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N-substituted 8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecanes as σ receptor ligands with potential neuroprotective effects

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ABSTRACT

Several libraries of similarly N-substituted 8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecanes (**9**), *N*-methyl-8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecanes (**14**), and *N*-methyl-11-aminopentacyclo [5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-ones (**13**) were synthesised and screened against a panel of CNS targets in order to develop structure–affinity relationships for cage-modified trishomocubane σ receptor ligands based on the N-substituted 4-azahexacyclo[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}]dodecan-3-ol (**8**) scaffold. In general, compared to the corresponding 4-azahexacyclo[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}]dodecan-3-ols, compounds of type **9** were potent σ receptor ligands with low levels of subtype selectivity, while the corresponding *N*-methyl-8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecanes showed reduced affinity but greater selectivity for σ_2 receptors. The *N*-methyl-11-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-ones demonstrated the poorest σ receptor affinities, suggesting that 4-azahexacyclo[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}]dodecan-3-ols interact with σ receptors in the bridged hemiaminal form rather than as the non-transannular, aminoketone tautomers. Several compounds of type **8**, **9**, and **14** were assessed for their ability to inhibit nitric oxide release in vitro, and demonstrated comparable or greater efficacy than 4-phenyl-1-(4-phenylbutyl)piperidine (PPBP), an established neuroprotective σ ligand with NOS inhibitory activity.

1. Introduction

Sigma (σ) receptors are unique mammalian proteins with two well-defined subtypes; σ_1 and σ_2.[1] Both σ_1 and σ_2 receptors are widely distributed in the central nervous system (CNS), as well as the periphery.[2–5] Each σ receptor subtype possesses distinct anatomical distribution, molecular weight, and ligand selectivity.[6] The σ_1 receptor has been cloned from numerous species and tissues, including human sources.[7,8] Perhaps the most well-defined activity of σ_1 receptors is their ability to modulate Ca^{2+} efflux by acting as molecular chaperones for type 3 inositol-1,4,5-triphosphate (IP_3) receptors at the mitochondria-associated endoplasmic reticulum membrane (MAM), thereby regulating interorganelle signalling and maintaining Ca^{2+} homeostasis.[9,10] However, σ_1 receptors are also known to translocate to the plasma membrane, where they regulate voltage-dependent Ca^{2+} channels and K^+ channels.[11,12] The ability of σ_1 receptors to modulate the activity of several neurotransmitter systems, including those of dopamine (DA),[13–15] 5-hydroxytryptamine (5-HT),[16] and norepinephrine (NE),[17,18] has also been demonstrated.

The putative σ_2 receptor binding site was only recently identified,[19] and relatively less is known about the physiological roles of σ_2 receptors. Like σ_1 receptors, σ_2 receptors modulate intracellular Ca^{2+} concentrations, although the mechanistic details have not been elucidated for the latter.[20–22] One of the most well-characterized activities of σ_2 receptors is their involvement in cell proliferation and apoptotic processes.[23] A wide variety of rodent and human tumour cell lines are known to overexpress σ_2 receptors,[24–26] and many σ ligands demonstrate antiproliferative activity in various tumour cell lines.[27–31] Radioligands with high affinity and high selectivity for σ_2 receptors have the potential to non-invasively assess the proliferative status of human solid tumours using imaging techniques such as positron emission tomography (PET) or single

Abbreviations: CNS, central nervous system; DTG, 1,3-di-*o*-tolylguanidine; DA, dopamine; DAT, dopamine transporter; HEK, human embryonic kidney; 5-HT, 5-hydroxytryptamine; IP_3, inositol-1,4,5-triphosphate; LPS, lipopolysccharide; MAM, mitochondria-associated endoplasmic reticulum membrane; NO, nitric oxide; NOS, nitric oxide synthase; NMDA, *N*-methyl-D-aspartate; NE, norepinephrine; NET, norepinephrine transporter; PCC, pyridinium chlorochromate; PPBP, 4-phenyl-1-(4-phenylbutyl)piperidine; PET, positron emission tomography; ROS, reactive oxygen species; SPECT, single photon emission computerised tomography; SERT, serotonin transporter; SAfiR, structure–affinity relationship; VGCCs, voltage-gated calcium channels.

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photon emission computerised tomography (SPECT), and several potential agents have been reported.[32–34]

The diverse pharmacology of σ receptors is consistent with their implication in virtually all major CNS disorders. There is compelling evidence that σ receptors are involved in the pathophysiology of anxiety, depression, neurodegeneration, motor dysfunction, pain, and substance abuse,[35,36] and agents targeting σ receptors have been under development as potential anxiolytics, antidepressants, and neuroprotective drugs with novel modes of action.[36,37] The role of σ receptors in neurodegenerative disease is suggested by their ability to regulate traditional neurodegenerative drug targets: *N*-methyl-D-aspartate (NMDA) receptors, voltage-gated calcium channels (VGCCs), and nitric oxide synthase (NOS). NMDA receptors and VGCCs, as Ca^{2+} ion channels, are directly inplicated in the excitotoxic process resulting from excessive neuronal Ca^{2+} influx.[38] NMDA receptor-mediated electrophysiology[39–44] and VGCC signalling [11] are both modulated by σ_1 receptors, consistent with the ability of σ_1 receptors to regulate intracellular Ca^{2+} concentrations through multiple mechanisms. NMDA-elicited neuronal responses were also potentiated by σ_2 receptors, indepdendent of σ_1 receptor activity.[45,46] One consequence of increased intracellular Ca^{2+} concentration in neurons is the activation of neuronal NOS (nNOS)—one of three NOS isoforms, along with epithelial NOS (eNOS) and inducible NOS (iNOS)—which produces the nitric oxide (NO) free radical as a neurotransmitter from substrate L-arginine, O_2, and NADPH.[47] Although NO is a precursor to other neurodegenerative reactive oxygen species (ROS), such as superoxide and peroxynitrite, excessive levels of NO itself are linked to neurodegenerative diseases.[48–50] NOS inhibitors remain an attractive target for the development of neuroprotective drugs, since they demonstrably attenuate neurotoxicity.[38,51]

Several structurally distinct, non-selective σ receptor ligands, including haloperidol (**1**, Fig. 1) and opipramole (**2**), were able to attenuate glutamate-induced activation of the NOS pathway in primary rat hippocampal cell cultures, suggesting possible neuroprotective applications.[52] Early selective σ receptor ligands, such as the subtype non-selective σ_1/σ_2 ligand 1,3-di-*o*-tolylguanidine (DTG, **3**), and σ_1-selective (+)-pentazocine (**4**), also demonstrably reduced post-ischemic brain injury in rats.[53–55] Similarly, one of the most well-studied neuroprotectants targeting σ receptors, 4-phenyl-1-(4-phenylbutyl)piperidine (PPBP, **5**), was shown to reduce brain injury after transient focal ischemia in rats and cats,[56–59] effects that were attributed to PPBP-mediated reductions in NO production.[60,61]

Polycyclic cage molecules have been proposed as a promising platform for the development of polypharmacological neuroprotective agents targeting NMDA receptors, VGCCs, and NOS, and these frequently possess confirmed σ receptor activity, or structural similarity to known σ receptor ligands.[38,62] Amantadine (**6**, Fig. 2) is an NMDA channel pore blocker currently in clinical use for the treatment of Parkinson's disease, which also acts as a functional agonist at σ_1 receptors.[63,64] NGP1-01 (**7a**) was developed as a dual antagonist of NMDA receptors and L-type VGCCs with neuroprotective effects against focal ischemia.[65–71] Although **7a** has never been screened for σ receptor activity, its ring-fluorinated analogue (**7b**) showed micromolar interaction with σ_1 and σ_2 receptors.[72] Isomerization of the hemiaminal ether of **7a** to give aza-bridged **8a** produced a high affinity σ receptor ligand (σ_1

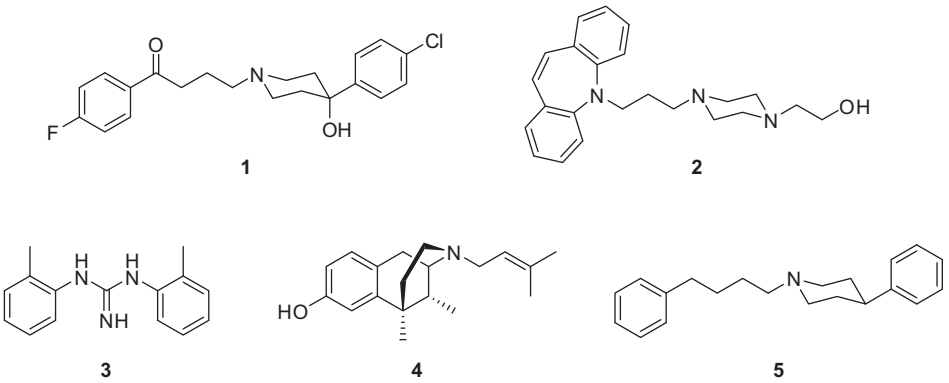


Figure 1. Early σ receptor ligands previously explored as neuroprotective agents.

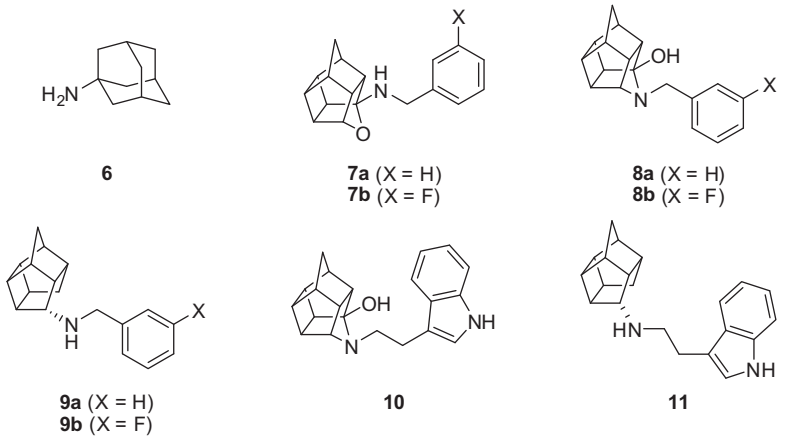


Figure 2. Polycyclic cage molecules with potential therapeutic activity in neurodegenerative diseases.

K_i = 337 nM, σ_2 K_i = 12 nM)[73] which nevertheless retained many of the neuroprotective properties of **7a**.[66] Interestingly, ring-fluorinated analogue **8b** showed diverse pharmacology in vitro, including inhibition of K^+ currents in locus coeruleus neurons and enhancement of amphetamine-stimulated DA release from striatal slices.[74,75] Additionally, **8b** and its analogues were able to alter cocaine-induced behavioral effects in rats, suggesting favorable physicochemical and pharmacokinetic profiles for in vivo applications.[76] Further modifications to the trishomocubane framework have produced **9a** which, along with several analogues, demonstrated anti-Parkinsonian activity in several animal models.[77] Although no mechanism for the activity of **9a** was proposed, ring-fluorinated analogue **9b** possessed affinity for the DA transporter (DAT) as well as σ receptors, with excellent selectivity over the NE transporter (NET), serotonin transporter (SERT), and dopamine receptors (D_1–D_5).[78] Most recently, pentacycloundecane conjugates of tryptamine (**10** and **11**) were found to act as NOS inhibitors.[79] The obvious structural similarities between **8a**, **9a**, **10**, **11** and various trishomocubanes previously reported by us prompted the systematic investigation of the relationship between structure and inhibitory NOS activity, with the aim of identifying potentially neuroprotective trishomocubanes.

We previously reported the σ receptor activity of numerous N-substituted 4-azahexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodecan-3-ols (**8**, Fig. 3), demonstrating the utility of the trishomocubane framework for developing selective σ receptor ligands.[73–76,80–85] Prior structure–affinity relationship (SAfiR) studies in our laboratories have focused on changes to σ receptor binding resulting from isomerization of the hemiaminal group of **8** to the analogous oxa-bridged hemiaminal ether, expansion the trishomocubane cage of **8** to the corresponding adamantane-derived hemiaminal, and steric reduction of **8** to the simplest azabicyclic subunit.[72,86,87] Taken together, these studies have allowed the generation of several pharmacophoric models for the interaction of compounds **8** with σ receptors,[73,88] however, all such models assume hemiaminals **8** interact with σ receptors in their transannularly-cyclized, aza-bridged form rather than as their tautomeric N-substituted 11-aminopentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecan-8-ones (**12**). X-ray crystallographic analysis of analogues of **8** indicates that they exist in the solid phase as the transannular hemiaminal, and this is supported by the absence of a characteristic carbonyl signal in the infrared (IR) spectra of such molecules.[73,89] The possibility that aminoketone tautomer **12** might exist in solution was prompted by the absence of a signal attributable to either the hemiaminal carbon of **8** (C3) or the corresponding carbonyl carbon of **12** (C8) in the ^{13}C NMR spectrum of **8** at 300 K. Preliminary exploration of the possibility of rapid tautomerism on the NMR timescale using variable temperature ^{13}C NMR has proven inconclusive, as has solution-phase Raman spectroscopy. Currently, the relative contribution of aminoketone **12** to the σ receptor affinity or activity of hemiaminal **8** is unknown, prompting the synthesis of tautomerically 'locked' analogues of **12** to explore this possibility.

The methylation of aminoketone **12** gives N-substituted *N*-methyl-11-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-ones (**13**) which may be considered tautomerically 'locked' analogues of **12** since they are unable to transannularly cyclize. Although compounds of type **13** retain the carbonyl group of **12**, a feature that may be important for σ receptor binding interactions, they also contain a tertiary amine that necessarily differs sterically and electronically from the secondary amine of **12**. Alternatively, deoxygenation of **12** gives N-substituted 8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecanes (**9**) with equivalent amine substitution, but lacking the carbonyl group. Conveniently, methylation of **9** gives the corresponding N-substituted *N*-methyl-8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecanes (**14**), thereby allowing delineation of the effects of σ receptor activity attributable to further alkylation of the amine of **12** (as is the case with **13**) or removal of the carbonyl group of **12** (as in **9**).

The aim of the present study was to prepare and characterize a library of analogously substituted trishomocubanes of type **8**, **9**, **13**, and **14**, and to identify SAfiRs for binding at σ_1 and σ_2 receptors, thereby estimating the contribution of tautomeric aminoketone **12** to the σ receptor affinity of **8**. Additionally, all ligands were screened against a panel other major CNS targets to determine general σ receptor selectivity profiles for **9**, **13**, and **14** compared to **8**. Finally, selected trishomocubanes with selectivity for σ_1/σ_2 receptors were assessed for potential neuroprotective properties by measuring their ability to reduce NO release from lipopolysccharide (LPS)-stimulated murine macrophages (RAW264.7 cells). Murine macrophages, along with monocytes, granulocytes, and lymphocytes, have been confirmed to express σ receptors.[90,91] Indeed, reduction of NO synthesis by the σ receptor ligand SR31747A was previously demonstrated in RAW murine macrophages.[91] This study aims to provide preliminary structure-activity relationships for the NO inhibition effected by various modifications of the cage framework of trishomocubane-derived σ receptor ligands.

