Tetrahedron 65 (2009) 563–578

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Parallel synthesis and spectroscopic analysis of a collection of heterocycles based on the diazabenz[*e*]aceanthrylene core structure

Alan M. Jones, Tomas Lebl, Stephen Patterson, Tanja van Mourik, Herbert A. Früchtl, Douglas Philp, Alexandra M.Z. Slawin, Nicholas J. Westwood *

School of Chemistry and Centre for Biomolecular Sciences, EaStChem, University of St Andrews, North Haugh, St Andrews, Fife, Scotland, KY16 9ST, UK

ARTICLE INFO

Article history:
Received 6 August 2008
Received in revised form
30 September 2008
Accepted 16 October 2008
Available online 1 November 2008

Keywords:
Heterocycles
Zipper reaction
Microwave
Variable temperature NMR analysis
Computational analysis

ABSTRACT

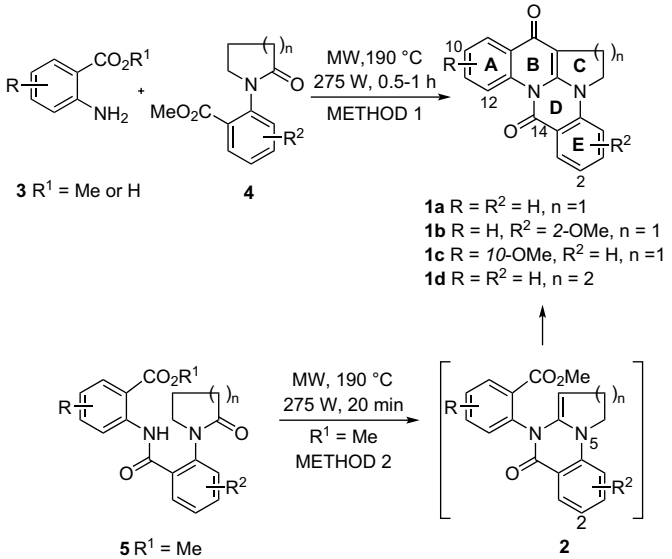
A practical strategy for the synthesis of diazabenz[*e*]aceanthrylene-based heterocycles is reported. The key step in this approach is a microwave-assisted condensation and cyclisation reaction between an anthranilic acid derivative and a 2′-carbomethoxy substituted *N*-aryl lactam. The scope of the reaction has been explored as a function of both the nature and position of substituents in both components and variations in lactam ring size. Interesting structural and spectroscopic variations observed across the compound collection are described and explored using NMR, X-ray crystallography and computational techniques.

© 2008 Elsevier Ltd. All rights reserved.

1. Introduction

We have previously reported the microwave-mediated synthesis of heterocycles **1a**–**1d** (Scheme 1).[1] Limited examples of three alternative synthetic approaches were described, the key step of each approach being an intramolecular attack on the anthranilate ester by the in situ generated *N*,*N*-dienamine functionality shown in general structure **2** (Scheme 1). This cyclisation reaction results in the formation of the second of two new six-membered rings (B and D rings in general structure **1**, Scheme 1). We also argued that to generate a diverse range of analogues, the two methods highlighted in Scheme 1 would be the most useful as they enable the preparation of differentially substituted analogues (where R differs from R^2 in **1**).[1] The first of these, method 1, combines anthranilates of general structure **3** and *N*-aryl lactams of general structure **4** directly in one pot, whereas method 2 requires an alternative synthesis of the more complex starting amide **5**, a proposed intermediate in method 1.[1,2]

Here we report the details of further studies on these two methods with a focus on exploring the reaction scope as a function of R, R^2 and *n*. We demonstrate that method 1 can tolerate a range of substituents in the A and E-rings (Scheme 1) and clear trends



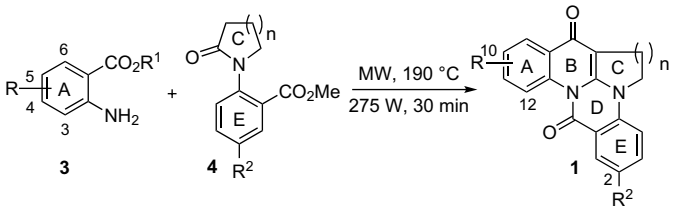
Scheme 1. Two routes for the synthesis of diazabenz[*e*]aceanthrylene-based heterocycles.

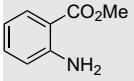
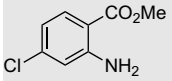
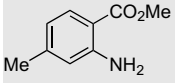
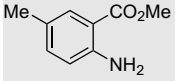
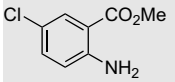
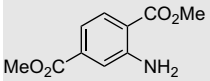
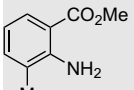
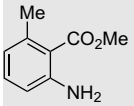
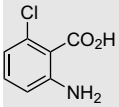
with regards to substituent position also emerged from these studies. Several limitations to method 1 were, however, identified. For example, when attempts were made to incorporate heteroaromatic and non-aromatic A-rings into the core structure, or to

* Corresponding author. Tel.: +44 (0)1334 463816; fax: +44 (0)1334 462595.
E-mail address: njw3@st-andrews.ac.uk (N.J. Westwood).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.10.049

Table 1
Exploring the reaction scope of method 1



		6(1) 7(1)	6(1) 7(2)	6(2) 7(1)	6(2) 7(2)
	**3**(1)	**1a** 67[a]; 70[b]	**1d** 78[a,+]	**1b** 18[a]; 93[b,+]	**1**(2,2,1) 59[a]; 74[b]
	**3**(2)	**1**(1,1,2) 53[b]	**1**(1,2,2) 33[b]	**1**(2,1,2) 81[b]	**1**(2,2,2) 60[b]
	**3**(3)	**1**(1,1,3) 46[b]	**1**(1,2,3) 55[b]	**1**(2,1,3) 34[b]	**1**(2,2,3) (≠)
	**3**(4)	**1**(1,1,4) 66[a]; 79[b]	**1**(1,2,4) 60[a]; 64[b]	**1**(2,1,4) 45[a]	**1**(2,2,4) 33[a]; 45[b]
	**3**(5)	**1**(1,1,5) 65[a]; 80[b]	**1**(1,2,5) 64[a]	**1**(2,1,5) (≠)	**1**(2,2,5) (≠)
	**3**(6)	**1**(1,1,6) 88[b]	**1**(1,2,6) 78[a]; 83	**1**(2,1,6) 57[a]	**1**(2,2,6) (≠)
	**3**(7)	**1**(1,1,7) 27[a]; 39[b]	**1**(1,2,7) 24[a]	**1**(2,1,7) 21[a]	**1**(2,2,7) 21[a]; 24[b]
	**3**(8)	**1**(1,1,8) (≠)	**1**(1,2,8) (≠)	**1**(2,1,8) 85[b]	**1**(2,2,8) 75[b]
	**3**(9)	**1**(1,1,9) 16[a]	**1**(1,2,9) 15[a]	**1**(2,1,9) 15[a]	**1**(2,2,9) (≠)

The compound numbers were assigned according to a literature protocol[4] that emphasises the structure of the components used (e.g., **1**(1,2,7) is made up from components **6**(1), **7**(2), **3**(7)); the isolated yield for each compound is also provided under varying reaction conditions.
The symbol (≠) indicates no product isolated, [+] cf. previously reported[1] unoptimised yields for synthesis of **1d** (28%) and **1b** (31%). HPLC analysis of the majority of the compounds described in Table 1 is provided.[3]
[a] Isolated yield after precipitation using diethyl ether.
[b] Isolated yield after purification by flash chromatography.

prepare analogues containing rings where $n>2$, method 1 failed. In most cases, these problems were overcome by the use of method 2. Several of the compounds that were prepared exhibited interesting spectroscopic properties, the details of which are also described here.

2. Results and discussion

2.1. Exploring the scope of method 1

The direct combination of a range of methyl anthranilates **3** (R^1=Me) and *N*-aryl lactams **4** was explored as a function of the type and position of substituents in **3**. Our previously reported[1] reaction conditions, further optimised by reduction of the reaction time to 30 min (cf. 1 h[1]) were used unless otherwise stated. This involved the mixing of the two reactants in a microwave tube followed by microwave irradiation at 190 °C, 275 W for 30 min under 'powermax' operating conditions.[3] No solvent is used in these reactions and given the melting points of the various anthranilates **3** and lactams **4**, it is assumed that a melt containing both reactants is formed. In most cases, the two reactants were briefly heated using a heat gun prior to running the reaction in the microwave. This caused them to both melt and mix effectively. Analysis of reactions after this brief period of heating outside the microwave indicated that no reaction had occurred prior to the microwave irradiation. Upon completion of the microwave reaction, the mixture was cooled and poured into diethyl ether whereupon, in most cases, precipitation of a pure sample of the desired product occurred (see Table S1 for details[3]). For those reactions where no precipitate was formed the reaction mixture was concentrated in vacuo and purified by standard chromatographic techniques. The results of these experiments are given in Table 1 and a description of the product numbering system used is provided in the table legend.[4]

Whilst care must be taken in interpreting the data presented in Table 1, as all reactions were carried out under one standard set of conditions and in several cases the yields reflect only the amount of product that precipitated following addition of the reaction mixture to diethyl ether, it was clear that both electron-withdrawing and electron-donating substituents were tolerated at C4 of **3**. For example, for the n=1 series both **1**(1,1,2) and **1**(1,1,3) were obtained in reasonable yield, 53% and 46%, respectively. The same two substituents at the C5-position also gave pure samples of the desired compounds in 66 and 65% yields for **1**(1,1,4) and **1**(1,1,5), respectively, when only the precipitated material was collected. These yields increased to 79% for **1**(1,1,4) and 80% for **1**(1,1,5) when purification of the crude reaction mixture by chromatography was employed. However, when methyl-5-bromoanthranilate was used in this reaction, none of the desired compound **1**(1,1,10) (Scheme 3c) was isolated presumably reflecting either the decreased nucleophilicity of the amino group in the presence of the *para*-bromo substituent,[5] or an alternative reaction path possibly involving homolytic cleavage of the aryl-bromine bond.[6] In practice, a sharp rise in pressure was observed during this particular microwave reaction along with extensive decomposition of the starting materials. Compound **1**(1,1,10) was subsequently prepared using method 2 (Scheme 3c). The inclusion of an ester functional group at C4 in **3** also proved successful giving **1**(1,1,6) in good yield despite the fact that the C4-ester group in **3**(6) could compete for reaction of the anthranilate amine with the ester functional group in **4**.[7] Subsequent further functionalisation of the A-ring substituents in several of the products, for example, **1**(1,1,2) and **1**(1,1,6), could be envisaged using standard chemical approaches.

For substrates **3** containing C4 or C5 substituents, the yields of the reaction remained good to average as the ring size of the lactam was varied from n=1 to n=2 in the R^2=H series. For example,

Table 2
Use of anthranilic acids in the two-component microwave approach

		3(1,R^1=H)	3(11)	3(12)	3(7, R1=H)
7(1)	6(1)	**1a** 67 146.5 °C Ref. 8a	**1**(1,1,11) 10 165–166.5 °C Ref. 8b	**1**(1,1,12) 37 189 °C Ref. 8c	**1**(1,1,7) 29 174–176 °C Ref. 8d
		3(3,R1 = H)	3(13)	3(14)	
7(1)	6(1)	**1**(1,1,3) 55 176–177.2 °C Ref. 8e	**1c**$^+$ 40 140–142 °C Ref. 8f	**1**(1,1,14) 10 213–214 °C Ref. 8g	

The compound numbers were assigned according to a literature protocol[4] (see Scheme and Table 1 legend for details); reaction yields and melting points of the starting anthranilate acids with references are provided. $^+$ cf. this yield with the previously reported[1] unoptimised yield for the synthesis of **1c** (20%).

1(1,2,4) was formed in 64% yield compared to 79% yield for the formation of **1**(1,1,4). However, when R^2 in aryl lactam **4** was changed to methoxy in both the n=1 and the n=2 series, the reaction yields fell and in several cases none of the desired product could be isolated for anthranilates containing a C4 or C5 substituent with the exception of anthranilate **3**(2).[9]

When substituents were incorporated at either the C3 or C6-position in **3** a reduction in the isolated yield was observed (cf. the following pairs of compounds, which have the substituents positioned in such a way that differences resulting from electronic effects would be expected to be minimal; **1**(1,1,4) vs **1**(1,1,7) and **1**(1,1,3) vs **1**(1,1,8) where none of the desired product was isolated). In the case of substitution at the C3-position in **3** the drop in yields was found to be independent of the ring size (n) of the lactam **4** used or the nature of R^2 in **4**. It is likely that the reduced yields in these reactions stem from increased steric hindrance to the expected initial reaction of the anthranilate amine with the lactam ester functionality in **4**. Despite the reduction in yield, analytically pure samples of compounds **1**(1,1,7), **1**(1,2,7), **1**(2,1,7) and **1**(2,2,7) were obtained and interesting observations relating to their structure and spectroscopic details are discussed in detail below. When a methyl substituent was incorporated at C6 in **3**, a remarkable result was obtained. Excellent yields of the desired compounds **1**(2,1,8) and **1**(2,2,8) were obtained in the series using **4** (R^2=OMe), whereas none of the desired compounds were obtained when lactam **4** (R^2=H) was used. This was the case in both the n=1 and n=2 series (cf. **1**(1,1,8) and **1**(2,1,8)). It is difficult to assign a clear explanation to this result. However, it is interesting to note that the C1-ester group in **3** (C6=Me) will be expected to adopt a preferred conformation in which the carbonyl group is no longer conjugated with the aromatic ring resulting in increased nucleophilicity of the anthranilate nitrogen for this substrate compared to **3** (C6=H). It is therefore likely that the initial reaction between the nitrogen in **3** and the ester group in **4** will proceed well for substrate **3** (C6=Me) regardless of the structure of **4**. However, the change in preferred conformation of the ester as a result of the presence of the C6-sustituent may result in difficulties in the final cyclisation step in which an intermediate of the general type **2** (Scheme 1) reacts to give **1**. The presence of the additional C2-electron-donating group in **2** (Scheme 1 for numbering) when the starting lactam **4** contains an electron-donating methoxy group may help to overcome the challenge of forming the final ring in this system. This may occur through an increase in electron density associated with N5 of the *N*,*N*-dienamine functionality and hence an increase in overall nucleophilicity associated with this functional group. In other words, in the absence of an increase in reactivity of the *N*,*N*-dienamine, the final cyclisation reaction to form **1** cannot occur. To date no intermediates have been isolated from this reaction to provide evidence to support this suggestion, with only extensive decomposition being observed when **4** (R^2=H) is used.

Whilst 22 novel heterocycles were prepared with relative ease using this approach, the synthesis of **1** containing, for example, heteroaryl A-rings (see Scheme 1 for numbering) including thiophene, pyrazine, nicotinic and isonicotinic rings was unsuccessful. In addition replacement of the A-ring with an aliphatic chain also failed.

2.2. Use of anthranilic acids in method 1

Although a significant number of anthranilates are commercially available, there is considerably more diversity available for anthranilic acids. To avoid having to convert the anthranilic acids to the corresponding esters prior to reaction with **4**, we decided to assess whether the acids could be used directly in this chemistry. Initial results were encouraging with the synthesis of **1a** being achieved in 67% (Table 2) using optimised conditions in which a 6:1 ratio of anthranilic acid/lactam was heated under microwave irradiation at 190 °C, 275 W for 60 min using 'powermax' conditions (see Table S2 for details[3]). This yield was comparable to that obtained when using the corresponding anthranilate ester (Table 1) although an increased amount of the anthranilic acid was used compared to the ester. It should be remembered, however, that the overall sequence using the anthranilic acids is typically one step shorter than with the corresponding esters and in the case of **3** (C6=Me) a significantly longer reaction sequence is required to convert the acid to the ester.[3] Using these reaction conditions, it was also possible to prepare 10 analogues in low to average yields (Tables 1 and 2).

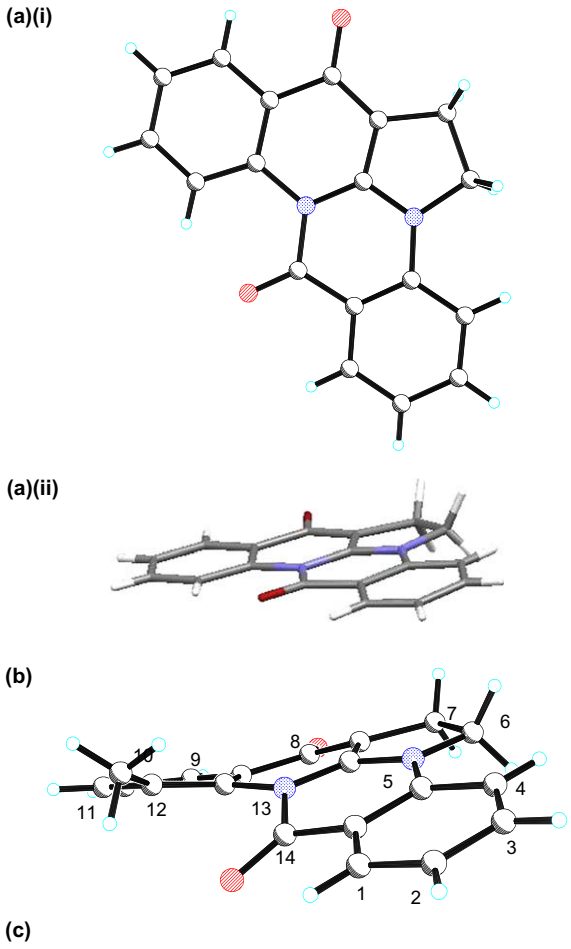
This approach, however, proved far from general with reactions proving unsuccessful when R=4-CO_2H, 4-NO_2, 5-OH, 5-I, 5-NO_2 and 6-Me in **3**. In addition, attempted reactions using nicotinic and isonicotinic acid failed. One possible explanation for the failure of these substrates comes from an observed correlation between the success of the reaction and the melting point of the anthranilic acid. Acids with melting points significantly above the reaction temperature (190 °C) failed (the melting points of the examples listed above range from 213 to 324 °C) whereas in cases where the melting point of the acid is below or close to the reaction temperature some success was observed (Table 2). Interestingly, preliminary studies using a CEM microwave equipped with a camera supported the view that in successful reactions a melt was formed between the reacting anthranilic acid and lactam (see Fig. S1[3]). Additional factors relating to a lack of solubility of the acid in the molten lactam **4**, reduced nucleophilicity of the anthranilic acid amino-functional group in the presence of electron-withdrawing substituents and possible decarboxylation of the anthranilic acid[10] leading to a dramatic increase in the reaction pressure may also play a role in limiting this particular approach.

