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A facile three-component [3+2]-cycloaddition/annulation domino protocol for the regio- and diastereoselective synthesis of novel penta- and hexacyclic cage systems, involving the generation of two heterocyclic rings and five contiguous stereocenters

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ABSTRACT

An expedient, three-component, [3+2]-cycloaddition/annulation domino protocol for the synthesis of a series of cage penta- and hexacyclic compounds in good to excellent yields is described. The ring systems thus generated contain as structural elements bridged, fused and spiro rings and were obtained with complete selectivity through the creation of two C–C and two C–N bonds, which led to the generation of two azaheterocyclic rings, four carbon and one nitrogen adjacent stereocentres, three of which are quaternary.

1. Introduction

Cage compounds, whose defining structural feature is the presence of a closed cavity, often behave as artificial receptors and are one of the key structures in the development of supramolecular chemistry. Because of these properties, the development of bioactive cage compounds is of considerable current interest.[1] Their preparation has traditionally required multi-step sequences, and for this reason there is a great interest in the development of simple, efficient, step-economic routes to cage frameworks. We describe in this paper a reaction illustrating the use of a three-component domino protocol to build structurally complex heterocyclic cage compounds in a single synthetic operation and with complete regio- and stereocontrol.

Multicomponent reactions (MCRs)[2] constitute an efficient and powerful tool for the construction of novel organic structures due to their valuable features of convergence, economy,[3] and eco-friendliness arising from minimization of waste, time, energy and cost. Because they provide expeditious and elegant access to libraries of molecules of high levels of complexity and diversity, they play a key role in combinatorial[4] and diversity-oriented synthesis.[5] In particular, three-component reactions involving [3+2]-cycloaddition of azomethine ylides to olefinic dipolarophiles[6,7] constitute a facile approach to the construction of five-membered heterocyclic rings of biological importance. Among them, pyrrolidines are particularly important because of their occurrence in a large number of natural products[8] and the remarkable biological properties of many of them.[9] Regarding the dipolarophile components, we initially chose piperidine-based frameworks, again because of the biological importance of heterocycles with piperidine substructures[10] and also because of their role as useful synthons for the construction of naturally occurring alkaloids.[11] In this context, we have recently explored the reaction between 1-substituted α,α′-bis(arylmethylidene)-cyclic ketones and azomethine ylides derived from cyclic ketones and α-amino acids[12] together with the antitubercular activity of the resulting products,[13] and report here its adaptation to the creation of cage structures via a one-pot, three-component protocol. As shown in Fig. 1, our strategy involves the combination

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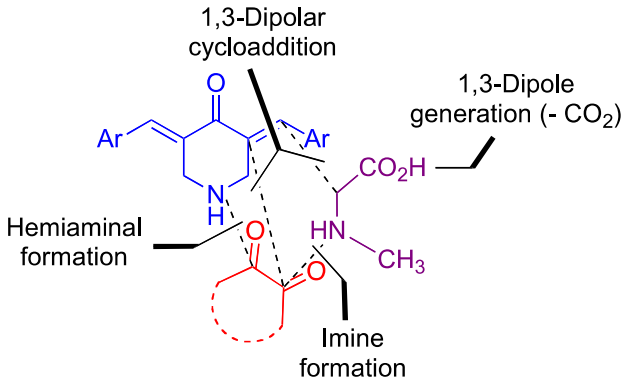
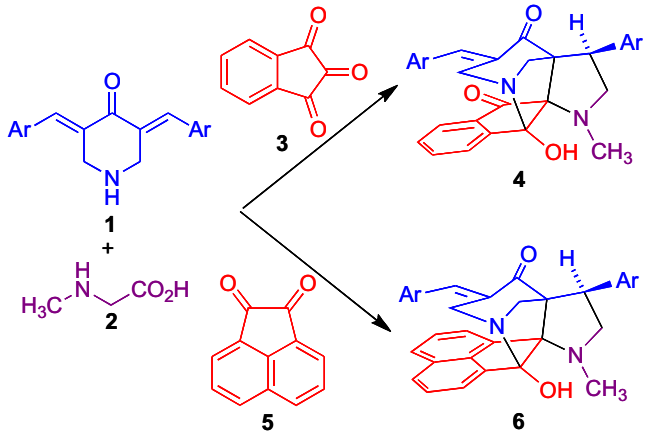


Fig. 1. Our strategy for the synthesis of heterocyclic cage compounds.

of a dipole generation-1,3-cycloaddition sequence with the generation of a hemiaminal bond in order to allow the creation of the bond that closes the cage. To this end, the starting α,α′-bis(arylmethylidene) ketone must have an unsubstituted nitrogen atom and the ketone involved in the generation of the dipole must contain a 1,2-dicarbonyl moiety.

2. Results and discussion

The three-component [3+2]-cycloaddition between the *N*-unsubstituted 3,5-bis[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones **1**,[14] sarcosine (**2**) and ninhydrin afforded derivatives of the hitherto unreported pentacyclic diazapentacyclo[12.3.1.$0^{2,10}$.$0^{3,8}$.$0^{10,14}$]octadeca-3(8),4,6-triene-9,15-dione system (compounds **4**), while similar reactions employing acenaphthoquinone **5** as the α-dicarbonyl component gave diazahexacyclo[10.7.1.1^{3,7}.$0^{2,11}$.$0^{7,11}$.$0^{16,20}$]henicosa-1(20),12,14,16,18-pentaen-6-ones **6**, both in good to excellent yields and isolated as the sole reaction products (Scheme 1). The reactions were initially performed by heating an equimolar mixture of the starting materials under reflux in methanol and were subsequently investigated also under microwave irradiation in a focused microwave synthesizer, as this technique has evolved as a valuable alternative to conventional heating for the introduction of energy into reactions and has clear benefits in many chemical transformations,[15] including cycloadditions,[16] in terms of rate accelerations and yield enhancements. As in the case of the thermal reactions, an equimolar mixture of the starting materials **1**–**3** or **1**, **2**, **5** in methanol was subjected to microwave irradiation for 6–8 min until completion of the reaction (TLC) and the products (**4** or **6**, respectively) were purified by crystallization. The results obtained for both methods are summarized in Table 1, and clearly show that microwave irradiation led to an enhancement in the yield of the product (81–96%) over the conventional thermal method (72–88%), although in the case **6f** both the conventional and the microwave-assisted reactions gave complex mixtures from which no identifiable compound could be isolated. This can be attributed to the presence of an *o*-methoxyphenol unit, which would render the compound very sensitive to air oxidation. As shown in Table 1, the domino reaction works well regardless of the position and electronic or steric properties of the substituents at the aromatic rings of compounds **1**.

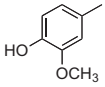
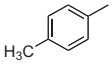
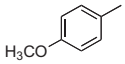
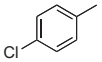
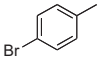


Scheme 1. Three-component synthesis of heterocyclic cage compounds **4** and **6**.