2. Results and discussion

The synthesis of a library of analogues of **8**, **9**, **13**, and **14** is shown in Scheme 1, and structures and yields of individual analogues are provided in Table 1. The sequence begins with the

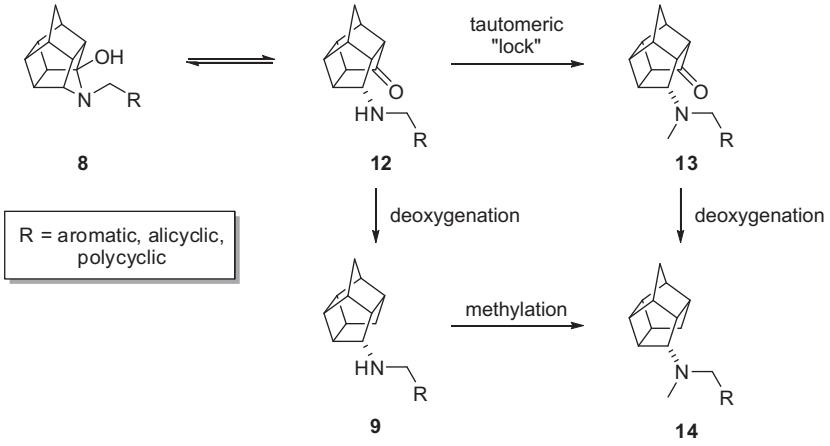
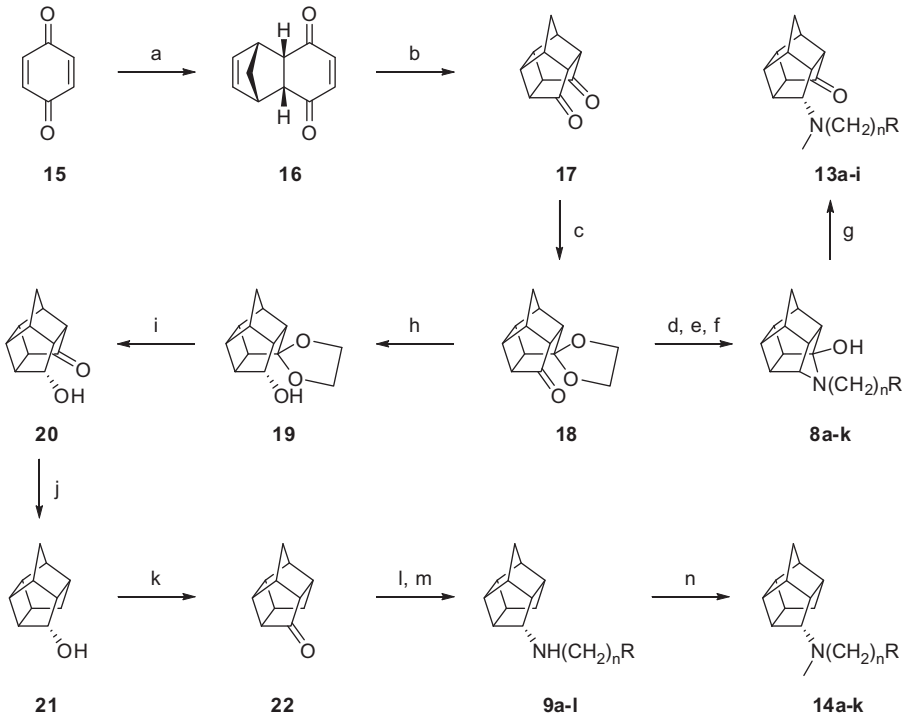


Figure 3. Trishomocubanes with demonstrated or potential activity at σ receptors.



Scheme 1. Reagents and conditions: (a) cyclopentadiene, PhMe, −10 °C to rt, 80%; (b) hν, hexane–acetone (90:10), rt, 14 h, 93%; (c) $HOCH_2CH_2OH$, *p*-TsOH (cat.), PhMe, reflux, Dean–Stark, 5 h, 93%; (d) $R(CH_2)_nNH_2$, EtOH, 100 °C, sealed tube, 18 h; (e) $NaBH_4$, EtOH, 0 °C to rt, 8 h; (f) 4 M aq HCl, Me_2CO, rt, 12 h, basic workup, 34–63% over three steps; (g) 37% aq CH_2O, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$, rt, 8–18 h, 65–97%; (h) $LiAlH_4$, Et_2O, reflux, 2 h, 92%; (i) 6% aq HCl, rt, 3.5 h, 99%; (j) $NH_2NH_2{\cdot}H_2O$, diethylene glycol, 105 °C, 2.5 h, then KOH, 190 °C, 4 h, 96%; (k) PCC, CH_2Cl_2, rt, 2 h, 93%; (l) $R(CH_2)_nNH_2$, EtOH, 100 °C, 18–24 h; (m) $NaBH_4$, EtOH, 0 °C to rt, 8 h, 66–94% over two steps; (n) 37% aq CH_2O, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$, rt, 14–22 h, 85–94%.

Diels–Alder reaction of 1,4-benzoquinone (**15**) and cyclopentadiene to give adduct **16**, which underwent intramolecular [2+2] photocyclization to yield Cookson's diketone (pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione, **17**).[92] Monoprotection of **17** as its ethylene acetal provided common precursor **18**.[93] Condensation of **18** with the appropriate primary amine, followed by sodium borohydride reduction of the formed imine and hydrolysis of the acetal, furnished hemiaminals **8a**–**k** in reasonable yield (34–63%) over three steps.[73] The generation of intramolecular hemiaminals **8a**–**k** indicates highly stereoselective delivery of the hydride to outside face of the carbonyl group. Reductive methylation of hemiaminals **8a**–**i** using aqueous formaldehyde solution and sodium triacetoxyborohydride gave the corresponding aminoketones **13a**–**i** in excellent yields (65–97%). The facile synthesis of **13a**–**i** indicates that **8a**–**i** partially exist as their aminoketone tautomers in solution or that the hemiaminal nitrogen of such compounds is sufficiently nucleophilic to allow facile tautomerisation in the presence of a suitable electrophile.

The aminoketone structure of **13a**–**i** was confirmed by the appearance of a carbonyl signal in the IR spectra (ν ~1720–1725 cm^{-1}) and ^{13}C NMR spectra (δ ~213–214 ppm). Additionally, X-ray crystallography of **13g** confirmed the relative stereochemistry of the cage, with *endo* configuration of the tertiary amine clearly apparent, as expected, and the carbonyl moiety adopting a slight deviation from planarity due to the rigidity of the trishomocubane framework.[94] The non-bonded interatomic distance between N1 and C18 in **13g** is 2.667 Å, substantially larger than the bonded distance of 1.513 Å between the corresponding atoms in hemiaminal **8g**, for example.[89,94]

The synthesis of **9a**–**l** and **14a**–**k** required an alternative route. Ketone **18** was reduced with lithium aluminium hydride to afford exclusively the *endo*-alcohol (**19**) due to steric occlusion of hydride delivery to the internal face of the ketone.[95] Hydrolysis of acetal **19** furnished ketol **20**, which exists in $CDCl_3$ solution in equilibrium with the tautomeric internal hemiacetal (not shown).[96] Wolff–Kishner reduction of **20** under Huang–Minlon conditions gave alcohol **21**, followed by oxidation with pyridinium chlorochromate (PCC) to yield desired ketone **22**.[96] This route was amenable to the synthesis of several grams of **22** in a single run, in yields of up to 81% over 4 steps, with minimal chromatography required. A more expeditious route to **22** involving Wolff–Kishner reduction of **18** followed by acetal hydrolysis proceeded in poorer overall yield, consistent with previously published reports.[96]

Condensation of **22** with the appropriate primary amines in ethanol at 100 °C in a sealed tube, followed by sodium borohydride reduction of the intermediate imines, gave the racemic secondary amines **9a**–**l** in good yields (66–94%). The sodium borohydride reduction of Schiff bases of **22** proceeded highly stereoselectively, with hydride delivered solely to the external face of the imine since internal delivery was sterically occluded by the geminal hydrogens of C11 of the polycyclic cage.[77] The newly installed *exo*-hydrogen of **9a**–**l** appears as an apparent triplet in the ^{1}H NMR spectrum, with vicinal coupling of a characteristic magnitude (^3J = 3.4 Hz) due to the dihedral angles imposed by the rigidity of the cage, entirely consistent with previous stereochemical assignments of related *endo*-8-substituted pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecanes.[97–99] Conversely, the *endo*-8-hydrogen of *exo*-8-substituted pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecanes exhibits a coupling constant of less than 1 Hz, displays little to no fine structure, and typically appears as a singlet.[97–99] Reductive methylation of **9a**–**k**, using similar methods to those used to generate **8a**–**i**, gave **14a**–**k** in 85–94% yield.

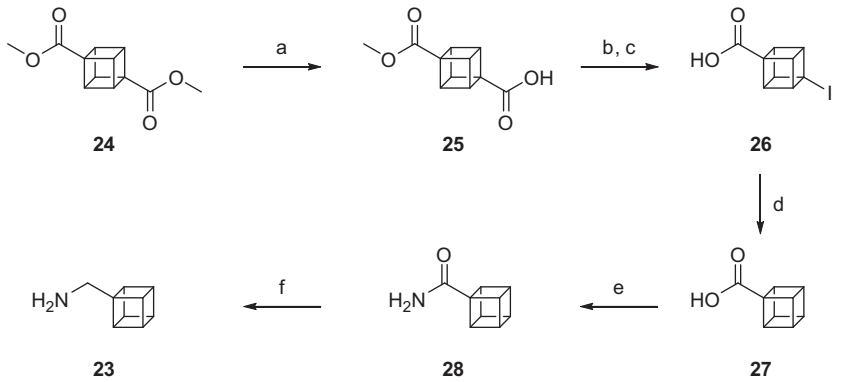
The requisite amines for steps (d) and (l) of Scheme 1 were generally commercially available, with the exception of those comprising **8i**, **9i**, and **9l**. The synthesis of **8i** and **9i** required 3-(3-fluorophenyl)propylamine[73] while **9l** required aminomethylcubane

Table 1
Binding affinities of compounds **8a–k**, **9a–l**, **13a–h**, and **14a–k** for σ_1 and σ_2 receptors and monoamine transporters (DAT, NET, SERT)

Compound	*n*	R	Yield (%)	K_i (nM ± SEM)[a]		σ_2 Selectivity	K_i (nM ± SEM)[a]		
				σ_1	σ_2		DAT	NET	SERT
8a[b]	1	Ph	63[c]	337 ± 21	12 ± 2	28.0	ND	ND	NA
8b[b]	1	3-FPh	34[c]	153 ± 17	31 ± 6	4.9	ND	ND	ND
8c[b]	1	3,4-$(OMe)_2$Ph	41[c]	228 ± 20	12.6 ± 2.2	18.1	NA	>10,000	4421 ± 322
8d[b]	1	3-Pyridyl	37[c]	>10,000	3234 ± 397	3.1	NA	NA	NA
8e[b]	2	Ph	61[c]	26 ± 2	68 ± 14	0.38	ND	ND	ND
8f[b]	2	3-FPh	52[c]	12 ± 1	48 ± 10	0.25	ND	ND	ND
8g[b]	2	2-Pyridyl	56[c]	1170 ± 186	26.8 ± 4.1	43.7	NA	ND	NA
8h[b]	3	3-FPh	55[c]	15 ± 1	6.3 ± 0.7	2.4	ND	ND	ND
8i	1	3,4,5-$(OMe)_3$Ph	61	4289 ± 395	>10,000		ND	ND	ND
8j	1	3,4-(OCH_2O)Ph	38	435 ± 51	259 ± 38		NA	ND	NA
8k[b]	1	Cyclohexyl	38[c]	6.7 ± 0.8	2.2 ± 0.3	3.0	NA	NA	ND
9a	1	Ph	83[d]	78 ± 3	19 ± 1	4.1	3480 ± 385	NA	NA
9b	1	3-FPh	79[d]	198 ± 20	19.0 ± 0.8	10.4	3443 ± 590	5883 ± 927	>10,000
9c	1	3,4-$(OMe)_2$Ph	94[d]	94 ± 9	25 ± 6	3.8	NA	NA	71 ± 9
9d	1	3-Pyridyl	66[d]	508 ± 61	105 ± 14	4.9	NA	NA	NA
9e	2	Ph	88[d]	49 ± 4	9.3 ± 0.6	5.3	2016 ± 217	NA	NA
9f	2	3-FPh	92[d]	66 ± 6	6.0 ± 0.5	11	1684 ± 250	3623 ± 432	>10,000
9g	2	2-Pyridyl	87[d]	21.5 ± 0.6	8.6 ± 0.8	2.5	1558 ± 88	NA	NA
9h	3	3-FPh	80[d]	24.9 ± 5	9.0 ± 0.4	2.8	>10,000	NA	NA
9i	1	3,4,5-$(OMe)_3$Ph	95[d]	1009 ± 59	627 ± 26	1.6	NA	NA	712 ± 61
9j	1	3,4-(OCH_2O)Ph	88[d]	17 ± 1	15 ± 1	1.1	NA	7352 ± 687	1993 ± 160
9k	1	Cyclohexyl	94[d]	4.0 ± 0.2	1.9 ± 0.2	2.1	NA	NA	NA
9l	1	Cubyl	91	3.0 ± 0.1	2.0 ± 0.1	1.5	126 ± 9	NA	NA
13a	1	Ph	88	568 ± 41	217 ± 11	2.6	NA	NA	NA
13b	1	3-FPh	65	303 ± 18	168 ± 11	1.8	4523 ± 299	NA	NA
13c	1	3,4-$(OMe)_2$Ph	89	1035 ± 39	471 ± 21	2.2	NA	NA	NA
13d	1	3-Pyridyl	70	734 ± 29	2626 ± 122	0.28	NA	NA	NA
13e	2	Ph	97	827 ± 89	172 ± 14	4.8	1293 ± 98	NA	NA
13f	2	3-FPh	91	405 ± 29	55 ± 3	7.4	NA	NA	NA
13g	2	2-Pyridyl	88	>10,000	633 ± 40	>15.8	NA	NA	NA
13h	3	3-FPh	75	133 ± 10	30 ± 2	4.4	NA	8533 ± 631	NA
14a	1	Ph	93	770 ± 57	50 ± 4	15.4	>10,000	NA	NA
14b	1	3-FPh	92	1571 ± 157	117 ± 8	13.4	1.2 ± 0.1	NA	NA
14c	1	3,4-$(OMe)_2$Ph	94	255 ± 9	27 ± 1	9.4	NA	NA	NA
14d	1	3-Pyridyl	86	970 ± 41	881 ± 35	1.1	NA	NA	NA
14e	2	Ph	90	773 ± 58	16 ± 1	48.3	NA	NA	NA
14f	2	3-FPh	93	1163 ± 89	39 ± 2	29.8	101 ± 5	NA	NA
14g	2	2-Pyridyl	85	448 ± 26	32 ± 2	14.0	NA	NA	NA
14h	3	3-FPh	88	429 ± 37	11 ± 1	39.0	NA	NA	NA
14i	1	3,4,5-$(OMe)_3$Ph	83	1217 ± 57	714 ± 33	1.7	>10,000	NA	>10,000
14j	1	3,4-(OCH_2O)Ph	91	209 ± 10	62 ± 2	3.4	NA	NA	>10,000
14k	1	Cyclohexyl	94	15 ± 1	14 ± 1	1.1	NA	NA	NA

[a] K_i values represent the mean ± SEM of four experiments.
[b] Data extracted from Ref. 72.
[c] Unoptimized yield over three steps.
[d] Unoptimized yield over two steps. ND = not determined. NA = <50% inhibition at 10 μM.