2.3. The structure of C12 substituted heterocycles

The ^{1}H NMR spectrum of **1a** has been reported by us[1] and others[2] to include a proton that experiences an unexpectedly strong downfield shift (δ, $CHCl_3$, 400 MHz, 9.52 ppm). We have suggested previously[1] that this signal corresponds to the C12-H in **1a** (Scheme 1) and is shifted downfield as a result of its proximity to the C14-carbonyl group. Here we provide further evidence in support of this proposal by reporting a small molecule X-ray structure of **1a** (Fig. 1a). By placing the C12-H in the idealised position, the planar nature of **1a** implies that the C12-H must be positioned within 2.52(1) Å of the C14 oxygen atom. In the light of this, it was surprising to us that it was possible to form analogues using C3-substituted anthranilates or anthranilic acids at all. X-ray crystallographic analysis of **1**(1,1,7) (Fig. 1b) showed that incorporation of a substituent at C12 in **1** can only be achieved at the expense of the planar structure of this heterocycle. The methyl group is accommodated via a distortion of the complete structure as exemplified by the C(12)–C(12a)–N(13)–C(14) torsional angle of 38° in **1**(1,1,7) compared with a value of 0.7° in **1a** (Fig. 1b and c, entry 1). The amide bond in **1**(1,1,7) is also forced to adopt a less than optimal arrangement with the torsional angle C(12a)–N(13)–C(14)–O(14) being 7.3° (Fig. 1c, entry 2). In addition, there is significant distortion of the A and B-rings in **1**(1,1,7), which is not observed in the structure of **1a** (Fig. 1c, entries 3–5). However, little or no distortion of the E-ring in **1**(1,1,7) is observed (Fig. 1c, entry 6).

It is also of interest to compare the ^{1}H NMR spectra of **1a** and **1**(1,1,7) as in the aliphatic region there is a noticeable line broadening of the signals corresponding to the C6- and C7-methylene in **1**(1,1,7) compared with the analogous signals in **1a** (Fig. 2a(i) and a(ii)). This broadening results from the restricted ability of the C12-methyl group in **1**(1,1,7) to pass the C14-carbonyl functionality. The restriction is apparently increased when a chlorine substituent is incorporated at the C12 position as the corresponding signals in the ^{1}H NMR analysis of **1**(1,1,12) are considerably broader and the methylene protons are now diastereotopic (Fig. 2a(iii)). Furthermore, the effect of incorporating a methyl group at the analogous position (C13) in the n=2 series is even more pronounced compared to the n=1 series with the diastereotopic nature of the C6-, C7- and C8- methylene protons in **1**(1,2,7) clearly differing from the situation for **1d** (cf. Fig. 2b(i) and b(ii)). In order to investigate this further, compounds **1**(1,1,7), **1**(1,1,12) and **1**(1,2,7) were studied by variable temperature ^{1}H NMR spectroscopy. Due to the poor solubility of **1**(1,1,12) in toluene and the fact that low temperature spectra were needed to analyse **1**(1,1,7) and **1**(1,1,12), it was not possible to study all the compounds in one solvent. Therefore, the low temperature spectra for **1**(1,1,7) and **1**(1,1,12) were recorded in CD_2Cl_2 and the ^{1}H NMR spectra for **1**(1,2,7) and **1**(1,1,7) were recorded in toluene-d_8 across the temperature range 318–373 K. The rate constants for the movement of the C12 (n=1) or C13 (n=2)-substituent past the C14 (n=1) or C15 (n=2)-carbonyl group at particular temperatures were determined by complete lineshape analysis of the variable temperature spectra using the Bruker TOPSPIN DNMR module. The temperature dependence of the rate constants was used to determine the activation parameters of the exchange process by fitting the experimental data to the Eyring equation. The plots of $\ln(k/T)$ against $1/T$ overall show a very good linear dependence (see Fig. S2[3]) and the resulting activation parameters $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are summarised in Figure 2c.

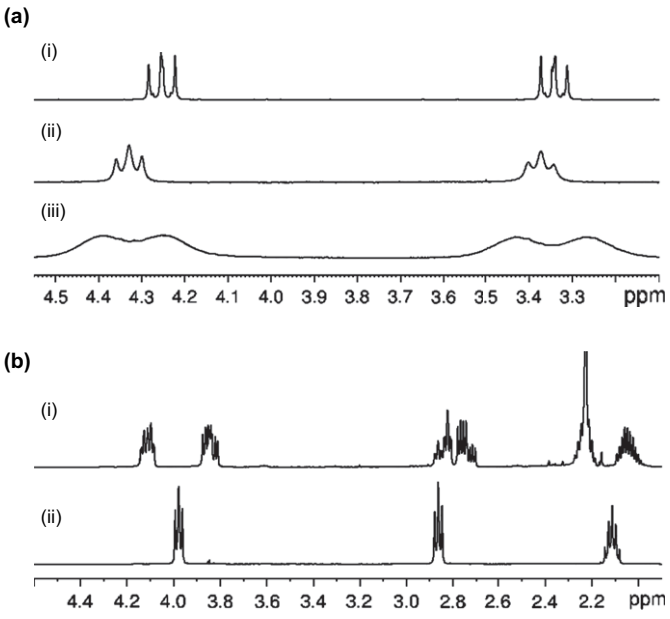
The Gibbs free energy of activation ($\Delta G^{\ddagger}$) clearly shows that, as suspected, substitution of C12-methyl in **1**(1,1,7) by chlorine in



(c)

Entry	Torsion Angle	1a	1(1,1,7)
1	C(12)-C(12a)-N(13)-C(14)	+0.7(3)	+37.7(2)
2	C(12a)-N(13)-C(14)-O(14)	-1.4(3)	+7.3(2)
3	C(9)-C(8a)-C(12a)-C(12)	-0.4(3)	-10.8(2)
4	C(8)-C(8a)-C(12a)-N(13)	+1.1(3)	-14.2(2)
5	O(8)-C(8)-C(8a)-C(9)	+0.5(3)	-6.9(3)
6	C(4)-C(3)-C(2)-C(1)	-2.1(3)	+1.3(3)

Figure 1. (a) X-ray crystal structure of **1a**. (b) X-ray crystal structure of **1**(1,1,7). (c) Analysis of key torsional angles (°) for **1a** and **1**(1,1,7). Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 697507 and 697508. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).



(c)

Compd. # 3-subst.; ring size	NMR solvent	$\Delta G^{\ddagger}_{298}$ kJ mol^{-1}	$\Delta H^{\ddagger}$ kJ mol^{-1}	$\Delta S^{\ddagger}$ JK^{-1} mol^{-1}	k_{298} s^{-1}	$t_{½}$ s
1(1,1,7) 12-Me; n=1	CD_2Cl_2	54.1	50.0	-14	2032	1.71×10^{-4}
1(1,1,7) 12-Me; n=1	d_8-PhMe	52.7	42.9	-33	3635	9.53×10^{-5}
1(1,1,12) 12-Cl; n=1	CD_2Cl_2	61.6	49.8	-39	100	3.43×10^{-3}
1(1,2,7) 13-Me; n=2	d_8-PhMe	74.2	65.9	-28	0.61	0.57

Figure 2. (a) Comparison of the aliphatic region (2×CH_2 triplets) for C(12)=H, Me and Cl for n=1. ^{1}H NMR spectra recorded in $CDCl_3$ at 298 K. (b) Comparison of the aliphatic region (3×CH_2) for C(13)=H and Me when n=2. ^{1}H NMR spectra recorded in $CDCl_3$ at 298 K. (c) Table of rate constants and barriers to rotation for C(12)=Me and Cl (n=1) and C(13)=Me (n=2).

1(1,1,12) reduces the ability of the substituent to pass the C14-carbonyl functionality. An increase in the lactam ring size whilst retaining the methyl substituent (cf. **1**(1,1,7) vs **1**(1,2,7)) gives a similar result. The change from n=1 to n=2 induces mainly a rise in the activation enthalpy ($\Delta H^{\ddagger}$=65.9 kJ mol^{-1} for **1**(1,2,7)) vs 42.9 kJ mol^{-1} for **1**(1,1,7)) while the activation entropies of the two compounds remain approximately the same. It seems likely that incorporation of the additional methylene group in the C-ring of **1**(1,2,7) forces the C13-methyl and C14-carbonyl closer together leading to a greater repulsive interaction as the methyl group tries to pass the carbonyl oxygen. On the contrary, comparison of the activation parameter data obtained for **1**(1,1,7) and **1**(1,1,12) in CD_2Cl_2 demonstrates that there is little difference in $\Delta H^{\ddagger}$ values but that the entropy of activation differs by 25 J K^{-1} mol^{-1} ($\Delta S^{\ddagger}$=−14 J K^{-1} mol^{-1} for **1**(1,1,7) vs −39 J K^{-1} mol^{-1} for **1**(1,1,12)).

Given this somewhat unexpected result, it was decided to establish computationally that the activation parameters derived from the ^{1}H NMR studies did, indeed, correspond to those associated with the racemisation process. Calculation of the ground state structures of **1**(1,1,7) and **1**(1,1,12) at the B3LYP/6-31G(d,p) level of theory afforded the geometries shown in Figure 3a and b. In the case of **1**(1,1,7), where X-ray data is available for comparison, the agreement between the diffraction and the calculated structures is excellent and, in particular, the torsion angle α (Fig. 3a) is reproduced well (calculated structure (49.6°) vs diffraction structure

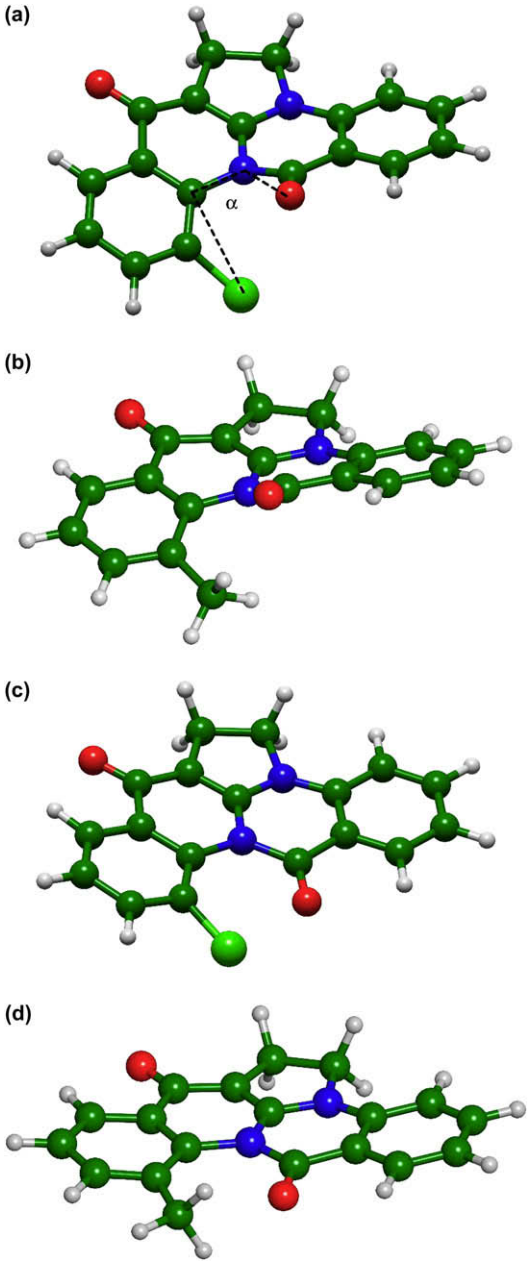


Figure 3. Ball and stick representations of (a) ground state of **1**(1,1,12); (b) ground state of **1**(1,1,7); (c) transition state for racemisation of **1**(1,1,12) and (d) transition state for racemisation of **1**(1,1,7). The key torsional parameter α indicates the degree of bending present in the fused ring framework. For the structures shown, α=(a) 53.4°, (b) 49.6°, (c) 1.2°, (d) 1.3°. Carbon atoms are green, oxygen atoms are red, nitrogen atoms are blue and hydrogen atoms are grey.

(47.4°)). The pathway for the racemisation process was then calculated. Using the semi-empirical RM1 method, the torsion angle α was progressively driven in 2° steps from +50° to −50°. Unsurprisingly, the maximum energy structures were all located around α=0°. Using the maximum energy structure, the transition state for racemisation was located at the RM1 level of theory and these structures were used as initial guesses for refinement of the transition state structures at the B3LYP/6-31G(d,p) level of theory. The calculated transition states for the racemisation of **1**(1,1,7) and **1**(1,1,12) are shown in Figure 3c and d, respectively. Using standard methods, the calculated $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ parameters were extracted for the racemisation process. For **1**(1,1,7), the calculated $\Delta G^{\ddagger}$ is 48.7 kJ mol^{-1} and for **1**(1,1,12), the calculated $\Delta G^{\ddagger}$ is

60.0 kJ mol^{-1}. These results are in good agreement with the experimental data, however, the question of the low value of $\Delta S^{\ddagger}$ for **1**(1,1,7) remained. The methyl group rotation is clearly restricted in the transition state for racemisation. It was reasoned that, if restricted rotation of the methyl group was also present in the ground state of **1**(1,1,7), the net change in entropy on moving from the **1**(1,1,7) ground state to the transition state would be less, i.e., the observed entropy change is influenced by a ground state effect in **1**(1,1,7). In simple aromatic compounds such as toluene, there is essentially no activation barrier for methyl group rotation. Therefore, the pathway for the rotation of the methyl group in **1**(1,1,7) was calculated using the semi-empirical RM1 method by driving the torsion angle of one of the methyl hydrogens with respect to the adjacent aromatic ring in 2° steps from 0° to 360°. The results (Fig. 4) indicate that there are three clearly preferred orientations for the methyl group and the barrier (at the RM1 level of theory) for their interconversion is around 12 kJ mol^{-1}. As before, this structure was then used as an initial guess for refinement of the transition state structure at the B3LYP/6-31G(d,p) level of theory. The calculated barrier ($\Delta G^{\ddagger}$) at this higher level of theory is larger than that suggested by the semi-empirical RM1 method at 28.7 kJ mol^{-1}. Armed with the knowledge that there is a significant barrier to methyl group rotation in the ground state of **1**(1,1,7), we looked for experimental evidence for restricted rotation to support the calculations. Close examination of the ^{1}H NMR data for **1**(1,1,7) reveals that the resonance arising from the methyl group has a significantly increased line width. At room temperature, the line width at half peak height for the singlet arising from the methyl group in toluene is 0.7 Hz. By contrast, the line width at half peak height for the singlet arising from the methyl group in **1**(1,1,7) is 2.5 Hz. This broadening is consistent with restricted rotation of the C12-methyl group in the ground state. This observation rationalises the apparently small $\Delta S^{\ddagger}$ for racemisation of **1**(1,1,7). Although the chiral nature of these compounds has been shown by ^{1}H NMR, resolution of enantiomers by chiral HPLC is impossible due to the relatively low barriers to interconversion ($t_{1/2}$ $^{298}_{\text{rac}}$ less than 1s, Fig. 2c).