The structures of products **4** and **6** were elucidated using elemental analysis, IR, ^{1}H, ^{13}C and 2D NMR spectroscopic data, as illustrated below for **4a**. The ^{1}H NMR spectrum of **4a** has a singlet at 2.26 ppm for the N–CH_3 hydrogens of the pyrrolidine ring, which show HMBC with a methylenic carbon, ascribable to 12-CH_2 (Fig. 2). From the C,H-COSY correlation of 12-CH_2, the triplet at 3.81 ppm (J=10.4 Hz) and the multiplet at 3.93–3.98 ppm were assigned to the 12-CH_2 hydrogens. The multiplicity of H-13 and its H,H-COSY correlation with 12-CH_2 hydrogens enabled the assignment of the former to the doublet of doublets at 4.86 ppm (J=10.0 and 5.2 Hz). The assignment of the doublet at 2.70 ppm (J=12.8 Hz) and the multiplet at 3.93–3.98 ppm to 18-CH_2 and that of the doublet at 3.43 ppm (J=16.4 Hz) and a doublet of doublets at 3.74 ppm (J=16.8, 2.4 Hz) to 17-CH_2 were done similarly on straightforward considerations. The arylmethylidene hydrogen, H-19 appears as a singlet at 7.11 ppm and the aromatic hydrogens appeared as doublets and multiplets at 6.78–7.68 ppm. The C=O of ninhydrin occurred at 201.5 ppm. These signal assignments are consistent with the HMBCs and H,H-COSY correlations depicted in Fig. 1. The fact that the H-13 benzylic hydrogen appears as a doublet of doublets at 4.86 ppm (J=10.0 and 5.6 Hz) clearly establishes the regiochemistry of the cycloaddition, as for the other possible regioisomer **9** that might have arisen from the cycloaddition, it should give a singlet. These findings were confirmed by X-ray crystallographic studies of **4a**, **4e**, **6a** and **6c** (Fig. 3 and Supplementary data),[17] which also reveal a retention of the stereochemistry of the benzylidene function of the dipolarophile **1** in the newly generated pyrrolidine ring during the cycloaddition reaction.

A mechanism proposed to rationalize the formation of the novel cage heterocycles is summarized in Scheme 2 for the case of the diazapentacycle **4**. The reaction of ninhydrin and sarcosine affords the azomethine ylide **7**, which adds to one of the C=C bonds of the bisdipolarophile **1** to form the corresponding cycloadduct **8**. The final annulation involves the reaction of the amino function with the neighbouring carbonyl group, resulting in the formation of a hemiaminal, that is, presumably stabilized by intramolecular hydrogen bonding. The remarkable product selectivity observed in this reaction depends on two factors, the first of which is the complete selectivity of the starting α-dicarbonyl compound towards sarcosine rather than the potentially competitive piperidine system, which is probably due to steric reasons. The second is the complete regioselectivity of the 1,3-dipolar cycloaddition, which can be viewed as the result of a preferential attack of the nucleophilic carbon of the azomethine ylide to the end of the enone fragment of the starting material **1** to give **8** instead of the alternative cycloaddition product **9**. While this is the expected regiochemical outcome of the reaction,[7d,18] the complete selectivity is somewhat unusual and can be explained by steric factors and also by the fact that, during the cycloaddition, a secondary orbital interaction between the nitrogen lone pair with the carbonyl function occurs, lowering the energy of activation for the cycloaddition and increasing the regioselectivity in favour of **8**. In a similar fashion, the reaction of the azomethine ylide generated in situ from the reaction of acenapthenequinone and sarcosine with compounds **2** also took place with complete regio- and product selectivity

Table 1
Comparison of the reaction times and yields for the thermal and microwave-assisted three-component domino reactions

Entry	Compound	Ar	Conventional conditions (MeOH, reflux, 60 min)		Microwave conditions (100 °C, 100 W)			
			4	**6**	**4**		**6**	
			Yield, %	Yield, %	Time, min	Yield, %	Time, min	Yield, %
1	**a**		86	88	6	94	5	96
2	**b**		85	86	5	92	5	94
3	**c**		82	81	5	93	6	92
4	**d**		83	82	5	90	6	90
5	**e**		80	84	7	92	8	93
6	**f**		72	0	8	81	—	0
7	**g**		86	85	5	95	6	94
8	**h**		80	83	6	92	8	90
9	**i**		87	86	6	96	5	91
10	**j**		84	82	5	95	6	90
11	**k**		85	87	5	94	6	92

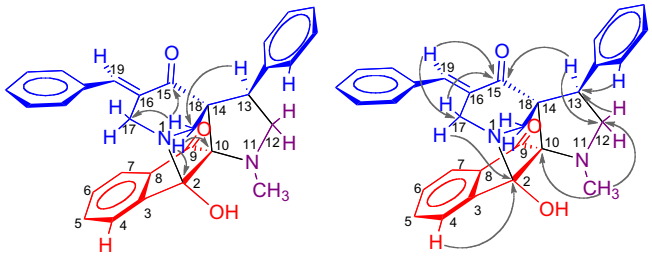


Fig. 2. HMBC correlations in compound **4a** (arbitrary numbering).

affording the hexacyclic ring system **6**. It is also pertinent to note that all the above reactions proceed with complete stereoselectivity, affording exclusively one stereoisomer despite of the presence of five stereocenters (this includes the tertiary nitrogen atom, which is stereogenic because it cannot undergo inversion).

3. Conclusions

In conclusion, we describe an expedient, three-component regio-, stereo- and product-selective domino protocol for the synthesis of novel cage diazapenta- and hexacyclic ring systems through a 1,3-dipole generation–cycloaddition–annulation sequence. The overall process involves the generation of two C–C and two C–N bonds and the creation of two new five-membered rings and five contiguous stereocentres, three of which are quaternary. Further studies on the synthetic applications of this methodology are currently in progress in our laboratories.

4. Experimental section

4.1. General

Melting points were taken using open capillary tubes and are uncorrected. A CEM microwave synthesizer (Model: Discover-S 908860) operating at 180/240 V and 50/60 Hz with consumption of 1100 W with microwave power maximum level of 300 W and microwave frequency of 2455 MHz was employed for the irradiation done in this work. ^{1}H, ^{13}C and two-dimensional NMR spectra were recorded on a Bruker 400 and 300 MHz instruments in $CDCl_3$ using TMS as internal standard. Standard Bruker software was used throughout. Chemical shifts are given in parts per million (δ-scale) and the coupling constants are given in Hertz. IR spectra were

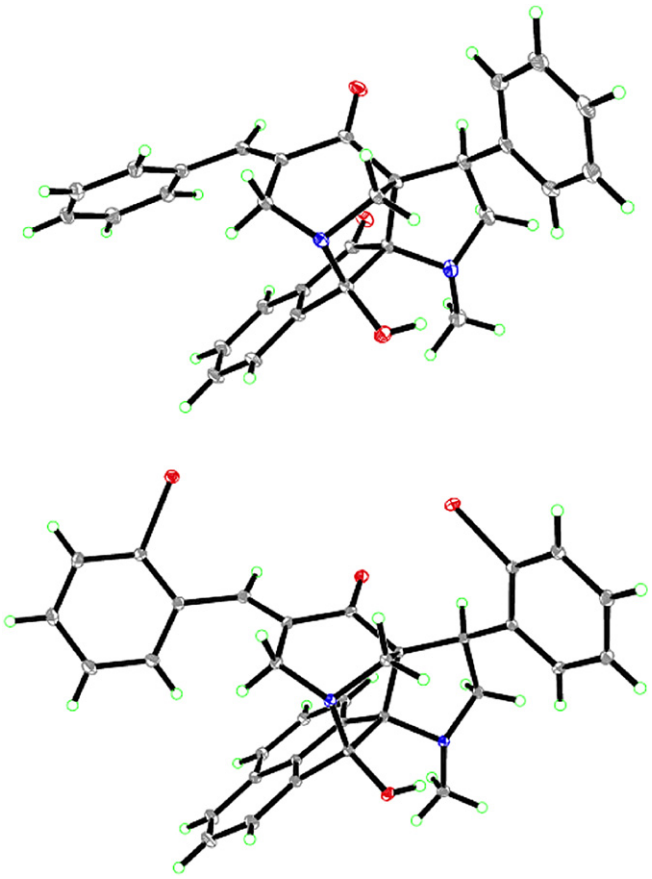
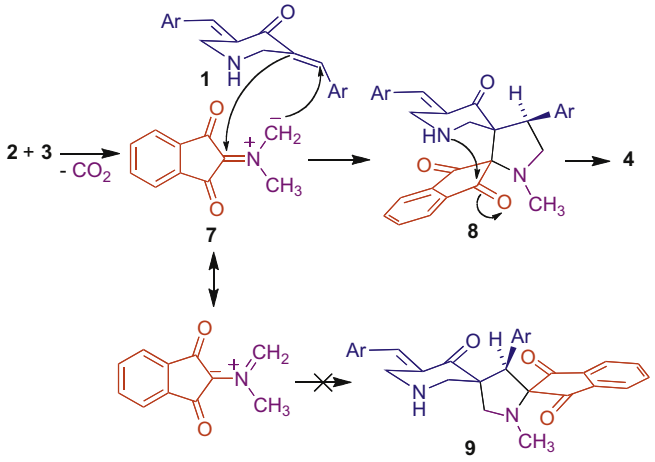


Fig. 3. ORTEP plost for compounds **4a** (top) and **6c** (bottom).