(**23**, Scheme 2). The synthetic route to the latter involved the conversion of cyclopentanone to dimethyl cubane-1,4-dicarboxylate (**24**) in 19% yield over six steps using the previously reported procedure of Bliese and Tsanaktsidis.[100] Diester **24** was monohydrolysed to acid–ester **25** and subjected to a Moriarty reaction, followed by saponification of the remaining ester to give



Scheme 2. Reagents and conditions: (a) NaOH, MeOH, THF, rt, 14 h, 92%; (b) $PhI(OAc)_2$, I_2, PhMe, 80 °C, 8 h; (c) aq NaOH, MeOH, THF, rt, 14 h, 74% over two steps; (d) *n*-BuLi, THF, −78 °C, 1 h, 70%; (e) (i)$(COCl)_2$, rt, 1 h, (ii) liq. NH_3, −78 °C, 1 h; (f) $LiAlH_4$, THF, reflux, 16 h, 77% over two steps.

4-iodocubanecarboxylic acid (**26**).[101,102] Treating **26** with *n*-butyllithium to facilitate lithium–halogen exchange, and methanol quench of the resultant carbanion, gave monofunctionalised cubanecarboxylic acid (**27**).[102] Cubanecarboxylic acid was converted to the corresponding amide (**28**) via the acid chloride.[103] Lithium aluminium hydride reduction of **28** gave the desired (aminomethyl)cubane (**23**) in 37% yield over six steps from **24**, a yield to comparable previous reports.[103] The amine was coupled to the pentacycloundecane cage, using the synthetic route described in Scheme 1, to give **9l** in 91% yield.

The amines thus synthesized (**8a–k**, **9a–l**, **13a–i**, and **14a–k**) were subjected to competitive radioligand-protein binding assays against a comprehensive panel of CNS receptors, transporters, and ion channels (see Table S1 for full binding profiles). Hemiaminals **8a–k** and aminoketones **13a–i** were screened as their free bases, while secondary and tertiary amines **9a–l** and **14a–k**, respectively, were screened as their hydrochloride salts. The binding affinities (K_i values) for **8a–k**, **9a–l**, **13a–i**, and **14a–k** at σ_1 and σ_2 receptors were determined using well-established in vitro competition assays and are presented in Table 1. Rat brain homogenates were used as a source of σ_1 receptors, whilst PC12 cells were used as a σ_2 receptor source, and the specific radioligands [^{3}H](+)-pentazocine and [^{3}H]DTG were used in the σ_1 and σ_2 receptor assays, respectively. The affinities of **8a–k**, **9a–l**, **13a–i**, and **14a–k** for DAT, NET, and SERT are also shown in Table 1. All transporter assays employed membranes from human embryonic kidney (HEK) cells expressing the human forms of the transporters, and the radioligands [^{3}H]WIN-35,428, [^{3}H]nisoxetine, and [^{3}H]citalopram were employed in the DAT, NET, and SERT assays, respectively.

Previous SAfiRs for the class of compounds **8** had indicated that benzylic derivatives, typified by the simplest member, **8a** (σ_2 K_i = 12 nM, σ_2/σ_1 = 28), generally displayed selectivity for the σ_2 receptor. Ring subsititution of **8a** with a 3-fluoro (**8b**) or 3,4-dimethoxy (**8c**) groups had relatively little effect. Fusing the dimethoxy groups of **8c** as a methylenedioxy bridge (**8j**) reduced σ_2 affinity and selectivity. Additional methoxy groups, as in 3,4,5-trimethoxy-substituted **8i**, or replacement of the phenyl ring with a 3-pyridyl unit (**8d**) essentially abolished affinity for either σ receptor. Although extending the distance between the aryl unit and the hemiaminal generally produced nanomolar dual σ_1/σ_2 ligands, such as **8e**, **8f**, and **8h** (σ_1 K_i = 12–26 nM, σ_2 K_i = 6.3–68 nM), replacement of the phenyl ring with a 2-pyridine unit in these homologues resulted in σ_2 selective ligand **8g** (σ_2 K_i = 26.8 nM, σ_2/σ_1 = 43.7). Finally, replacement of the phenyl ring of **8a** with its alicyclic equivalent, cyclohexane, gave the most potent, subtype non-selective σ receptor ligand in the series, **8k** (σ_1 K_i = 6.7 nM, σ_2 K_i = 2.2 nM). Excluding anomalous micromolar σ ligands **8d** and **8i**, the remaining ligands showed a comparable range of binding affinities for σ_1 (K_i = 6.7–1170 nM) and σ_2 (K_i = 2.2–259 nM) receptors.

When compared to their hemiaminal counterparts **8a–8k**, the N-substituted 8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane derivatives (**9a–l**) showed increased affinity for one or both σ receptor subtypes. Unlike **8a–8k**, all ligands showed a slight preference for σ_2 receptors irrespective of the distance between aryl group and the nitrogen atom. The three benzylic compounds **9a–9k**, displayed σ_2 binding constants (σ_2 K_i = 19–25 nM), entirely comparable to the range of demonstrated for the analogous hemiaminals **8a–8c** (σ_2 K_i = 12.6–31.0 nM), but reduced σ_2 selectivity (σ_2/σ_1 = 3.8–10.4) due to increased σ_1 binding. Increasing the distance between the aryl group and the polycarbocyclic amine produced somewhat σ_2 selective compounds, with phenethyl (**9e**), 3-fluorophenethyl (**9f**) and 3-(3-fluorophenyl)propyl (**9h**) analogues all possessing a moderate preference for the σ_2 receptor (K_i = 6.0–9.3 nM, σ_2/σ_1 = 2.8–11.0). Surprisingly, a 2-pyridylethyl subunit (**9g**) produced a compound that was nearly equipotent at both σ_1 (K_i = 21.5 nM) and σ_2 (K_i = 8.6 nM) sites. The poor subtype selectivity of **9g**, some of the lowest in the series, was unexpected in light of the high level of σ_2 selectivity displayed by the corresponding hemiaminal **8g**. Congeners of **9** containing a 3-picolyl (**9d**: σ_1 K_i = 508 nM, σ_2 K_i = 105 nM), 3,4,5-trimethoxybenzyl (**9i**: σ_1 K_i = 1009 nM, σ_2 K_i = 627 nM) or 3,4-methylenedioxybenzyl substituent (**9j**: σ_1 K_i = 17 nM, σ_2 K_i = 15 nM) each showed order of magnitude improvements in σ binding when compared to **8d**, **8i**, and **8j**. The low nanomolar affinity of cyclohexylmethyl hemiaminal **8k** was retained by similarly-substituted **9k** (σ_1 K_i = 4.0 nM, σ_2 K_i = 1.9 nM), and this was further improved by incorporation of a bulky, polycyclic cubane moiety (**9l**: σ_1 K_i = 3.0 nM, σ_2 K_i = 2.0 nM).

When compared to their **8** or **9** counterparts, **13a–13h** showed a dramatic loss of affinity for both σ receptor subtypes. With the exception of 3-picolyl derivative **13d**, all arylmethyl-substituted aminoketones showed only a slight preference for the σ_2 subtype, and low-to-moderate affinity for this site. The σ_2 affinity of benzylic **13a–c** (σ_2 K_i = 168–471 nM) was an order of magnitude lower than the corresponding **8a–c** (σ_2 K_i = 12–31 nM) or **9a–c** (σ_2 K_i = 19–25 nM), and σ_1 binding was also reduced, albeit to a lesser extent, resulting in low affinity, subtype non-selective ligands. The phenethyl (**13e**), 3-fluorophenethyl (**13f**) and 3-(3-fluorophenyl)propyl (**13h**) analogues showed reduced σ_2 binding (K_i = 30–172 nM) when compared to **9e**, **9f**, and **9h**, but similar selectivity profiles (σ_2/σ_1 = 4.4–7.4) due to reduction in σ_1 affinity.

In agreement with the trend observed for **9a–9k**, **14a–14k** were all found to interact preferentially with σ_2 receptors, regardless of the distance between the tertiary amine and aryl functional groups. Overall, **14a–14k** showed weaker σ_2 binding than their des-methyl counterparts, but the degree of selectivity for the σ_2 subtype was much higher. The cyclohexylmethyl derivative **14k** had approximately equal binding affinities at both σ_1 and σ_2 receptors (K_i = 15 nM and 14 nM, respectively), a lack of σ subtype discrimination consistent with the selectivity of both the normethyl derivative **9k** and the corresponding hemiaminal **8k**.

Comparing trends across the different trishomocubanes, the 4-azahexacyclo[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}]dodecan-3-ol framework could be suitably functionalised to provide high affinity, selective σ_2 ligands, or nanomolar dual σ_1/σ_2 ligands. Analogous subsitution of the 8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane cage generally produced ligands with higher affinities, but lower subtype selectivities than their 4-azahexacyclo[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}]dodecan-3-ol counterparts, with selectivity restored by methylation to the corresponding *N*-methyl-8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecanes. The improved subtype selectivity of series **14**, largely arising from reductions in σ_1 binding, was accompanied by a marginal decrease in σ_2 affinity, although nanomolar ligands could still be obtained. The *N*-methyl-11-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]-undecan-8-ones showed vastly inferior σ binding compared to their consonant compounds of types **8**, **9**, and **14**.

Taken together, these data suggest that the carbonyl group of aminoketones **12**, the tautomeric form of hemiaminals **8**, is unlikely to contribute to σ binding. The secondary amines **9**, deoxygenated analogues of the aminoketone tautomers **12**, were all found to bind to both σ receptor subtypes with greater affinity than the hemiaminals **8** themselves. Increasing the degree of substitution of the amine (**14**) led to a dramatic reduction in σ_1 binding, but a much smaller decrease in σ_2 affinity, suggesting that tertiary amines are better tolerated by the σ_2 receptor than the σ_1.

Several structurally diverse trishomocubanes with differing σ_1/σ_2 binding profiles (**8a–c**, **8f**, **8g**, **9a**, **9b**, **9e**, **9f**, **9h**, **9j**, **9k**, **9l**, **14e**, **14f**, **14h**, and **14k**) were assessed for neuroprotective potential by comparing with PPBP their ability to reduce NO release from LPS-stimulated murine macrophages (RAW264.7 cells). PPBP is a

selective σ_1 ligand and a potent inhibitor of NO release,[60] properties which confer demonstrable neuroprotective effects in vivo.[56,57,61,104] PPBP demonstrated a significant inhibition of NO production at all tested concentrations (20, 30, 50 and 100 μM). On the other hand, DTG was unable to significantly inhibit NO release at concentrations up to 200 μM (results not shown), contrary to a previous report of NO inhibition by DTG with an IC_{50} value of 166 μM, albeit in a different cell line.[55]

Of the 18 trishomocubanes assayed, half demonstrated significant dose-dependent inhibition of NO production (expressed as nitrite) comparable to, or greater than, PPBP (see Table 2). Compounds **8b**, **9h** and **9l** demonstrated the greatest inhibition of NO production with similar activities at 30 μM (17.3, 17.9 and 18.1% NO inhibition respectively). **8b** led to the highest inhibition of NO production (43.2%) at 100 μM without affecting cell viability. Compounds **8f**, **8g**, **9a**, **9b**, and **9j** did not significantly inhibit NO release from LPS-stimulated cells at any concentration up to 100 μM.

The benzylic derivatives **8a**–**c** demonstrated superior NO inhibitory activity over their analogues of type **9**. The phenethyl homologue of **8b**, **8f**, was inactive despite higher affinity for both σ receptor subtypes. The highly selective σ_2 ligand **8g** also failed to inhibit NO release. Curiously, the same trend was not observed for **9a** and **9b**, which failed to inhibit NO production despite the similarity of their binding profiles to those of **8a** and **8b**. Unlike 4-azahexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodecan-3-ols containing a two- or three-carbon tether, **9e**, **9f**, and **9h** showed potent NO inhibition at 30, 50, and 100 μM, although **9h** affected cell viability at 100 μM.

Substitution of the aromatic ring of **9a** for an alicyclic ring, to give low nanomolar dual σ_1/σ_2 ligand **9k**, resulted in 10.2% inhibition at 30 μM. Similar levels of NO inhibition were observed with cubane-derived **9l**, the most potent subtype non-selective σ ligand in the series, at 30 μM. Unfortunately, the limited solubility of this highly lipophilic compound prevented further assessment at 50 or 100 μM

Compounds **9h** and **14k** led to significant inhibition of NO release at 100 μM (48.5%) and 75 μM (88.3%), respectively, but morphological observation suggested these compounds, along with **14e**, **14f**, and **14h**, were cytotoxic. This was confirmed by examination of cell viability, as shown in Table 3. A notable decline in cell viability was seen with **14k**, **14e**, **14f**, and **14h**, all of which possess a tertiary amine and, excepting **14k**, have been identified as selective σ_2 receptor ligands. **14k** shows equal affinity for both receptor subtypes, which might explain its unique ability among these four structurally related ligands to demonstrate NO inhibition at 50 μM without significantly affecting cell viability.

Table 2
Percentage inhibition of NO

Compound	Inhibition of NO release[a] (%)		
	30 μM	50 μM	100 μM
PPBP[b]	9.0***	13.6***	23.7***
8a	7.6	12.6*	27.2**
8b	17.3***	25.1***	43.2***
8c	12.3**	17.7***	28.4***
9k	10.2**	7.7**	ND
9e	7	9.5**	17.5***
9f	11.9*	12.5*	23***
9h	17.9**	24.3***	Cell death
9l	18.1***	ND	ND
14k	0	30	ND

Average of 3-independent experiments, each carried out in triplicate and calculated from sodium nitrite standard curve.
[a] Threshold for statistical significance: *p <0.05; **p <0.01; ***p <0.001.
[b] Vehicle DMSO conc 0.2%. ND = not determined due to insufficient solubility.

Table 3
Percentage reduction in cell viability

Compound	Cell viability[a] (%)	
	50 μM	100 μM
9h	83.14	69.28*
14e	90.41	50.35**
14f	82.98	60.69*
14h	88.65	53.76*
14k	79.40	50.86**[b]

[a] Threshold for statistical significance: *p <0.05; **p <0.01.
[b] Concentration = 75 μM due to solubility limitations.

3. Conclusions

Several libraries of similarly N-substituted 8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecanes (**9a**–**l**), *N*-methyl-8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecanes (**14a**–**k**), and *N*-methyl-11-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-ones (**13a**–**i**) were synthesised to explore the effects of cage modification of the 4-azahexacyclo[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}]dodecan-3-ol scaffold on σ receptor binding. Compounds of type **9** were generally potent σ receptor ligands with low levels of subtype selectivity, while those of type **14** showed reduced affinity but greater selectivity for σ_2 receptors. The N-substituted *N*-methyl-11-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-ones (**13**) demonstrated the lowest σ receptor affinities. Taken together, this data suggests that 4-azahexacyclo[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}]dodecan-3-ols interact with σ receptors in their hemiaminal, rather than tautomeric aminoketone, form. Additionally, trishomocubanes containing tertiary rather than secondary amines appear to be better tolerated by σ_2 than σ_1 receptors.

Several compounds of type **8**, **9**, and **14** were compared to confirmed neuroprotective σ ligand PPBP for their ability to inhibit nitric oxide release in LPS-stimulated murine macrophages. In general, structures of type **8**, **9**, and **14** demonstrated comparable or greater inhibition of NO release than PPBP, suggesting potential roles for these trishomocubanes as neuroprotectants.