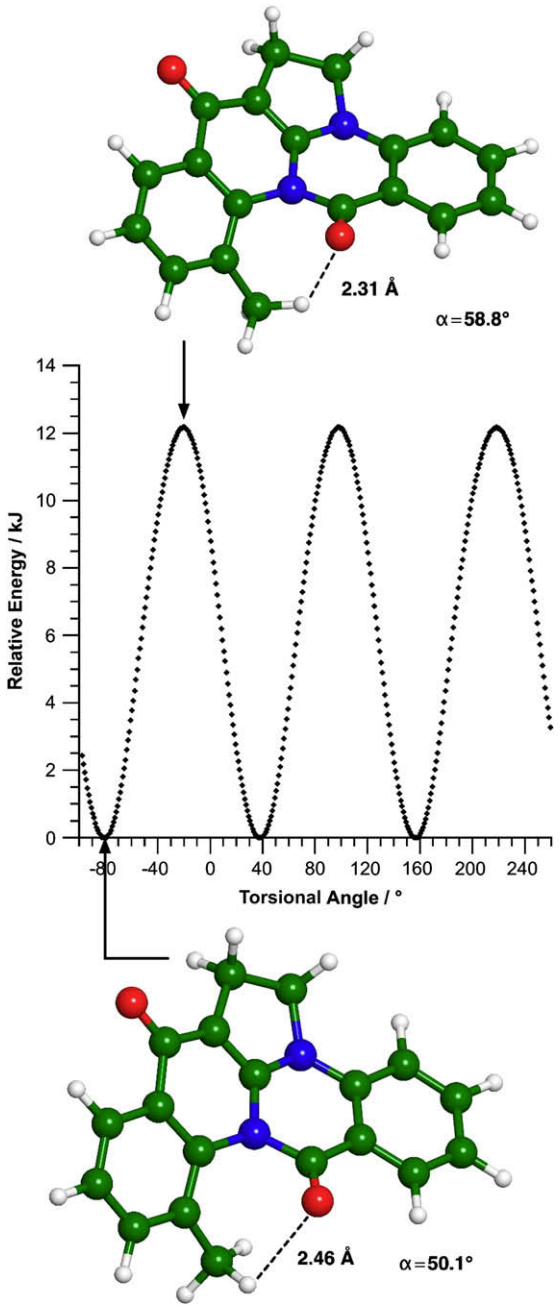
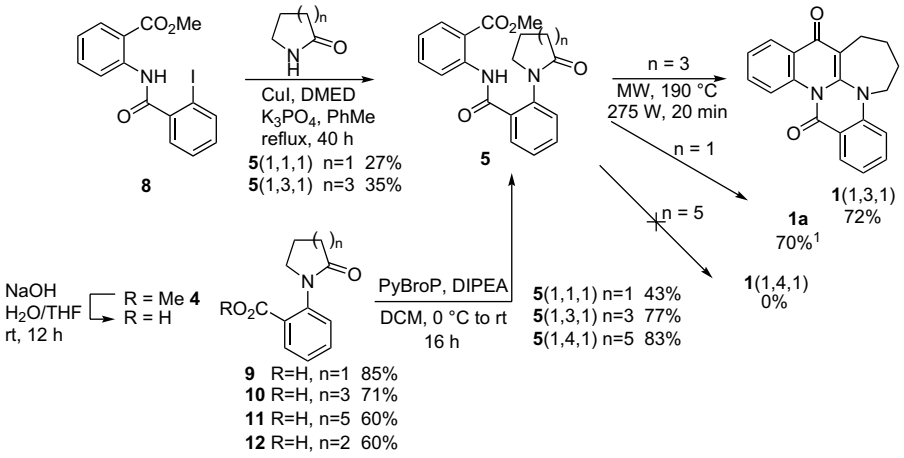


Figure 4. Torsional energy profile for the rotation of the methyl group in **1**(1,1,7) at the RM1 level of theory. The torsion angle is the angle subtended between the C–H bond in the methyl group and the C–C bond in the adjacent aromatic ring. The torsional parameter α is defined in the same manner as in Figure 3 and indicates the degree of bending present in the fused ring framework. The distance shown is that between the carbonyl oxygen atom and the nearest hydrogen atom on the methyl group. Carbon atoms are green, oxygen atoms are red, nitrogen atoms are blue and hydrogen atoms are grey.

2.4. Applications of method 2

During the exploration of the scope of method 1 both with anthranilic esters and acids, several limitations were identified. In particular, attempts to incorporate a 5-Br-substituent, a range of heteroatomic A-rings and large ring lactams **4** (n>2) failed despite significant attempts to optimise the microwave reaction conditions. A probable explanation for these observations is failure of the initial amide bond forming reaction to generate intermediates of the general structure **5** (Scheme 1). It was, therefore, decided to focus on alternative methods of forming this amide bond. We have previously reported[1] the formation of this bond through reaction of *o*-iodo-benzoyl chloride with methyl anthranilate **3** (R=H, R^1=Me) to give **8** in excellent yield (Scheme 2). Although the subsequent N-arylation of 2-pyrrolidinone using **8** resulted in formation of the *N*-aryl-lactam **5** in low yield, we demonstrated that **5** was efficiently converted to **1a** under microwave irradiation conditions. Here we report that this reaction sequence can also be used to prepare **1**(1,3,1) (Scheme 2), a compound containing a seven-membered ring, by initial N-arylation of δ-caprolactam with **8**, followed by microwave irradiation of **5**(1,3,1) to give **1**(1,3,1) in 72% yield for the key zipper reaction (Scheme 2). It is of interest to note that attempts to form **1**(1,3,1) using method 1 resulted in formation of only trace amounts of the desired product (see Fig. S3[3]).

In an attempt to avoid the low yielding copper-catalysed N-arylation reaction, the lactam esters **4** (n=1, 2 or 3) were hydrolysed to give the corresponding carboxylic acids **9**–**11** in good yield (Scheme 2). Subsequent amide bond coupling with methyl anthranilate **3**(R=H, R^1=Me) using PyBroP resulted in formation of the desired cyclisation precursors in moderate to good yields, providing improved access compared to our previous route.[1] The use of carbodiimide-based reagents in this reaction was less successful consistent with PyBroP's reported improved performance compared to other coupling reagents when weak amine nucleophiles are used.[11] Whilst access to **5**(1,4,1) was achieved in good yield, attempts to cyclise **5**(1,4,1) proved unsuccessful with no reaction occurring under the standard microwave conditions. Extensive decomposition resulted from the use of more forcing microwave conditions or high temperatures in a sealed tube.[12]



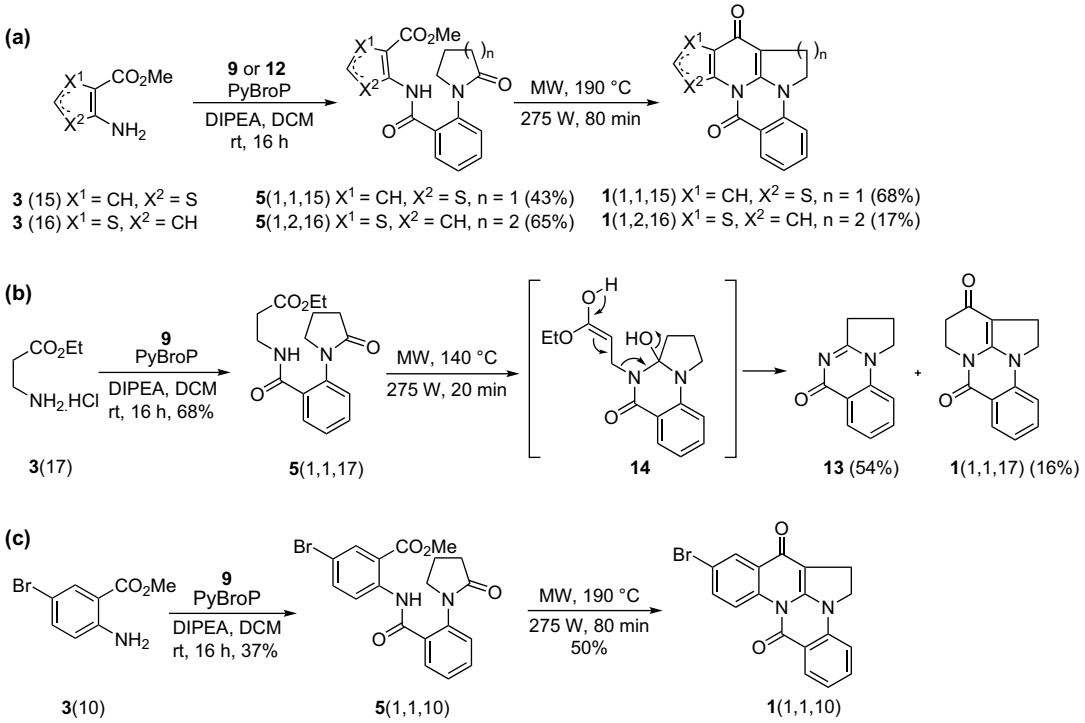
Scheme 2. Alternative approaches for the synthesis of **1**(1,3,1) using method 2.

Having established a relatively rapid method for preparing substrates for method 2, this approach was successfully applied to the synthesis of thiophene and isothiophene containing heterocycles **1**(1,1,15) and **1**(1,2,16) (Scheme 3a), compounds that were not accessible using method 1. PyBroP-mediated coupling of **3**(15) with **9** and **3**(16) with **12** (Scheme 2) led to the formation of **5**(1,1,15) and **5**(1,2,16), respectively. Compound **5**(1,1,15) was converted in 68% yield to the desired compound **1**(1,1,15) and **1**(1,2,16) was formed from **5**(1,2,16), albeit in significantly lower yield. The reduced yield for formation of **1**(1,2,16) was interesting and may have its origins in an analogous effect to that observed when a C6-substituent is present in **3** as discussed above (e.g., for formation of **1**(1,1,7)). Attempts to use method 2 as a means of incorporating nitrogen atoms in ring-A of **1** proved unsuccessful for both the pyridine and pyrazine cases with the sequence failing at the amide bond forming stage.

However, it was possible to replace the A-ring in **1** with a simple alkyl backbone by using β-amino acid ester **3**(17) (Scheme 3b). The major compound **13**[13] formed in this reaction presumably results from a β-elimination reaction under the MW conditions as shown for the proposed intermediate **14** (Scheme 3b). Method 2 also allowed the synthesis of the 10-Br containing **1**(1,1,10) in acceptable yield through microwave reaction of the **5**(1,1,10) (Scheme 3c). It has not been possible to prepare **1**(1,1,10) using method 1.

2.5. Computational analysis of observed ^{1}H chemical shifts

Use of method 2 enabled the synthesis of **1**(1,3,1) (Scheme 2) allowing a detailed comparison of the ^{1}H NMR spectra obtained for **1a** (n=1), **1d** (n=2) and **1**(1,3,1) (n=3), compounds that differ only in the number of methylene groups present in the C-ring (Fig. 5a). A



Scheme 3. Examples of the use of method 2 for the synthesis of (a) sulfur containing heterocycles (thiophene and isothiophene), (b) heterocycles in which the aromatic A-ring has been replaced by an alkyl chain and (c) **1** containing an EWG in the 5-position to access **1**(1,1,14), **1**(1,2,15), **1**(1,1,16) and **1**(1,1,10).

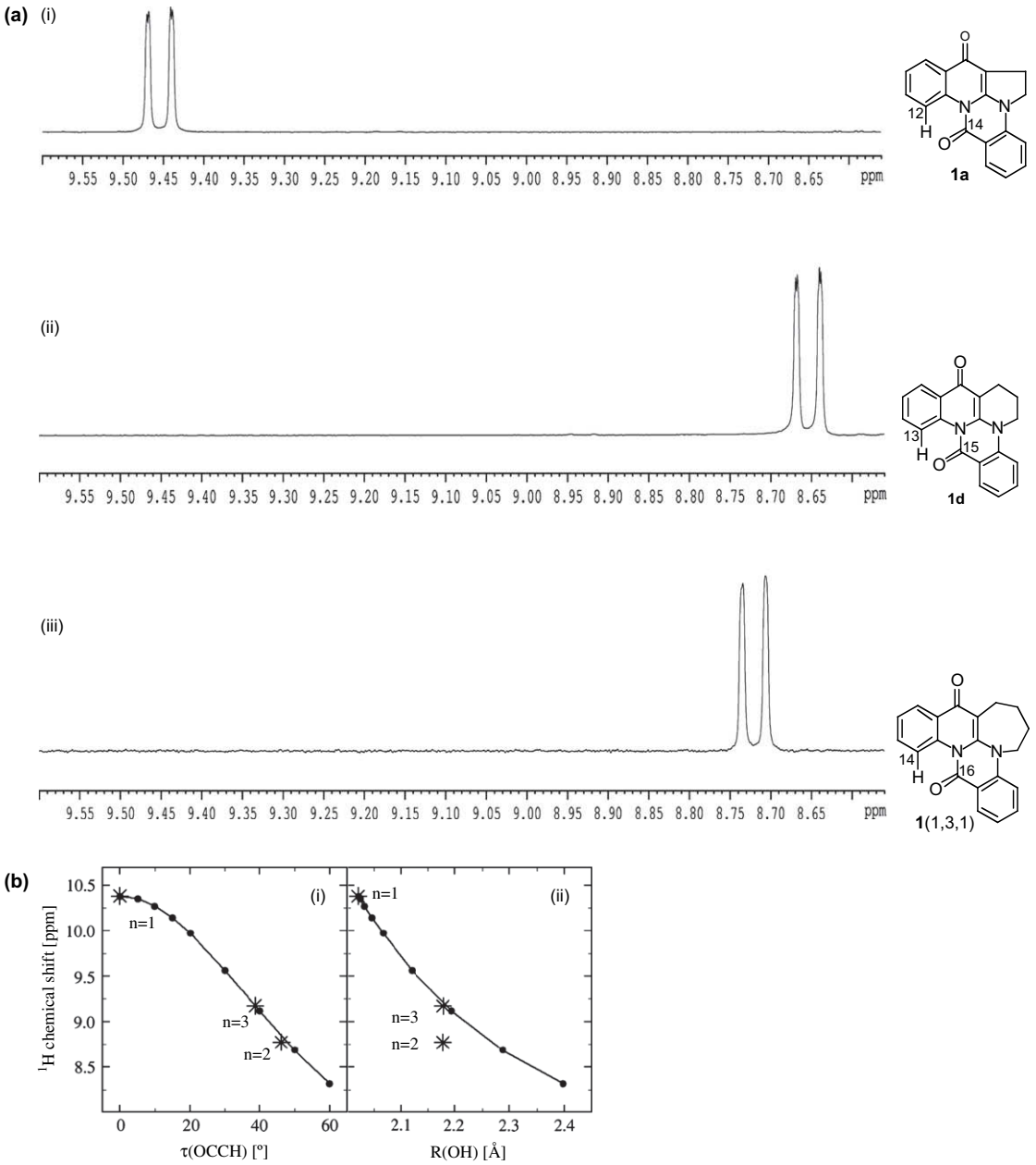


Figure 5. (a) ^{1}H NMR analysis of three closely related heterocyclic structures as a function of the size of the C-ring in **1**. A significant downfield shift is observed for the C12H proton in **1a** (n=1) compared to other ring sizes. (b) Computational studies at the B3LYP level to explore the dependence of the chemical shift of the signal corresponding to the A-ring *ortho*-proton as a function of (i) τ(O14–C14–C12–H12) dihedral angle and (ii) O–H distance in the n=1 system (solid circles). The calculated chemical shifts of the signal for the A-ring *ortho*-proton in **1a** (n=1), **1d** (n=2) and **1**(1,3,1) (n=3) are represented by *(n=x).

striking difference in the ^{1}H NMR spectrum of **1a** compared with **1d** and **1**(1,3,1) was observed with the chemical shift of the signal corresponding to the *ortho*-proton in the A-ring being significantly more downfield for **1a** (9.52 ppm) than for **1d** (8.66 ppm) and **1**(1,3,1) (8.70 ppm) (Fig. 3a). We became interested in the origins of this variation and decided to probe this using computational analysis at the B3LYP/6-31G(d,p) level of theory.

To investigate if the large change in chemical shift observed for the *ortho*-proton in the A-ring on going from **1a** (C12H) to **1d** (C13H) and **1**(1,3,1) (C14H) was due to a move away from a planar structure in **1d** and **1**(1,3,1), we computed theoretical chemical shift values not only for the three compounds, but also for an artificially twisted version of the n=1 system. To this end, we optimised the structure of **1a** with the O14–C14–C12–H12 dihedral angle (Fig. 5a) frozen at step intervals between 0° and 60°. The computational studies suggested that to accommodate variation in this dihedral angle, the structure of **1a** distorts away from the planar structure, in agreement with our previous X-ray crystallographic studies in the n=2 system.[1] Figure 5b shows the calculated chemical shifts for the A-ring *ortho*-proton in the artificially generated geometries in comparison to the chemical shift values calculated for the fully optimised structures of **1a**, **1d** and **1**(1,3,1). In Figure 5b(i) the dependence of the calculated chemical shift on the O14–C14–C12–H12 dihedral angle is shown. The chemical shifts calculated for **1d** (n=2) and **1**(1,3,1) (n=3) systems are extremely close to the curve of the distorted **1a** (n=1) system, confirming that the change in chemical shift is nearly entirely due to the non-planarity of the ring systems. These calculations also agree with the trend observed in the chemical shift of the A-ring *ortho*-proton in practice (i.e., in order of decreasing parts per million value **1a**>**1**(1,3,1)>**1d**).

Figure 5b(ii) shows calculated chemical shifts plotted as a function of the O–H distance. Interestingly, for **1d** (n=2) and **1**(1,3,1) (n=3) the calculations show near-identical O–H distances, but significantly different chemical shift values for the C13H in **1d** and C14H in **1**(1,3,1), respectively. We can conclude from this that the torsional angle used in these calculations is a better predictor of the change in the chemical shift of the A-ring *ortho*-proton than the mere distance from the oxygen atom, consistent with a complex view of the carbonyl deshielding cone that contains subtle differences in deshielding strength as the cone is traversed.[14]

3. Conclusions

These studies have shown that it is possible to access rapidly a wide range of structures based on the diazabenz[*e*]aceanthrylene core structure using two complementary microwave-assisted approaches. We have explored the scope of these reactions particularly focussing on variation of substituents in both the anthranilic esters and acids **3** and the *N*-aryl lactam esters **4** in method 1. Subsequent studies on the chemical reactivity of these heterocyclic systems will be reported in the near future. During the course of these studies a range of interesting structural and spectroscopic issues arose and these have been investigated further with the aid of NMR, X-ray crystallographic and computational techniques.

4. Experimental

4.1. General

Chemicals and solvents were purchased from the Aldrich Chemical Company, Fisher Chemicals and Lancaster and were used as received unless otherwise stated. Air and moisture sensitive reactions were carried out under an inert atmosphere of dried argon and glassware was oven-dried (145 °C).