Scheme 2. A mechanistic proposal to explain the formation of compounds **4** through a domino sequence.

recorded on a Perkin–Elmer system 2000 FT IR instrument (KBr). Single crystal X-ray data set for **4a**, **4e**, **6a** and **6c** was collected on Bruker APEXII DUO CCD area detector diffractometer with Mo Kα (λ=0.71073 Å) radiation. Scan range was $2.8°\leq\theta\leq35.8°$ (**4a**), $2.3°\leq\theta\leq32.6°$ (**4e**), $2.6°\leq\theta\leq29.9°$ (**6a**), $3.3°\leq\theta\leq35.1°$ (**6c**). Elemental analyses were performed on a Perkin Elmer 2400 Series II Elemental CHNS analyser. Column chromatography was performed on silica gel (230–400 mesh) using petroleum ether–ethyl acetate as eluent.

4.2. Synthesis of compounds 4 and 6. General procedures

Conventional heating method. A mixture of 3,5-bis[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinone (**1**, 0.364 mmol), sarcosine (**2**, 0.364 mmol) and ninhydrin/acenaphthenequinone (**3**/**5**, 0.364 mmol) was dissolved in methanol (5 mL) and heated under reflux for 1 h. After completion of the reaction as evident from TLC, the mixture was poured into water (50 mL). The precipitated solid was filtered and washed with water to give the products **4** or **6**, which were purified by recrystallisation from ethyl acetate.

Microwave irradiation method. A mixture of 3,5-bis[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones (**1**, 0.364 mmol), sarcosine (**2**, 0.364 mmol) and ninhydrin/acenaphthenequinone (**3**/**5**, 0.364 mmol) was dissolved in methanol (1 mL) and irradiated for 6–8 min in a CEM microwave synthesizer (100 °C, 100 W). After completion of the reaction as evident from TLC, the mixture was poured into water. The precipitated solid was filtered and washed with water to afford the products **4** or **6**, which were purified by recrystallisation from ethyl acetate.

*4.2.1. 2-Hydroxy-11-methyl-13-phenyl-16-[(E)-phenyl-methylidene]-1,11-diazapentacyclo[12.3.1.0^{2,10}.0^{3,8}.0^{10,14}]octadeca-3(8),4,6-triene-9,15-dione (**4a**).* Pale yellow crystals; (0.158 g, 94%); mp 159–160 °C; IR (KBr) ν_{max} 3333, 1708, 1680, 1601 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.26 (s, 3H, N–CH_3), 2.70 (d, *J*=12.8 Hz, 1H, H-18$_{ax}$), 3.43 (d, *J*=16.8 Hz, 1H, H-17$_{ax}$), 3.74 (dd, *J*=16.8, 2.4 Hz, 1H, H-17$_{eq}$), 3.81 (t, *J*=10.4 Hz, 1H, H-12), 3.93–3.98 (m, 2H, H-12 and H-18$_{eq}$), 4.86 (dd, *J*=10.0, 5.2 Hz, 1H, H-13), 6.79 (d, *J*=6.4 Hz, 2H, aromatic), 7.11 (s, 1H, H-19), 7.14–7.34 (m, 7H, aromatic), 7.40–7.45 (m, 3H, aromatic), 7.52 (d, *J*=7.6 Hz, 1H, aromatic), 7.67 (d, *J*=7.6 Hz, 1H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 38.2, 41.2, 53.5, 59.7, 64.1, 75.0, 91.8, 97.2, 123.2, 125.6, 127.3, 128.4, 128.5, 128.9, 129.4, 130.1, 130.6, 133.9, 134.6, 135.9, 136.4, 138.2, 139.7, 149.3, 195.9, 201.5. Anal. Calcd for $C_{30}H_{26}N_2O_3$: C, 77.90; H, 5.67; N, 6.06. Found: C, 78.07; H, 5.33; N, 6.07.

*4.2.2. 13-(2-Chlorophenyl)-16-[(E)-(2-chlorophenyl)-methylidene]-2-hydroxy-11-methyl-1,11-diaza-pentacyclo[12.3.1.0^{2,10}.0^{3,8}.0^{10,14}]octadeca-3(8),4,6-triene-9,15-dione (**4b**).* Pale yellow crystals; (0.142 g, 92%); mp 112–113 °C; IR (KBr) ν_{max} 3389, 1706, 1678, 1601 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.22 (s, 3H, N–CH_3), 2.80 (d, *J*=12.8 Hz, 1H, H-18$_{ax}$), 3.10 (d, *J*=17.6 Hz, 1H, H-17$_{ax}$), 3.63–3.75 (m, 3H, H-17$_{eq}$, H-18$_{eq}$, H-12), 4.06–4.13 (m, 1H, H-12), 5.01–5.03 (m, 1H, H-13), 6.48 (d, *J*=7.6 Hz, 1H, aromatic), 6.97–7.01 (m, 1H, aromatic), 7.10–7.38 (m, 6H, aromatic), 7.44 (s, 1H, H-19), 7.47–7.51 (m, 1H, aromatic), 7.62–7.71 (m, 3H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 36.9, 37.2, 53.0, 59.4, 65.9, 74.0, 90.8, 96.9, 124.0, 125.2, 126.4, 127.5, 128.6, 129.0, 129.9, 130.0, 130.3, 130.4, 130.6, 132.7, 134.6, 134.7, 135.1, 136.1, 136.2, 139.2, 148.8, 193.7, 201.7. Anal. Calcd for $C_{30}H_{24}Cl_2N_2O_3$: C, 67.80; H, 4.55; N, 5.27. Found: C, 67.98; H, 4.27; N, 5.19.

*4.2.3. 13-(2-Bromophenyl)-16-[(E)-(2-bromophenyl)-methylidene]-2-hydroxy-11-methyl-1,11-diaza-pentacyclo[12.3.1.0^{2,10}.0^{3,8}.0^{10,14}]octadeca-3(8),4,6-triene-9,15-dione (**4c**).* Pale yellow crystals; (0.134 g, 93%); mp 141–142 °C; IR (KBr) ν_{max} 3380, 1712, 1603 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.21 (s, 3H, N–CH_3), 2.81 (d, *J*=12.8 Hz, 1H, H-18$_{ax}$), 3.08 (dt, *J*=17.6, 1.6 Hz, 1H, H-17$_{ax}$), 3.63–3.68 (m, 2H, H-12 and H-18$_{eq}$), 3.74 (dd, *J*=17.6, 3.2 Hz, 1H, H-17$_{eq}$), 4.07–4.12 (m, 1H, H-12), 4.97 (dd, *J*=8.4, 1.6 Hz, 1H, H-13), 6.45–6.47 (m, 1H, aromatic), 7.04–7.15 (m, 3H, H-19 and aromatic), 7.28–7.57 (m, 7H, aromatic), 7.63–7.75 (m, 2H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 37.1, 39.5, 53.0, 59.4, 66.5, 74.1, 90.9, 97.0, 124.2, 125.1, 125.2, 125.3, 127.0, 128.1, 128.9, 129.2, 130.0, 130.5, 130.6, 133.2, 133.8, 134.3, 134.4, 136.1, 136.2, 138.3, 141.2, 148.9, 193.5, 201.6. Anal. Calcd

for $C_{30}H_{24}Br_2N_2O_3$: C, 58.09; H, 3.90; N, 4.52. Found: C, 57.82; H, 3.65; N, 4.34.