4. Materials and methods

4.1. General chemistry details

All reactions were conducted under a positive pressure of nitrogen or argon, unless otherwise stated. Tetrahydrofuran and toluene were dried over, and distilled from, sodium wire. Dichloromethane, ethanol, and methanol were dried over, and distilled from, calcium hydride. Temperature quoted as 0 °C was achieved with a cooling bath of ice-water. 3-Fluorocinnamic acid was purchased from Matrix Scientific (Columbia, SC, USA). All other commercial reagents were purchased from Sigma–Aldrich and used without further purification. Flash column chromatography employed Merck Kieselgel 60 (230–400 mesh) silica gel, unless otherwise stated. Solvents for chromatography were distilled prior to use. Melting point ranges were determined on a Stanford Research Systems Optimelt MPA100 automated melting point system using open capillaries and are uncorrected. Infrared absorption spectra were recorded on a Bruker ALPHA FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded at 300 ± 1 K, unless otherwise stated, on Bruker Avance DRX200, DRX300 or DRX400 spectrophotometers, as reported. ^{1}H chemical shifts (δ_H ppm) are reported relative to residual non-deuterated solvent resonance. The data is presented as chemical shift, relative integral, multiplicity (s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, t = triplet, q = quartet, m = multiplet range). Coupling

constants (J_{HH} Hz) and assignments are reported where possible. ^{13}C chemical shifts (δ_C ppm) are reported relative to perdeuterated solvent resonance and assigned as quaternary (C), tertiary (CH), secondary (CH_2), or primary (CH_3) where possible. Coupling constants (J_{CF} Hz) are reported for fluorinated compounds. Unambiguous assignment is reported where additional data from DEPT, COSY, NOESY, DQF-COSY, HSQC, or HMBC experiments is available. Low-resolution mass spectrometry (LRMS) was performed using electrospray ionization (ESI) and recorded on a Finnigan LCQ ion trap spectrometer. High-resolution electrospray ionization mass spectrometry (HRMS) was performed by the Mass Spectrometry Unit at the Research School of Chemistry, Australia National University, using a Bruker Apex 4.7 T Fourier transform ion cyclotron resonance (FTICR) mass spectrometer. The molecular ion and major fragment peaks are reported as percentages relative to base peak intensity. Elemental analyses were performed by the Campbell Microanalytical Laboratory, University of Otago, Otago, New Zealand.

4.1.1. General procedure for the synthesis of N-substituted 4-azahexacyclo[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}]dodecan-3-ols (8a–k)[55]

A solution of **18** (655 mg, 3.00 mmol) and the appropriate amine (3.00 mmol, 1.0 equiv) in EtOH (6 mL) was heated at 100 °C in a sealed tube for 14–20 h. The solution cooled (0 °C), $NaBH_4$ (159 mg, 4.20 mmol, 1.4 equiv) was added, and the mixture stirred at rt for 8 h. EtOH was evaporated under reduced pressure, H_2O (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo. To this crude material, acetone (25 mL) and 4 M aq HCl (15 mL) were added. After stirring at rt for 12 h, the mixture was diluted with H_2O (200 mL), basified to pH 14 with 1 M aq NaOH, and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The crude products were purified by recrystallisation from *i*-PrOH, unless otherwise stated, to yield the desired compounds. The characterization of **8a–k** was previously reported.[73]

4.1.2. General procedure for the synthesis of N-substituted 8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecanes (9a–l)

A solution of **22** (320 mg, 2.00 mmol.) and the appropriate arylalkylamine (2.20 mmol, 1.1 equiv) in EtOH (4 mL) was heated in a sealed pressure tube at 100 °C for 18–24 h. The solution was cooled (0 °C) and $NaBH_4$ (106 mg, 2.80 mmol, 1.4 equiv) was added in one portion. The mixture was allowed to warm to rt and stirred for 8 h. The solvent was evaporated under reduced pressure and the residue suspended in H_2O (75 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL), washed with brine (25 mL), dried (Na_2SO_4) and the solvent evaporated to give the crude product. Purification was achieved by flash chromatography on silica gel, eluting with $CHCl_3$–MeOH-28% aq NH_4OH (90:9:1), unless stated otherwise. NMR, IR, and mass spectrometry were performed on the freebase of each compound. The amines were converted to their HCl salts and recrystallised from *i*-PrOH or *i*-PrOH-Et_2O to give satisfactory elemental analyses.

4.1.2.1. *N*-Benzyl-8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (9a).

Treating **22** (320 mg, 2.00 mmol) with benzylamine (295 μL, 2.70 mmol, 1.35 equiv) as described above gave **9a** (416 mg, 83%) as a colourless oil: mp (HCl salt) 250 °C (dec); R_f 0.48 (silica gel, CH_2Cl_2–MeOH-28% aq NH_4OH; 90:9:1); **IR** (thin film); 3328 (br), 2951, 2861, 2797, 1602, 1494, 1452, 1349, 1134, 735, 697; ^1H NMR (400 MHz, $CDCl_3$); δ 7.35–7.29 (4H, m), 7.25–7.20 (1H, m), 3.78 (2H, s), 2.79 (1H, t, J = 3.5 Hz), 2.70–2.65 (1H, m), 2.59–2.54 (3H, m), 2.49–2.44 (1H, m), 2.34–2.32 (1H, m), 2.24–2.19 (3H, m), 1.68 (1H, d, J = 10.3 Hz), 1.38 (1H, br s, NH), 1.17 (1H, d, J = 10.3 Hz), 1.02 (1H, dt, J = 11.6, 3.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$); δ 141.6 (quat.), 128.4, 128.1, 126.8, 61.8, 53.6 (CH_2), 47.4, 44.8, 44.4, 42.2, 42.1, 41.1, 37.9, 36.5, 34.9 (CH_2), 28.9 (CH_2); m/z (+ESI) 252.00 ([M+H]$^+$, 100); Anal. ($C_{18}H_{21}N$·HCl): calcd C 75.11, H 7.70, N 4.87; found, C 75.34, H 7.70, N 4.82.

4.1.2.2. *N*-(3-Fluorobenzyl)-8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (9b).

Treating **22** (320 mg, 2.00 mmol) with 3-fluorobenzylamine (228 μL, 2.00 mmol, 1.0 equiv) as described above gave, **9b** (424 mg, 79%) as a colourless oil: mp (HCl salt) 256 °C (dec); R_f 0.70 (silica gel, $CHCl_3$–MeOH-28% aq NH_4OH; 90:9:1); IR (thin film); 3339, 2954, 1586, 1489, 1443, 1250, 1155, 899, 792, 733, 694; ^1H NMR (400 MHz, $CDCl_3$); δ 7.28–7.23 (1H, m), 7.11–7.06 (2H, m), 6.93–6.89 (1H, m), 3.77 (2H, s), 2.76 (1H, t, J = 3.4 Hz), 2.69–2.64 (1H, m), 2.59–2.52 (3H, m), 2.48–2.43 (1H, m), 2.34–2.32 (1H, m), 2.24–2.18 (3H, m), 1.67 (1H, d, J = 10.3 Hz), 1.58 (1H, br s, NH), 1.16 (1H, d, J = 10.3 Hz), 1.02 (1H, dt, J = 11.7, 3.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$); δ 163.1 (d, $^1J_{CF}$ = 245.2 Hz, quat.), 144.2 (d, $^3J_{CF}$ = 6.2 Hz, quat.), 129.8 (d, $^3J_{CF}$ = 8.2 Hz), 123.6 (d, $^4J_{CF}$ = 2.5 Hz), 114.9 (d, $^2J_{CF}$ = 21.2 Hz), 113.7 (d, $^2J_{CF}$ = 21.1 Hz), 61.7, 53.1 (CH_2), 47.4, 44.8, 44.3, 42.2, 42.0, 41.0, 37.8, 36.4, 34.8 (CH_2), 28.9 (CH_2); m/z (+ESI) 270.00 ([M+H]$^+$, 100); Anal. ($C_{18}H_{20}NF$·HCl): calcd C 70.69, H 6.92, N 4.58; found, C 70.75, H 6.70, N 4.58.

4.1.2.3. *N*-(3,4-Dimethoxybenzyl)-8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (9c).

Treating **22** (320 mg, 2.00 mmol) with 3,4-dimethoxybenzylamine (327 μL, 2.20 mmol, 1.1 equiv) as described above gave **9c** (585 mg, 94%) as a colourless oil: mp (HCl salt) 237 °C (dec); R_f 0.67 (silica gel, CH_2Cl_2–MeOH-28% aq NH_4OH; 90:9:1); IR (thin film); 2952, 2773, 1583, 1505, 1446, 1426, 1414, 1266, 1223, 1148, 1002, 943, 910, 831, 746, 653; ^1H NMR (400 MHz, $CDCl_3$); δ 6.91 (1H, d, J = 1.7 Hz), 6.84 (1H, dd, J = 8.1, 1.7 Hz), 6.80 (1H, d, J = 8.1 Hz), 3.89 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.72 (2H, s), 2.77 (1H, t, J = 3.4 Hz), 2.69–2.64 (1H, m), 2.59–2.52 (3H, m), 2.48–2.43 (1H, m), 2.32 (1H, d, J = 9.3 Hz), 2.23–2.16 (3H, m), 1.67 (1H, d, J = 10.3 Hz), 1.44 (1H, br s, NH), 1.16 (1H, d, J = 10.3 Hz), 1.02 (1H, dt, J = 11.7, 3.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$); δ 149.0 (quat.), 148.0 (quat.), 134.4 (quat.), 120.0, 111.5, 111.2, 61.8, 56.1 (CH_3), 56.0 (CH_3), 53.4 (CH_2), 47.4, 44.8, 44.4, 42.2, 42.1, 41.0, 38.0, 36.5, 34.8 (CH_2), 28.9 (CH_2); m/z (+ESI) 311.80 ([M + H]$^+$, 100); Anal. ($C_{20}H_{25}NO_2$·HCl): calcd C 69.05, H 7.53, N 4.03; found, C 69.07, H 7.52, N 4.11.

4.1.2.4. *N*-(3-Pyridyl)methyl-8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (9d).

Treating **22** (320 mg, 2.00 mmol) with (3-pyridyl)methylamine (262 μL, 2.20 mmol, 1.1 equiv) as described above gave **9d** (335 mg, 66%) as a colourless oil: mp (2HCl salt) 240 °C (dec); R_f 0.64 (silica gel, $CHCl_3$–MeOH-28% aq NH_4OH; 90:9:1); IR (thin film); 3480, 3375, 2963, 2941, 2866, 1633, 1562, 1479, 1427, 1374, 1331, 1269, 1230, 992, 911, 833, 776, 689; ^1H NMR (400 MHz, $CDCl_3$); δ 8.55 (1H, d, J = 1.6 Hz), 8.47 (1H, dd, J = 4.8, 1.6 Hz), 7.68 (1H, d, J = 7.8 Hz), 7.23 (1H, dd, J = 7.8, 4.8 Hz), 3.78 (2H, s), 2.77(1H, t, J = 3.4 Hz), 2.68–2.63 (1H, m), 2.59–2.51 (3H, m), 2.48–2.43 (1H, m), 2.31 (1H, d, J = 9.2 Hz), 2.23–2.18 (3H, m), 1.67 (1H, d, J = 10.3 Hz), 1.50 (1H, br s, NH), 1.16 (1H, d, J = 10.3 Hz), 1.01 (1H, dt, J = 11.7, 3.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$); δ 149.7, 148.4, 136.9 (quat.), 135.8, 123.4, 61.9, 51.1 (CH_2), 47.4, 44.8, 44.4, 42.2, 42.0, 41.1, 37.9, 36.5, 34.8 (CH_2), 28.8 (CH_2); m/z (+ESI) 253.00 ([M+H]$^+$, 100); Anal. ($C_{17}H_{20}N_2$·2HCl): calcd C 62.77, H 6.82, N 8.61; found: C, 62.85; H, 7.01; N, 8.54.

4.1.2.5. *N*-(2-(Phenyl)ethyl)-8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (9e).

Treating **22** (320 mg, 2.00 mmol) with phenethylamine (277 μL, 2.20 mmol, 1.1 equiv) as described above

gave **9e** (465 mg, 88%) as a colourless oil: **mp** (HCl salt) 260 °C (dec); R_f 0.72 (silica gel, CH_2Cl_2–MeOH-28% aq NH_4OH; 90:9:1); **IR** (thin film); 3342 (br), 2919, 2861, 2799, 1603, 1453, 1351, 1136, 747, 697; ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.31–7.27 (2H, m), 7.22–7.18 (3H, m), 2.89–2.73 (5H, m), 2.66–2.62 (1H, m), 2.60–2.53 (2H, m), 2.49–2.44 (1H, m), 2.31–2.28 (1H, m), 2.23–2.16 (4H, m), 1.67 (1H, d, J = 10.3 Hz), 1.18 (1H, br s, NH), 1.16 (1H, d, J = 10.3 Hz), 0.96 (1H, dt, J = 11.9, 3.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$); δ 140.6 (quat.), 128.8, 128.5, 126.1, 61.8, 50.7 (CH_2), 47.4, 44.8, 44.3, 42.1, 42.0, 40.9, 37.9, 37.0 (CH_2), 36.4, 34.9 (CH_2), 28.8 (CH_2); m/z (+ESI) 265.87 ([M+H]$^+$, 100); Anal. ($C_{19}H_{23}N$·HCl): calcd C 75.60, H 8.01, N 4.64; found, C 75.73, H 7.94, N 4.63.

4.1.2.6. *N*-(2-(3-Fluorophenyl)ethyl)-8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (9f). Treating **22** (320 mg, 2.00 mmol) with 2-(3-fluorophenyl)ethylamine (261 μL, 2.00 mmol, 1.0 equiv) as described above gave **9f** (521 mg, 92%) as a colourless oil: mp (HCl salt) 272 °C (dec); R_f 0.65 (silica gel, $CHCl_3$–MeOH-28% aq NH_4OH; 90:9:1); IR (thin film); 3329 (br), 2950, 2861, 2799, 1615, 1588, 1487, 1449, 1352, 1248, 1139, 781, 692; ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.26–7.21 (1H, m), 6.98 (1H, d, J = 7.7 Hz), 6.93–6.86 (2H, m), 2.88–2.72 (5H, m), 2.66–2.62 (1H, m), 2.58–2.53 (2H, m), 2.49–2.44 (1H, m), 2.29 (1H, d, J = 9.5 Hz), 2.22–2.18 (3H, m), 1.67 (1H, d, J = 10.4 Hz), 1.18 (1H, br s, NH, obscured), 1.16 (1H, d, J = 10.4 Hz), 0.96 (1H, dt, J = 11.9, 3.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$); δ 163.1 (d, $^1J_{CF}$ = 245.3 Hz, quat.), 143.2 (d, $^3J_{CF}$ = 7.2 Hz, quat.), 129.9 (d, $^3J_{CF}$ = 8.4 Hz), 124.5 (d, $^4J_{CF}$ = 2.6 Hz), 115.6 (d, $^2J_{CF}$ = 20.8 Hz), 113.0 (d, $^2J_{CF}$ = 20.9 Hz), 61.8, 50.3 (CH_2), 47.4, 44.8, 44.3, 42.1, 42.0, 41.0, 37.9, 36.8 (CH_2), 36.4, 34.8 (CH_2), 28.8 (CH_2); m/z (+ESI) 283.80 ([M+H]$^+$, 100); Anal. ($C_{19}H_{22}NF$·HCl): calcd C 71.35, H 7.25, N 4.38; found, C 71.64, H 7.05, N 4.39.