Analytical thin-layer chromatography (TLC) was performed on pre-coated TLC plates SIL G-25 UV_{254} (layer 0.25 mm silica gel with fluorescent indicator UV_{254}) (Aldrich). Developed plates were air-dried and analysed under a UV lamp, Model UVGL-58 (Mineralight LAMP, Multiband $UV_{254/365}$ nm) and where necessary, stained with a solution of ceric ammonium molybdate, ninhydrin or iodine on silica to aid identification. Flash column chromatography was performed using silica gel (40–63 μm) (Fluorochem). Copper(I) iodide catalyst was purified according to a literature method.

Melting points were determined using an Electrothermal 9100 capillary melting point apparatus. Values are quoted to the nearest 1 °C and are uncorrected.

^{1}H NMR spectra were recorded on a Bruker Avance 300 (300.1 MHz) spectrometer. ^{13}C NMR spectra using the DEPTQ sequence were recorded on a Bruker Avance 300 (75.5 MHz) spectrometer. Chemical shifts (δ) are recorded using the residual solvent as the internal reference in all cases ($CDCl_3$ δH 7.27 ppm, δC 77.0 ppm). Coupling constants (J) are quoted to the nearest 0.1 Hz. The following abbreviations are used; s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublets of doublets; dt, doublet of triplets; t, triplet; m, multiplet and br, broad. IR spectra were recorded on a Perkin Elmer Spectrum GX FT-IR spectrometer.

Low resolution and high resolution (HR) electrospray mass spectral (ES-MS) analyses were recorded on a high performance orthogonal acceleration reflecting TOF mass spectrometer, coupled to a Waters 2975 HPLC. Only the major peaks are reported and intensities are quoted as percentages of the base peak.

The purity of precipitated products was measured using liquid chromatography mass spectrometry (LCMS). The LCMS system includes a Waters 2996 photodiode array detector, Waters 2795 Alliance HT Separations Module, Micromass LCT, Thinkcenter IBM running MassLynx™ 4.0.Global. Separations were performed using a Waters Xterra™ RP_{18} (5 μm, 3.0×50 mm) HPLC column.

Microwave-assisted reactions were performed using a CEM Discover microwave operated in 'powermax' mode.

The geometries of the n=1, n=2 and n=3 pentacycles were optimised using density functional theory (DFT) using the B3LYP[15] functional and the 6-31+G(d) basis set. The shielding tensors were computed using the gauge-independent atomic orbital (GIAO)[16,17] method, employing the B97-2[18] functional and the 6-311G(d,p) basis set. The 1*H* isotropic chemical shifts were referenced to tetramethylsilane (TMS), the shielding tensor of which was determined with the same methodology. All calculations were performed with the Gaussian 03 program package[19] on the EaStCHEM Research Computing Facility.

4.2. General procedure for the synthesis of 1(1–2,1–4,1–17)

4.2.1. Ester route

A mixture of the methyl anthranilate **3**(1–8,10,14–16) (4.00 mmol) and the *N*-aryl lactam **4**(1–2,1–2) (1.00 mmol) in a sealed glass microwave tube was heated to 190 °C, (maximum 275 W), with air flowing through the reaction chamber, for 30 min. Upon cooling the reaction mixture was added to diethyl ether (30.0 mL) and the resultant precipitate filtered. The precipitate was purified by flash column chromatography over silica gel (99:1, chloroform/methanol) to afford the title compound. An analytically pure sample of **1** was prepared by recrystallisation from acetic acid.

4.2.2. Acid route

A mixture of the anthranilic acid **3**(1,3,7,9,11–13) (6.00 mmol) and methyl 2-(2-oxo-pyrrolidin-1-yl)-benzoate **4**(1,1) (1.00 mmol) in a sealed glass microwave tube was heated to 190 °C, (maximum 275 W), with air flowing through the reaction chamber, for 60 min. Upon cooling the reaction mixture was added to chloroform (30.0 mL) and washed with saturated sodium hydrogen carbonate solution (2×30.0 mL). The organic layer was then dried ($MgSO_4$), filtered and concentrated in vacuo to give a solid, which was purified by flash column chromatography (99:1, chloroform/methanol) to afford the title compound. An analytically pure sample of **1** was prepared by recrystallisation from acetic acid.

4.2.3. Intramolecular cyclisation

Compound **5** (1.00 mmol) was heated in a sealed glass microwave tube to 190 °C, (maximum 275 W) for 20 min (unless otherwise stated). The resultant yellow/brown solid was purified by column chromatography over silica gel (99:1, chloroform/methanol) to give a yellow solid **1a**, **1**(1,1,10), **1**(1,3,1), **1**(1,1,15), **1**(1,2,16) or **1**(1,1,17).

4.3. General procedure for the synthesis of 5

4.3.1. PyBroP amide bond coupling

To a solution of 2-(*N*-lactam)-benzoic acid **9**–**12** (1.5 mmol), methyl anthranilate **3** (1.0 mmol), and PyBroP® (0.70 g, 1.5 mmol) coupling reagent in DCM (8 mL) was treated under stirring with DIPEA (0.70 mL, 4.0 mmol) at 0 °C. The ice bath was removed after 1 min and the stirring continued at room temperature for 15 h. The mixture was poured into ethyl acetate (300 mL) and the solution treated with $NaHCO_3$ (10% w/v) (100 mL) and the solution extracted with ethyl acetate (3×150 mL). The organic layer was washed with brine (100 mL) and then dried ($MgSO_4$). The solvent was removed in vacuo to yield a bright yellow powder. The powder was purified by flash column chromatography on silica gel (6:4 ethyl acetate/hexane) to give the title compound **5** as a pale brown oil.

4.3.2. **1**(2,2,1) 2-Methoxy-6,7,8-trihydro-9H,15H-5,14-diaza-dibenzo[a,de]anthracen-9,15-dione

Yield **1**(2,2,1) (0.246 g, 0.74 mmol, 74%) (LCMS purity 99%) as a brown powder using ester route. Mp 209–210 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.65 (dd, ^3J=9.0 Hz, ^4J=1.0 Hz, 1H, C13-*H*), 8.39 (dd, ^3J=8.0 Hz, ^4J=2.0 Hz, 1H, C10-*H*), 7.73 (d, ^3J=3.0 Hz, 1H, C1-*H*), 7.61–7.54 (m, 1H, C12-*H*), 7.50–7.44 (m, 1H, C11-*H*), 7.34–7.29 (m, 1H, C3-*H*), 7.26–7.20 (m, 1H, C4-*H*), 4.00 (t, ^3J=6.0 Hz, 2H, C6-H_2), 3.91 (s, 3H, OCH_3), 2.90 (t, ^3J=6.0 Hz, 2H, C8-H_2), 2.18–2.09 (m, 2H, C7-H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=175.0 (C9), 160.3 (C15), 155.3 (C2), 144.5 (C5a), 135.5 (C4a), 135.2 (C13a), 129.8 (C12), 126.4 (C9a), 126.3 (C11), 125.3 (C10), 125.0 (C3), 122.3 (C13), 116.0 (C15a), 114.6 (C4), 110.2 (C1), 101.6 (C8a), 56.0 (OCH$_3$), 47.1 (C6), 20.1 (C8), 19.8 (C7); IR (KBr): ν_{max}=2936 (m), 1699 (s) (C=O), 1610 (s), 1591 (s), 1534 (m), 1483 (m), 1146 (w) (C–O), 759 (m) (Ar–H) cm^{-1}; LRMS (ES$^+$): *m*/*z* (%) 333.01 (100) [M+H]$^+$; HRMS (ES$^+$): *m*/*z* calcd for $C_{20}H_{17}N_2O_3$ [M+H]$^+$: 333.1239; found: 333.1228.

4.3.3. **1**(1,1,2) 11-Chloro 8,14-dioxo-6,7-dihydro-8H,14H-5,13-diazabenz[e]aceanthrylene

Yield **1**(1,1,2) (0.171 g, 0.53 mmol, 53%) (LCMS purity 94%) as a pale brown powder using the ester route. Mp 276 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.59 (d, ^4J=2.0 Hz, 1H, C12-*H*), 8.37 (d, ^3J=8.5 Hz, 1H, C9-*H*), 8.26 (d, ^3J=8.0 Hz, ^4J=1.5 Hz, 1H, C1-*H*), 7.76–7.70 (m, 1H, C3-*H*), 7.42 (dd, ^3J=8.5 Hz, ^4J=2.0 Hz, 1H, C10-*H*), 7.30–7.24 (m, 1H, C2-*H*), 6.97 (d, ^3J=8.0 Hz, 1H, C4-*H*), 4.30 (t, ^3J=9.5 Hz, 2H, C6-H_2), 3.36 (t, ^3J=9.5 Hz, 2H, C7-H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=171.7 (C8), 159.7 (C14), 148.8 (C5a), 139.0 (C4a), 137.5 (C12a), 136.6 (C3), 130.1 (C1), 127.0 (C10), 126.6 (C9), 123.8 (C11), 122.8 (C2), 121.1 (C12), 120.7 (C8a), 115.0 (C14a), 112.4 (C4), 102.8 (C7a), 47.1 (C6), 22.8 (C7); IR (KBr): ν_{max}=1707 (s) (C=O), 1604 (s), 1582 (s), 1498 (s), 1466 (m), 1425 (w), 1324 (w), 1157 (w) (C–O), 746 (m) (Ar–H) cm^{-1}; LRMS (ES$^+$): *m*/*z* (%) 323.04 (100) [M+H]$^+$, 345.03 (20) [M+Na]$^+$, 667.07 [2M+Na]$^+$; HRMS (ES$^+$): *m*/*z* calcd for $C_{18}H_{11}N_2O_2NaCl$ [M+Na]$^+$: 345.0407; found: 345.0402.

4.3.4. **1**(1,2,2) 12-Chloro 6,7,8-trihydro-9H,15H-5,14-diaza-dibenzo[a,de]anthracen-9,15-dione

Yield **1**(1,2,2) (0.11 g, 0.33 mmol, 33%) (LCMS purity 99%) as a brown powder using the ester route. Mp 241–242 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.68 (d, ^4J=2.0 Hz, 1H, C13-*H*), 8.25–8.20 (m, 2H, C10-*H*, C1-*H*), 7.69–7.63 (m, 1H, C3-*H*), 7.36 (dd, ^3J=8.5 Hz, ^4J=2.0 Hz, 1H, C11-*H*), 7.24–7.18 (m, 2H, C2-*H*, C4-*H*), 3.95 (t, ^3J=6.0 Hz, 2H, C6-H_2), 2.81 (t, ^3J=6.0 Hz, 2H, C8-H_2), 2.12–2.02 (m, 2H, C7-H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=174.3 (C9), 160.2 (C15), 144.2 (C5a), 140.7 (C4a), 136.4 (C3), 136.2 (C13a), 136.1 (C9a), 129.6 (C10), 126.8 (C11), 126.7 (C1), 124.1 (C12), 122.9 (C2), 122.3 (C13), 115.3 (C15a), 112.8 (C4), 102.6 (C8a), 47.0 (C6), 20.0 (C8), 19.7 (C7); IR (KBr): ν_{max}=3445 (w) (OH), 1708 (s) (C=O), 1582 (w), 1521 (s), 1473 (s), 1369 (m), 1320 (w), 1286 (w) (C–O), 1179 (w) (C–O), 746 (m) (Ar–H) cm^{-1}; LRMS (ES$^+$): *m*/*z* (%) 337.09 (100) [M^{35}Cl+H]$^+$; HRMS (ES$^+$): *m*/*z* calcd for $C_{19}H_{14}ClN_2O_2$ [M+H]$^+$: 337.0744; found: 337.0741.

4.3.5. **1**(2,1,2) 2-Methoxy-11-chloro-8,14-dioxo-6,7-dihydro-8H,14H-5,13-diazabenz[e]aceanthrylene

Yield **1**(2,1,2) (0.183 g, 0.81 mmol, 81%) as a yellow powder using the ester route. Mp 308–309 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.63 (s, 1H, C12-*H*), 8.42 (d, ^3J=8.4 Hz, 1H, C9-*H*), 7.71 (d, ^4J=2.9 Hz, 1H, C1-*H*), 7.47 (dd, ^3J=8.4 Hz, ^4J=2.9 Hz, 1H, C10-*H*), 7.35 (dd, ^3J=8.8 Hz, ^4J=2.9 Hz, 1H, C3-*H*), 6.94 (d, ^3J=8.8 Hz, 1H, C4-*H*), 4.30 (t, ^3J=8.8 Hz, 2H, C6-H_2), 3.92 (s, 3H, ArOCH_3), 3.37 (t, ^3J=8.8 Hz, 2H, C7-H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=171.2 (C8), 159.9 (C14), 155.8 (C2), 148.6 (C5a), 136.9 (C4a), 136.5 (C11), 133.2 (C12a), 129.2 (C10), 127.2 (C9), 126.4 (C8a), 126.1 (C3), 121.2 (C12), 115.1 (C14a), 114.2 (C4), 110.8 (C1), 102.2 (C7a), 56.1 (OCH$_3$), 47.7 (C6), 23.3 (C7); IR (KBr): ν_{max}=2949 (m), 1709 (s) (C=O), 1700 (m) (C=O), 1601 (s), 1557 (w), 1499 (m), 1318 (m), 1158 (m) (C–O) cm^{-1}; LRMS (CI$^+$): *m*/*z* (%) 353.07 (100) [M+H]$^+$; HRMS (ES$^+$): *m*/*z* calcd for $C_{19}H_{14}N_2O_3Cl$ [M+H]$^+$: 353.0693; found: 353.0692.

4.3.6. **1**(2,2,2) 2-Methoxy-12-chloro-6,7,8-trihydro-9H,15H-5,14-diaza-dibenzo[a,de]anthracen-9,15-dione

Yield **1**(2,2,2) (0.220 g, 0.60 mmol, 60%) as a yellow powder using the ester route. Mp 233–234 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.75 (d, ^4J=2.0 Hz, 1H, C13-*H*), 8.29 (d, ^3J=8.6 Hz, 1H, C10-*H*), 7.70 (d, ^4J=3.0 Hz, 1H, C1-*H*), 7.41 (dd, ^3J=8.6 Hz, ^4J=2.0 Hz, 1H, C11-*H*), 7.32 (dd, ^3J=9.0 Hz, ^4J=3.0 Hz, C3-*H*), 7.23 (d, ^3J=9.0 Hz, 1H, C4-*H*), 4.00 (t, ^3J=6.0 Hz, 2H, C6-H_2), 3.91 (s, 3H, ArOCH_3), 2.87 (t, ^3J=6.0 Hz, 2H, C8-H_2), 2.12 (qt, ^3J=6.0 Hz, 2H, C7-H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=174.2 (C9), 160.7 (C15), 155.5 (C2), 145.2 (C5a), 136.2 (C12), 136.0 (C13a), 135.2 (C4a), 126.9 (C11), 126.8 (C10), 125.5 (C3), 124.9 (C9a), 122.3 (C13), 115.9 (C15a), 114.8 (C4), 110.3 (C1), 101.9 (C8a), 56.2 (ArOCH_3), 47.2 (C6), 20.1 (C7), 19.9 (C8); IR (KBr): ν_{max}=2950 (m) (CH), 1664 (s) (C=O), 1599 (m), 1497 (m), 1353 (m), 1099 (m) (C–O), 766 (m) (Ar–H) cm^{-1}; LRMS (CI$^+$): *m*/*z* (%) 367.09 (100) [M+H]$^+$; HRMS (CI$^+$): *m*/*z* calcd for $C_{20}H_{16}N_2O_3Cl$ [M+H]$^+$: 367.0849; found: 367.0854.

4.3.7. **1**(1,1,3) 12-Methyl-8,14-dioxo-6,7-dihydro-8H,14H-5,13-diazabenz[e]aceanthrylene

Yield **1**(1,1,3) (0.139 g, 0.46 mmol, 46%) as a yellow powder using the ester route. Mp 286 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.26 (s, 1H, C12-*H*), 8.26 (d, ^3J=8.0 Hz, 1H, C9-*H*), 8.19 (dd, ^3J=8.0 Hz, ^4J=1.3 Hz, 1H, C1-*H*), 7.67 (ddd, ^3J=7.7 Hz, ^3J=7.7 Hz, ^4J=1.3 Hz, 1H, C3-*H*), 7.22–7.16 (m, 2H, C10-*H*, C2-*H*), 6.90 (d, ^3J=8.2 Hz, 1H, C4-*H*), 4.23 (t, ^3J=8.8 Hz, 2H, C6-H_2), 3.31 (t, ^3J=8.8 Hz, 2H, C7-H_2), 2.47 (s, 3H, ArCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=172.7 (C8), 160.2 (C14), 148.4 (C5a), 141.7 (C12a), 138.8 (C4a), 136.6 (C11), 136.2 (C3), 130.0 (C1), 127.8 (C10), 125.5 (C8a), 125.4 (C9), 122.4 (C2), 121.3 (C12), 114.7 (C14a), 112.3 (C4), 101.2 (C7a), 47.3 (C6), 23.5 (C7), 22.4 (ArCH_3); IR (KBr): ν_{max}=2924 (m), 1717 (s) (C=O), 1705 (m) (C=O), 1599 (m), 1556 (m), 1497 (m), 1308 (m), 1143 (m) (C–O) cm^{-1}; LRMS (CI$^+$): *m*/*z* (%) 303.11 (100) [M+H]$^+$; HRMS (CI$^+$): *m*/*z* calcd for $C_{19}H_{15}N_2O_2$ [M+H]$^+$: 303.1134; found: 303.1128.