*4.2.4. 13-(2-Fluorophenyl)-16-[(E)-(2-fluorophenyl)-methylidene]-2-hydroxy-11-methyl-1,11-diazapentacyclo[12.3.1.0^{2,10}.0^{3,8}.0^{10,14}]octadeca-3(8),4,6-triene-9,15-dione (**4d**).* Pale Yellow solid; (0.144 g, 90%); mp 131–132 °C; IR (KBr) ν_{max} 3384, 1718, 1676, 1600 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.23 (s, 3H, N–CH_3), 2.84 (d, J=12.6 Hz, 1H, H-18$_{ax}$), 3.19 (d, J=17.6 Hz, 1H, H-17$_{ax}$), 3.63–3.68 (m, 2H, H-12 and H-17$_{eq}$), 3.86–3.89 (m, 1H, H-12), 3.96 (dd, J=12.6 Hz, 1H, H-18$_{eq}$), 4.95 (dd, J=8.8, 4.8 Hz, 1H, H-13), 6.56–6.59 (m, 1H, aromatic), 6.86–6.92 (m, 2H, aromatic), 7.00–7.05 (m, 2H, aromatic), 7.09–7.18 (m, 3H, H-19 and aromatic), 7.23–7.27 (m, 2H, aromatic), 7.40–7.44 (m, 1H, aromatic), 7.58–7.64 (m, 2H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 35.6, 37.8, 53.4 (J_{CF}=4.0 Hz), 59.7, 63.6, 74.8, 91.2, 97.1, 115.8 ($^2J_{CF}$=21.7 Hz), 116.3 ($^2J_{CF}$=22.3 Hz), 122.3 ($^2J_{CF}$=13.9 Hz), 123.4, 123.8 ($^4J_{CF}$=3.4 Hz), 124.7 ($^4J_{CF}$=3.2 Hz), 125.5, 126.8 ($^2J_{CF}$=14.5 Hz), 129.1 ($^3J_{CF}$=8.3 Hz), 130.5, 130.6, 131.2, 131.3 ($^3J_{CF}$=8.3 Hz), 135.7, 136.0, 136.4, 149.0, 160.6 ($^1J_{CF}$=250.2 Hz), 161.4 ($^1J_{CF}$=244.8 Hz), 194.7, 201.7. Anal. Calcd for $C_{30}H_{24}F_2N_2O_3$: C, 72.28; H, 4.85; N, 5.62. Found: C, 72.51; H, 4.67; N, 5.71.

*4.2.5. 2-Hydroxy-11-methyl-13-(3-nitrophenyl)-16-[(E)-(3-nitrophenyl)-methylidene]-1,11-diazapentacyclo-[12.3.1.0^{2,10}.0^{3,8}.0^{10,14}]octadeca-3(8),4,6-triene-9,15-dione (**4e**).* Pale yellow solid; (0.140 g, 92%); mp 188–189 °C; IR (KBr) ν_{max} 3391, 1702, 1603 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.30 (s, 3H, N–CH_3), 2.72 (d, J=12.4 Hz, 1H, H-18$_{ax}$), 3.42 (d, J=18.0 Hz, 1H, H-17$_{ax}$), 3.76 (dd, J=18.0, 2.8 Hz, 1H, H-17$_{eq}$), 3.89 (t, J=10.4 Hz, 1H, H-12), 3.95–3.99 (m, 2H, H-12 and H-18$_{eq}$), 4.96 (dd, J=10.0, 5.6 Hz, 1H, H-13), 7.10 (d, J=8.4 Hz, 2H, aromatic), 7.25–7.28 (m, 1H, aromatic), 7.38–7.42 (m, 1H, aromatic), 7.46–7.57 (m, 3H, H-19 and aromatic), 7.60 (d, J=8.0 Hz, 1H, aromatic), 7.69 (d, J=7.6 Hz, 1H, aromatic), 7.81 (d, J=8.0 Hz, 1H, aromatic), 8.06–8.14 (m, 2H, aromatic), 8.29–8.31 (m, 1H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 38.2, 41.1, 53.2, 59.5, 63.6, 74.9, 91.7, 97.3, 122.7, 123.0, 123.3, 123.9, 124.1, 125.8, 129.6, 130.0, 130.9, 135.0, 135.2, 135.3, 135.9, 136.3, 136.4, 136.6, 141.6, 148.2, 148.9, 149.1, 195.2, 201.3. Anal. Calcd for $C_{30}H_{24}N_4O_7$: C, 65.21; H, 4.38; N, 10.14. Found: C, 65.05; H, 4.34; N, 9.96.

*4.2.6. 2-Hydroxy-13-(4-hydroxy-3-methoxyphenyl)-16-[(E)-(4-hydroxy-3-methoxyphenyl)methylidene]-11-methyl-1,11-diazapentacyclo [12.3.1.0^{2,10}.0^{3,8}.0^{10,14}]octadeca-3(8),4,6-triene-9,15-dione (**4f**).* Colourless crystals; (0.123 g, 81%); mp 164–165 °C; IR (KBr) ν_{max} 3382, 1718, 1679, 1601 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.27 (s, 3H, N–CH_3), 2.77 (d, J=15.2 Hz, 1H, H-18$_{ax}$), 3.42–3.50 (m, 1H, H-17$_{ax}$), 3.74–0.79 (m, 2H, H-17$_{eq}$ and H-12), 3.08 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.93–4.04 (m, 2H, H-12 and H-18$_{eq}$), 4.81 (dd, J=10.2, 6.0 Hz, 1H, H-13), 6.41–6.47 (m, 2H, aromatic), 6.72–6.75 (m, 1H, aromatic), 6.95 (s, 1H, H-19), 7.22–7.27 (m, 1H, aromatic), 7.51–7.53 (m, 2H, aromatic), 7.87–7.92 (m, 2H, aromatic), 8.00–8.04 (m, 2H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 38.4, 40.6, 41.2, 41.4, 54.5, 59.7, 70.1, 74.5, 91.7, 97.5, 111.8, 111.9, 113.1, 114.7, 120.5, 124.8, 125.7, 127.1, 130.6, 131.0, 131.2, 136.3, 136.7, 138.7, 140.3, 144.9, 146.4, 146.8, 147.4, 149.2. 195.8, 201.2. Anal. Calcd for $C_{32}H_{30}N_2O_7$: C, 69.30; H, 5.45; N, 5.05. Found: C, 69.52; H, 5.23; N, 4.94.

