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Microwave-assisted methods for the synthesis of pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecylamines

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Abstract

Efficient methodologies for the preparation of pentacyclo[5..4.0.0^{2,6}.0^{3,10}.0^{5,9}] undecane (PCU) amine derivatives are described via microwave-assisted synthesis. The obtained results revealed that microwave-assisted synthetic procedures under controlled conditions (power, temperature and time) are very convenient, high yielding, efficient and low-cost methods for the preparation of PCU amine derivatives. The new methods show several advantages including operational simplicity, good performance, significant reduction in reaction time, less by-product formation and easier purification.

The synthesis, chemical and biological applications of saturated polycyclic hydrocarbon 'cage' compounds have, in recent years, become an intense area of research interest. The pharmacology and medicinal potential of these compounds were realized with the discovery that the cage-like molecule, 1-amino-adamantane or amantadine (1, Fig. 1), an antiviral agent, could be used as a symptomatic treatment option for Parkinson's disease patients.[1,2] The pharmacological mechanism of amantadine as an anti-Parkinson's agent, at least in part, has generally been attributed to its ability to increase extracellular dopamine (DA) levels via reuptake inhibition and DA release.[1,2] A distinct structural similarity (Fig. 1) exists between amantadine (1) and the polycyclic pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecyl (PCU) amines 3 and 4.[3,4] PCU amines are derived from the Cookson's diketone cage structure (2; pentacyclo[5.4.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione), which is obtained via the intramolecular photocyclization of the Diels Alder adduct of p-benzoquinone and cyclopentadiene.[5]

The first account of biological activity for PCU amines was published in 1986, detailing L-type calcium channel inhibition by 8-benzylamino-8,11-oxapentacycloundecane (NGP1-01, 8, Scheme 1).[6] Early on in the synthesis of 8, it was first assumed that the aza-derivative 9 was formed. However, two independent studies based on X-ray crystallographic data later showed that when the imine 7 was reduced with sodium borohydride ($NaBH_4$), the oxa-derivative 8 was formed, whereas reduction with sodium cyanoborohydride ($NaBH_3CN$) led to the aza-derivative 9.[4,7] The PCU structures are now known to have a variety of pharmacological activities which include, amongst others, antiviral,[3] anti-Parkinson's,[8–11] calcium and sodium channel antagonism,[10–12] sigma receptor antagonism[13–15] and nitric oxide synthase inhibition.[16,17] These polycyclic structures have also been used as effective scaffolds with the ability to promote favourable pharmacokinetic and pharmacodynamic properties to conjugated privileged moieties.[18] Based on the above and the number of publications describing the chemical and biological applications of these PCU-amines, we set out to improve on the current synthetic methods to increase the throughput of these drug-like molecules.

The advantages of using microwave dielectric heating for performing organic reactions are well known, for example remarkable reduction of reaction time, improved yields, cleaner reactions and reduction or elimination of hazardous solvents compared to reactions performed under conventional thermal heating.[19–21] This Letter reports a new microwave-assisted synthesis of pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane amines. We used two well known benzylamine derived PCUs (8 and 9)[4,6,7] to develop the microwave-assisted methods (MWAMs) and compare them to methods reported in the literature. These methods could then be used in the development and synthesis of other distinct cage-derived molecules and to improve the throughput thereof. The experiments were performed under pressurized conditions in a closed vessel (unless otherwise specified) using a CEM Discover LabMate (model number 908010) with IntelliVent™ pressure control system and CEM Synergy™ software. The reported microwave conditions were optimized by varying the applied power, temperature and solvents used.