4.3.8. **1**(1,2,3) 12-Methyl-6,7,8-trihydro-9H,15H-5,14-diaza-dibenzo[a,de]anthracen-9,15-dione

Yield **1**(1,2,3) (0.194 g, 0.55 mmol, 55%) as a yellow powder using the ester route. Mp 162–163 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.47 (s, 1H, C13-*H*), 8.31 (dd, ^3J=8.3 Hz, ^4J=1.9 Hz, 1H, C10-*H*), 8.27 (d, ^3J=8.0 Hz, 1H, C1-*H*), 7.73 (ddd, ^3J=7.3 Hz, ^3J=7.3 Hz, ^4J=1.7 Hz, 1H, C3-*H*), 7.31–7.25 (m, 3H, C11-*H*, C2-*H*, C4-*H*), 4.03 (t, ^3J=6.0 Hz, 2H, C6-H_2), 2.90 (t, ^3J=6.0 Hz, 2H, C8-H_2), 2.52 (s, 3H, ArCH_3), 2.16 (qt, ^3J=6.0 Hz, 2H, C7-H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=175.7 (C9), 160.5 (C15), 144.5 (C5a), 140.9 (C13a), 140.7 (C4a), 136.0 (C3), 135.8 (C12), 129.6 (C1), 127.8 (C11), 125.4 (C10), 124.3 (C9a), 122.6 (C2), 122.4 (C13), 115.7 (C15a), 112.7 (C4), 102.3 (C8a), 47.0 (C6), 22.3 (ArCH_3), 20.3 (C7), 19.9 (C8); IR (KBr): ν_{max}=2925 (m) (CH), 1671 (s) (C=O), 1599 (m), 1535 (m), 1475 (m), 1320 (w), 1173 (m) (C–O), 773 (m) cm^{-1}; LRMS (CI$^+$): *m*/*z* (%) 317.13 (100) [M+H]$^+$; HRMS (CI$^+$): *m*/*z* calcd for $C_{20}H_{17}N_2O_2$ [M+H]$^+$: 317.1290; found: 317.1290.

4.3.9. **1**(2,1,3) 2-Methoxy-11-methyl-8,14-dioxo-6,7-dihydro-8H,14H-5,13-diazabenz[e]aceanthrylenes

Yield **1**(2,1,3) (0.077 g, 0.23 mmol, 34%) as a yellow powder using the ester route. Mp 116–117 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.22 (s, 1H, C12-*H*), 8.24 (d, ^3J=8.0 Hz, 1H, C9-*H*), 7.56 (d, ^4J=3.0 Hz, 1H, C1-*H*), 7.23 (dd, ^3J=9.0 Hz, ^4J=3.0 Hz, 1H, C3-*H*), 7.17 (d, ^3J=8.0 Hz, 1H, C10-*H*), 6.81 (d, ^3J=9.0 Hz, 1H, C4-*H*), 4.15 (t,

^3J=8.8 Hz, 2H, C6-H_2), 3.83 (s, 3H, ArOCH_3), 3.27 (t, ^3J=8.8 Hz, 2H, C7-H_2), 2.43 (s, 3H, ArCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=171.9 (C8), 160.0 (C14), 155.4 (C2), 148.3 (C5a), 141.4 (C12a), 136.3 (C4a), 133.0 (C11), 127.8 (C10), 127.4 (C8a), 125.6 (C9), 125.2 (C3), 121.1 (C12), 115.1 (C14a), 114.1 (C4), 110.4 (C1), 101.6 (C7a), 56.1 (ArOCH_3), 47.5 (C6), 23.4 (C7), 22.1 (ArCH_3); IR (KBr): ν_{max}=2947 (m), 1718 (s) (C=O), 1701 (m) (C=O), 1607 (s), 1556 (m), 1499 (w), 1318 (w), 1153 (m) (C–O) cm^{-1}; LRMS (CI$^+$): *m*/*z* (%) 333.12 (100) [M+H]$^+$; HRMS (CI$^+$): *m*/*z* calcd for $C_{20}H_{17}N_2O_3$ [M+H]$^+$: 333.1239; found: 333.1236.

4.3.10. **1**(1,1,4) 10-Methyl 8,14-dioxo-6,7-dihydro-8H,14H-5,13-diazabenz[e]aceanthrylene

Yield **1**(1,1,4) (0.239 g, 0.79 mmol, 79%) (LCMS purity 99%) as a yellow solid using the ester route or (0.110 g, 0.36 mmol, 36%) using the acid route. Mp 299 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.36 (d, ^3J=9.0 Hz, 1H, C12-*H*), 8.25–8.22 (m, 2H, C9-*H*, C1-*H*), 7.64 (ddd, ^3J=7.0 Hz, ^3J=7.0 Hz, ^4J=1.5 Hz, 1H, C3-*H*), 7.41 (dd, ^3J=9.0 Hz, ^4J=1.5 Hz, 1H, C11-*H*), 7.26–7.20 (m, 1H, C2-*H*), 6.90 (dd, ^3J=7.0 Hz, ^4J=1.5 Hz, 1H, C4-*H*), 4.30 (t, ^3J=9.0 Hz, 2H, C6-H_2), 3.34 (t, ^3J=9.0 Hz, 2H, C7-H_2), 2.42 (s, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=172.6 (C8), 159.9 (C14), 148.4 (C5a), 138.6 (C4a), 136.6 (C12a), 136.0 (C3), 134.3 (C10), 131. 9 (C11), 130.0 (C1), 127.4 (C8a), 125.3 (C9), 122.5 (C2), 120.8 (C12), 114.9 (C14a), 112.2 (C4), 102.2 (C7a), 47.3 (C6), 234 (C7), 20.9 (*C*H$_3$); IR (KBr): ν_{max}=2924 (m) (CH_2), 1708 (s) (C=O), 1583 (m), 1549 (m), 1499 (s), 1451 (w), 1324 (w), 751 (m) (Ar–H) cm^{-1}; LRMS (ES$^+$): *m*/*z* (%) 303.11 (100) [M+H]$^+$; HRMS (ES$^+$): *m*/*z* calcd for $C_{19}H_{15}N_2O_2Na$ [M+H]$^+$: 303.1134; found: 303.1140.

4.3.11. **1**(1,2,4) 11-Methyl 6,7,8-trihydro-9H,15H-5,14-diaza-dibenzo[a,de]anthracen-9,15-dione

Yield **1**(1,2,4) (0.203 g, 0.64 mmol, 64%) as a pale brown powder using the ester route. Mp 260 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.56 (d, ^3J=9.0 Hz, 1H, C13-*H*), 8.28 (dd, ^3J=8.0 Hz, ^4J=1.5 Hz, 1H, C1-*H*), 8.17–8.15 (m, 1H, C10-*H*), 7.73–7.67 (m, 1H, C3-*H*), 7.39 (ddd, ^3J=9.0 Hz, ^4J=2.5 Hz, 1H, C12-*H*), 7.28–7.22 (m, 2H, C2-*H*, C4-*H*), 4.01 (t, ^3J=6.0 Hz, 2H, C6-H_2), 2.89 (t, ^3J=6.0 Hz, 2H, C8-H_2), 2.48 (s, 3H, CH_3), 2.18–2.09 (m, 2H, C7-H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=175.5 (C9), 160.2 (C15), 144.3 (C5a), 140.7 (C4a), 136.2 (C13a), 135.8 (C3), 133.5 (C9a), 131.2 (C12), 129.4 (C1), 126.1 (C11), 124.8 (C10), 122.5 (C2), 122.1 (C13), 115.4 (C15a), 112.7 (C4), 102.3 (C8a), 46.8 (C6), 21.0 (*C*H$_3$), 20.1 (C8), 19.8 (C7); IR (KBr): ν_{max}=3449 (w) (OH), 2949 (w) (CH_2), 2361 (w) (CH_2), 1703 (s) (C=O), 1588 (s), 1533 (s), 1474 (s), 1360 (m), 1152 (m) (C–O), 746 (m) (Ar–H) cm^{-1}; LRMS (ES$^+$): *m*/*z* (%) 339.13 (50) [M+Na]$^+$, 655.25 (100) [2M+Na]$^+$; HRMS (ES$^+$): *m*/*z* calcd for $C_{40}H_{32}N_4O_4Na$ [2M+Na]$^+$: 655.2321; found: 655.2327.

4.3.12. **1**(2,1,4) 2-Methoxy-10-methyl-8,14-dioxo-6,7-dihydro-8H,14H-5,13-diazabenz[e]aceanthrylene

Yield **1**(2,1,4) (0.146 g, 0.45 mmol, 45%) (LCMS purity 90%) as a yellow powder using the ester route. Mp 305–306 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.43 (d, ^3J=9.0 Hz, 1H, C12-*H*), 8.32 (d, ^3J=2.0 Hz, 1H, C9-*H*), 7.75 (d, ^3J=3.0 Hz, 1H, C1-*H*), 7.47 (dd, ^3J=9.0 Hz, ^4J=2.0 Hz, 1H, C11-*H*), 7.35 (dd, ^3J=9.0 Hz, ^4J=3.0 Hz, 1H, C3-*H*), 6.96 (d, ^3J=9.0 Hz, 1H, C4-*H*), 4.31 (t, ^3J=9.0 Hz, 2H, C6-H_2), 3.92 (s, 3H, OCH_3), 3.40 (t, ^3J=9.0 Hz, 2H, C7-H_2), 2.50 (s, 3H, ArCH_3); ^{13}C NMR (125.5 MHz, CD_3COOD): δ=173.4 (C8), 156.6 (C14), 156.1 (C2), 147.0 (C5a), 137.2 (C4a), 136.7 (C11), 135.8 (C12a), 132.1 (C10), 131.8 (C12), 128.0 (C8a), 125.6 (C9), 122.5 (C3), 115.2 (C14a), 115.0 (C14), 110.4 (C1), 103.8 (C7a), 56.7 (OCH_3), 48.2 (C6), 22.5 (C7), 21.5 (ArCH_3); IR (KBr): ν_{max}=3024 (m), 2925 (m), 1691 (s) (C=O), 1629 (m), 1583 (s), 1548 (m), 1507 (s), 1284 (m), 1167 (w) (C–O) cm^{-1}; LRMS (ES$^+$): *m*/*z* (%) 333.06 (45) [M+H]$^+$, 355.03 (100) [M+Na]$^+$, 687.15 (90) [2M+Na]$^+$; HRMS (ES$^+$): *m*/*z* calcd for $C_{20}H_{17}N_2O_3$ [M+H]$^+$: 333.1239; found: 333.1237.

4.3.13. **1**(2,2,4) 2-Methoxy-11-methyl-6,7,8-trihydro-9H,15H-5,14-diaza-dibenzo[a,de]anthracen-9,15-dione

Yield **1**(2,2,4) (0.166 g, 0.45 mmol, 45%) (LCMS purity 90%) as a brown powder using the ester route. Mp 255 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.57 (d, ^3J=9.0 Hz, 1H, C13-*H*), 8.17 (d, ^3J=2.0 Hz, 1H, C10-*H*), 7.73 (d, ^3J=3.0 Hz, 1H, C1-*H*), 7.39 (dd, ^3J=9.0 Hz, ^4J=2.0 Hz, 1H, C12-*H*), 7.33–7.29 (m, 1H, C3-*H*), 7.26–7.20 (m, 1H, C4-*H*), 4.00 (t, ^3J=6.0 Hz, 2H, C6-H_2), 3.91 (s, 3H, ArOCH_3), 2.89 (t, ^3J=6.0 Hz, 2H, C8-H_2), 2.50 (s, 3H, ArCH_3), 2.17–2.08 (m, 2H, C7-H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=175.4 (C9), 160.5 (C15), 155.3 (C2), 144.5 (C5a), 136.4 (C13a), 135.2 (C4a), 133.5 (C11), 131.1 (C12), 126.4 (C9a), 125.0 (C3 & C10), 122.2 (C13), 116.1 (C15a), 114.5 (C4), 110.2 (C1), 101.6 (C8a), 56.0 (OCH_3), 47.1 (C6), 21.1 (ArCH_3), 20.3 (C8), 20.0 (C7); IR (KBr): ν_{max}=2923 (m), 1701 (s) (C=O), 1604 (m), 1587 (s), 1522 (m), 1472 (m), 1291 (w) cm^{-1}; LRMS (ES$^+$): *m*/*z* (%) 369.13 (100) [M+Na]$^+$, 715.29 (30) [2M+Na]$^+$; HRMS (ES$^+$): *m*/*z* calcd for $C_{21}H_{18}N_2O_3Na$ [M+Na]$^+$: 369.1215; found 369.1217.

4.3.14. **1**(1,1,5) 10-Chloro 8,14-dioxo-6,7-dihydro-8H,14H-5,13-diazabenz[e]aceanthrylene

Yield **1**(1,1,5) (0.258 g, 0.80 mmol, 80%) (LCMS purity 96%) as a pale brown powder using the ester route. Mp 301 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.52 (d, ^3J=9.5 Hz, 1H, C12-*H*), 8.45 (d, ^4J=2.5 Hz, 1H, C9-*H*), 8.29 (d, ^3J=8.5 Hz, ^4J=1.5 Hz, 1H, C1-*H*), 7.76 (ddd, ^3J=8.5 Hz, ^3J=8.5 Hz, ^4J=1.5 Hz, 1H, C3-*H*), 7.58 (dd, ^3J=9.5 Hz, ^4J=2.5 Hz 1H, C11-*H*), 7.30 (d, ^3J=8.5 Hz, 1H, C2-*H*), 7.00 (d, ^3J=8.5 Hz, 1H, C4-*H*), 4.34 (t, ^3J=9.0 Hz, 2H, C6-H_2), 3.40 (t, ^3J=9.0 Hz, 2H, C7-H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=171.2 (C8), 157.8 (C14), 148.8 (C5a), 138.6 (C4a), 136.4 (C3), 132.9 (C12a), 130.8 (C11), 130.2 (C1), 125.2 (C9), 123.8 (C10), 122.9 (C2), 122.7 (C12), 120.7 (C8a), 114.5 (C14a), 112.4 (C4), 102.8 (C7a), 47.4 (C6), 23.4 (C7); IR (KBr): ν_{max}=3449 (w) (OH), 2360 (w) (CH_2), 1706 (s) (C=O), 1604 (s), 1583 (s), 1541 (m), 1497 (m), 1324 (m), 1161 (m) (C–O), 747 (m) (Ar–H) cm^{-1}; LRMS (ES$^+$): *m*/*z* (%) 345.08 (70) [M+Na]$^+$, 667.12 (100) [2M (^{35}Cl^{35}Cl)+Na]$^+$, 669.12 [2M (^{35}Cl^{37}Cl)+Na]$^+$; HRMS (ES$^+$): *m*/*z* calcd for $C_{36}H_{22}N_4O_4NaCl$ [2M+Na]$^+$: 667.0916; found: 667.0906.

4.3.15. **1**(1,2,5) 11-Chloro 6,7,8-trihydro-9H,15H-5,14-diaza-dibenzo[a,de]anthracen-9,15-dione

Yield **1**(1,2,5) (0.215 g, 0.64 mmol, 64%) (LCMS purity 99%) as a pale brown powder using the ester route. Mp 236 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.64 (d, ^3J=9.0 Hz, 1H, C13-*H*), 8.32 (d, ^4J=3.0 Hz, 1H, C10-*H*), 8.28 (dd, ^3J=8.0 Hz, ^4J=1.5 Hz, 1H, C1-*H*), 7.77–7.71 (m, 1H, C3-*H*), 7.50 (dd, ^3J=9.0 Hz, ^4J=3.0 Hz, 1H, C12-*H*), 7.32–7.26 (m, 2H, C2-*H*, C4-*H*), 4.03 (t, ^3J=6.0 Hz, 2H, C6-H_2), 2.88 (t, ^3J=6.0 Hz, 2H, C8-H_2), 2.19–2.10 (m, 2H, C7-H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=174.5 (C9), 160.5 (C15), 144.9 (C5a), 141.0 (C4a), 136.5 (C3), 134.3 (C13a), 132.6 (C9a), 130.4 (C10), 130.0 (C12), 128.0 (C11), 125.1 (C1), 124.4 (C2), 123.3 (C13), 115.7 (C15a), 113.2 (C4), 103.0 (C8a), 47.4 (C6), 20.4 (C8), 20.2 (C7); IR (KBr): ν_{max}=3449 (w) (OH), 1707 (s) (C=O), 1585 (w), 1526 (s), 1476 (s), 1406 (m), 1363 (m), 1321 (w), 1289 (w) (C–O), 1181 (w) (C–O), 1087 (w), 756 (m) (Ar–H) cm^{-1}; LRMS (ES$^+$): *m*/*z* (%) 337.07 (100) [M^{35}Cl+H]$^+$, 339.07 (30) [M^{37}Cl+H]$^+$; HRMS (ES$^+$): *m*/*z* calcd for $C_{19}H_{14}ClN_2O_2$ [M+H]$^+$: 337.0744; found: 337.0742.

4.3.16. **1**(1,1,6) 11-Methyl carboxylate-8,14-dioxo-6,7-dihydro-8H,14H-5,13-diazabenz[e]aceanthrylene

Yield **1**(1,1,6) (0.305 g, 0.88 mmol, 88%) (LCMS purity 78%) as a dark yellow powder using the ester route. Mp 160 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.14 (d, ^4J=1.5 Hz, 1H, C12-*H*), 8.48 (d, ^3J=8.0 Hz, 1H, C9-*H*), 8.25 (dd, ^3J=8.0 Hz, ^4J=1.5 Hz, 1H, C1-*H*), 8.08 (dd, ^3J=8.0 Hz, ^4J=1.5 Hz, 1H, C10-*H*), 7.71–7.65 (m, 1H, C3-*H*), 7.25–7.19 (m, 1H, C2-*H*), 6.93 (d, ^3J=8.0 Hz, 1H, C4-*H*), 4.27 (t,

^3J=9.5 Hz, 2H, C6-H_2), 3.94 (s, 3H, CO_2CH_3), 3.33 (t, ^3J=9.5 Hz, 2H, C7-H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=171.7 (C8), 166.7 (CO_2Me), 160.1 (C14), 149.5 (C5a), 138.7 (C4a), 136.8 (C3), 136.2 (C12a), 135.5 (C8a), 132.3 (C11), 130.5 (C10), 127.5 (C1), 126.1 (C9), 123.5 (C2), 123.0 (C12), 114.9 (C14a), 112.9 (C4), 103.9 (C7a), 53.0 (CO_2CH_3), 47.8 (C6), 23.7 (C7); IR (KBr): ν_{max}=3422 (w) (OH), 2924 (m) (CH_2), 1719 (s) (C=O), 1584 (s), 1535 (m), 1497 (s), 1429 (m), 1324 (w), 1261 (m) (C–O), 1164 (m) (C–O), 756 (m) (Ar–H) cm^{-1}; LRMS (ES$^+$): *m*/*z* (%) 369.13 (100) [M+Na]$^+$, 715.28 (50) [2M+Na]$^+$; HRMS (ES$^+$): *m*/*z* calcd for $C_{20}H_{14}N_2O_4Na$ [M+Na]$^+$: 369.0851; found: 369.0852.