*4.2.7. 2-Hydroxy-11-methyl-13-(4-methylphenyl)-16-[(E)-(4-methylphenyl)-methylidene]-1,11-diazapentacyclo-[12.3.1.0^{2,10}.0^{3,8}.0^{10,14}] octadeca-3(8),4,6-triene-9,15-dione (**4g**).* Pale yellow crystals; (0.152 g, 95%); mp 195–196 °C; IR (KBr) ν_{max} 3380, 1708, 1679, 1598 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.27 (s, 3H, N–CH_3), 2.29 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.73 (d, J=12.8 Hz, 1H, H-18$_{ax}$), 3.46 (d, J=17.6 Hz, 1H, H-17$_{ax}$), 3.75–3.81 (m, 2H, H-17$_{eq}$, H-12), 3.93–4.04 (m, 2H, H-12 and H-18$_{eq}$), 4.85 (dd, J=10.0, 5.6 Hz, 1H, H-13), 6.73 (d, J=8.0 Hz, 2H, aromatic), 6.99 (d, J=8.0 Hz, 2H, aromatic), 7.12–7.15 (m, 3H, H-19 and aromatic), 7.21–7.24 (m, 1H, aromatic), 7.34 (d, J=7.6 Hz, 2H, aromatic), 7.45–7.49 (m, 1H, aromatic), 7.53 (d, J=8.0 Hz, 1H, aromatic), 7.71 (d, J=7.6 Hz, 1H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 21.4, 21.8, 38.3, 41.1, 53.6, 59.4, 64.0, 74.7, 91.9, 97.2, 123.3, 125.6, 128.5, 129.3, 129.6, 130.4, 130.6, 131.8, 132.6, 136.0, 136.3, 136.4, 136.9, 138.5, 139.9, 149.3, 195.9, 201.5. Anal. Calcd for $C_{32}H_{30}N_2O_3$: C, 78.34; H, 6.16; N, 5.71. Found: C, 78.50; H, 6.03; N, 5.58.

*4.2.8. 2-Hydroxy-13-(4-methoxyphenyl)-16-[(E)-(4-methoxyphenyl)-methylidene]-11-methyl-1,11-diaza-pentacyclo [12.3.1.0^{2,10}.0^{3,8}.0^{10,14}]-octadeca-3(8),4,6-triene-9,15-dione (**4h**).* Yellow solid; (0.142 g, 92%); mp 153–154 °C; IR (KBr) ν_{max} 3195, 1712, 1678, 1595 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.26 (s, 3H, N–CH_3), 2.73 (d, J=12.4 Hz, 1H, H-18$_{ax}$), 3.43 (d, J=17.6 Hz, 1H, H-17$_{ax}$), 3.72–3.77 (m, 1H, H-17$_{eq}$), 3.77 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.82–3.98 (m, 3H, H-12 and H-18$_{eq}$), 4.83 (dd, J=10.0, 6.0 Hz, 1H, H-13), 6.71 (d, J=8.8 Hz, 2H, aromatic), 6.81–6.86 (m, 4H, aromatic), 7.09 (s, 1H, H-19), 7.19–7.23 (m, 1H, aromatic), 7.35 (d, J=8.4 Hz, 2H, aromatic), 7.45–7.51 (m, 2H, aromatic), 7.71 (d, J=7.6 Hz, 1H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 38.4, 40.8, 53.6, 55.7, 59.3, 64.0, 74.6, 91.9, 97.3, 114.0, 114.2, 123.2, 125.6, 127.3, 129.6, 130.6, 131.2, 131.4, 132.4, 136.0, 136.3, 138.2, 149.3, 158.8, 160.7, 195.9, 201.4. Anal. Calcd for $C_{32}H_{30}N_2O_5$: C, 73.55; H, 5.79; N, 5.36. Found: C, 73.27; H, 5.94; N, 5.47.

*4.2.9. 13-(4-Chlorophenyl)-16-[(E)-(4-chlorophenyl)-methylidene]-2-hydroxy-11-methyl-1,11-diazapentacyclo[12.3.1.0^{2,10}.0^{3,8}.0^{10,14}]octadeca-3(8),4,6-triene-9,15-dione (**4i**).* Pale yellow solid; (0.148 g, 96%); mp 188–189 °C; IR (KBr) ν_{max} 3367, 1715, 1689, 1598 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.26 (s, 3H, N–CH_3), 2.70 (d, J=12.8 Hz, 1H, H-18$_{ax}$), 3.39 (d, J=17.2 Hz, 1H, H-17$_{ax}$), 3.73 (dd, J=17.2, 2.4 Hz, 1H, H-17$_{eq}$), 3.80 (t, J=10.4 Hz, 1H, H-12), 3.88–3.95 (m, 2H, H-12 and H-18$_{eq}$), 4.82 (dd, J=10.0, 5.6 Hz, 1H, H-13), 6.73 (d, J=8.4 Hz, 2H, aromatic), 7.03 (s, 1H, H-19), 7.15 (d, J=8.4 Hz, 2H, aromatic), 7.23–7.30 (m, 3H, aromatic), 7.37 (d, J=8.4 Hz, 2H, aromatic), 7.47–7.53 (m, 2H, aromatic), 7.69 (d, J=7.6 Hz, 1H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 38.3, 40.8, 53.5, 59.5, 63.8, 74.7, 91.7, 97.2, 123.2, 125.7, 128.8, 129.1, 129.9, 130.8, 131.4, 132.8, 133.1, 134.2, 135.6, 136.3, 136.9, 138.0, 149.1, 195.7, 201.4. Anal. Calcd for $C_{30}H_{24}Cl_2N_2O_3$: C, 67.80; H, 4.55; N, 5.27. Found: C, 68.04; H, 4.69; N, 5.38.

*4.2.10. 13-(4-Bromophenyl)-16-[(E)-(4-bromophenyl)-methylidene]-2-hydroxy-11-methyl-1,11-diazapentacyclo[12.3.1.0^{2,10}.0^{3,8}.0^{10,14}]octadeca-3(8),4,6-triene-9,15-dione (**4j**).* Pale yellow crystals; (0.135 g, 95%); mp 184–185 °C; IR (KBr) ν_{max} 3392, 1710, 1679, 1600 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.26 (s, 3H, N–CH_3), 2.70 (d, J=12.8 Hz, 1H, H-18$_{ax}$), 3.39 (d, J=17.6 Hz, 1H, H-17$_{ax}$), 3.72 (dd, J=17.6, 2.4 Hz, 1H, H-17$_{eq}$), 3.80 (t, J=10.4 Hz, 1H, H-12), 3.87–3.95 (m, 2H, H-12 and H-18$_{eq}$), 4.81 (dd, J=10.0, 5.6 Hz, 1H, H-13), 6.66 (d, J=8.4 Hz, 2H, aromatic), 7.02 (s, 1H, H-19), 7.24–7.32 (m, 5H, aromatic), 7.44 (d, J=8.4 Hz, 2H, aromatic), 7.48–7.53 (m, 2H, aromatic), 7.69 (d, J=8.0 Hz, 1H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 38.2, 40.9, 53.4, 59.5, 63.8, 74.7, 91.7, 97.3, 123.2, 123.9, 125.7, 130.3, 130.8, 131.5, 131.8, 132.0, 132.1, 132.3, 133.8, 134.3, 135.8, 136.2, 136.9, 149.2, 195.6, 201.3. Anal. Calcd for $C_{30}H_{24}Br_2N_2O_3$: C, 58.09; H, 3.90; N, 4.52. Found: C, 57.90; H, 3.78; N, 4.64.