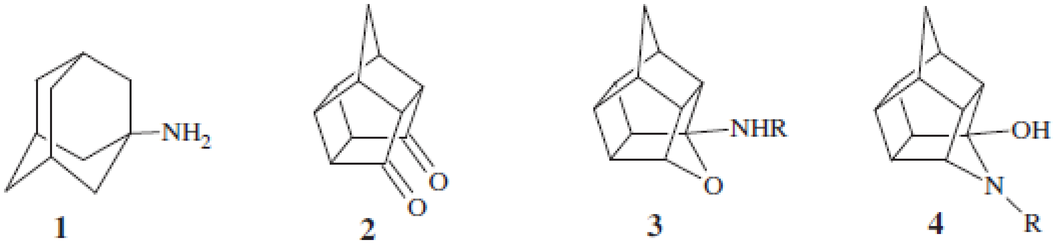
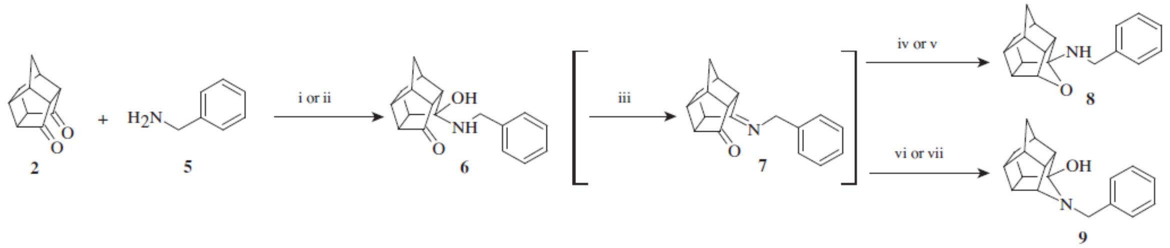


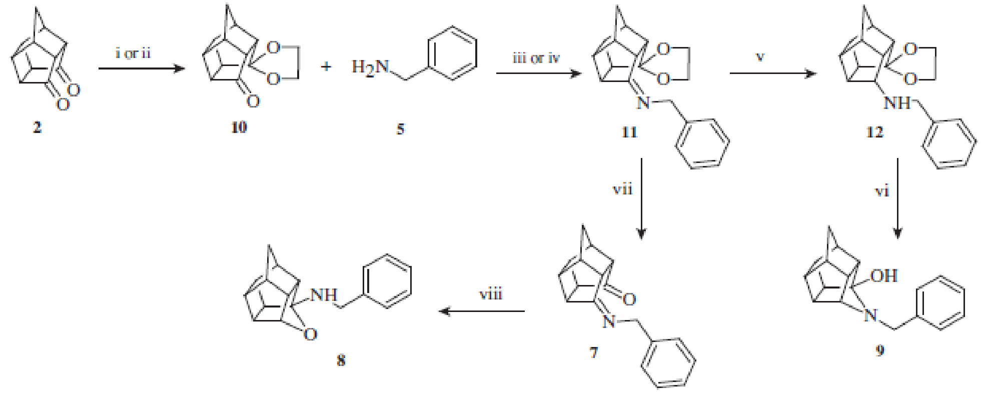
Figure 1. Representative polycyclic-cage moieties.



Scheme 1. Reagents and conditions: for the synthesis of oxa-PCU (**8**) and aza-PCU (**9**): (i) THF, 0 °C, 30 min; (ii) MW, 80 °C, 100 W, 100 psi, 10 min, quantitative yield; (iii) benzene, Dean–Stark reflux, 1 h; (iv) THF/MeOH, $NaBH_4$, rt, 8 h 36%; (v) EtOH, $NaBH_4$, rt, 8 h, 71%; (vi) MeOH/AcOH, $NaCNBH_3$, rt, 2 h, 42%; (vii) EtOH/AcOH, $NaCNBH_3$, rt, 2 h, 69%.

The conventional methods described in the literature[4] for the synthesis of compounds 8 and 9 (Scheme 1; steps i, iii, iv or vi) proceeded via the incorporation of benzylamine through amination, Dean–Stark dehydration and reductive amination using $NaBH_4$ or $NaCNBH_3$ to give the oxa-derivative, 8, and the aza-derivative, 9 in 36% and 42% yields, respectively. Comparing the above process to our newly developed MWAM, the yields of both 8 and 9 were significantly improved to 71% and 69%, respectively, (Scheme 1; steps ii, v or vii). The main differences between the two methods were the aminative combination of 2 and 5 through MW irradiation and the omission of the Dean–Stark dehydration step. Bypassing the latter step avoided the use of the toxic solvent, benzene, contributing to a greener approach. In the MW combination step the reaction time was decreased from 30 to 10 min. Following analysis by thin-layer chromatography (TLC), it was found that in the MWAM, all the reagents were consumed within the specified time, unlike in the traditional method where the reagents were still present after extended reaction times. Increasing the reaction time to a maximum of 8 h did not increase consumption of the reactants in the conventional method; this was true when either EtOH or THF was used as the solvent. The Dean–Stark dehydration step (Scheme 1, step iii) was also found to be unnecessary in the synthesis of both 8 and 9 when anhydrous solvents were used in the conventional methods, and transannular cyclization still proceeded with yields in the same range (37–43%) as specified in the literature.[4] The use of EtOH as the solvent in the MW reactions made it possible to set up this synthesis as a one-pot process, which makes the process more convenient and efficient. Also of interest was the fact that crystallization of amine 8 from the MW reaction proceeded without the need for prior purification through column chromatography, as was the case for 8 prepared via the conventional reaction.