4.1.2.7. *N*-(2-(2-Pyridyl)ethyl)-8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (9g). Treating **22** (320 mg, 2.00 mmol) with 2-(2-pyridyl)ethylamine (262 μL, 2.20 mmol, 1.10 equiv) as described above gave **9g** (463 mg, 87%) as a colourless oil: **mp** (2HCl salt) 172 °C (dec); R_f 0.30 (silica gel, $CHCl_3$–MeOH-28% aq NH_4OH; 90:9:1); **IR** (thin film); 3302, 2963, 1633, 1563, 1478, 1432, 1373, 1337, 1269, 1230, 1035, 999, 831, 773, 687, 627; ^{1}H NMR (400 MHz, $CDCl_3$); δ 8.52 (1H, dd, J = 5.0, 1.8 Hz), 7.58 (1H, td, J = 7.6, 1.8 Hz), 7.17 (1H, d, J = 7.6 Hz), 7.10 (1H, dd, J = 7.6, 5.0 Hz), 3.01–2.93 (4H, m), 2.74 (1H, t, J = 3.5 Hz), 2.66–2.61 (1H, m), 2.60–2.52 (1H, m), 2.48–2.43 (1H, m), 2.29 (1H, d, J = 9.5 Hz), 2.24–2.16 (4H, m), 1.66 (1H, d, J = 10.3 Hz), 1.62 (1H, br s, NH), 1.15 (1H, d, J = 10.3 Hz), 0.95 (1H, dt, J = 11.9, 3.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$); δ 160.8 (quat.), 149.4, 136.4, 123.4, 121.2, 61.8, 49.0 (CH_2), 47.4, 44.8, 44.2, 42.1, 42.0, 40.9, 39.2 (CH_2), 37.8, 36.4, 34.8 (CH_2), 28.8 (CH_2); m/z (+ESI) 267.07 ([M+H]$^+$, 100); Anal. ($C_{18}H_{22}N_2$·2HCl): calcd C 71.35, H 7.25, N 4.38; found: C, 71.64; H, 7.35; N, 4.39.

4.1.2.8. *N*-(3-(3-Fluorophenyl)propyl)-8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (9h). Treating **22** (320 mg, 2.00 mmol) with 3-(3-fluorophenyl)propylamine (306 mg, 2.00 mmol, 1.0 equiv) as described above gave **9h** (475 mg, 80%) as a colourless oil: mp (HCl salt) 236 °C (dec); R_f 0.70 (silica gel, $CHCl_3$–MeOH-28% aq NH_4OH; 94:5.4:0.6); **IR** (thin film); 2952, 2867, 2673, 1613, 1583, 1485, 1444, 1416, 1260, 1143, 1038, 896, 782, 745, 694; ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.25–7.19 (1H, m), 6.96 (1H, d, J = 7.6 Hz), 6.90–6.84 (2H, m), 2.68–2.64 (4H, m), 2.63–2.52 (4H, m), 2.49–2.44 (1H, m), 2.37–2.31 (2H, m), 2.30–2.18 (3H, m), 1.80–1.73 (2H, m), 1.68 (1H, d, J = 10.4 Hz), 1.17 (1H, d, J = 10.4 Hz), 1.17 (1H, br s, NH, obscured), 1.01 (1H, dt, J = 12.0, 3.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$); δ 163.1 (d, $^1J_{CF}$ = 245.0 Hz, quat.), 145.2 (d, $^3J_{CF}$ = 7.2 Hz, quat.), 129.7 (d, $^3J_{CF}$ = 8.3 Hz), 124.2 (d, $^4J_{CF}$ = 2.5 Hz), 115.4 (d, $^2J_{CF}$ = 20.7 Hz), 112.6 (d, $^2J_{CF}$ = 21.0 Hz), 62.2, 48.8 (CH_2), 47.4, 44.8, 44.4, 42.1, 42.0, 41.0, 38.0, 36.5, 34.9 (CH_2), 33.6 (CH_2), 32.2 (CH_2), 28.9 (CH_2); m/z (+ESI) 298.07 ([M + H]$^+$, 100); Anal. ($C_{20}H_{24}NF$·HCl): calcd C 71.95, H 7.55, N 4.20; found, C 72.14, H 7.55, N 4.25.

4.1.2.9. *N*-(3,4,5-Trimethoxybenzyl)-8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (9i). Treating **22** (320 mg, 2.00 mmol) with 3,4,5-trimethoxybenzylamine (342 μL, 2.00 mmol, 1.0 equiv) as described above gave **9i** (652 mg, 95%) as a colourless oil: mp (HCl salt) 252 °C (dec); R_f 0.65 (silica gel, $CHCl_3$–MeOH-28% aq NH_4OH; 95:4.5:0.5); IR (thin film); 3394, 2952, 2782, 1588, 1421, 1329, 1243, 1123, 997, 780, 690; ^{1}H NMR (400 MHz, $CDCl_3$); δ 6.58 (2H, s), 3.86 (6H, s, 2 × OCH_3), 3.83 (3H, s, OCH_3), 3.72 (2H, s), 2.78 (1H, t, J = 3.3 Hz), 2.70–2.64 (1H, m), 2.59–2.53 (3H, m), 2.48–2.43 (1H, m), 2.33 (1H, d, J = 8.0 Hz), 2.24–2.18 (3H, m), 1.67 (1H, d, J = 10.3 Hz), 1.43 (1H, br s, NH), 1.17 (1H, d, J = 10.3 Hz), 1.02 (1H, dt, J = 11.6, 3.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$); δ 153.2 (2 × quat.), 137.5 (quat.), 136.8 (quat.), 104.8, 62.0, 61.0 (CH_3), 56.2 (2 × CH_3), 54.0 (CH_2), 47.4, 44.8, 44.4, 42.147, 42.072, 41.0, 38.0, 36.5, 34.8 (CH_2), 28.9 (CH_2); m/z (+ESI) 341.93 ([M+H]$^+$, 100), 181.00 ([$ArCH_2$]$^+$, 57); Anal. ($C_{21}H_{27}NO_3$·HCl): calcd C 66.74, H 7.47, N 3.71; found, C 66.55, H 7.59, N 3.70.

4.1.2.10. *N*-(3,4-Methylenedioxybenzyl)-8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (9j). Treating **22** (320 mg, 2.00 mmol) with piperonylamine (249 μL, 2.00 mmol, 1.0 equiv) as described above gave **9j** (520 mg, 88%) as a colourless oil: mp (HCl salt) 232 °C (dec); R_f 0.47 (silica gel, $CHCl_3$–MeOH-28% aq NH_4OH; 95:4.5:0.5); IR (thin film); 3382, 2952, 2866, 2777, 1585, 1481, 1437, 1252, 1106, 1040, 937, 895, 809, 777, 707; ^{1}H NMR (400 MHz, $CDCl_3$); δ 6.86 (1H, d, J = 1.3 Hz), 6.76 (1H, dd, J = 7.9, 1.3 Hz), 6.73 (1H, d, J = 7.9 Hz), 5.92 (2H, s, OCH_2O), 3.67 (2H, s), 2.76 (1H, t, J = 3.4 Hz), 2.69–2.64 (1H, m), 2.59–2.50 (3H, m), 2.48–2.43 (1H, m), 2.32 (1H, d, J = 8.4 Hz), 2.23–2.17 (3H, m), 1.67 (1H, d, J = 10.3 Hz), 1.44 (1H, br s, NH), 1.16 (1H, d, J = 10.3 Hz), 1.01 (1H, dt, J = 11.7, 3.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$); δ 147.7 (quat.), 146.4 (quat.), 135.7 (quat.), 121.0, 108.7, 108.1, 100.9 (CH_2), 61.6, 53.4 (CH_2), 47.4, 44.8, 44.4, 42.2, 42.1, 41.1, 37.9, 36.5, 34.8 (CH_2), 28.9 (CH_2); m/z (+ESI) 296.20 ([M + H]$^+$, 100), 135.07 ([$ArCH_2$]$^+$, 11); Anal. ($C_{19}H_{21}NO_2$·HCl): calcd C 68.77, H 6.68, N 4.22; found, C 68.63, H 6.78, N 4.25.

4.1.2.11. *N*-(Cyclohexyl)methyl-8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (9k). Treating **22** (641 mg, 4.00 mmol) with (cyclohexyl)methylamine (453 mg, 4.00 mmol, 1.0 equiv) as described above gave **9k** (967 mg, 94%) as a glass/microcrystalline solid: mp (HCl salt) 265 °C (dec); R_f 0.45 (silica gel, $CHCl_3$–MeOH-28% aq NH_4OH; 96:3.6:0.4); IR (thin film); 3427, 2964, 2925, 2852, 2808, 1595, 1453, 1415, 1268, 1231, 1112, 1029, 985, 890, 777, 706, 595; ^{1}H NMR (400 MHz, $CDCl_3$); δ 2.68–2.63 (2H, m), 2.57–2.53 (2H, m), 2.48–2.43 (1H, m), 2.42–2.37 (2H, m), 2.35–2.30 (2H, m), 2.22–2.16 (3H, m), 1.75–1.63 (6H, m), 1.43–1.33 (1H, m), 1.28–1.09 (5H, m), 0.98 (1H, dt, J = 12.0, 3.7 Hz), 0.93–0.83 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$); δ 62.1, 56.4 (CH_2), 47.4, 44.8, 44.3, 42.1, 42.0, 41.0, 38.5, 37.9, 36.5, 34.9 (CH_2), 31.7 (CH_2), 28.9 (CH_2) 26.9 (CH_2), 26.3 (CH_2); m/z (+ESI) 258.27 ([M+H]$^+$, 100); Anal. ($C_{18}H_{27}N$·HCl): calcd C 73.57, H 9.60, N 4.77; found: C 73.47, H 9.75, N 4.81.

4.1.2.12. *N*-(Cubyl)methyl-8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (9l). Treating **22** (160 mg, 1.00 mmol) with (cubyl)methylamine (133 mg, 1.00 mmol, 1.0 equiv) as described above gave **9l** (249 mg, 91%) as a colourless oil: mp (HCl salt) 281 °C (dec); R_f 0.24 (silica gel, $CHCl_3$–MeOH-28% aq NH_4OH; 90:9:1); IR (thin film); 3407, 2957, 2863, 2758, 2664, 1575, 1444, 1373, 1326, 1300, 1268, 1230, 1039, 838, 811, 775, 682; ^{1}H NMR

(400 MHz, $CDCl_3$); δ 4.04–4.00 (1H, m), 3.90–3.87 (3H, m), 3.81–3.78 (3H, m), 2.76–2.73 (3H, m), 2.69–2.64 (1H, m), 2.60–2.53 (2H, m), 2.36–2.31 (2H, m), 2.24–2.19 (2H, m), 1.67 (1H, d, J = 10.3 Hz), 1.17 (1H, br s, NH, obscured), 1.16 (1H, d, J = 10.2 Hz), 0.98 (1H, dt, J = 12.0, 3.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$); δ 62.0, 58.6 (quat.), 51.5 (CH_2), 48.6, 47.8 (3 × CH), 47.4, 44.8, 44.6 (3 × CH), 44.1, 42.1, 42.0, 41.0, 37.7, 36.5, 34.9 (CH_2), 28.9 (CH_2); m/z (+ESI) 278.13 ([M+H]$^+$, 100); Anal. ($C_{20}H_{23}N$·HCl): calcd C 76.53, H 7.71, N 4.46; found, C 76.86, H 7.91, N 4.56.

4.1.3. General procedure for the synthesis of N-substituted *N*-methyl-11-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-ones (13a–i)

A solution of the appropriate N-substituted 4-azahexacyclo[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}]dodecan-3-ol **8** (0.50 mmol) and 37% aq formaldehyde (45 μL, 0.60 mmol, 1.2 equiv) in $ClCH_2CH_2Cl$ (5 mL) was treated with $NaBH(OAc)_3$ (530 mg, 2.50 mmol, 5.0 equiv) and the mixture stirred for 8–18 h. The reaction was quenched with 1 M aq NaOH (5 mL), and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried (Na_2SO_4) and the solvent evaporated to give the crude product. Purification was achieved by flash chromatography on silica gel, eluting with $CHCl_3$–MeOH-28% aq NH_4OH (90:9:1), unless otherwise stated.

4.1.3.1. *N*-Benzyl-*N*-methyl-11-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-one (13a).

Treating **8a** (133 mg, 0.500 mmol) as described above gave **13a** (123 mg, 88%) as a white crystalline solid: mp 103–105 °C; R_f 0.51 (silica gel, $CHCl_3$–MeOH-28% aq NH_4OH; 90:9:1); IR (thin film); 2965, 2784, 1725 (C=O), 1496, 1454, 1342, 1051, 743, 700; ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.25–7.19 (4H, m), 7.16–7.12 (1H, m), 3.53 (1H, d, J = 12.7 Hz), 3.45 (1H, d, J = 12.7 Hz), 3.04–2.99 (1H, m), 2.87–2.77 (2H, m), 2.74–2.69 (1H, m), 2.60 (1H, t, J = 3.7 Hz), 2.48–2.43 (3H, m), 2.35–2.31 (1H, m), 2.00 (3H, s), 1.80 (1H, d, J = 10.8 Hz), 1.43 (1H, d, J = 10.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$); δ 213.9 (C=O), 139.0 (quat.), 128.9, 128.4, 126.9, 66.4, 60.6 (CH_2), 51.5, 50.1, 46.4, 42.1, 41.7, 41.3, 40.9, 40.3, 38.4 (CH_2), 37.1; m/z (+ESI) 280.27 ([M + H]$^+$, 100); Anal. ($C_{19}H_{21}NO$): calcd C 81.68, H 7.58, N 5.01; found, C 81.42, H 7.69, N 5.07.

4.1.3.2. *N*-(3-Fluorobenzyl)-*N*-methyl-11-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-one (13b).

Treating **8b** (142 mg, 0.501 mmol) as described above gave **13b** (97 mg, 65%) as a white crystalline solid: mp 96.5–98.5 °C; R_f 0.68 (silica gel, $CHCl_3$–MeOH-28% aq NH_4OH; 90:9:1); IR (thin film); 2967, 2786, 1727 (C=O), 1588, 1487, 1449, 1342, 1255, 1136, 1051, 948, 786, 747, 690; ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.29–7.23 (1H, m), 7.07–7.05 (1H, m), 7.01–6.98 (1H, m), 6.92–6.88 (1H, m), 3.59 (1H, d, J = 13.3 Hz), 3.51 (1H, d, J = 13.3 Hz), 3.11–3.06 (1H, m), 2.91–2.86 (2H, m), 2.82–2.77 (1H, m), 2.67 (1H, t, J = 3.7 Hz), 2.56–2.50 (3H, m), 2.41–2.38 (1H, m), 2.07 (3H, s), 1.87 (1H, d, J = 10.8 Hz), 1.50 (1H, d, J = 10.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$); δ 214.1 (C=O), 163.0 (d, $^1J_{CF}$ = 245.3 Hz, quat.), 141.8 (d, $^3J_{CF}$ = 7.1 Hz, quat.), 129.9 (d, $^3J_{CF}$ = 8.1 Hz), 124.4 (d, $^4J_{CF}$ = 2.7 Hz), 115.7 (d, $^2J_{CF}$ = 21.5 Hz), 113.8 (d, $^2J_{CF}$ = 21.1 Hz), 66.4, 60.2 (CH_2), 51.5, 50.1, 46.4, 42.1, 41.7, 41.3, 40.9, 40.4, 38.4 (CH_2), 37.1; m/z (+ESI) 298.13 ([M + H]$^+$, 100); Anal. ($C_{19}H_{20}NOF$): calcd C 76.74, H 6.78, N 4.71; found, C 76.73, H 6.97, N 4.72.

4.1.3.3. *N*-(3,4-Dimethoxybenzyl)-*N*-methyl-11-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-one (13c).