*4.2.11. 13-(4-Fluorophenyl)-16-[(E)-(4-fluorophenyl)-methylidene]-2-hydroxy-11-methyl-1,11-diazapentacyclo[12.3.1.0^{2,10}.0^{3,8}.0^{10,14}]octadeca-3(8),4,6-triene-9,15-dione (**4k**).* Pale yellow crystals; (0.150 g, 94%); mp 189–190 °C; IR (KBr) ν_{max} 3363, 1720, 1668, 1605 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.26 (s, 3H, N–CH_3), 2.71 (d, J=12.6 Hz, 1H, H-18$_{ax}$), 3.39 (d, J=17.4 Hz, 1H, H-17$_{ax}$), 3.71–3.84

(m, 2H, H-17_{eq} and H-12), 3.93–3.98 (m, 2H, H-12 and H-18_{eq}), 4.84 (dd, J=10.2, 5.7 Hz, 1H, H-13), 5.64 (br s, 1H, OH), 6.80–6.91 (m, 4H, aromatic), 6.97–7.05 (m, 3H, H-19 and aromatic), 7.20–7.25 (m, 1H, aromatic), 7.38–7.53 (m, 4H, aromatic), 7.69 (d, J=7.5 Hz, 1H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 38.2, 40.7, 53.5, 59.5, 64.1, 74.8, 91.8, 97.2, 115.6 ($^2J_{CF}$=21.5 Hz), 115.7 ($^2J_{CF}$=21.1 Hz), 123.2, 125.6, 130.0 ($^3J_{CF}$=7.8 Hz), 130.6, 130.7, 132.2 ($^2J_{CF}$=8.5 Hz), 133.6, 135.2 ($^4J_{CF}$=3.3 Hz), 136.1, 136.4, 137.0, 149.2, 162.2 ($^1J_{CF}$=244.0 Hz), 163.3 ($^1J_{CF}$=249.8 Hz), 195.8, 201.4. Anal. Calcd for $C_{30}H_{24}F_2N_2O_3$: C, 72.28; H, 4.85; N, 5.62. Found: C, 72.64; H, 4.57; N, 5.64.

*4.2.12. 2-Hydroxy-10-methyl-8-phenyl-5-[(E)-phenyl-methylidene]-3,10-diazahexacyclo-[10.7.1.1^{3,7}.0^{2,11}. 0^{7,11}.0^{16,20}]henicosa-1(19),12(20),-13,15,17-pentaen-6-one (**6a**).* Pale yellow crystals; (0.170 g, 96%); mp 144–145 °C; IR (KBr) ν_{max} 3445, 1685, 1599 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.04 (s, 3H, N–CH_3), 2.72 (d, J=12.4 Hz, 1H, H-21_{ax}), 3.40 (d, J=17.6 Hz, 1H, H-4_{ax}), 3.64 (dd, J=17.6, 2.4 Hz, 1H, H-4_{eq}), 3.73 (t, J=10.4 Hz, 1H, H-9), 4.06 (dd, J=12.8, 2.4 Hz, 1H, H-21_{eq}), 4.11–4.15 (m, 1H, H-9), 4.97 (dd, J=10.0, 6.4 Hz, 1H, H-8), 6.33 (s, 1H, H-22), 6.42 (d, J=8.0 Hz, 2H, aromatic), 7.06–7.11 (m, 3H, aromatic), 7.24–7.28 (m, 2H, aromatic), 7.33–7.36 (m, 3H, aromatic), 7.49–7.57 (m, 5H, aromatic), 7.70 (d, J=8.4 Hz, 1H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 38.8, 41.5, 53.5, 57.9, 63.0, 74.0, 94.6, 103.0, 121.4, 123.4, 126.1, 126.2, 127.4, 127.9, 128.1, 128.2, 128.7, 128.8, 128.9, 130.0, 131.3, 133.9, 134.3, 136.3, 136.4, 137.1, 138.9, 139.7, 197.4. Anal. Calcd for $C_{33}H_{28}N_2O_2$: C, 81.79; H, 5.82; N, 5.78. Found: C, 81.95; H, 5.91; N, 5.70.

*4.2.13. 8-(2-Chlorophenyl)-5-[(E)-(2-chlorophenyl)-methylidene]-2-hydroxy-10-methyl-3,10-diaza-hexacyclo[10.7.1.1^{3,7}.0^{2,11}.0^{7,11}.0^{16,20}] henicosa-1(20),12,14,16,18-pentaen-6-one (**6b**).* Pale yellow solid; (0.150 g, 94%); mp 194–195 °C; IR (KBr) ν_{max} 3402, 1699, 1610 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.94 (s, 3H, N–CH_3), 2.82 (d, J=12.4 Hz, 1H, H-21_{ax}), 3.13 (d, J=17.6 Hz, 1H, H-4_{ax}), 3.66 (dd, J=17.6, 2.4 Hz, 1H, H-4_{eq}), 3.83–3.94 (m, 3H, H-9 and H-21_{eq}), 5.21 (dd, J=8.4, 3.2 Hz, 1H, H-8), 5.85 (br s, 1H, OH), 6.03 (d, J=7.6 Hz, 1H, aromatic), 6.79 (s, 1H, H-22), 6.90–6.94 (m, 1H, aromatic), 7.02–7.06 (m, 1H, aromatic), 7.30 (d, J=8.0 Hz, 1H, aromatic), 7.21–7.25 (m, 1H, aromatic), 7.34–7.47 (m, 4H, aromatic), 7.54–7.60 (m, 2H, aromatic), 7.70 (d, J=8.0 Hz, 1H, aromatic), 7.77 (d, J=8.4 Hz, 2H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 37.3, 37.7, 52.4, 57.5, 65.2, 72.6, 94.1, 102.5, 121.1, 124.0, 126.3, 126.4, 127.5, 128.2, 128.4, 128.6, 129.1, 129.6, 129.7, 129.9, 130.4, 131.4, 133.0, 133.8, 134.3, 134.4, 134.7, 136.0, 137.1, 138.8, 139.2, 194.9. Anal. Calcd for $C_{33}H_{26}Cl_2N_2O_2$: C, 71.61; H, 4.73; N, 5.06. Found: C, 71.84; H, 4.56; N, 5.21.

*4.2.14. 8-(2-Bromophenyl)-5-[(E)-(2-bromophenyl)-methylidene]-2-hydroxy-10-methyl-3,10-diazahexacyclo[10.7.1.1^{3,7}.0^{2,11}.0^{7,11}.0^{16,20}]henicosa-1(20),12,14,16,18-pentaen-6-one (**6c**).* Pale yellow crystals; (0.135 g, 92%); mp 186–187 °C; IR (KBr) ν_{max} 3405, 1708, 1613 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.93 (s, 3H, N–CH_3), 2.84 (d, J=12.6 Hz, 1H, H-21_{ax}), 3.12 (d, J=18.0 Hz, 1H, H-4_{ax}), 3.64 (dd, J=18.0, 2.7 Hz, 1H, H-4_{eq}), 3.78–3.94 (m, 3H, H-9 and H-21_{eq}), 5.16 (dd, J=8.4, 3.3 Hz, 1H, H-8), 5.84 (br s, 1H, OH), 5.93–5.96 (m, 1H, aromatic), 6.80 (s, 1H, H-22), 6.93–6.98 (m, 2H, aromatic), 7.11–7.17 (m, 1H, aromatic), 7.31–7.61 (m, 7H, aromatic), 7.73 (d, J=8.1 Hz, 1H, aromatic), 7.78 (d, J=8.1 Hz, 2H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 37.6, 40.1, 52.0, 57.2, 65.5, 72.4, 94.1, 102.5, 121.1, 124.1, 124.2, 125.4, 126.5, 126.6, 126.9, 128.1, 128.3, 128.4, 128.9, 129.3, 129.5, 130.0, 131.4, 133.0, 133.8, 133.9, 135.0, 135.9, 136.2, 137.1, 138.9, 141.0, 194.6. Anal. Calcd for $C_{33}H_{26}Br_2N_2O_2$: C, 61.70; H, 4.08; N, 4.36. Found: C, 61.53; H, 4.30; N, 4.21.