An alternative method for the synthesis of the aza-PCU compound (9), as described by Kassiou et al. in 1996,[15] was also used and optimized through MWAMs (Scheme 2). This required the synthesis of the ketal-derivative 10 of PCU (Scheme 2, step i or ii). The ketal was synthesized by reacting 2 and ethylene glycol under Dean–Stark dehydration conditions using toluene to produce 10. Using the MWAM we achieved a 12-fold reduction in reaction time compared to the conventional reaction, and also increased the yield of 10 from 88% to 95% (Table 1). In the conventional method, ketal 10 is reacted with benzylamine by amination in a sealed tube at 100 °C to yield the ketal-imine PCU (11), which was subsequently reduced using $NaBH_4$ and the final aza-PCU (9) was obtained in 29% yield through transannular cyclization using 3 M HCl/acetone (Scheme 2, Steps iii and v–vi). The requirement for more extreme conditions suggests that the ketal group has an effect, either steric or electronic, on the adjacent carbonyl making nucleophilic attack more difficult. For these reasons we set out to optimize the process at the aminative conjugation step where MW irradiation could be used (Scheme 2, step iv). The reaction conditions were maintained at 100 °C, 150 W and 150 psi for 30 min to produce the imine 11 (TLC analysis indicated completion of the reaction).



Scheme 2. Reagents and conditions: for the synthesis of oxa-PCU (**8**) and aza-PCU (**9**) using alternative methods: (i) ethylene glycol, toluene, Dean–Stark reflux, 6 h, 88%; (ii) ethylene glycol, MW, open vessel, 110 °C, 100 W, toluene, Dean–Stark reflux, 30 min, 95%; (iii) EtOH, 100 °C, sealed tube, 18 h; (iv) EtOH, MW, 100 °C, 150 W, 150 psi, 30 min, quantitative yield; (v) EtOH, $NaBH_4$, rt, 8 h; (vi) acetone, 3 M $HCl_{(aq)}$, 6 h, 29% from conventional synthesis, 58% from MW synthesis; (vii) EtOH, 6% HCl, rt, 6 h; (viii) EtOH, $NaBH_4$, rt, 8 h, 21%.

Table 1
Summary of the reaction conditions and outcomes of the conventional methods compared to the microwave-assisted methods

Product[a]	Organic solvents used	Time (h)	Yield (%)	Method	Purification method(s)[b]	R_f[c]	Mp (°C)
8[4]	THF (10 mL), MeOH (6 mL)	18.5	36	Conventional, dehydration, reductive amination	Column chromatography [hexane:CH_2Cl_2, (1:1)], crystallization from EtOH	0.23	70-71
8[22]	EtOH (5 mL)	8.17	71	MW-assisted, reductive amination	Crystallization from EtOH	0.23	70-71
8[23]	EtOH (5 mL)	14.5	21	Via ketal-PCU (**10**), MW-assisted, hydrolysis, reductive amination	Column chromatography [hexane:CH_2Cl_2, (1:1)], crystallization from EtOH	0.23	70-71
9[4]	THF (10 mL), MeOH (6 mL)	8.5	42	Conventional, dehydration, reductive amination	Crystallization from isopropanol	0.16	158
9[24]	EtOH (5 mL)	2.17	69	MW-assisted, reductive amination	Crystallization from isopropanol	0.16	158
9[15]	EtOH (10 mL), acetone (30 mL)	32	29	Via ketal-PCU (**10**), traditional, reductive amination, transannular cyclization	Crystallization from isopropanol	0.16	158
9[25]	EtOH (5 mL), acetone (25 mL)	14.5	58	Via ketal-PCU (**10**), MW-assisted, reductive amination, transannular cyclization	Crystallization from isopropanol	0.16	158
10[26]	Toluene (15 mL)	6	88	Conventional, thermal heating	Crystallization from hexane	0.55	71
10[27]	Toluene (15 mL)	0.5	95	MW-assisted	Crystallization from hexane	0.55	71

