.9, 42.0, 46.1, 46.2, 47.7, 48.4, 72.6, 72.8, 79.1, 83.3, 122.36, 122.40, 131.0 (4 × C), 132.40 (2 × C), 132.41 (2 × C), 139.0, 139.1, 158.81, 158.84, 174.9, 176.6. HRMS (ESI, m/z) for $C_{29}H_{38}Br_2N_8O_4$ $[M + 2H]^{2+}$ calc. 361.0764; found 361.0769.

5,6-Bis(allyloxy) bicyclo[2.2.1]heptane-3-*endo*-2-*exo*-dicarboxamidoethylguanidine hydrogen chloride (16i). Compound **16i** was prepared from Boc-protected diguanidine **15i** (126 mg, 0.15 mmol) according to general procedure E as a yellow solid (24 mg, 31%); m.p: 79.9–85.9 °C. ^{1}H NMR (500 MHz, CD_3OD) δ 1.52 (1H, d, J = 10.3 Hz, H7a), 1.92 (1H, d, J = 9.3 Hz, H7s), 2.44 (1H, br s, H2), 2.59 (1H, d, J = 3.5 Hz, H1), 2.66 (1H, d, J = 5.2 Hz, H4), 3.16 (1H, app. t, J = 5.1 Hz, H3), 3.30–3.46 (8H, m, 4 × CH_2), 3.57 (1H, d, J = 6.0 Hz, H5), 3.63 (1H, d, J = 5.4 Hz, H6), 4.00–4.09 (4H, m, 2 × CH_2O), 5.13–5.32 (4H, m, 2 × CH_2CH), 5.86–5.98 (2H, m, 2 × CH_2CH), 7.45–7.48 (2H, m, 2 × NH). ^{13}C NMR (125 MHz, CD_3OD) δ 34.2, 39.6, 39.7, 42.0, 42.2, 46.1, 46.2, 47.9, 48.4, 72.7, 72.8, 79.4, 83.3, 117.1, 117.2, 136.2 (2 × C), 158.87, 158.92, 175.0, 176.7. HRMS (ESI, m/z) for $C_{21}H_{36}N_8O_4$ $[M + 2H]^{2+}$ calc. 233.1503; found 233.1502.

Crystallography

Intensity data were collected with an CCD diffractometer using Cu-Kα radiation, the temperature during data collection was maintained at 130.0(1) using an Oxford Cryosystems cooling device. The structure was solved by direct methods and difference Fourier synthesis.[53] Thermal ellipsoid plots were generated using the program ORTEP-3 (ref. 54) integrated within the WINGX[55] suite of programs. Disordered solvent, assumed to be ethanol was removed using the Squeeze procedure.[56]

Disk diffusion – zone of inhibition assay

A stock solution of 10 mg mL^{-1} was made for each compound under observation using DMSO as a solvent. Each of these stock solutions was then diluted by a factor of 1 : 2 to bring the concentration to 5 mg mL^{-1}. The diluted solutions were then filter-sterilized using a 0.2 μm Nylon filter, and 10 μL of the 5 mg mL^{-1} stock was pipetted onto a blank disk (*i.e.* 50 μg per disk; Oxoid Limited, Hampshire, UK). All bacterial isolates were matched to a 0.5 McFarland standard (in 0.9% NaCl) before they were swabbed onto nutrient agar. The controls used were a 10 μg colistin disk (Oxoid), 10 μL of DMSO and a plate swabbed with saline from the dispenser used.

Minimum inhibitory concentration (MIC) determination

Bacteria were obtained from American Type Culture Collection (ATCC; Manassas, VA, USA) as listed in Table S2 (see ESI†). Bacteria were cultured in Nutrient broth (NB; Bacto Laboratories, catalog no. 234000) or Muller-Hinton broth (MHB; Bacto Laboratories, catalog no. 211443) at 37 °C overnight with shaking (∼180 RPM). A sample of each culture was diluted 50-fold in fresh MHB and incubated at 37 °C for 1.5–3 h with shaking (∼180 RPM). Compound stock solutions were prepared as 10 mg mL^{-1} in DMSO and colistin was dissolved in Milli-Q water at 5.12 mg mL^{-1}. The compounds, at twice the final desired concentration, were serially diluted 2-fold across the wells of 96-well plates (Non-Binding Surface, Corning, catalog no. 3641). Mid-log phase bacterial cultures (after 1.5–3 h incubation) were diluted to a final concentration of 5 × 10^5 colony forming units (CFU) per mL, and 50 μL was added to each well giving a final compound concentration range of 32 μg mL^{-1} to 0.015 μg mL^{-1} (DMSO ≤ 1%). MICs were determined visually after 20 h of incubation at 37 °C, with the MIC defined as the lowest compound concentration at which no bacterial growth was visible.

Cytotoxicity evaluation

HEK293 (ATCC CRL-1573) and HepG2 (ATCC HB-8065) cells were seeded as 3000 cells per well in a 384-well plate in DMEM medium (GIBCO-Invitrogen #11995-073), in which 10% of FBS was added. Cells were incubated for 24 h at 37 °C, 5% CO_2 to allow cells to attach to the plates. A concentration series of compounds was then added into each well. The cells were incubated with the compounds for 24 h at 37 °C, 5% CO_2. After the incubation, 10 μM resazurin (dissolved in PBS) was added to each well. The plates were then incubated for 2 h at 37 °C, 5% CO_2. The fluorescence intensity was read using Polarstar Omega with excitation/emission 560/590. The data was analysed by Prism software. Results are presented as the average percentage of control ± SD for each set of duplicate wells using the following equation:

$$\text{Percentage viability} = (\text{FITEST} - \text{FI}_{\text{Negative}}/\text{FI}_{\text{UNTREATED}} - \text{FI}_{\text{Negative}}) \times 100.$$

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