Treating **8c** (130 mg, 0.400 mmol) as described above gave **13c** (121 mg, 89%) as a pale yellow oil: mp 114–116 °C; R_f 0.49 (silica gel, $CHCl_3$-MeOH-28% aq NH_4OH; 90:9:1); IR (thin film); 2959, 2834, 2781, 1722 (C=O), 1513, 1454, 1340, 1260, 1235, 1154, 1028, 804, 742; ^{1}H NMR (400 MHz, $CDCl_3$); δ 6.96 (1H, d, J = 1.8 Hz), 6.75 (1H, d, J = 8.1 Hz), 6.70 (1H, dd, J = 8.1, 1.8 Hz), 3.97 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.46 (2H, br s), 3.11–3.05 (1H, m), 2.91–2.84 (2H, m), 2.80–2.75 (1H, m), 2.66 (1H, t, J = 3.9 Hz), 2.53–2.48 (3H, m), 2.40–2.36 (1H, m), 2.04 (3H, s), 1.86 (1H, d, J = 10.8 Hz), 1.49 (1H, d, J = 10.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$); δ 214.1 (C=O), 149.3 (quat.), 148.0 (quat.), 132.2 (quat.), 120.3, 112.1, 110.6, 66.6, 60.3 (CH_2), 56.2 (CH_3), 56.0 (CH_3), 51.5, 50.1, 46.3, 42.1, 41.7, 41.4, 40.9, 40.2, 38.4 (CH_2), 37.1; m/z (+ESI) 340.00 ([M+H]$^+$, 100), 151.00 ([$ArCH_2$]$^+$, 35); Anal. ($C_{21}H_{25}NO_3$): calcd C 74.31, H 7.42, N 4.13; found, C 74.01, H 7.59, N 4.17.

4.1.3.4. *N*-(3-Pyridyl)methyl-*N*-methyl-11-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-one (13d).

Treating **8d** (107 mg, 0.40 mmol) as described above gave **13d** (78 mg, 70%) as a pale yellow oil: R_f 0.42 (silica gel, $CHCl_3$–MeOH-28% aq NH_4OH; 90:9:1); ^{1}H NMR (400 MHz, $CDCl_3$); δ 8.46 (1H, dd, J = 4.8, 1.7 Hz), 8.39 (1H, d, J = 1.7 Hz), 7.72 (1H, dt, J = 7.8, 1.7 Hz), 7.28 (1H, dd, J = 7.8, 4.8 Hz), 3.53 (2H, br s), 3.12–3.06 (1H, m), 2.93–2.87 (2H, m), 2.82–2.77 (1H, m), 2.68 (1H, t, J = 4.0 Hz), 2.58–2.49 (3H, m), 2.41–2.37 (1H, m), 2.05 (3H, s), 1.87 (1H, d, J = 10.9 Hz), 1.50 (1H, d, J = 10.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$); δ 214.3 (C=O), 149.7, 148.7, 137.1, 134.6 (quat.), 123.9, 66.5, 57.6 (CH_2), 51.4, 50.0, 46.4, 42.1, 41.7, 41.2, 40.9, 40.3, 38.4 (CH_2), 37.1; m/z (+ESI) 281.27 ([M+H]$^+$, 100); HRMS (+ESI) calcd for $C_{18}H_{20}N_2O$ [M+H]$^+$: 281.16484, found: 209.16496.

4.1.3.5. *N*-Methyl-N-(2-(Phenyl)ethyl)-11-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-one (13e).

Treating **8e** (140 mg, 0.500 mmol) as described above gave **13e** (142 mg, 97%) as a white crystalline solid: mp 97–99 °C; R_f 0.39 (silica gel, $CHCl_3$–MeOH-28% aq NH_4OH; 90:9:1); IR (thin film); 2964, 2863, 2786, 1727 (C=O), 1496, 1453, 1341, 1213, 1056, 743, 700; ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.28–7.25 (2H, m), 7.19–7.15 (3H, m), 3.03–2.97 (1H, m), 2.87–2.69 (7H, m), 2.66–2.62 (2H, m), 2.50–2.44 (2H, m), 2.36–2.32 (1H, m), 2.31 (3H, s), 1.85 (1H, d, J = 10.8 Hz), 1.48 (1H, d, J = 10.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$); δ 212.8 (C=O), 140.7 (quat.), 128.8, 128.5, 126.0, 64.5, 57.3 (CH_2), 51.6, 50.1, 46.3, 42.0, 41.6, 41.5, 40.8, 40.1, 38.5 (CH_2), 37.2, 31.6 (CH_2); m/z (+ESI) 294.13 ([M + H]$^+$, 100); Anal. ($C_{20}H_{23}NO$): calcd C 81.87, H 7.90, N 4.77; found, C 81.59, H 8.06, N 4.81.

4.1.3.6. *N*-(2-(3-Fluorophyl)ethyl)-*N*-methyl-11-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-one (13f).

Treating **8f** (942 mg, 3.17 mmol) as described above gave **13f** (902 mg, 91%) as a white crystalline solid: mp 90–91.5 °C; R_f 0.43 (silica gel, $CHCl_3$–MeOH-28% aq NH_4OH; 90:9:1); IR (thin film); 2970, 2861, 1721 (C=O), 1582, 1484, 1426, 1343, 1229, 1141, 1059, 981, 939, 906, 791; ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.25–7.19 (1H, m), 6.93 (1H, d, J = 7.9 Hz), 6.89–6.85 (2H, m), 3.02–2.97 (1H, m), 2.87–2.67 (7H, m), 2.66–2.62 (2H, m), 2.50 (1H, t, J = 4.2 Hz), 2.47–2.43 (1H, m), 2.35–2.31 (1H, m), 2.30 (3H, s), 1.86 (1H, d, J = 10.8 Hz), 1.48 (1H, d, J = 10.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$); δ 213.1 (C=O), 163.0 (d, $^1J_{CF}$ = 245.3 Hz, quat.), 143.4 (d, $^3J_{CF}$ = 7.4 Hz, quat.), 129.9 (d, $^3J_{CF}$ = 8.3 Hz), 124.5 (d, $^4J_{CF}$ = 2.6 Hz), 115.6 (d, $^2J_{CF}$ = 20.8 Hz), 112.9 (d, $^2J_{CF}$ = 21.1 Hz), 64.6, 57.1 (CH_2), 51.6, 50.1, 46.4, 42.1, 41.6, 41.4, 40.8, 40.2, 38.5 (CH_2), 37.2, 31.7 (CH_2); m/z (+ESI) 312.13 ([M+H]$^+$, 100); Anal. ($C_{20}H_{22}NOF$): calcd C 77.14, H 7.12, N 4.50; found, C 76.90, H 7.19, N 4.55.

4.1.3.7. *N*-Methyl-N-(2-(2-pyridyl)ethyl)-11-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-one (13g).

Treating **8g** (140 mg, 0.500 mmol) as described above gave **13g** (129 mg, 88%) as a pale yellow oil: R_f 0.34 (silica gel, $CHCl_3$–MeOH-28% aq NH_4OH; 90:9:1); ^{1}H NMR (400 MHz, $CDCl_3$); δ 8.49 (1H, dd, J = 4.9, 1.8 Hz), 7.57 (1H, td, J = 7.7, 1.8 Hz), 7.14 (1H, d, J = 7.7), 7.08 (1H, dd,

J = 7.7, 4.9 Hz), 3.03–2.98 (1H, m), 2.90–2.79 (6H, m), 2.75–2.70 (1H, m), 2.65–2.61 (2H, m), 2.46 (1H, t, J = 4.7 Hz), 2.43–2.39 (1H, m), 2.32–2.29 (1H, m), 2.28 (3H, s), 1.82 (1H, d, J = 10.8 Hz), 1.45 (1H, d, J = 10.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$); δ 213.0 (C=O), 160.7 (quat.), 149.3, 136.5, 123.5, 121.2, 64.4, 55.5 (CH_2), 51.5, 50.0, 46.3, 42.0, 41.6, 41.4, 40.7, 40.1, 38.4 (CH_2), 37.1, 34.0 (CH_2); m/z (+ESI) 295.20 ([M+H]$^+$, 100), 202.13 ([M−PyCH$_2$]$^+$, 18); HRMS (+ESI) calcd for $C_{19}H_{22}N_2O$ [M + H]$^+$: 295.18049, found: 209.18056.

4.1.3.8. *N*-(3-(3-Fluorophenyl)propyl)-*N*-methyl-11-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-one (13h). Treating **8h** (156 mg, 0.500 mmol) as described above gave **13h** (122 mg, 75%) as a pale yellow oil: R_f 0.28 (silica gel, $CHCl_3$–MeOH-28% aq NH_4OH; 90:9:1); IR (thin film); 2967, 2863, 2786, 1720 (C=O), 1615, 1587, 1487, 1451, 1342, 1251, 1139, 946, 784, 692; ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.24–7.18 (1H, m), 6.97 (1H, d, J = 7.6 Hz), 6.92–6.83 (2H, m), 2.97–2.91 (1H, m), 2.85–2.71 (3H, m), 2.66–2.54 (3H, m), 2.51–2.39 (5H, m), 2.33–2.29 (1H, m), 2.19 (3H, s), 1.83 (1H, d, J = 10.8 Hz), 1.76–1.68 (5H, m), 1.46 (1H, d, J = 10.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$); δ 213.2 (C=O), 163.0 (d, $^1J_{CF}$ = 244.8 Hz, quat.), 145.2 (d, $^3J_{CF}$ = 7.1 Hz, quat.), 129.7 (d, $^3J_{CF}$ = 8.3 Hz), 124.2 (d, $^4J_{CF}$ = 2.3 Hz), 115.3 (d, $^2J_{CF}$ = 20.7 Hz), 112.6 (d, $^2J_{CF}$ = 21.1 Hz), 65.5, 54.9 (CH_2), 51.6, 50.0, 46.3, 42.0, 41.6, 41.4, 40.8, 40.0, 38.4 (CH_2), 37.2, 33.4 (CH_2) 27.2 (CH_2); m/z (+ESI) 326.33 ([M+H]$^+$, 100); HRMS (+ESI) calcd for $C_{21}H_{24}NOF$ [M + H]$^+$: 326.19147, found: 326.19164.

4.1.4. General procedure for the synthesis of N-substituted *N*-methyl-8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecanes (14a–k)

A solution of the appropriate N-substituted 8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane **9** (0.692 mmol) and 37% aq formaldehyde (78 μL, 1.00 mmol, 1.5 equiv) in $ClCH_2CH_2Cl$ (6.9 mL), was treated with $NaBH(OAc)_3$ (734 mg, 3.46 mmol, 5.0 equiv) and the mixture stirred for 14–22 h. The reaction was quenched with 1 M aq NaOH (5 mL), and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried (Na_2SO_4) and the solvent evaporated to give the crude product. Purification was achieved by flash chromatography on silica gel, eluting with $CHCl_3$–MeOH-28% aq NH_4OH (99.5:0.45:0.05), unless otherwise stated. Spectroscopic analyses were performed on the freebase of each compound. The compounds were converted to their HCl salts, and recrystallised from *i*-PrOH or *i*-PrOH-Et_2O, to give satisfactory elemental analyses.

4.1.4.1. *N*-Benzyl-*N*-methyl-8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (14a). Treating **9a** (174 mg, 0.692 mmol) as described above gave **14a** (170 mg, 93%) as a colourless oil: mp (HCl salt) 209–212 °C; R_f 0.46 (silica gel, $CHCl_3$–MeOH-28% aq NH_4OH; 99.5:0.45:0.05); IR (thin film); 2952, 2862, 2838, 1494, 1453, 1350, 1217, 1180, 1146, 1048, 915, 738, 698; ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.32–7.28 (4H, m), 7.24–7.20 (1H, m), 3.46 (2H, br s), 2.96 (1H, d, J = 11.1 Hz), 2.74–2.66 (2H, m), 2.61–2.56 (1H, m), 2.53–2.49 (1H, m), 2.41–2.33 (2H, m), 2.29 (1H, t, J = 3.4 Hz), 2.27–2.23 (2H, m), 2.05 (3H, s), 1.70 (1H, d, J = 10.3 Hz), 1.21 (1H, d, J = 10.3 Hz), 1.01 (1H, dt, J = 11.1, 3.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$); δ 140.6 (quat.), 128.9, 128.2, 126.7, 69.1, 61.4 (CH_2), 47.4, 44.8, 43.3, 42.44, 42.38, 41.1, 41.0, 37.3, 36.8, 35.1 (CH_2), 28.9 (CH_2); m/z (+ESI) 266.07 ([M+H]$^+$, 100); Anal. ($C_{19}H_{23}N$·HCl): calcd C 75.60, H 8.01, N 4.64; found, C 75.35, H 8.15, N 4.66.

4.1.4.2. *N*-(3-Fluorobenzyl)-*N*-methyl-8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (14b). Treating **9b** (173 mg, 0.642 mmol) as described above gave **14b** (167 mg, 92%) as a colourless oil: mp (HCl salt) 217–220 °C; R_f 0.30 (silica gel, $CHCl_3$–MeOH-28% aq NH_4OH; 99.5:0.45:0.05); IR (thin film); 2961, 2867, 1587, 1489, 1453, 1265, 1231, 1155, 1048, 914, 791, 758, 678; ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.27–7.22 (1H, m), 7.08–7.03 (2H, m), 6.93–6.88 (1H, m), 3.45 (2H, br s), 2.90 (1H, d, J = 11.1 Hz), 2.70–2.64 (2H, m), 2.60–2.56 (1H, m), 2.53–2.48 (1H, m), 2.38–2.24 (5H, m), 2.05 (3H, s), 1.69 (1H, d, J = 10.3 Hz), 1.20 (1H, d, J = 10.3 Hz), 1.01 (1H, dt, J = 11.0, 3.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$); δ 163.1 (d, $^1J_{CF}$ = 244.8 Hz, quat.), 143.5 (d, $^3J_{CF}$ = 6.9 Hz, quat.), 129.6 (d, $^3J_{CF}$ = 8.2 Hz), 124.2 (d, $^4J_{CF}$ = 2.4 Hz), 115.5 (d, $^2J_{CF}$ = 21.1 Hz), 113.5 (d, $^2J_{CF}$ = 21.2 Hz), 69.0, 61.0 (CH_2), 47.3, 44.8, 43.2, 42.4, 42.3, 41.2, 41.0, 37.2, 36.7, 35.0 (CH_2), 28.9 (CH_2); m/z (+ESI) 284.27 ([M+H]$^+$, 100); Anal. ($C_{19}H_{22}NF$): calcd C 71.35, H 7.25, N 4.38; found, C 71.30, H 7.33, N 4.44.

4.1.4.3. *N*-(3,4-Dimethoxybenzyl)-*N*-methyl-8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (14c). Treating **9c** (152 mg, 0.488 mmol) as described above gave **14c** (149 mg, 94%) as a colourless oil: mp (HCl salt) 195.5–198 °C; R_f 0.32 (silica gel, $CHCl_3$–MeOH-28% aq NH_4OH; 99.5:0.45:0.05); IR (thin film); 2952, 1606, 1520, 1453, 1390, 1344, 1268, 1251, 1163, 1025, 964, 901, 814, 768; ^{1}H NMR (400 MHz, $CDCl_3$); δ 6.89 (1H, s), 6.82–6.78 (2H, m), 3.872 (3H, s, OCH_3), 3.866 (3H, s, OCH_3), 3.40 (2H, br s), 2.94 (1H, d, J = 11.0 Hz), 2.72–2.64 (2H, m), 2.60–2.55 (1H, m), 2.52–2.47 (1H, m), 2.39–2.31 (2H, m), 2.27 (1H, t, J = 3.4 Hz), 2.24 (2H, br s), 2.05 (3H, s), 1.68 (1H, d, J = 10.3 Hz), 1.19 (1H, d, J = 10.3 Hz), 1.00 (1H, dt, J = 11.0, 3.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$); δ 148.9 (quat.), 147.8 (quat.), 133.4 (quat.), 120.6, 112.0, 110.8, 69.0, 61.1 (CH_2), 56.0 (OCH_3), 55.9 (OCH_3), 47.3, 44.7, 43.2, 42.4, 42.3, 41.2, 41.0, 37.3, 36.8, 35.0 (CH_2), 28.8 (CH_2); m/z (+ESI) 326.00 ([M + H]$^+$, 100), 151.00 ([ArCH$_2$]$^+$, 30); Anal. ($C_{21}H_{27}NO_2$·HCl): calcd C 69.69, H 7.80, N 3.87; found, C 69.72, H 7.90, N 3.90.