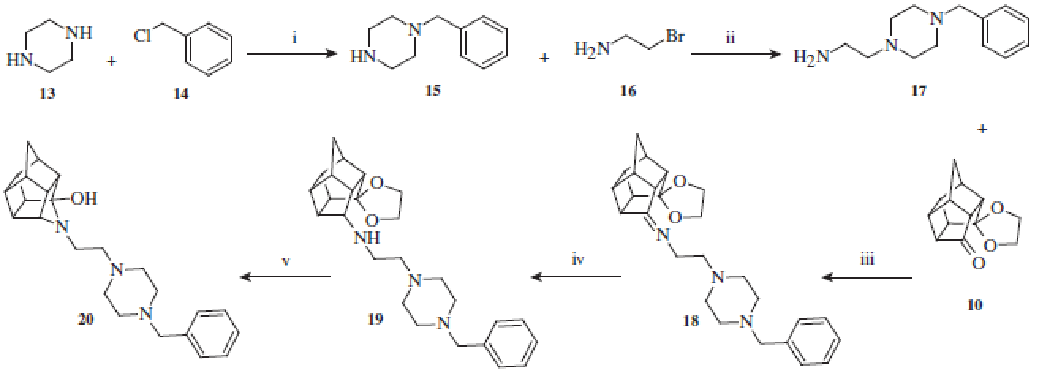
[a] All syntheses were performed using 1 g of the diketone-PCU (**2**) and percentage yield calculations were performed from this point.
[b] Before purification a work up step was performed which involved aqueous extraction of the compound into methylene chloride.
[c] Mobile phases used: compounds **8** and **9** [hexane:CH_2Cl_2, (1:1)]; Compound **10** [EtOAc:hexane (40:60)].

A 36-fold reduction in reaction time was achieved for this step and following the same procedure as described above (Scheme 2, steps v–vi), we were able to synthesize azaCU 9 in 58% yield, which represents a doubling of the yield compared to the conventional method (Table 1).

We further developed an alternative synthetic route for the synthesis of oxa-PCUs (Scheme 2, steps vii–viii). Compound 8 was synthesized by reacting 5 with 10 using the MWAM as described for 9 to produce the imine-ketal PCU (11). This imine-ketal PCU was hydrolysed using a 6% $HCl_{(aq)}$ solution to yield 7. Further reduction using $NaBH_4$ yielded the oxa-PCU (8) in 21% yield. Although the yield was poor, this new method represents a valuable addition to the array of synthetic routes available to synthesize oxa-PCUs and might be of specific value for regiospecific synthesis, and where highly reactive reagents are used and reaction at both ketone moieties of the diketone-PCU (2) is unavoidable. With protection of one carbonyl group by means of a ketal-moiety it should be possible to produce a mono-substituted oxa-PCU compound.

It should also be noted that the MWAMs required smaller volumes or completely omitted the use of toxic solvents compared to the conventional methods, thus contributing to green chemistry. The compounds produced through the MWAMs were of a higher purity compared to the conventional methods, therefore the purification procedures required less solvents and consumables. Ethanol was also used in the majority of the reaction steps in the MWAMs, which is less toxic and less hazardous than the solvents used in the conventional methods.

The newly developed MWAMs were further used to demonstrate the relevance and advantages thereof to synthesize a novel PCU amine (compound 20, Scheme 3).[28] The synthesis commenced from a series of microwave-assisted S_N2 reactions to produce the intermediate 2-(4-benzylpiperazin-1-yl)ethanamine (17) in 92% yield. Compound 17 was reacted with the ketal-PCU (10) through the same MWAM developed for compound 11. The reaction conditions were maintained at 100 °C, 150 W and 150 psi for 30 min to produce the imine (18) on completion of the reaction (as per TLC analysis). The subsequent reaction steps were the same as for compound 9 and yielded the final compound, *N*-[2-(4-benzylpiperazin-1-yl)ethyl]-4-azahexacyclo [5.4.1.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}]dodecan-3-ol (20) in 53% yield. The yield, as is the case for all the synthetic routes described, was calculated from the amount of diketonePCU (2) used. The reaction time required for the whole sequence using the MWAM was 14.5 h. The synthetic sequence described for compound 20 was also performed using the conventional method of thermal heating. Compound 20 was successfully synthesized using this approach, but the sequence required more than 100 h for completion and yielded only 10% of the final compound.