4.3.17. *1(1,2,6) 12-Methyl carboxylate 6,7,8-trihydro-9H,15H-5,14-diaza-dibenzo[a,de]anthracen-9,15-dione*

Yield **1**(1,2,6) (0.296 g, 0.83 mmol, 83%) (LCMS purity 93%) as a bright orange powder using the ester route. Mp 97–98 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.36 (d, ^4J=1.5 Hz, 1H, C13-*H*), 8.45 (d, ^3J=8.0 Hz, 1H, C10-*H*), 8.34 (dd, ^3J=8.0 Hz, ^4J=2.0 Hz, 1H, C1-*H*), 8.11 (dd, ^3J=8.0 Hz, ^4J=1.5 Hz, 1H, C11-*H*), 7.79–7.73 (m, 1H, C3-*H*), 7.35–7.29 (m, 2H, C2-*H*, C4-*H*), 4.06 (t, ^3J=6.0 Hz, 2H, C6-H_2), 4.00 (s, 3H, CO_2CH_3), 2.92 (t, ^3J=6.0 Hz, 2H, C8-H_2), 2.22–2.13 (m, 2H, C7-H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=174.6 (C9), 166.4 (CO_2CH_3), 160.1 (C15), 145.0 (C5a), 140.6 (C4a), 136.1 (C3), 134.5 (C13a), 131.1 (C9a), 129.7 (C10), 128.9 (C12), 126.6 (C11), 125.6 (C1), 124.1 (C2), 123.1 (C13), 115.5 (C15a), 112.9 (C4), 103.2 (C8a), 52.6 (CO_2CH_3), 47.0 (C6), 20.0 (C8), 19.8 (C7); IR (KBr): ν_{max}=3449 (m) (OH), 2363 (w) (CH_2), 1719 (s) (C=O), 1588 (s), 1528 (m), 1475 (s), 1362 (w), 1260 (m) (C–O), 755 (m) (Ar–H) cm^{-1}; LRMS (ES$^+$): *m*/*z* (%) 383.07 (100) [M+Na]$^+$, 743.20 (15) [2M+Na]$^+$; HRMS (ES$^+$): *m*/*z* calcd for $C_{21}H_{16}N_2O_4Na$ [M+Na]$^+$: 383.1008; found: 383.1013.

4.3.18. *1(2,1,6) 2-Methoxy-11-methyl carboxylate-8,14-dioxo-6,7-dihydro-8H,14H-5,13-diazabenz[e]aceanthrylene*

Yield **1**(2,1,6) (0.214 g, 0.57 mmol, 57%) as a yellow solid using the ester route. Mp 206–207 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.28 (d, ^4J=1.2 Hz, 1H, C12-*H*), 8.63 (d, ^3J=8.4 Hz, 1H, C9-*H*), 8.23 (dd, ^3J=8.4 Hz, ^4J=1.2 Hz, 1H, C10-*H*), 7.82 (d, ^4J=2.6 Hz, 1H, C1-*H*), 7.40 (dd, ^3J=9.0 Hz, ^4J=2.6 Hz, 1H, C3-*H*), 7.02 (d, ^3J=9.0 Hz, 1H, C4-*H*), 4.38 (t, ^3J=8.7 Hz, 2H, C6-H_2), 4.02 (s, 3H, CO_2CH_3), 3.94 (s, 3H, OCH_3), 3.44 (t, ^3J=8.7 Hz, 2H, C7-H_2); ^{13}C NMR (125.5 MHz, CD_3COOD): δ=169.3 (C8), 166.2 (CO_2Me), 159.4 (C14), 156.4 (C2), 149.8 (C5a), 135.2 (C14a), 132.1 (C11a), 131.5 (C12a), 129.4 (C8a), 127.0 (C9), 125.7 (C3), 125.1 (C10), 122.2 (C12), 115.6 (C14a), 115.4 (C4), 109.9 (C1), 104.5 (C7a), 55.4 (OCH_3), 52.2 (CO_2CH_3), 48.1 (C6), 22.7 (C2); IR (KBr): ν_{max}=2923 (m), 1701 (s) (C=O), 1600 (m), 1540 (m), 1581 (m), 1506 (m), 1363 (m), 1327 (m), 1281 (w), 1160 (m), 764 (m) (Ar–H) cm^{-1}; LRMS (ES$^+$): *m*/*z* (%) 377.10 (100) [M+H]$^+$; HRMS (ES$^+$): *m*/*z* calcd for $C_{21}H_{17}N_2O_5$ [M+H]$^+$: 377.1137; found: 377.1147.

4.3.19. *1(1,1,7) 12-Methyl-8,14-dioxo-6,7-dihydro-8H,14H-5,13-diazabenz[e]aceanthrylene*

Yield **1**(1,1,7) (0.082 g, 0.27 mmol, 27%) (LCMS purity 95%) as a yellow powder using the ester route. Mp 238–239 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.27–8.22 (m, 1H, C9-*H*), 8.18 (dd, ^3J=8.0 Hz, ^4J=1.5 Hz, 1H, C1-*H*), 7.73 (ddd, ^3J=7.5 Hz, ^3J=7.5 Hz, ^4J=1.5 Hz, 1H, C3-*H*), 7.48–7.45 (m, 2H, C10-*H*, C11-*H*), 7.27–7.21 (m, 1H, C2-*H*), 6.98 (d, ^3J=7.5 Hz, 1H, C4-*H*), 4.30 (t, ^3J=9.0 Hz, 2H, C6-H_2), 3.33 (t, ^3J=9.0 Hz, 2H, C7-H_2), 2.32 (s, 3H, ArCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=173.9 (C8), 158.5 (C14), 151.0 (C5a), 140.2 (C4a), 136.2 (C3), 134.0 (C10), 133.9 (C12a), 132.4 (C12), 130.4 (C8a), 130.1 (C1), 127.2 (C11), 123.7 (C9), 123.0 (C2), 116.2 (C14a), 113.3 (C4), 102.5 (C7a), 48.6 (C6), 24.0 (C7), 22.9 (ArCH_3); IR (KBr): ν_{max}=3339 (m) (OH), 1712 (s) (C=O), 1602 (m), 1556 (s), 1492 (s), 1320 (m), 1157 (m) (C–O), 747 (m) (Ar–H) cm^{-1}; LRMS (ES$^+$): *m*/*z* (%) 325.29 (100) [M+Na]$^+$, 627.09 (25) [2M+Na]$^+$; HRMS (ES$^+$): *m*/*z* calcd for $C_{19}H_{14}N_2O_2Na$ [M+Na]$^+$: 325.0953; found: 325.0944.

4.3.20. *1(1,2,7) 13-Methyl 6,7,8-trihydro-9H,15H-5,14-diaza-dibenzo[a,de]anthracen-9,15-dione*

Yield **1**(1,2,7) (0.075 g, 0.24 mmol, 24%) (LCMS purity 94%) as a brown powder using the ester route. Mp 194–195 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.22 (dd, ^3J=8.0 Hz, ^4J=2.0 Hz, 1H, C10-*H*), 8.20–8.16 (m, 1H, C1-*H*), 7.76–7.70 (m, 1H, C3-*H*), 7.47–7.45 (m, 2H, C11-*H*, C12-*H*), 7.29–7.24 (m, 2H, C2-*H*, C4-*H*), 4.19–4.10 (m, 1H, C6-*H*), 3.93–3.84 (m, 1H, C6-*H*), 2.93–2.72 (m, 2H, C8-H_2), 2.33–2.21 (m, 1H, C7-*H*), 2.25 (s, 3H, ArCH_3), 2.15–2.00 (m, 1H, C7-*H*); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=176.6 (C9), 158.6 (C15), 145.4 (C5a), 141.2 (C4a), 138.2 (C13a), 135.6 (C3), 135.0 (C9a), 133.0 (C12), 132.2 (C13), 129.1 (C10), 126.5 (C11), 123.0 (C1), 122.4 (C2), 115.8 (C15a), 112.8 (C4), 102.9 (C8a), 46.2 (C6), 21.4 (ArCH_3), 20.4 (C8), 19.5 (C7); IR (KBr): ν_{max}=2933 (m), 1709 (s) (C=O), 1601 (s), 1538 (m), 1417 (m), 1225 (m), 755 (w) (Ar–H) cm^{-1}; LRMS (ES$^+$): *m*/*z* (%) 339.15 (100) [M+Na]$^+$, 655.31 (90) [2M+Na]$^+$; HRMS (ES$^+$): *m*/*z* calcd for $C_{20}H_{16}N_2O_2Na$ [M+Na]$^+$: 339.1109; found: 339.1108.

4.3.21. *1(2,1,7) 2-Methoxy-12-methyl-8,14-dioxo-6,7-dihydro-8H,14H-5,13-diazabenz[e]aceanthrylene*

Yield **1**(2,1,7) (0.070 g, 0.21 mmol, 21%) (LCMS purity 94%) as a light yellow powder using the ester route. Mp 239.0 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.30–8.24 (m, 1H, C9-*H*), 7.65 (d, ^3J=3.0 Hz, 1H, C1-*H*), 7.49–7.47 (m, 2H, C10-*H*, C11-*H*), 7.33 (dd, ^3J=9.0 Hz, ^4J=3.0 Hz, 1H, C3-*H*), 6.97 (d, ^3J=9.0 Hz, 1H, C4-*H*), 4.30 (t, ^3J=9.0 Hz, 2H, C6-H_2), 3.91 (s, 3H, OCH_3), 3.35 (t, ^3J=9.0 Hz, 2H, C7-H_2), 2.32 (s, 3H, ArCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=173.0 (C8), 158.1 (C14), 155.4 (C2), 150.7 (C5a), 134.2 (C4a), 133.5 (C12a), 133.2 (C11), 132.0 (C12), 130.2 (C8a), 126.8 (C10), 124.8 (C3), 123.3 (C9), 116.3 (C14a), 114.6 (C4), 110.9 (C1), 101.6 (C7a), 56.0 (OCH_3), 48.7 (C6), 23.6 (C7), 22.5 (ArCH_3); IR (KBr): ν_{max}=2930 (m), 1702 (s) (C=O), 1632 (m), 1608 (m), 1589 (m), 1559 (m), 1505 (s), 1319 (m), 1029 (w), 767 (m) (Ar–H) cm^{-1}; LRMS (ES$^+$): *m*/*z* (%) 333.14 (100) [M+H]$^+$; HRMS (ES$^+$): *m*/*z* calcd for $C_{20}H_{17}N_2O_3$ [M+H]$^+$: 333.1239; found: 333.1234.

4.3.22. *1(2,2,7) 2-Methoxy-13-methyl-6,7,8-trihydro-9H,15H-5,14-diaza-dibenzo[a,de]anthracen-9,15-dione*

Yield **1**(2,2,7) (0.083 g, 0.24 mmol, 24%) as a red powder using the ester route. Mp 233–234 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.19–8.14 (m, 1H, C10-*H*), 7.64 (d, ^3J=3.0 Hz, 1H, C1-*H*), 7.44–7.42 (m, 2H, C11-*H*, C12-*H*), 7.32–7.28 (m, 1H, C3-*H*), 7.22–7.18 (m, 1H, C4-*H*), 4.17–4.08 (m, 1H, C6-*H*), 3.91 (s, 3H, ArOCH_3), 3.86–3.77 (m, 1H, C6-*H*), 2.90–2.70 (m, 2H, C8-H_2), 2.92–2,16 (m, 1H, C7-*H*), 2.23 (s, 3H, ArCH_3), 2.12–1.97 (m, 1H, C7-*H*); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=175.9 (C9), 159.1 (C15), 155.2 (C2), 145.7 (C5a), 135.4 (C4a), 134.9 (C13a), 132.9 (C12), 132.1 (C13), 128.7 (C9a), 126.5 (C11), 124.3 (C3), 122.9 (C10), 116.5 (C15a), 114.6 (C4), 110.3 (C1), 101.9 (C8a), 56.0 (ArOCH_3), 46.3 (C6), 21.5 (ArCH_3), 20.4 (C7), 19.5 (C8); IR (KBr): ν_{max}=2935 (m), 1706 (s) (C=O), 1604 (s), 1592 (m), 1533 (s), 1427 (m), 1038 (m), 771 (m) (Ar–H) cm^{-1}; LRMS (ES$^+$): *m*/*z* (%) 347.10 (100) [M]$^+$, 348.14 (30) [M+H]$^+$, 369.17 (45) [M+Na]$^+$; HRMS (ES$^+$): *m*/*z* calcd for $C_{21}H_{18}N_2O_3Na$ [M+Na]$^+$: 369.1215; found: 369.1219.

4.3.23. *1(2,1,8) 2-Methoxy-9-methyl-8,14-dioxo-6,7-dihydro-8H,14H-5,13-diazabenz[e]aceanthrylene*

Yield **1**(2,1,8) (0.284 g, 0.85 mmol, 85%) as a yellow powder using the ester route. Mp 339–340 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.33 (d, ^3J=8.6 Hz, 1H, C12-*H*), 7.75 (d, ^4J=3.0 Hz, 1H, C1-*H*), 7.51 (dd, ^3J=8.6 Hz, ^4J=1.4 Hz, 1H, C11-*H*), 7.34 (dd, ^3J=8.8 Hz, ^4J=3.0 Hz, 1H, C3-*H*), 7.30 (d, ^3J=8.6 Hz, 1H, C10-*H*), 6.93 (d, ^3J=9.0 Hz, 1H, C4-*H*), 4.28 (t, ^3J=8.8 Hz, 2H, C6-H_2), 3.92 (s, 3H, ArOCH_3), 3.35 (t,

^3J=8.8 Hz, 2H, C7-H_2), 3.03 (s, 3H, ArCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=176.9 (C8), 159.1 (C14), 155.1 (C2), 148.0 (C5a), 140.0 (C4a), 136.6 (C12a), 134.3 (C9), 129.2 (C11), 129.0 (C10), 125.4 (C3), 122.4 (C8a), 119.2 (C12), 113.5 (C4), 113.4 (C14a), 110.9 (C1), 101.4 (C7a), 55.9 (OCH_3), 51.5 (C6), 31.0 (C6), 24.4 (ArCH_3); IR (KBr): ν_{max}=2945 (m), 1717 (s) (C=O), 1700 (m) (C=O), 1601 (w), 1556 (m), 1499 (m), 1318 (m), 1159 (m) (C–O) cm^{-1}; LRMS (CI$^+$): *m*/*z* (%) 333.12 (100) [M+H]$^+$; HRMS (ES$^+$): *m*/*z* calcd for $C_{20}H_{17}N_2O_3$ [M+H]$^+$: 333.1239; found: 333.1234.

4.3.24. **1**(2,2,8) 2-Methoxy-10-methyl-6,7,8-trihydro-9H,15H-5,14-diaza-dibenzo[a,de]anthracen-9,15-dione

Yield **1**(2,2,8) (0.261 g, 0.75 mmol, 75%) as a yellow powder using ester route. Mp 147–148 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.23 (d, ^3J=8.7 Hz, 1H, C13-*H*), 7.67 (d, ^4J=3.1 Hz, 1H, C1-*H*), 7.38–7.33 (m, 1H, C11-*H*), 7.24 (dd, ^3J=9.2 Hz, ^4J=3.1 Hz, 1H, C3-*H*), 7.18 (dd, ^3J=7.4 Hz, ^4J=1.0 Hz, 1H, C12-*H*), 7.14 (d, ^3J=9.2 Hz, 1H, C4-*H*), 3.90 (t, ^3J=6.0 Hz, 2H, C6-H_2), 3.83 (s, 3H, ArOCH_3), 2.89 (s, 3H, ArCH_3), 2.77 (t, ^3J=6.0 Hz, 2H, C8-H_2), 2.08 (qt, ^3J=6.0 Hz, 2H, C7-H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=178.1 (C9), 160.7 (C15), 155.3 (C2), 143.4 (C5a), 139.4 (C13a), 136.7 (C9a), 135.5 (C4a), 129.7 (C12), 128.5 (C11), 125.4 (C10), 124.9 (C3), 121.0 (C13), 116.0 (C15a), 114.3 (C4), 110.5 (C1), 102.6 (C8a), 55.9 (ArOCH_3), 46.5 (C6), 23.7 (ArCH_3), 20.4 (C7), 19.8 (C8); IR (KBr): ν_{max}=2948 (m), 1719 (s) (C=O), 1698 (m) (C=O), 1601 (m), 1559 (w), 1499 (m), 1318 (w), 1158 (m) (C–O) cm^{-1}; LRMS (CI$^+$): *m*/*z* (%) 347.14 (100) [M+H]$^+$; HRMS (CI$^+$): *m*/*z* calcd for $C_{21}H_{19}N_2O_3$ [M+H]$^+$: 347.1396; found: 347.1390.