*4.2.15. 8-(2-Fluorophenyl)-5-[(E)-(2-fluorophenyl)-methylidene]-2-hydroxy-10-methyl-3,10-diaza-hexacyclo[10.7.1.1^{3,7}.0^{2,11}.0^{7,11}.0^{16,20}] henicosa-1(20),12,14,16,18-pentaen-6-one (**6d**).* Pale yellow crystals; (0.150 g, 90%); mp 146–147 °C; IR (KBr) ν_{max} 3408, 1693, 1602 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.98 (s, 3H, N–CH_3), 2.87 (d, J=12.8 Hz, 1H, H-21_{ax}), 3.19 (d, J=17.8 Hz, 1H, H-4_{ax}), 3.64 (dd, J=17.8, 2.0 Hz, 1H, H-4_{eq}), 3.75 (t, J=10.4 Hz, 1H, H-9), 4.01–4.12 (m, 2H, H-9 and H-21_{eq}), 5.10 (dd, J=10.0, 5.2 Hz, 1H, H-8), 6.18–6.21 (m, 1H, aromatic), 6.40 (s, 1H, H-22), 6.75–6.82 (m, 2H, aromatic), 7.02–7.16 (m, 3H, aromatic), 7.20–7.30 (m, 2H, aromatic), 7.35 (d, J=7.2 Hz, 1H, aromatic), 7.51–7.60 (m, 4H, aromatic), 7.73 (d, J=8.0 Hz, 1H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 35.5, 38.3, 53.3 (J_{CF}=3.7 Hz), 57.9, 62.9, 73.7, 94.2, 102.7, 115.5 ($^2J_{CF}$=21.9 Hz), 116.3 ($^2J_{CF}$=22.7 Hz), 121.2, 122.2 ($^2J_{CF}$=13.9 Hz), 123.5, 124.6 ($^4J_{CF}$=3.3 Hz), 126.2, 127.0 ($^2J_{CF}$=14.2 Hz), 127.8, 128.1, 128.7 ($^4J_{CF}$=3.3 Hz), 129.0 ($^3J_{CF}$=8.3 Hz), 130.4, 130.5, 130.8 ($^3J_{CF}$=8.4 Hz), 131.2, 135.5, 136.1, 137.1, 138.8, 160.2 ($^1J_{CF}$=250.3 Hz), 161.4 ($^1J_{CF}$=245.4 Hz), 195.9. Anal. Calcd for $C_{33}H_{26}F_2N_2O_2$: C, 76.14; H, 5.03; N, 5.38. Found: C, 76.40; H, 5.17; N, 5.21.

*4.2.16. 2-Hydroxy-10-methyl-8-(3-nitrophenyl)-5-[(E)-(3-nitrophenyl)-methylidene]-3,10-diaza-hexacyclo[10.7.1.1^{3,7}.0^{2,11}.0^{7,11}.0^{16,20}] henicosa-1(20),12,14,16,18-pentaen-6-one (**6e**).* Pale yellow solid; (0.147 g, 93%); mp 202–203 °C; IR (KBr) ν_{max} 3414, 1703, 1606 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.09 (s, 3H, N–CH_3), 2.74 (d, J=12.4 Hz, 1H, H-21_{ax}), 3.30 (d, J=17.2 Hz, 1H, H-4_{ax}), 3.64 (dd, J=17.2, 2.4 Hz, 1H, H-4_{eq}), 3.83 (t, J=10.4 Hz, 1H, H-9), 4.07 (d, J=12.4 Hz, 1H, H-21_{eq}), 4.18 (dd, J=10.8, 6.4 Hz, 1H, H-9), 5.06 (dd, J=10.0, 6.4 Hz, 1H, H-8), 6.04 (br s, 1H, OH), 6.21 (s, 1H, aromatic), 6.72 (d, J=7.6 Hz, 1H, aromatic), 7.13 (s, 1H, H-22), 7.21–7.31 (m, 2H, aromatic), 7.37 (d, J=6.8 Hz, 1H, aromatic), 7.49–7.70 (m, 4H, aromatic), 7.84 (d, J=8.4 Hz, 1H, aromatic), 7.88 (d, J=7.6 Hz, 1H, aromatic), 8.00 (d, J=8.0 Hz, 1H, aromatic), 8.15 (d, J=8.0 Hz, 1H, aromatic), 8.39 (s, 1H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 38.8, 41.3, 53.4, 58.0, 62.5, 74.3, 94.7, 103.0, 110.0, 121.6, 122.7, 123.3, 123.4, 124.5, 126.2, 126.5, 128.1, 128.4, 129.2, 130.0, 131.3, 133.2, 134.9, 135.6, 135.9, 136.7, 137.0, 138.6, 141.7, 147.9, 148.8, 196.9. Anal. Calcd for $C_{33}H_{26}N_4O_6$: C, 68.98; H, 4.56; N, 9.75. Found: C, 68.84; H, 4.33; N, 9.89.

*4.2.17. 2-Hydroxy-10-methyl-8-(4-methylphenyl)-5-[(E)-(4-methylphenyl)-methylidene]-3,10-diazahexacyclo-[10.7.1.1^{3,7}.0^{2,11}.0^{7,11}.0^{16,20}] henicosa-1(20),12,14,16,18-pentaen-6-one (**6g**).* Pale yellow crystals; (0.158 g, 94%); mp 130–131 °C; IR (KBr) ν_{max} 3415, 1683, 1604 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.02 (s, 3H, N–CH_3), 2.22 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.72 (d, J=12.4 Hz, 1H, H-21_{ax}), 3.40 (d, J=17.2 Hz, 1H, H-4_{ax}), 3.61–3.70 (m, 2H, H-9 and H-4_{eq}), 4.04–4.11 (m, 2H, H-9 and H-21_{eq}), 4.93 (dd, J=10.4, 6.8 Hz, 1H, H-8), 6.36 (d, 2H, H-aromatic), 6.87 (d, J=8.0 Hz, 2H, aromatic), 7.13 (d, J=8.0 Hz, 2H, aromatic), 7.22–7.33 (m, 2H, aromatic), 7.38 (d, J=7.6 Hz, 2H, aromatic), 7.49–7.54 (m, 2H, aromatic), 7.57 (d, J=6.8 Hz, 1H, aromatic), 7.66 (d, J=8.4 Hz, 1H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 21.5, 21.7, 38.9, 41.4, 53.5, 57.7, 62.9, 73.8, 94.7, 103.1, 121.4, 123.4, 126.0, 126.2, 127.9, 128.0, 128.6, 129.0, 129.5, 130.2, 131.3, 131,6. 132.9, 136.4, 136.5, 136.9, 137.1, 139.0, 197.3. Anal. Calcd for $C_{35}H_{32}N_2O_2$: C, 82.00; H, 6.29; N, 5.46. Found: C, 82.29; H, 6.17; N, 5.67.