4.1.4.4. *N*-Methyl-N-(3-pyridyl)methyl-8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (14d). Treating **9d** (44 mg, 0.17 mmol) as described above gave **14d** (40 mg, 86%) as a pale yellow oil: R_f 0.23 (silica gel, $CHCl_3$–MeOH-28% aq NH_4OH; 99.5:0.45:0.05); ^{1}H NMR (400 MHz, $CDCl_3$); δ 8.51–8.47 (2H, m), 7.63 (1H, d, J = 7.4 Hz), 7.24–7.20 (1H, m), 3.45 (2H, br s), 2.85 (1H, d, J = 11.1 Hz), 2.71–2.62 (2H, m), 2.60–2.54 (1H, m), 2.53–2.46 (1H, m), 2.39–2.21 (5H, m), 2.04 (3H, s), 1.68 (1H, d, J = 10.3 Hz), 1.19 (1H, d, J = 10.3 Hz), 0.99 (1H, d, J = 11.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$); δ 150.4, 148.3, 136.5, 135.9 (quat.), 123.3, 69.0, 58.6 (CH_2), 47.3, 44.8, 43.2, 42.4, 42.3, 41.1, 41.0, 37.2, 36.7, 35.0 (CH_2), 28.8 (CH_2); m/z (+ESI) 267.35 ([M + H]$^+$, 100); Anal. ($C_{18}H_{22}N_2$·2HCl): calcd C 63.72, H 7.13, N 8.26; found: C, 63.90; H, 7.21; N, 8.33.

4.1.4.5. *N*-Methyl-N-(2-(phenyl)ethyl)-8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (14e). Treating **9e** (160 mg, 0.603 mmol) as described above gave **14e** (152 mg, 90%) as a colourless oil: mp (HCl salt) 186.5–188.5 °C; R_f 0.17 (silica gel, $CHCl_3$–MeOH-28% aq NH_4OH; 99.5:0.45:0.05); IR (thin film); 2951, 2866, 1463, 1367, 1230, 1028, 913, 790, 728, 694; ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.29–7.26 (2H, m), 7.20–7.16 (3H, m), 2.75–2.71 (2H, m), 2.66–2.51 (6H, m), 2.49–2.44 (1H, m), 2.33–2.30 (1H, m), 2.27–2.23 (5H, m), 2.22–2.19 (2H, m), 1.66 (1H, d, J = 10.3 Hz), 1.17 (1H, d, J = 10.3 Hz), 0.85 (1H, dt, J = 11.1, 3.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$); δ 141.5 (quat.), 128.9, 128.3, 125.8, 68.1, 58.2 (CH_2), 47.4, 44.7, 43.2, 42.41, 42.35, 41.01, 40.95, 37.2, 36.8, 35.0 (CH_2), 33.3 (CH_2), 28.5 (CH_2); m/z (+ESI) 280.07 ([M + H]$^+$, 100); Anal. ($C_{20}H_{25}N$·HCl): calcd C 76.05, H 8.30, N 4.43; found, C 75.97, H 8.32, N 4.51.

4.1.4.6. *N*-(2-(3-Fluorophenyl)ethyl)-*N*-methyl-8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (14f). Treating **9f** (221

mg, 0.780 mmol) as described above gave **14f** (215 mg, 93%) as a colourless oil: mp (HCl salt) 190–193 °C; R_f 0.20 (silica gel, $CHCl_3$–MeOH-28% aq NH_4OH; 99.5:0.45:0.05); IR (thin film); 2952, 1614, 1587, 1487, 1454, 1423, 1368, 1230, 1145, 1013, 912, 861, 776, 686; ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.25–7.19 (1H, m), 6.96 (1H, d, J = 7.6 Hz), 6.92–6.84 (2H, m), 2.74–2.70 (2H, m), 2.64–2.52 (6H, m), 2.49–2.44 (1H, m), 2.31–2.27 (1H, m), 2.25–2.19 (7H, m), 1.66 (1H, d, J = 10.3 Hz), 1.17 (1H, d, J = 10.3 Hz), 0.83 (1H, dt, J = 11.0, 3.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$); δ 163.0 (d, $^1J_{CF}$ = 244.8 Hz, quat.), 144.1 (d, $^3J_{CF}$ = 7.0 Hz, quat.), 129.6 (d, $^3J_{CF}$ = 8.3 Hz), 124.5 (d, $^4J_{CF}$ = 2.6 Hz), 115.7 (d, $^2J_{CF}$ = 20.8 Hz), 112.6 (d, $^2J_{CF}$ = 21.1 Hz), 68.1, 57.8 (CH_2), 47.3, 44.7, 43.2, 42.4, 42.3, 40.94, 40.89, 37.2, 36.7, 35.0 (CH_2), 33.1 (CH_2), 28.5 (CH_2); m/z (+ESI) 298.20 ([M+H]$^+$, 100); Anal. ($C_{20}H_{24}NF{\cdot}HCl$): calcd C 71.95, H 7.55, N 4.20; found, C 71.80, H 7.61, N 4.24.

4.1.4.7. *N*-Methyl-N-(2-(2-pyridyl)ethyl)-8-aminopentacyclo [5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (14g). Treating **9g** (38 mg, 0.14 mmol) as described above gave **14g** (34 mg, 85%) as a pale yellow oil: R_f 0.19 (silica gel, $CHCl_3$–MeOH-28% aq NH_4OH; 99.5:0.45:0.05); ^{1}H NMR (400 MHz, $CDCl_3$); δ 8.50 (1H, d, J = 2.8 Hz), 7.55 (1H, t, J = 7.5 Hz), 7.16 (1H, d, J = 7.5 Hz), 7.08–7.05 (1H, m), 2.94–2.72 (4H, m), 2.66–2.60 (1H, m), 2.54–2.38 (4H, m), 2.32–2.12 (8H, m), 1.63 (1H, d, J = 10.2 Hz), 1.14 (1H, d, J = 10.2 Hz), 0.77 (1H, d, J = 9.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$); δ 161.4 (quat.), 149.3, 136.2, 123.4, 121.0, 68.1, 56.4 (CH_2), 47.3, 44.7, 43.1, 42.4, 42.3, 40.9, 40.8, 37.1, 36.7, 35.6 (CH_2), 34.9 (CH_2), 28.4 (CH_2); m/z (+ESI) 281.21 ([M + H]$^+$, 100); Anal. ($C_{19}H_{24}N_2{\cdot}2HCl$): calcd C 64.59, H 7.42, N 7.93; found: C, 64.79; H, 7.70; N, 8.01.

4.1.4.8. *N*-(3-(3-Fluorophenyl)propyl)-*N*-methyl-8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (14h). Treating **9h** (150 mg, 0.504 mmol) as described above gave **14h** (139 mg, 88%) as a colourless oil: mp (HCl salt) 178–180 °C; R_f 0.15 (silica gel, $CHCl_3$–MeOH-28% aq NH_4OH; 99.5:0.45:0.05); IR (thin film); 2952, 1615, 1587, 1486, 1454, 1423, 1368, 1269, 1159, 1014, 954, 893, 861, 777, 744, 688; ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.25–7.20 (1H, m), 6.97 (1H, d, J = 7.6 Hz), 6.92–6.84 (2H, m), 2.74 (2H, d, J = 11.0 Hz), 2.65–2.61 (4H, m), 2.58–2.53 (1H, m), 2.49–2.44 (1H, m), 2.39–2.26 (4H, m), 2.24–2.13 (6H, m), 1.77–1.70 (2H, m), 1.67 (1H, d, J = 10.3 Hz), 1.18 (1H, d, J = 10.3 Hz), 0.94 (1H, dt, J = 10.9, 3.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$); δ 163.0 (d, $^1J_{CF}$ = 244.8 Hz, quat.), 145.6 (d, $^3J_{CF}$ = 7.0 Hz, quat.), 129.7 (d, $^3J_{CF}$ = 8.3 Hz), 124.2 (d, $^4J_{CF}$ = 2.5 Hz), 115.4 (d, $^2J_{CF}$ = 20.7 Hz), 112.5 (d, $^2J_{CF}$ = 21.0 Hz), 68.9, 55.6 (CH_2), 47.4, 44.7, 43.2, 42.4 (2 × CH), 40.9, 40.8, 37.2, 36.8, 35.0 (CH_2), 33.5 (CH_2), 28.8 (CH_2), 28.7 (CH_2); m/z (+ESI) 312.07 ([M+H]$^+$, 100); Anal. ($C_{21}H_{26}NF{\cdot}HCl$): calcd C 72.50, H 7.82, N 4.03; found, C 72.42, H 7.94, N 4.10.

4.1.4.9. *N*-Methyl-N-(3,4,5-trimethoxybenzyl)-8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (14i). Treating **9i** (103 mg, 0.302 mmol) as described above gave **14i** (89 mg, 83%) as a colourless oil: mp (HCl salt) 204–206 °C; R_f 0.37 (silica gel, $CHCl_3$–MeOH-28% aq NH_4OH; 99.5:0.45:0.05); IR (thin film); 2953, 1592, 1484, 1463, 1403, 1387, 1337, 1243, 1131, 988, 953, 813, 781, 678; ^{1}H NMR (400 MHz, $CDCl_3$); δ 6.56 (2H, s), 6.82–6.78 (2H, m), 3.85 (6H, s, 2 × OCH_3), 3.83 (3H, s, OCH_3), 3.39 (2H, br s), 2.94 (1H, d, J = 11.0 Hz), 2.71–2.64 (2H, m), 2.60–2.55 (1H, m), 2.52–2.47 (1H, m), 2.38–2.31 (2H, m), 2.28 (1H, t, J = 3.3 Hz), 2.24 (2H, br s), 2.08 (3H, s), 1.69 (1H, d, J = 10.3 Hz), 1.20 (1H, d, J = 10.3 Hz), 1.01 (1H, dt, J = 10.9, 3.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$); δ 153.1 (quat.), 136.7 (quat.), 136.6 (quat.), 105.3, 69.0, 61.7 (CH_2), 61.0 (CH_3), 56.1 (2 × CH_3), 47.3, 44.7, 43.3, 42.4, 42.3, 41.4, 41.0, 37.3, 36.7, 35.0 (CH_2), 28.7 (CH_2); m/z (+ESI) 356.00 ([M + H]$^+$, 100), 181.00 ([$ArCH_2$]$^+$, 44); Anal. ($C_{22}H_{29}NO_3{\cdot}HCl$): calcd C 67.42, H 7.72, N 3.57; found, C 67.37, H 7.73, N 3.61.

4.1.4.10. *N*-Methyl-N-(3,4-methylenedioxybenzyl)-8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (14j). Treating **9j** (59 mg, 0.20 mmol) as described above gave **14j** (56 mg, 91%) as a white crystalline solid: mp (freebase) 66–68 °C; R_f 0.29 (silica gel, $CHCl_3$-MeOH-28% aq NH_4OH; 99.5:0.45:0.05); IR (thin film); 2953, 2862, 2836, 2776, 1502, 1488, 1239, 1040, 933, 807; ^{1}H NMR (400 MHz, $CDCl_3$); δ 6.85 (1H, s), 6.73 (2H, br s), 5.93 (2H, s, OCH_2O), 3.36 (2H, br s), 2.91 (1H, d, J = 11.1 Hz), 2.73–2.65 (2H, m), 2.61–2.56 (1H, m), 2.53–2.48 (1H, m), 2.39–2.32 (2H, m), 2.27–2.23 (3H, m), 2.04 (3H, s), 1.70 (1H, d, J = 10.3 Hz), 1.20 (1H, d, J = 10.3 Hz), 1.00 (1H, dt, J = 11.0, 3.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$); δ 147.7 (quat.), 146.3 (quat.), 134.6 (quat.), 121.7, 109.3, 107.9, 100.9 (CH_2), 68.9, 61.1 (CH_2), 47.4, 44.8, 43.2, 42.4, 42.3, 41.0, 40.9, 37.2, 36.7, 35.0 (CH_2), 28.9 (CH_2); m/z (+ESI) 310.00 ([M+H]$^+$, 100), 135.00 ([$ArCH_2$]$^+$, 28); Anal. ($C_{20}H_{23}NO_2$): calcd C 77.64, H 7.49, N 4.53; found, C 77.31, H 7.53, N 4.55.

4.1.4.11. *N*-(Cyclohexyl)methyl-*N*-methyl-8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (14k). Treating **9k** (227 mg, 0.882 mmol) as described above gave **14k** (226 mg, 94%) as a colourless oil: mp (HCl salt) 228–235 °C; R_f 0.53 (silica gel, $CHCl_3$–MeOH-28% aq NH_4OH; 99.5:0.45:0.05); IR (thin film); 2955, 2919, 2848, 1633, 1563, 1447, 1372, 1332, 1270, 1229, 1105, 1024, 1001, 982, 952, 897, 782, 688; ^{1}H NMR (400 MHz, $CDCl_3$); δ 2.77 (1H, d, J = 11.0 Hz), 2.65–2.57 (2H, m), 2.56–2.50 (1H, m), 2.47–2.42 (1H, m), 2.32–2.23 (2H, m), 2.22–2.17 (2H, m), 2.12–1.95 (6H, m), 1.80–1.57 (6H, m), 1.46–1.35 (1H, m), 1.27–1.10 (4H, m), 0.90–0.77 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$); δ 69.5, 63.9 (CH_2), 47.4, 44.6, 43.2, 42.4, 42.3, 41.3, 40.9, 37.3, 36.8, 36.1, 35.1 (CH_2), 32.0 (CH_2), 28.7 (CH_2), 27.1 (CH_2), 26.4 (CH_2); m/z (+ESI) 272.13 ([M + H]$^+$, 100); Anal. ($C_{19}H_{29}N{\cdot}HCl$): calcd C 74.12, H 9.82, N 4.55; found, C 74.22, H 9.95, N 4.63.

4.1.4.12. (1*R*,2*S*,7*R*,8*S*)-Tricyclo[6.2.1.0^{2,7}]undeca-4,9-diene-3,6-dione (16)[92,105]. A cooled (−10 °C) suspension of **6** (24.0 g, 222 mmol) in toluene (170 mL) was treated dropwise with a cooled (−72 °C) solution of freshly cracked cyclopentadiene (21.2 mL, 260 mmol, 1.17 equiv) in toluene (30 mL). The mixture was stirred at −10 °C for 1 h and allowed to warm to rt. The solvent was removed in vacuo and hexanes (100 mL) added to the residue. The precipitate was filtered and recrystallised from methanol to yield **7** (30.9 g, 80%) as yellow needles, the spectroscopic properties of which corresponded with those previously reported:[92,105] mp 77–78 °C; (lit. 76.0–78.5 °C)[92]; ^{1}H NMR (200 MHz, $CDCl_3$); δ 6.56 (2H, s, COCH=CHCO), 6.07–6.05 (2H, m, CHC*H*=C*H*CH), 3.56–3.52 (2H, m), 3.22–3.20 (2H, m, C*H*COCH=CHCOC*H*), 1.61–1.40 (2H, m).