4.3.25. **1**(1,1,9) 9-Chloro 8,14-dioxo-6,7-dihydro-8H,14H-5,13-diazabenz[e]aceanthrylene

Yield **1**(1,1,9) (0.052 g, 0.16 mmol, 16%) as a yellow solid using the acid route. Mp 187 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.42 (d, ^3J=8.0 Hz, ^4J=2.0 Hz, 1H, C12-*H*), 8.29 (dd, ^3J=8.0 Hz, ^4J=1.5 Hz, 1H, C1-*H*), 7.76–7.70 (m, 1H, C11-*H*), 7.55–7.50 (m, 2H, C10-*H*, C3-*H*), 7.29–7.23 (m, 1H, C2-*H*), 6.97 (d, ^3J=8.0 Hz, 1H, C4-*H*), 4.29 (t, ^3J=9.1 Hz, 2H, C6-H_2), 3.36 (t, ^3J=9.1 Hz, 2H, C7-H_2); ^{13}C NMR (75.5 MHz, CD_3COOD): δ=171.3 (C8), 159.2 (C14), 149.4 (C5a), 137.6 (C3), 137.0 (C4a), 134.2 (C12a), 132.7 (C1), 131.9 (C11), 130.1 (C10), 127.4 (C8a), 123.8 (C9), 119.8 (C12), 115.9 (C4), 114.4 (C14a), 102.3 (C7a), 51.9 (C6), 31.5 (C7); IR (KBr): ν_{max}=2951 (m) (CH_2), 1723 (s) (C=O), 1600 (s), 1548 (w),1492 (m), 1459 (m), 1384 (m), 1261 (w) (C–O), 1119 (w) (C–O), 751 (w) (Ar–H) cm^{-1}; LRMS (ES$^+$): *m*/*z* (%) 345.09 (100) [M+Na]$^+$; HRMS (ES$^+$): *m*/*z* calcd for $C_{18}H_{11}N_2O_2NaCl$ [M+Na]$^+$: 345.0407; found: 345.0412.

4.3.26. **1**(1,2,9) 10-Chloro 6,7,8-trihydro-9H,15H-5,14-diaza-dibenzo[a,de]anthracen-9,15-dione

Yield **1**(1,2,9) (0.051 g, 0.15 mmol, 15%) as a yellow powder using the acid route. Mp 126–127 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.36 (dd, ^3J=8.5 Hz, ^4J=1.5 Hz, 1H, C13-*H*), 8.27 (dd, ^3J=8.0 Hz, ^4J=1.5 Hz, 1H, C1-*H*), 7.75–7.66 (m, 1H, C12-*H*), 7.46–7.40 (m, 2H, C3-*H*, C11-*H*), 7.28–7.21 (m, 2H, C2-*H*, C4-*H*), 3.98 (t, ^3J=6.0 Hz, 2H, C6-H_2), 2.84 (t, ^3J=9.0 Hz, 2H, C8-H_2), 2.19–2.10 (m, 2H, C7-H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=174.6 (C9), 160.2 (C15), 143.4 (C5a), 140.8 (C4a), 137.6 (C13a), 136.3 (C3), 132.4 (C10), 129.7 (C12), 129.6 (C1), 129.0 (C11), 123.6 (C9a), 122.6 (C2), 121.9 (C13), 115.1 (C15a), 112.8 (C4), 104.0 (C8a), 46.3 (C6), 20.2 (C8), 19.7 (C7); IR (KBr): ν_{max}=1706 (s) (C=O), 1582 (m), 1471 (s), 1403 (m), 1359 (m), 1289 (w) (C–O), 1179 (w) (C–O), 1082 (w), 754 (m) (Ar–H) cm^{-1}; LRMS (ES$^+$): *m*/*z* (%) 359.09 (100) [M+Na]$^+$, 695.21 (10) [2M+Na]$^+$; HRMS (ES$^+$): *m*/*z* calcd for $C_{19}H_{13}N_2O_2NaCl$ [M+Na]$^+$: 359.0563; found: 359.0563.

4.3.27. **1**(2,1,9) 2-Methoxy-9-chloro-8,14-dioxo-6,7-dihydro-8H,14H-5,13-diazabenz[e]aceanthrylene

Yield **1**(2,1,9) (0.053 g, 0.15 mmol, 15%) as a yellow powder using the ester route. Mp 309 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.42 (dd, ^3J=8.0 Hz, ^4J=1.5 Hz, 1H, C12-*H*), 7.72 (d, ^3J=3.0 Hz, 1H, C1-*H*), 7.56–7.46 (m, 2H, C10-*H*, C11-*H*), 7.35 (dd, ^3J=9.0 Hz, ^4J=3.0 Hz, 1H, C3-*H*), 6.98 (d, ^3J=9.0 Hz, 1H, C4-*H*), 4.28 (t, ^3J=9.0 Hz, 2H, C6-H_2), 3.91 (s, 3H, OCH_3), 3.35 (t, ^3J=9.0 Hz, 2H, C7-H_2); ^{13}C NMR (75.5 MHz, CD_3COOD): δ=175.3 (C8), 160.4 (C14), 159.9 (C2), 149.6 (C5a), 146.1 (C9), 141.8 (C4a), 131.1 (C11), 130.5 (C10), 130.2 (C12a), 127.3 (C8a), 126.1 (C3), 120.7 (C12), 116.1 (C4), 113.4 (C14a), 111.0 (C1), 103.7 (C7a), 55.6 (*C*H_3), 48.6 (C6), 23.5 (C7); IR (KBr): ν_{max}= 2939 (w), 1693 (s) (C=O), 1615 (s), 1592 (s), 1580 (s), 1507 (s), 1458 (w), 1231 (m), 1063 (m), 761 (m) (Ar–H) cm^{-1}; LRMS (ES$^+$): *m*/*z* (%) 375.05 (100) [M+Na]$^+$; HRMS (ES$^+$): *m*/*z* calcd for $C_{19}H_{14}N_2O_3Cl$ [M+H]$^+$: 353.0693; found: 353.0691.

4.3.28. **1**(1,1,10) 10-Bromo 8,14-dioxo-6,7-dihydro-8H,14H-5,13-diazabenz[e]aceanthrylene

Methyl 5-bromo-2-[2-(2-oxo-pyrrolidin-1-yl)-benzoylamino]-benzoate **5**(7) (0.17 g, 0.40 mmol) was heated in a sealed glass microwave tube to 190 °C, (maximum 275 W) for 80 min. The resultant yellow/brown solid was purified by flash column chromatography over silica gel (1:99, methanol/chloroform) to afford the title compound **1**(1,1,10) (0.073 g, 0.20 mmol, 50%) (LCMS purity 96%) as a yellow powder. Mp 346–347 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.48 (d, ^3J=9.5 Hz, 1H, C12-*H*), 8.67 (d, ^4J=2.5 Hz, 1H, C9-*H*), 8.33 (dd, ^3J=8.0 Hz, ^4J=1.5 Hz, 1H, C1-*H*), 7.80–7.75 (m, 2H, C11-*H*, C3-*H*), 7.30 (ddd, ^3J=8.0 Hz, ^3J=8.0 Hz, ^4J=1.5 Hz, 1H, C2-*H*), 7.02 (d, ^3J=8.0 Hz, 1H, C4-*H*), 4.36 (t, ^3J=9.0 Hz, 2H, C6-H_2), 3.42 (t, ^3J=9.0 Hz, 2H, C7-H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=171.1 (C8), 157.6 (C14), 148.7 (C5a), 138.6 (C4a), 136.5 (C3), 133.4 (C12a), 131.3 (C11), 130.3 (C1), 128.3 (C9), 122.8 (C2), 122.7 (C12), 121.0 (C8a), 120.1 (C10), 114.6 (C14a), 112.5 (C4), 102.7 (C7a), 47.4 (C6), 23.5 (C7); IR (KBr): ν_{max}=2924 (w), 1715 (s) (C=O), 1700 (s) (C=O), 1600 (s), 1580 (s), 1498 (s), 1325 (m), 1160 (m) (C–O), 749 (m) (Ar–H) cm^{-1}; LRMS (CI$^+$): *m*/*z* (%) 367.10 (100) [M^{79}Br+H]$^+$, 369.01 (70) [M^{81}Br+H]$^+$; HRMS (CI$^+$): *m*/*z* calcd for $C_{18}H_{12}N_2O_2^{79}Br$ [M+H]$^+$: 367.0082; found: 367.0078.

4.3.29. **1**(1,1,11) 12-Methoxy 8,14-dioxo-6,7-dihydro-8H,14H-5,13-diazabenz[e]aceanthrylene

Yield **1**(1,1,11) (0.031 g, 0.10 mmol, 10%) using the acid route. Mp 251–252 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.19 (m, ^3J=8.5 Hz, 1H, C9-*H*), 8.00 (d, ^3J=8.0 Hz, 1H, C1-*H*), 7.71–7.67 (m, 1H, C3-*H*), 7.55–7.49 (m, 2H, C10-*H*, C11-*H*), 7.26–7.22 (m, 1H, C2-*H*), 6.98 (d, ^3J=8.0 Hz, 1H, C4-*H*), 4.30 (t, ^3J=9.0 Hz, 2H, C6-H_2), 3.87 (s, 3H, CH_3), 3.35 (t, ^3J=9.0 Hz, 2H, C7-H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=173.0 (C8), 157.0 (C14), 152.4 (C12), 150.5 (C5a), 139.4 (C4a), 135.4 (C3), 131.2 (C12a), 129.7 (C1), 127.6 (C10), 124.2 (C8a), 122.6 (C2), 117.5 (C11), 116.2 (C14a), 114.4 (C9), 113.1 (C4), 102.0 (C5a), 56.7 (OCH_3), 48.2 (C6), 23.8 (C7); IR (KBr): ν_{max}=2949 (m), 1718 (s) (C=O), 1700 (m) (C=O), 1601 (s), 1559 (s), 1499 (m), 1318 (m), 1158 (m) (C–O) cm^{-1}; LRMS (ES$^+$): *m*/*z* (%) 341.11 (100) [M+Na]$^+$; HRMS (ES$^+$): *m*/*z* calcd for $C_{19}H_{14}N_2O_3Na$ [M+Na]$^+$: 341.0902; found: 341.0903.

4.3.30. **1**(1,1,12) 12-Chloro 8,14-dioxo-6,7-dihydro-8H,14H-5,13-diazabenz[e]aceanthrylene

Yield **1**(1,1,12) (0.144 g, 0.45 mmol, 45%) (LCMS purity 97%) as a pale brown powder using the acid route. Mp 271–272 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.21 (d, ^3J=8.0 Hz, ^4J=1.5 Hz, 1H, C9-*H*), 8.09 (dd, ^3J=8.0 Hz, ^4J=1.0 Hz, 1H, C1-*H*), 7.64–7.55 (m, 2H, C10-*H*, C11-*H*), 7.42–7.35 (m, 1H, C3-*H*), 7.20–7.14 (m, 1H, C2-*H*), 6.89 (d, ^3J=8.0 Hz, 1H, C4-*H*), 4.45–3.96 (m, 2H, C6-H_2), 3.45–3.03 (m, 2H, C7-H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=171.9 (C8), 157.0 (C14), 150.8 (C5a), 139.3 (C4a), 135.9 (C3), 132.6 (C11), 131.8 (C12a), 131.7 (C12), 129.7 (C1), 127.8 (C8a), 127.5 (C10), 124.3 (C9), 123.1 (C2), 115.8 (C14a), 113.2 (C4), 102.5 (C7a), 48.4 (C6), 23.6 (C7); IR (KBr): ν_{max}=1776 (s) (C=O), 1753 (m) (C=O), 1720 (s) (C=O), 1578 (s), 1536 (s), 1489 (s), 1397 (m), 1318 (m), 1158 (m), 749 (s) (Ar–H) cm^{-1}; LRMS (ES$^+$): *m*/*z* (%) 323.04 (100) [M^{35}Cl+H]$^+$, 325.06

(30) $[M^{37}Cl+H]^+$; HRMS (ES^+): *m/z* calcd for $C_{18}H_{12}N_2O_2Cl$ $[M+H]^+$: 323.0587; found: 323.0589.

4.3.31. *1(1,1,14) 8,16-Dioxo-6,7-dihydro-8H,16H-5,15-diazanaphtho[e]aceanthrylene*

Yield **1**(1,1,14) (0.035 g, 0.010 mmol, 10%) as a yellow solid using the acid route. Mp 232 °C (dec); ^1H NMR (300 MHz, $CDCl_3$): δ=10.05 (s, 1H, C14-*H*), 8.96 (s, 1H, C9-*H*), 8.56 (s, 1H, C1-*H*), 8.23 (d, ^3J=8.0 Hz, 1H, C3-*H*), 8.01–7.95 (m, 2H, C10-*H*, C13-*H*), 7.71–7.63 (m, 1H, C12-*H*), 7.59–7.48 (m, 1H, C11-*H*), 7.25–7.13 (m, 1H, C2-*H*), 6.95–6.89 (m, 1H, C4-*H*), 4.18 (t, ^3J=9.0 Hz, 2H, C6-H_2), 3.36 (t, ^3J=9.0 Hz, 2H, C7-H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=170.1 (C8), 158.8 (C16), 149.8 (C5a), 140.3 (C14a), 138.3 (C4a), 136.0 (C3), 133.3 (C13a), 130.7 (C9a), 129.9 (C1), 128.8 (C10), 127.8 (C12), 126.9 (C9), 126.5 (C8a), 123.1 (C2), 121.3 (C13), 120.2 (C11), 115.0 (C16a), 113.2 (C14), 112.5 (C4), 101.2 (C7a), 47.5 (C6), 23.2 (C7); IR (KBr): ν_{max}=1708 (m) (C=O), 1611 (m), 1579 (m), 1546 (s), 1484 (m), 1353 (m), 1150 (w) (C–O), 743 (m) (Ar–H) cm^{-1}; LRMS (ES^+): *m/z* (%) 339.11 (100) $[M+H]^+$; HRMS (ES^+): *m/z* calcd for $C_{22}H_{15}N_2O_2$ $[M+H]^+$: 339.1134; found: 339.1141.

4.3.32. *1(1,3,1) 6,7,8,9-Tetrahydro-10H,16H-5,15-diaza-dibenzo[a,de]anthracen-10,16-dione*

Methyl 2-(2-(2-oxoazepan-1-yl)benzamido)benzoate **5**(1,3,1) (0.73 g, 2.00 mmol) was heated in a sealed glass microwave tube to 190 °C, (maximum 275 W), for 30 min. The resultant yellow/brown solid was purified by flash column chromatography over silica gel (1:99, methanol/chloroform) to afford the title compound **1**(1,3,1) (0.455 g, 1.44 mmol, 72%) as a yellow powder. Mp 187–188 °C; ^1H NMR (300 MHz, $CDCl_3$): δ=8.70 (dd, ^3J=8.5 Hz, ^4J=1.0 Hz, 1H, C11-*H*), 8.35 (dd, ^3J=8.5 Hz, ^4J=1.0 Hz, 1H, C12-*H*), 8.26 (dd, ^3J=8.0 Hz, ^4J=1.5 Hz, 1H, C1-*H*), 7.68 (ddd, ^3J=8.0 Hz, ^3J=8.0 Hz, ^4J=1.5 Hz, 1H, C3-*H*), 7.60 (ddd, ^3J=7.2 Hz, ^3J=7.2 Hz, ^4J=1.9 Hz, 1H, C14-*H*), 7.45 (ddd, ^3J=7.2 Hz, ^3J=7.2 Hz, ^4J=1.0 Hz, 1H, C13-*H*), 7.21 (ddd, ^3J=7.2 Hz, ^3J=7.2 Hz, ^4J=1.0 Hz, 1H, C4-*H*), 7.17 (d, ^3J=8.7 Hz, 1H, C2-*H*), 4.17 (t, ^3J=6.2 Hz, 2H, C6-H_2), 3.05–3.00 (m, 2H, C9-H_2), 2.16 (qt, ^3J=6.4 Hz, 2H, C7-H_2), 2.02–1.92 (m, 2H, C8-H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=177.5 (C10), 160.1 (C16), 149.6 (C5a), 142.0 (C4a), 136.1 (C10a), 136.1 (C14a), 136.0 (C3), 130.7 (C14), 129.8 (C1), 126.1 (C13), 125.9 (C12), 122.4 (C11), 122.2 (C4), 114.9 (C16a), 112.4 (C2), 111.3 (C9a), 51.6 (C6), 25.4 (C7), 23.8 (C9), 22.8 (C8); IR (KBr): ν_{max}=2935 (m), 1715 (s) (C=O), 1701 (m) (C=O), 1603 (s), 1560 (m), 1499 (m), 1313 (m), 1153 (m) (C–O) cm^{-1}; LRMS (CI^+): *m/z* (%) 317.13 (100) $[M+H]^+$; HRMS (CI^+): *m/z* calcd for $C_{20}H_{17}N_2O_2$ $[M+H]^+$: 317.1290; found: 317.1287.