*4.2.18. 2-Hydroxy-8-(4-methoxyphenyl)-5-[(E)-(4-methoxy-phenyl) methylidene]-10-methyl-3,10-diazahexacyclo-[10.7.1.1^{3,7}.0^{2,11}.0^{7,11}.0^{16,20}] henicosa-1(20),12,14,16,18-pentaen-6-one (**6h**).* Yellow solid; (0.146 g, 90%); mp 158–159 °C; IR (KBr) ν_{max} 3412, 1686, 1605 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.01 (s, 3H, N–CH_3), 2.73 (d, J=12.4 Hz, 1H, H-21_{ax}), 3.39 (d, J=17.6 Hz, 1H, H-4_{ax}), 3.63–3.68 (m, 1H, H-4_{eq}), 3.69 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.79–3.82 (m, 1H, H-9), 4.03–4.12 (m, 2H, H-9 and H-21_{eq}), 4.92 (dd, J=10.4, 6.8 Hz, 1H, H-8), 6.33 (s, 1H, H-22), 6.47 (d, J=8.8 Hz, 2H, aromatic), 6.60 (d, J=8.8 Hz, 2H, aromatic), 6.86 (d, J=8.8 Hz, 2H, aromatic), 7.26–7.32 (m, 2H, aromatic), 7.40 (d, J=8.8 Hz, 2H, aromatic), 7.47–7.53 (m, 2H, aromatic), 7.58 (d, J=6.8 Hz,

1H, aromatic), 7.65 (d, J=8.0 Hz, 1H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 38.9, 41.1, 53.5, 55.5, 55.6, 57.5, 62.8, 73.7, 94.6, 103.1, 113.7, 114.2, 121.3, 123.4, 125.9, 126.1, 127.1, 127.8, 128.0, 129.7, 131.2, 131.4, 131.5, 132.1, 136.2, 136.4, 137.1, 139.0, 158.8, 160.1, 197.2. Anal. Calcd for $C_{35}H_{32}N_2O_4$: C, 77.18; H, 5.92; N, 5.14. Found: C, 77.56; H, 6.07; N, 5.21.

*4.2.19. 8-(4-Chlorophenyl)-5-[(E)-(4-chlorophenyl)-methylidene]-2-hydroxy-10-methyl-3,10-diazahexacyclo[10.7.1.1^{3,7}.0^{2,11}.0^{7,11}.0^{16,20}]henicosa-1(20),12,14,16,18-pentaen-6-one (**6i**).* Pale yellow solid; (0.145 g, 91%); mp 205–206 °C; IR (KBr) ν_{max} 3380, 1687, 1611 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.06 (s, 3H, N–CH_3), 2.73 (d, J=12.4 Hz, 1H, H-21$_{ax}$), 3.37 (d, J=17.6 Hz, 1H, H-4$_{ax}$), 3.64 (dd, J=17.6, 2.8 Hz, 1H, H-4$_{eq}$), 3.72 (t, J=9.6 Hz, 1H, H-9), 4.04 (dd, J=12.4, 1.6 Hz, 1H, H-21$_{eq}$), 4.10 (dd, J=10.8, 6.8 Hz, 1H, H-9), 4.94 (dd, J=10.0, 6.4 Hz, 1H, H-8), 6.12 (br s, 1H, OH), 6.23 (s, 1H, H-22), 6.36 (d, J=8.4 Hz, 2H, aromatic), 7.08 (d, J=8.4 Hz, 2H, aromatic), 7.32–7.35 (m, 4H, aromatic), 7.45 (d, J=8.8 Hz, 2H, aromatic), 7.54–7.59 (m, 3H, aromatic), 7.72 (d, J=8.4 Hz, 1H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 38.8, 41.0, 53.5, 57.8, 62.8, 74.0, 94.6, 102.9, 121.5, 123.3, 126.1, 126.3, 128.0, 128.1, 128.5, 129.1, 130.0, 131.2, 131.3, 132.7, 133.2, 134.3, 134.8, 134.9, 136.1, 137.1, 138.0, 138.8, 197.2. Anal. Calcd for $C_{33}H_{26}Cl_2N_2O_2$: C, 71.61; H, 4.73; N, 5.06. Found: C, 71.38; H, 4.92; N, 5.21.

*4.2.20. 8-(4-Bromophenyl)-5-[(E)-(4-bromophenyl)-methylidene]-2-hydroxy-10-methyl-3,10-diazahexacyclo[10.7.1.1^{3,7}.0^{2,11}.0^{7,11}.0^{16,20}]henicosa-1(20),12,14,16,18-pentaen-6-one (**6j**).* Pale yellow solid; (0.133 g, 90%); mp 197–198 °C; IR (KBr) ν_{max} 3408, 1692, 1602 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.02 (s, 3H, N–CH_3), 2.69 (d, J=12.8 Hz, 1H, H-21$_{ax}$), 3.33 (d, J=17.2 Hz, 1H, H-4$_{ax}$), 3.59 (dd, J=17.2, 2.4 Hz, 1H, H-4$_{eq}$), 3.70 (t, J=10.8 Hz, 1H, H-9), 3.97–4.07 (m, 2H, H-9 and H-21$_{eq}$), 4.89 (dd, J=10.4, 6.4 Hz, 1H, H-8), 6.20 (s, 1H, H-22), 6.26 (d, J=8.4 Hz, 2H, aromatic), 7.20 (d, J=8.4 Hz, 2H, aromatic), 7.28–7.32 (m, 2H, aromatic), 7.36 (d, J=8.4 Hz, 2H, aromatic), 7.45 (d, J=8.8 Hz, 2H, aromatic), 7.52–7.57 (m, 3H, aromatic), 7.69 (d, J=8.4 Hz, 1H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 38.8, 41.1, 53.4, 57.8, 62.7, 73.9, 94.6, 103.0, 121.2, 121.5, 123.2, 123.3, 126.1, 126.3, 128.0, 128.1, 130.4, 131.2, 131.3, 131.4, 132.0, 133.1, 134.4, 134.9, 136.1, 137.0, 138.5, 138.9, 197.0. Anal. Calcd for $C_{33}H_{26}Br_2N_2O_2$: C, 61.70; H, 4.08; N, 4.36. Found: C, 61.84; H, 4.17; N, 4.43.

*4.2.21. 8-(4-Fluorophenyl)-5-[(E)-(4-fluorophenyl)-methylidene]-2-hydroxy-10-methyl-3,10-diaza-hexacyclo[10.7.1.1^{3,7}.0^{2,11}.0^{7,11}.0^{16,20}] henicosa-1(20),12,14,16,18-pentaen-6-one (**6k**).* Pale yellow solid; (0.152 g, 92%); mp 186–187 °C; IR (KBr) ν_{max} 3446, 1694, 1600 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.04 (s, 3H, N–CH_3), 2.72 (d, J=12.8 Hz, 1H, H-21$_{ax}$), 3.36 (d, J=17.4 Hz, 1H, H-4$_{ax}$), 3.63 (dd, J=17.4, 2.4 Hz, 1H, H-4$_{eq}$), 3.73 (t, J=10.4 Hz, 1H, H-9), 4.04 (dd, J=12.8, 2.4 Hz, 1H, H-21$_{eq}$), 4.06–4.11 (m, 1H, H-9), 4.94 (dd, J=10.4, 6.8 Hz, 1H, H-8), 6.25 (s, 1H, H-22), 6.40–6.43 (m, 2H, aromatic), 6.77–6.81 (m, 2H, aromatic), 7.02–7.06 (m, 2H, aromatic), 7.27–7.33 (m, 2H, aromatic), 7.45–7.58 (m, 5H, aromatic), 7.71 (d, J=8.4 Hz, 1H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 38.8, 40.9, 53.5, 57.8, 62.9, 74.0, 94.6, 103.0, 115.3 ($^2J_{CF}$=21.5 Hz), 115.7 ($^2J_{CF}$=21.0 Hz), 121.4, 123.3, 126.1, 128.0, 130.2 ($^3J_{CF}$=7.8 Hz), 130.4 ($^4J_{CF}$=3.1 Hz), 131.2, 131.9 ($^3J_{CF}$=8.3 Hz), 133.7, 135.0, 135.2 ($^4J_{CF}$=3.0 Hz), 136.3, 137.1, 138.9, 162.1 ($^1J_{CF}$=244.0 Hz), 162.7 ($^1J_{CF}$=248.9 Hz), 197.3. Anal. Calcd for $C_{33}H_{26}F_2N_2O_2$: C, 76.14; H, 5.03; N, 5.38. Found: C, 76.01; H, 5.19; N, 5.29.

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.02.058. These data include MOL files and InChIKeys of the most important compounds described in this article.

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