Scheme 3. Microwave-assisted synthesis of a novel PCU amine-derived sigma-1 receptor antagonist **20** utilizing the newly developed MWAM. Reagents and conditions: (i) CH_3CN, 100 °C, 150 W, 100 psi, 5 min, 94%; (ii) CH_3CN, 100 °C, 150 W, 100 psi, 10 min, 92% yield from **14**; (iii) EtOH, 100 °C, 150 W, 150 psi, 30 min, quantitative yield; (iv) EtOH, $NaBH_4$, rt, 8 h; (v) acetone, 3 M $HCl_{(aq)}$, 6 h, 53%.

A sevenfold reduction in reaction time was thus achieved using the MWAM and the yield was improved significantly. Novel compound 20 was shown to be a potent sigma-1 receptor inhibitor (IC_{50} = 0.139 lM, K_i = 67.26 nM), and preliminary studies have indicated that it has some degree of *N*-methyl-D-aspartate receptor and voltage-dependent calcium channel inhibitory activity. Compound 20 may thus find application as a potential neuro-active drug by modulating certain neuroprotective targets for a number of neurological disorders. This one example serves as an illustration of how MWAM can be used to reduce reaction times, improve yields and increase the throughput of PCU-derivatives, which might serve as potential drugs.

These new MWAMs can be utilized to optimize the reaction conditions and improve on the synthesis of PCU derived molecules with high efficiency and throughput. In addition, the microwave process, when compared with the conventional methods, has several advantages, viz: reduction of the reaction time, less by-product formation and easier purification. Based on the above and on the number of research groups currently studying the chemistry and biology of polycyclic cage moieties, these MWAMs should contribute to the synthetic approaches towards cage-derived organic compounds and should aid in the design and discovery of new PCU derivatives.

References and notes

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22. *Synthesis of* 8*:* Pentacyclo[5.4.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione (2, 1 g, 4.59 mmol) and benzylamine (5, 0.49 g, 4.59 mmol) were dissolved in EtOH (5 mL) and transferred to a sealed microwave vessel (10 mL capacity). The mixture was placed in a CEM Discover Labmate microwave reactor and irradiated for 10 min at 100 W, 80 °C and 100 psi. The mixture was removed from the microwave reactor and $NaBH_4$ (0.4 g, 10.56 mmol) was added portionwise in excess. This mixture was stirred at room temperature for 8 h,

after which the solvents were removed in vacuo, the residue suspended in H_2O (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were washed with H_2O (2 x 20 mL), dried ($MgSO_4$) and evaporated in vacuo to yield a light-yellow oil. Crystallization from EtOH rendered the final product 8 as a colourless microcrystalline solid (yield: 0.852 g, 3.21 mmol, 71%, mp: 70–71 °C). The physical characteristics of this compound were exactly the same as those described in the literature.[4,7]

23. *Synthesis of* 8 *via the ketal derivative* 10 *of PCU:* A mixture of 10 (1.0 g, 4.59 mmol) and benzylamine (5, 0.49 g, 4.59 mmol) in EtOH (5 mL) was transferred to a sealed microwave vessel (10 mL capacity). The mixture was placed in a CEM Discover Labmate microwave reactor and irradiated for 30 min at 150 W, 100 °C, and 100 psi. The solution was cooled and 6% $HCl_{(aq)}$ solution (20 mL) was added gradually and the mixture stirred at room temperature for 3.5 h. The solvents were removed in vacuo, the residue produced was suspended in H_2O (20 mL), made basic with 1 M NaOH solution and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were dried ($MgSO_4$) and evaporated in vacuo to yield a light-yellow oil. The oil was dissolved in EtOH (10 mL) and $NaBH_4$ (0.4 g, 10.56 mmol) was added portionwise in excess. This mixture was stirred at room temperature for 8 h after which the solvents were removed in vacuo. The residue was suspended in H_2O (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were washed with H_2O (2 x 20 mL), dried ($MgSO_4$) and evaporated in vacuo to yield a light-yellow oil. Purification was carried out using flash column chromatography with the solvent system; hexane: CH_2Cl_2 (1:1) to obtain the product as a white solid. Crystallization from EtOH rendered the final product 8 as a colourless microcrystalline solid (yield: 0.255 g, 0.96 mmol, 21%, mp: 70–71 °C). The physical characteristics of this compound were exactly the same as those described in the literature.[4,7]