4.1.4.13. Pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione (Cookson's diketone, 17)[92]. A solution of **7** (13.0 g, 74.6 mmol) in hexanes-acetone (90:10, 250 mL) was saturated with argon (1 h) and irradiated for 14 h by a UV-B photoreactor (emission λ_{max} ~313 nm, 192 W), through a Pyrex filter (reaction glassware). The solvent was evaporated under reduced pressure and crude material recrystallised from hexanes–EtOAc (~80:20) to give **8** as a white crystalline solid (12.1 g, 93%) of consistent spectroscopic properties to those previously reported:[92] mp 243–244 °C (lit. 243.0–243.5 °C)[92]; ^{1}H NMR (200 MHz, $CDCl_3$); δ 3.23–3.13 (2H, m), 2.98–2.91 (2H, m), 2.82–2.79 (2H, m), 2.74–2.68 (2H, m), 2.05 (1H, d, J = 11.3 Hz), 1.88 (1H, d, J = 11.3 Hz).

4.1.4.14. Pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione ethylene acetal (18)[93]. A mixture of **8** (15.0 g, 86.0 mmol), ethylene glycol (4.80 mL, 86.0 mmol, 1.0 equiv) and *p*-TsOH·H_2O (164 mg, 0.86 mmol, 0.01 equiv) in toluene (172 mL) was refluxed under Dean–Stark conditions for 5 h, allowed to cool, and neutralised with satd aq $NaHCO_3$ (75 mL). The layers were separated

and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude material was recrystallised from Et_2O to yield **9** (17.5 g, 93%) as colourless crystals, the physical and spectroscopic properties of which were in accord with previously reported data:[93] mp 78.5–80 °C (lit. 73.0–73.5 °C)[93]; ^{1}H NMR (300 MHz, $CDCl_3$); δ 3.97–3.83 (4H, m, CH_2CH_2), 3.00–2.93 (1H, m), 2.85–2.78 (2H, m), 2.69–2.42 (5H, m), 1.88 (1H, d, J = 11.5 Hz), 1.58 (1H, d, J = 11.5 Hz).

4.1.4.15. *endo*-11-Hydroxypentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8-one ethylene acetal (19)[95].

To a suspension of lithium aluminium hydride (114 mg, 3.00 mmol, 1.5 equiv) in Et_2O (20 mL) was added **9** (436 mg, 2.00 mmol), portionwise. The mixture was heated at reflux for 2 h, cooled (0 °C) and quenched by the successive dropwise addition of H_2O (0.114 mL), 15% aq NaOH (0.114 mL), and H_2O (0.342 mL). The mixture was filtered, the filtrate dried (Na_2SO_4) and the solvent evaporated. The crude material was purified by flash chromatography on silica gel, eluting with hexanes–EtOAc (50:50), to yield **10** (404 mg, 92%) as a colourless oil that crystallised on standing. The spectroscopic properties of **14** were in accord with those previously published:[95] R_f 0.48 (silica gel, hexanes–EtOAc; 50:50); mp 61–63 °C (lit. mp[95] 61.5–63 °C); ^{1}H NMR (300 MHz, $CDCl_3$); δ 5.35 (1H, d, J = 12.2 Hz), 4.04–3.83 (4H, m), 3.67 (1H, dt, J = 12.2, 3.6 Hz), 2.75–2.44 (6H, m), 2.37–2.34 (1H, m), 2.23–2.17 (1H, m), 1.65 (1H, d, J = 10.7 Hz), 1.16 (1H, d, J = 10.7 Hz).

4.1.4.16. *endo*-11-Hydroxypentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8-one (20)[96].

A solution of **10** (2.590 g, 11.76 mmol) in 6% aq HCl (60 mL) was stirred for 3.5 h. The solution was diluted with H_2O (60 mL) and extracted with CH_2Cl_2 (4 × 30 mL). The combined organic layers were dried (Na_2SO_4) and the solvent evaporated. Purification of the crude material by flash chromatography on silica gel, eluting with hexanes–EtOAc (50:50), furnished **11** as a microcrystalline solid (2.049 g, 99%) possessing spectroscopic properties in agreement with those reported previously:[96] mp 252–255 °C (lit. mp[96] 255 °C); R_f 0.34 (silica gel, hexanes–EtOAc; 50:50); ^{1}H NMR (200 MHz, $CDCl_3$); δ 4.63 (½H, t, J = 5.3 Hz, C*H*OH), 4.11 (½H, t, J = 3.5 Hz, C*H*OH), 3.90 (½H, br s, OH), 3.05–2.39 (8H, m), 1.90 (½H, d, J = 10.5 Hz), 1.88 (½H, d, J = 10.8 Hz), 1.61 (½H, d, J = 11.7 Hz), 1.49 (½H, d, J = 11.2 Hz).

4.1.4.17. Pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8-ol (21)[96].

A solution of **11** (1.24 g, 7.06 mmol) and hydrazine monohydrate (2.48 mL, 51.2 mmol, 7.25 equiv) in diethylene glycol (24 mL) was heated at 105 °C for 2.5 h. Solid potassium hydroxide (1.74 g, 31.1 mmol, 4.4 equiv) was added portionwise and the solution was distilled until the temperature of the distillate reached 190 °C. The solution was heated at 190 °C for 4 h, allowed to cool, and diluted with H_2O (50 mL). The aqueous phase was extracted with Et_2O (4 × 25 mL) and the combined organic layers washed successively with 2 M aq HCl (25 mL), satd aq $NaHCO_3$ (25 mL), and brine (25 mL). The organic phase was dried (Na_2SO_4) and the solvent evaporated. Purification of the crude material by flash chromatography on silica gel, eluting with hexanes–EtOAc (80:20), gave **12** as a microcrystalline white solid (1.10 g, 96%) with spectroscopic properties corresponding to those previously reported:[96] mp 232–234 °C (lit. mp[96] 231–232 °C); R_f 0.39 (silica gel, hexanes–EtOAc; 80:20); ^{1}H NMR (200 MHz, $CDCl_3$); δ 3.97–3.91 (1H, m), 2.78–2.21 (9H, m), 1.70 (1H, d, J = 10.3 Hz), 1.17 (1H, d, J = 11.1 Hz), 1.08 (1H, dt, J = 11.8, 3.8 Hz).

4.1.4.18. Pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8-one (22)[96].

A solution of **12** (1.58 g, 9.72 mmol) in CH_2Cl_2 (10 mL) was added to a suspension of pyridinium chlorochromate (4.19 g, 19.4 mmol, 2.0 equiv) in CH_2Cl_2 (20 mL) in one portion. The mixture was stirred for 2 h and diluted with Et_2O (150 mL). The organic phase was decanted and the black precipitate washed with Et_2O (2 × 25 mL). The combined organic layers were filtered through a Florisil pad and the solvent evaporated. Purification of the crude material by flash chromatography on silica gel, eluting with hexanes-EtOAc (80:20), gave **13** as a crystalline solid (1.45 g, 93%), the spectroscopic properties of which matched those previously described:[96] mp 194.5–196 °C (lit. mp[96] 194–195 °C); R_f 0.63 (silica gel, hexanes–EtOAc; 80:20); ^{1}H NMR (200 MHz, $CDCl_3$); δ 3.04–2.25 (8H, m), 1.86 (1H, d, J = 10.8 Hz), 1.53 (1H, d, J = 10.5 Hz), 1.45 (2H, br s).

4.1.4.19. Pentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octane-1-methanamine (23)[103].

Solid **27** (633 mg, 4.27 mmol) was dissolved in $(COCl)_2$ (6.41 mL) and stirred for 1 h. Excess $(COCl)_2$ was removed under reduced pressure and the obtained residue was dissolved in CH_2Cl_2 (20 mL) in a flask fitted with a cold finger containing dry-ice/acetone. Ammonia was condensed into the flask (ca. 10 mL) and the mixture allowed to reflux for 1 h. The cold finger was removed and the NH_3 and CH_2Cl_2 were evaporated under a stream of N_2. The residue was treated with H_2O (50 mL) and the aqueous phase extracted with $CHCl_3$ (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), the solvent evaporated under reduced pressure, and the obtained amide dried in vacuo. Crude amide **28** was added portionwise to a cooled (0 °C) suspension of $LiAlH_4$ (648 mg, 17.1 mmol, 4.0 equiv) in THF (80 mL). The mixture was heated at reflux for 16 h, cooled to 0 °C, and quenched by the addition of H_2O (0.65 mL), 15% aq NaOH (0.65 mL), and H_2O (1.95 mL). The mixture was filtered, the filtrate evaporated, and the residue subjected to flash chromatography on silica gel, eluting with $CHCl_3$–MeOH-28% aq NH_4OH (90:9:1), to furnish **23** as a pale yellow oil (440 mg, 77% over two steps). The spectroscopic data for **23** were in accord with those previously reported:[103] R_f 0.10 (silica gel, $CHCl_3$–MeOH-28% aq NH_4OH; 90:9:1); ^{1}H NMR (200 MHz, $CDCl_3$); δ 4.09–3.99 (1H, m), 3.92–77 (6H, m), 2.83 (2H, s, CH_2), 1.25 (2H, br s, NH_2).

4.1.4.20. Pentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octane-1,4-dicarboxylic acid methyl ester (25)[106].

A 2.5 M solution of NaOH in MeOH (7.60 mL, 19.1 mmol, 1.05 equiv) was added dropwise to a solution of **24** (4.00 g, 18.2 mmol) in THF (125 mL) at rt. The mixture was stirred for 14 h and the solvent evaporated in vacuo without heating. The residue was diluted with H_2O (45 mL) and extracted with $CHCl_3$ (3 × 15 mL). The aqueous layer was acidified to pH 3 with 32% aq HCl, extracted with $CHCl_3$ (1 × 60 mL, 2 × 35 mL), and the combined organic layers dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give **25** as a colourless crystalline solid (3.46 g, 92%) with spectroscopic properties matching those previously reported:[106] mp 183–184.5 °C; (lit. mp[106] 182–183 °C); ^{1}H NMR (200 MHz, $CDCl_3$); δ 4.30–4.24 (6H, m, CH), 3.72 (3H, s, CH_3).

4.1.4.21. 4-Iodopentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octane-1-carboxylic acid (26)[102].

A suspension of **25** (3.46 g, 16.8 mmol) in toluene (265 mL) was treated with $PhI(OAc)_2$ (16.2 g, 50.4 mmol, 3.0 equiv) and I_2 (12.7 g, 50.4 mmol, 3 equiv) was stirred at 80 °C for 8 h. After cooling to rt, *n*-pentane (135 mL) was added to the reaction mixture. The solution was washed with satd aq Na_2SO_3 (2 × 45 mL), H_2O (45 mL), and brine (45 mL), dried ($MgSO_4$), and the solvent reduced in vacuo. The remaining liquid was dissolved in THF (90 mL), and treated with a solution of NaOH (679 mg, 17.0 mmol, 1.01 equiv) in MeOH (65 mL) and H_2O (20 mL). After stirring at rt for 14 h, the solution was evaporated to near-dryness, dissolved in H_2O (45 mL), and acidified to pH 1 with 32% aq HCl. The precipitated solid was filtered, washed with H_2O (5 mL), and

dried under vacuum to constant weight furnishing **26** (3.42 g, 74%) as an off-white solid with spectroscopic properties matching those reported:[102] mp 209 °C (dec); (lit. mp[102] 215 °C, dec); ^{1}H NMR (200 MHz, CD_3OD); δ 4.38–4.32 (3H, m), 4.28–4.21 (3H, m).

4.1.4.22. Pentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octane-1-carboxylic acid (27)[102]. A cooled (−78 °C) solution of **26** (1.12 g, 4.09 mmol) in THF (410 mL) was treated dropwise with a 1.90 M solution of *n*-BuLi in THF (17.0 mL, 32.3 mmol, 7.89 equiv) and stirred at −78 °C for 1 h. Cold MeOH (40 mL) was added dropwise and the solution allowed to warm to rt. Hexanes (300 mL) were added and the solution extracted with H_2O (3 × 200 mL). The combined aqueous layers were acidified to pH 1 with 32% aq HCl, and extracted with $CHCl_3$ (3 × 200 mL). The combined organic phases were dried ($MgSO_4$), and the solvent removed in vacuo to give **27** as a white solid (423 mg, 70%), the spectroscopic properties of which corresponded with those described previously:[102] mp 124–126 °C; (lit. mp[102] 124–125 °C); ^{1}H NMR (200 MHz, $CDCl_3$); δ 4.33–4.27 (3H, m), 4.07–3.99 (4H, m).

4.2. General pharmacology details

4.2.1. Reagents

High glucose Dulbecco's modified Eagle media (DMEM), phosphate-buffered saline (PBS), dimethyl sulfoxide (DMSO), lipopolysaccharide (LPS) from *Escherichia coli*, Griess reagent (modified), sodium nitrite, 4-phenyl-1-(4-phenylbutyl)piperidine (PPBP) and DTG were all purchased from Sigma-Aldrich. Penicillin/streptomycin and fetal bovine serum (FBS) were supplied from Invitrogen and CellTiter-Blue (CTB) was purchased from Promega.

4.2.2. Cell culture

RAW264.7 mouse monocyte-macrophage cells were obtained from American type culture collection (ATCC) and maintained in DMEM supplemented with 10% heat-inactivated FBS (10% DMEM). Cells were grown in 75 cm^2 flasks in a humidified 5% CO_2 incubator at 37 °C. The medium was routinely changed every 2–3 days.

4.2.3. Determination of NO production

All compounds were initially dissolved in DMSO at 1000 times the indicated doses. Final DMSO concentrations were 0.1% (0.2% for PPBP) and did not affect cell function. RAW264.7 cells were gently scraped, centrifuged, resuspended in 10% DMEM and seeded in 96-well plates at 2 × 10^5 cells/well for 5 h. The supernatant was aspirated and cells were washed once with serum-free DMEM containing 100 U/mL penicillin and 100 μg/mL streptomycin, hereafter referred to as conditioned medium. For nitric oxide (NO) production assays, the cells were then treated with a 150 μL solution of 1 μg/mL LPS in conditioned medium containing various concentrations of test compounds (1–100 μM) and incubated for 20–24 h. Due to limited solubility, some compounds were not tested up to 100 μM (**14k**: 75 μM; **9k**: 50 μM; **9l**: 30 μM). RAW264.7 cells were treated with 1 μg/mL LPS to induce NO production. All of the tested compounds, at the highest available concentration, had no effect on NO release when added to the cells without LPS stimulation. NO production was determined by measuring the amount of nitrite in cell culture supernatant mixed with equal volumes of Griess reagent (modified) and incubated in the dark for 10 min. The absorbance was read at 540 nm using a POLARstar Omega microplate reader (BMG Labtech). The nitrite levels were calculated from a serial dilution standard curve (range 0.5–65 μM) generated with sodium nitrite.

4.2.4. Determination of cell viability

RAW264.7 cells were harvested and plated as described in Section 4.2.3. Cells were treated with a 100 μL solution of selected concentrations of compounds in conditioned medium and incubated for 24 h. Cell viability was assessed using the CellTiter-Blue assay as per the manufacturer's protocol.

4.2.5. Statistical analysis

For NO determination, the results were expressed as the mean ± standard error of the mean (±SEM) of at least three independent experiments, each conducted in triplicate. Data were analyzed statistically by the randomized block ANOVA and Dunnett's post-hoc test.[107] For cell viability assays, data were expressed as percentage of vehicle-treated control, and differences between groups were analyzed using one-way ANOVA with Dunnett's post-hoc test. In all cases, a value of p <0.05 was the criterion of statistical significance.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2013.07.045.

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