24. *Synthesis of* 9*:* Pentacyclo[$5.4.0^{2,6}.0^{3,10}.0^{5,9}$]undecane-8,11-dione (2, 1 g, mmol) and benzylamine (5, 0.49 g, 4.59 mmol) were dissolved in EtOH (5 mL) and transferred to a sealed microwave vessel (10 mL capacity). The mixture was placed in a CEM Discover Labmate microwave reactor and irradiated for 10 min at 100 W, 80 °C, and 100 psi. The mixture was removed from the microwave reactor and EtOH (20 mL), AcOH (1.5 mL) and $NaBH_3CN$ (0.66 g, 10.56 mmol) were added. This mixture was stirred at room temperature for 2 h after which it was concentrated in vacuo, and H_2O (20 mL) was added to the residue. The resulting suspension was stirred, and solid sodium bicarbonate was added portionwise until evolution of carbon dioxide ceased. Excess solid sodium bicarbonate (0.4 g) was added and the aqueous suspension was extracted with CH_2Cl_2 (4 x 20 mL). The combined extracts were washed with H_2O (2 x 100 mL), dried over $MgSO_4$, filtered, and

concentrated in vacuo. A yellow microcrystalline solid was thereby obtained. This material was recrystallized from isopropanol to afford compound 9 (yield: 0.838 g, 3.16 mmol, 69%, mp: 158 °C) as a colourless microcrystalline solid. The physical characteristics of this compound were exactly the same as those described in the literature.[4,7]

25. *Synthesis of* 9 *via the ketal derivative* 10 *of PCU:* A mixture of 10 (1.0 g, 4.59 mmol) and benzylamine (0.49 g, 4.59 mmol) in EtOH (5 mL) was transferred to a sealed microwave vessel (10 mL capacity). The mixture was placed in a CEM Discover Labmate microwave reactor and irradiated for 30 min at 150 W, 100 °C, and 150 psi. The solution was cooled, $NaBH_4$ (0.35 g, 9.17 mmol) was added gradually and the mixture was stirred at room temperature for 8 h. The solution was concentrated in vacuo, H_2O (20 mL) was added and the solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and concentrated in vacuo. To the crude residue was added acetone (25 mL) and aqueous 4 M HCl (15 mL) with stirring at room temperature for 12 h. H_2O was added (250 mL) and the solution was basified to pH 14 with aqueous 1 M NaOH and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extract was dried over $MgSO_4$ and concentrated to give the crude residue, which was recrystallized from isopropanol to yield the desired product 9 (yield: 0.708 g, 2.67 mmol, 58%, mp: 71 °C). The physical characteristics of this compound were exactly the same as those described in the literature.[4,7]
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27. *Synthesis of* 10*:* Pentacyclo[5.4.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione (1 g, 4.59 mmol), ethylene glycol (0.45 mL) and *p*-TsOH (0.04 g, 1.9 mmol) were dissolved in toluene (15 mL) and placed in a CEM Discover Labmate microwave reactor set to the open vessel function and refluxed using a Dean–Stark apparatus for 30 min at 100 W and 110 °C. The reaction was allowed to cool followed by addition of an aqueous solution of 10% (m/v) Na_2CO_3 (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The organic layer was dried using anhydrous Na_2SO_4, filtered and the solvent evaporated in vacuo. The crude residue was purified via recrystallization from hexane to afford 10 as a white microcrystalline solid (yield: 0.951 g, 4.36 mmol, 95%, mp: 71 °C). The physical characteristics of this compound were exactly the same as those described in the literature.[26]
28. *Synthesis of* 20*: Step 1*: Benzyl chloride (1 g, 7.96 mmol) was added to a stirred suspension of piperazine (3.42 g, 39.8 mmol) and K_2CO_3 (1.32 g, 9.56 mmol) in CH_3CN (3 mL). The mixture was transferred to a sealed microwave vessel (10 mL capacity) and placed in a CEM Discover Labmate microwave reactor and allowed to react for 5 min at 150 W, 100 °C and 100 psi. The CH_3CN was removed in vacuo and CH_2Cl_2 (20 mL) was added.

The crude product was washed with H_2O (5 x 20 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated in vacuo to yield the desired compound, 2-(piperazin-1-yl)ethanamine (15), as a viscous yellow oil (1.319 g, 7.48 mmol, 94%). The physical characteristics of compound 15 were exactly the same as those described in the literature. [29] *Step 2*: 2-bromoethanamine (0.192 g, 1.55 mmol) was added to a suspension of 15 (1.30 g, 7.38 mmol) and K_2CO_3 (0.257 g, 1.86 mmol) in CH_3CN (5 mL). The reaction was placed in the microwave reactor and allowed to react for 10 min at 150 W, 100 °C and 100 psi. The mixture was concentrated in vacuo, added to $CHCl_3$ (20 mL) and washed with H_2O (3 x 25 mL). The organic solution was dried over $MgSO_4$, filtered and evaporated in vacuo to afford the desired product, 2-(4-benzylpiperazin-1-yl)ethanamine (17), as a clear oil with low viscosity (0.312 g, 1.55 mmol, 92%). Physical data: ^{1}H NMR (200 MHz, $CDCl_3$): d$_H$:15,16), 3.72 (s, 2H, H-10), 2.78 (t, J = 6.7 Hz, 2H, H-7), 2.48 (s, 4H, H-3, 5), 1.86 (t, J = 6.7 Hz, 2H, H-8), 1.24 (s, 4H, H-2, 6). *Step 3*: pentacyclo [5.4.0.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}]undecane-8,11-dione ethylene acetal (10, 200 mg, 0.917 mmol) and 2-(4-benzylpiperazin-1-yl)ethanamine (17, 200 mg, 0.913 mmol) were reacted under microwave conditions. The reactants were dissolved in EtOH (5 mL) at a maximum temperature of 100 °C, power setting of 150 W and pressure of 150 psi for 30 min. The mixture was allowed to cool and used directly in the next step. The cooled solution of *N*-[2-(4-benzylpiperazin-1-yl)ethyl]-4-pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-11-ethylene acetal (18) was dissolved in EtOH (5 mL) and $NaBH_4$ (159 mg, 4.20 mmol) was added. The mixture was stirred at room temperature for 8 h after which the EtOH was evaporated under reduced pressure. H_2O (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with brine (10 mL) and concentrated in vacuo. To this crude material, acetone (25 mL) and 4 M aq HCl (15 mL) were added. After stirring at room temperature for 6 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 x 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by recrystallization from EtOH to yield the desired compound 20 as colourless crystals (Yield: 0.183 mg, 0.485 mmol, 53%). Physical data: ^{1}H NMR (200 MHz, $CDCl_3$) d$_H$: 7.26–7.16 (m, 5H, H-23, 24, 25, 26, 27), 3.43 (s, 2H, H-21), 3.43 (t, J = 4.7 Hz, 2H, H-13), 2.96–2.30 (m, 19H, H-1, 2, 3, 4, 5, 6, 7,8, 9, 10, 11, 14, 16, 17, 19, 20), 1.76:1.44 (AB-q, J_{AB} = 10.4 Hz, 2H, H-4a, 4b). ^{13}C NMR (50 MHz, $CDCl_3$) d$_C$: 137.98, 129.12, 128.21, 127.05, 70.79, 62.75, 58.66, 56.90, 52.75, 53.42, 51.53, 46.62, 45.68, 45.40, 43.32, 43.25, 42.15, 41.88, 41.69. IR (t$_{max}$): 3243, 2950, 2813, 1320, 1284 cm^{-1}. HR-MS (ESI, 15 eV): 378.2546 (M+H^{+}).

29. Stein, S.E., ‘‘Gas-phase infrared database’’ in NIST Chemistry WebBook, NIST standard reference Database number 69, Eds. Linstrom, P.J.; Mallard, W.G. and Technology, Gaithersburg MD, 20899, http://webbook.nist.gov, (retrieved January 31, 2013).