4.3.33. *1(1,1,15) 8,13-Dioxo-6,7-dihydro-8H,13H-5,12-diazathieno[3,2-e]aceanthrylene*

Methyl 2-[2-(2-oxo-pyrrolidin-1-yl)-benzoylamino]-thiophene-3-carboxylate **5**(1,1,15) (0.05 g, 0.15 mmol) was heated in a sealed glass microwave tube to 190 °C, (maximum 275 W) for 80 min. The resultant yellow/brown solid was purified by flash column chromatography over silica gel (1:199, methanol/chloroform) to afford the title compound **1**(1,1,15) (0.030 g, 0.10 mmol, 68%) (LCMS purity 96%) as a pale yellow powder. Mp 316–317 °C; ^1H NMR (300 MHz, $CDCl_3$): δ=8.26 (dd, ^3J=8.0 Hz, ^4J=1.5 Hz, 1H, C1-*H*), 7.71 (ddd, ^3J=8.0 Hz, ^3J=8.0 Hz, ^3J=1.5 Hz, 1H, C3-*H*), 7.60 (d, ^3J=6.0 Hz, 1H, C9-*H*), 7.25–7.19 (m, 2H, C2-*H*, C4-*H*), 6.97 (d, ^3J=6.0 Hz, 1H, C10-*H*), 4.36 (t, ^3J=8.5 Hz, 2H, C6-H_2), 3.39 (t, ^3J=8.5 Hz, 2H, C7-H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=171.2 (C8), 161.8 (C13), 156.2 (C11a), 146.1 (C5a), 139.5 (C4a), 136.8 (C3), 130.0 (C10), 122.8 (C1), 122.5 (C2), 121.2 (C9), 120.0 (C8a), 112.6 (C4), 112.2 (C13a), 48.3 (C6), 23.9 (C7); IR (KBr): ν_{max}=3423 (s) (OH), 1702 (s) (C=O), 1561 (s), 1528 (m), 1490 (m), 752 (m) (Ar–H) cm^{-1}; LRMS (ES^+): *m/z* (%) 295.05 (100) $[M+H]^+$; HRMS (ES^+): *m/z* calcd for $C_{16}H_{11}N_2O_2S$ $[M+H]^+$: 295.0541; found: 295.0533.

4.3.34. *1(1,2,16) 8,13-Dioxo-6,7-dihydro-8H,13H-5,12-diazathieno[2,3-e]aceanthrylene*

Yield **1**(1,2,16) (0.032 g, 0.10 mmol, 17%) as a brown powder using the zipper route on a 0.6 mmol scale. Mp 210–211 °C; ^1H NMR (300 MHz, $CDCl_3$): δ=8.60 (d, ^3J=5.6 Hz, 1H, C12-*H*), 8.30 (dd, ^3J=7.6 Hz, ^4J=1.7 Hz, 1H, C1-*H*), 7.72 (ddd, ^3J=7.2 Hz, ^3J=7.2 Hz, ^4J=1.7 Hz, 1H, C3-*H*), 7.61 (d, ^3J=5.6 Hz, 1H, C11-*H*), 7.30–7.23 (m, 2H, C2-*H*, C4-*H*), 4.05 (t, ^3J=6.0 Hz, 2H, C6-H_2), 2.94 (t, ^3J=6.0 Hz, 2H, C8-H_2), 2.15 (qt, ^3J=6.0 Hz, 2H, C7-H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=171.6 (C9), 158.6 (C14), 143.0 (C5a), 140.8 (C4a), 136.7 (C12a), 136.1 (C3), 130.9 (C9a), 129.4 (C11), 128.9 (C12), 123.7 (C1), 122.5 (C2), 113.8 (C14a), 112.8 (C4), 102.9 (C8a), 47.4 (C6), 20.0 (C8), 19.8 (C7); IR (KBr): ν_{max}=2926 (m) (CH), 1696 (s) (C=O), 1596 (m), 1499 (s), 1366 (m), 1197 (m) (C–O), 767 (m) (Ar–H) cm^{-1}; LRMS (CI^+): *m/z* (%) 309.07 (100) $[M+H]^+$; HRMS (CI^+): *m/z* calcd for $C_{17}H_{13}N_2O_2S$ $[M+H]^+$: 309.0693; found: 309.0698.

4.3.35. *1(1,1,17) 1,2,3,4,5,7-Hexahydropyrrolo[1,2-a]pyrido[2,1-b]quinazoline-3,7-dione*

Ethyl 3-[2-(2-oxo-pyrrolidin-1-yl)-benzoylamino]-propionate **5**(1,1,17) (0.05 g, 0.15 mmol) dissolved in methanol (0.5 mL) in a sealed glass microwave tube was heated to 100 °C, (maximum 275 W), with air flowing through the reaction chamber, for 30 min. Upon cooling the reaction mixture was purified by flash column chromatography over silica gel (98:2, chloroform/methanol) to afford the title compound **1**(1,1,17) (0.006 g, 0.025 mmol, 16%) as a pale brown powder. Mp 139 °C (dec); ^1H NMR (300 MHz, $CDCl_3$): δ=8.12 (dd, ^3J=7.5 Hz, ^4J=1.5 Hz 1H, C8-*H*), 7.63 (ddd, ^3J=7.5 Hz, ^3J=7.5 Hz, ^4J=1.5 Hz, 1H, C10-*H*), 7.19 (ddd, ^3J=7.5 Hz, ^3J=7.5 Hz, ^4J=1.0 Hz, 1H, C9-*H*), 6.87 (d, ^3J=7.5 Hz, 1H, C11-*H*), 4.25 (t, ^3J=7.5 Hz, 2H, C1-H_2), 4.10 (t, ^3J=9.0 Hz, 2H, C5-H_2), 3.07 (t, ^3J=9.0 Hz, 2H, C4-H_2), 2.63 (t, ^3J=7.5 Hz, 2H, C2-H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=184.1 (C3), 152.8 (C7), 139.2 (C11a), 135.4 (C10), 129.5 (C8), 122.7 (C9), 115.3 (C12a), 113.9 (C7a), 112.6 (C11), 93.7 (C2a), 46.7 (C5), 40.6 (C1), 34.4 (C2), 22.5 (C4); IR (KBr): ν_{max}=2922 (m), 2361 (m), 1685 (s) (C=O), 1602 (s), 1561 (m), 1523 (m), 1183 (m) (C–O), 762 (s) (Ar–H) cm^{-1}; LRMS (CI^+): *m/z* (%) 241.10 (100) $[M+H]^+$, 240.09 (30) $[M]^+$; HRMS (ES^+): *m/z* calcd for $C_{14}H_{13}N_2O_2$ $[M+H]^+$: 241.0977; found: 241.0976.

4.3.36. *5(1,3,1) Methyl 2-(2-(2-oxoazepan-1-yl)benzamido)benzoate*

Using the PyBroP procedure the title compound was afforded (0.81 g, 0.77 mmol, 77%) as a pale brown oil. ^1H NMR (300 MHz, $CDCl_3$): δ=11.34 (s, 1H, N*H*), 8.78 (dd, ^3J=9.5 Hz, ^4J=1.0 Hz, 1H, C3-*H*), 8.05 (dd, ^3J=8.0 Hz, ^4J=1.5 Hz, 1H, C6′-*H*), 7.73 (dd, ^3J=8.0 Hz, ^4J=1.5 Hz, 1H, C6-*H*), 7.57 (ddd, ^3J=8.0 Hz, ^3J=7.5 Hz, ^4J=1.5 Hz, 1H, C4′-*H*), 7.51 (ddd, ^3J=9.5 Hz, ^3J=8.0 Hz, ^4J=1.5 Hz, 1H, C4-*H*), 7.39 (ddd, ^3J=8.0 Hz, ^3J=8.0 Hz, ^4J=1.5 Hz, 1H, C5′-*H*), 7.25 (dd, ^3J=8.0 Hz, ^4J=1.5 Hz, 1H, C3′-*H*), 7.12 (ddd, ^3J=8.0 Hz, ^3J=7.5 Hz, ^4J=1.5 Hz, 1H, C5-*H*), 3.94–3.64 (m, 2H, NCH_2CH$_2$), 3.90 (s, 3H, CO_2CH_3), 2.67–2.57 (m, 2H, CH_2CH_2CO), 2.04–1.63 (m, 6H, CH_2CH_2CO, $NCH_2CH_2CH_2$, $NCH_2CH_2CH_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=176.1 (N*C*OCH$_2$), 168.4 (*C*O$_2$CH$_3$), 166.5 (Ar*C*ONH), 142.9 (C2), 141.6 (C2′), 134.6 (C1′), 134.5 (C4), 131.7 (C4′), 130.9 (C6), 128.3 (C6′), 128.1 (C5′), 127.4 (C3′), 122.9 (C5), 120.7 (C3), 115.9 (C1), 53.8 (NCH$_2$CH$_2$), 52.5 (CO_2CH_3), 37.6 (CH_2CH_2CO), 30.2 ($NCH_2CH_2CH_2$), 28.4 (NCH_2CH_2), 23.2 (CH_2CH_2CO); IR (KBr): ν_{max}=3426 (s) (NH), 2953 (m), 2849 (w), 1638 (s) (C=O), 1159 (m) (C–O), 749 (m) (Ar–H) cm^{-1}; LRMS (ES^+): *m/z* (%) 389.22 (100) $[M+Na]^+$; HRMS (ES^+): *m/z* calcd for $C_{21}H_{22}N_2O_4Na$ $[M+Na]^+$: 389.1477; found: 389.1471. An analytical sample of **5**(1,3,1) was prepared by recrystallisation from ethyl acetate/hexanes. Anal. Calcd for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65. Found: C, 68.95; H, 6.02; N, 7.60.

*4.3.37. **5**(1,4,1) Methyl 2-(2-(2-oxoazonan-1-yl)-benzamido)benzoate*

Using the PyBroP procedure the title compound was afforded (0.18 g, 0.46 mmol, 83%) as a pale brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=11.31 (s, 1H, N*H*), 8.75 (dd, ^3J=8.0 Hz, ^4J=1.5 Hz, 1H, C3-*H*), 8.02 (dd, ^3J=8.0 Hz, ^4J=1.5 Hz, 1H, C6-*H*), 7.73 (dd, ^3J=7.5 Hz, ^4J=1.5 Hz, 1H, C6′-*H*), 7.55 (ddd, ^3J=8.0 Hz, ^3J=8.0 Hz, ^4J=1.5 Hz, 1H, C4-*H*), 7.49 (dd, ^3J=7.5 Hz, ^4J=1.5 Hz, 1H, C4′-*H*), 7.40 (ddd, ^3J=7.5 Hz, ^3J=7.5 Hz, ^4J=1.5 Hz, 1H, C5′-*H*), 7.31 (dd, ^3J=7.5 Hz, ^4J=1.5 Hz, 1H, C3′-*H*), 7.10 (ddd, ^3J=8.0 Hz, ^3J=8.0 Hz, ^4J=1.5 Hz, 1H, C5-*H*), 4.15–3.53 (m, 2H, C9″-H_2), 3.88 (s, 3H, CO_2CH_3), 2.83–2.37 (m, 2H, C3″-H_2), 1.91–1.54 (m, 10H, C4″-H_2, C8″-H_2, C7″-H_2, C6″-H_2, C5″-H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=176.2 ($NCOCH_2$), 168.3 (CO_2CH_3), 166.4 (Ar*C*ONH), 141.3 (C2), 141.2 (C2′), 134.6 (C1′), 134.5 (C4), 131.4 (C4′), 131.0 (C6), 129.8 (C3′), 128.8 (C6′), 127.9 (C5′), 123.0 (C5), 120.7 (C3), 116.0 (C1), 53.2 (C9″), 52.5 (CO_2CH_3), 34.2 (C3″), 28.2 (C5″), 27.6 (C6″), 25.3 (C7″), 24.7 (C4″), 23.1 (C8″); IR (KBr): ν_{max}=3296 (m) (NH), 2929 (s) (CH), 1679 (s) (C=O), 1606 (m), 1588 (m), 1450 (m), 1270 (m), 1093 (m) (C–O) cm^{-1}; LRMS (ES$^+$): *m*/*z* (%) 417.08 (100) [M+Na]$^+$, 811.17 (100) [2M+Na]$^+$; HRMS (ES$^+$): *m*/*z* calcd for $C_{23}H_{26}N_2O_4Na$ [M+Na]$^+$: 417.1790; found: 417.1784. An analytical sample of **5**(1,4,1) was prepared by recrystallisation from ethyl acetate/hexanes. Anal. Calcd for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10. Found: C, 69.97; H, 6.73; N, 7.03.

*4.3.38. **5**(1,1,15) Methyl 2-[2-(2-oxo-pyrrolidin-1-yl)-benzoylamino]-thiophene-3-carboxylate*

Using the PyBroP procedure the title compound was afforded (0.14 g, 0.41 mmol, 41%) as a pale brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=11.45 (s, 1H, N*H*), 7.78 (dd, ^3J=8.0 Hz, ^4J=1.5 Hz, 1H, C6′-*H*), 7.50 (ddd, ^3J=7.5 Hz, ^3J=7.5 Hz, ^4J=1.5 Hz, 1H, C4′-*H*), 7.36–7.30 (m, 2H, C3′-*H*, C5′-*H*), 7.15 (d, ^3J=6.0 Hz, 1H, C4-*H*), 6.70 (dd, ^3J=6.0 Hz, ^4J=1.0 Hz, 1H, C5-*H*), 3.85 (t, ^3J=7.0 Hz, 2H, CH_2N), 3.80 (s, 3H, CO_2CH_3), 2.45 (t, ^3J=8.0 Hz, 2H, CH_2CO), 2.19–2.10 (m, 2H, $CH_2CH_2CH_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=176.0 ($NCOCH_2$), 166.3 (CO_2CH_3), 164.4 (Ar*C*ONH), 149.3 (C2), 137.7 (C2′), 132.8 (C4′), 131.2 (C1′), 129.8 (C6′), 127.9 (C4), 126.9 (C5′), 124.3 (C3′), 116.7 (C5), 113.5 (C3), 52.5 (CO_2CH_3), 51.4 (NCH_2), 31.9 (CH_2CO), 19.0 ($CH_2CH_2CH_2$); IR (KBr): ν_{max}=2928 (m) (CH_2), 1635 (s) (C=O), 1535 (m), 1489 (w), 1303 (m), 1224 (m), 843 (w), 749 (m) cm^{-1}; LRMS (ES$^+$): *m*/*z* (%) 367.04 (100) [M+Na]$^+$; HRMS (ES$^+$): *m*/*z* calcd for $C_{17}H_{16}N_2O_4NaS$ [M+Na]$^+$: 367.0728; found: 367.0737.

*4.3.39. **5**(1,2,16) Methyl 3-(2-(2-oxopiperidin-1-yl)benzamido)thiophene-2-carboxylate*

Using the PyBroP procedure the title compound was afforded (0.23 g, 0.68 mmol, 68%) as a pale brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.54 (br s, 1H, N*H*), 8.22 (d, ^3J=5.4 Hz, 1H, C5-*H*), 7.73 (dd, ^3J=7.5 Hz, ^4J=1.5 Hz, 1H, C6′-*H*), 7.54 (ddd, ^3J=7.5 Hz, ^3J=7.5 Hz, ^4J=1.5 Hz, 1H, C4′-*H*), 7.48 (d, ^3J=5.4 Hz, 1H, C4-*H*), 7.40 (ddd, ^3J=7.5 Hz, ^3J=7.5 Hz, ^4J=1.5 Hz, 1H, C5′-*H*), 7.27 (dd, ^3J=7.5 Hz, ^4J=1.5 Hz, 1H, C3′-*H*), 3.86 (s, 3H, CO_2CH_3), 3.75–3.65 (m, 2H, NCH_2), 2.50–2.43 (m, 2H, $COCH_2$), 1.98–1.85 (m, 4H, NCH_2CH_2, $COCH_2CH_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=170.8 ($NCOCH_2$), 164.8 (CO_2CH_3), 164.6 (Ar*C*ONH), 144.6 (C3), 141.8 (C2′), 132.2 (C4), 131.6 (C4′), 128.8 (C3′), 128.5 (C6′), 128.4 (C5′), 128.3 (C1′), 122.6 (C5), 111.1 (C2), 52.3 (NCH_2), 52.2 (CO_2CH_3), 32.7 (CH_2CO), 23.4 ($COCH_2$), 21.4 (NCH_2CH_2); IR (KBr): ν_{max}=3418 (s) (NH), 2954 (m), 2844 (w), 1648 (s) (C=O), 1451 (w), 1110 (m) (C–O), 1017 (w), 856 (m) cm^{-1}; LRMS (ES$^+$): *m*/*z* (%) 381.06 (100) [M+Na]$^+$; HRMS (ES$^+$): *m*/*z* calcd for $C_{18}H_{18}N_2O_4NaS$ [M+Na]$^+$: 381.0885; found: 381.0885.

*4.3.40. **5**(1,1,17) Ethyl 3-[2-(2-oxo-pyrrolidin-1-yl)-benzoylamino]-propionate*

Using the PyBroP procedure the title compound was afforded (0.208 g, 0.68 mmol, 68%) as a pale brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.53 (dd, ^3J=8.0 Hz, ^4J=1.5 Hz, 1H, C3′-*H*), 7.46 (ddd, ^3J=8.0 Hz, ^3J=8.0 Hz, ^4J=1.5 Hz, 1H, C5′-*H*), 7.34 (dd, ^3J=8.0 Hz, ^4J=1.5 Hz, 1H, C4′-*H*), 7.20 (dd, ^3J=8.0 Hz, ^4J=1.5 Hz, 1H, C6′-*H*), 6.82 (s, 1H, N*H*), 4.16 (q, ^3J=7.0 Hz, 2H, CH_3CH_2O), 3.81 (t, ^3J=7.0 Hz, 2H, C5-*H*), 3.64 (dt, J_{CH}=J_{NH}=6.0 Hz, 2H, CH_2NH), 2.60 (t, ^3J=6.0 Hz, 2H, C3-*H*), 2.53 (t, ^3J=8.0 Hz, 2H, CO_2CH_2), 2.25–2.15 (m 2H, C4-*H*), 1.25 (t, ^3J=7.0 Hz, 3H, CH_3CH_2O); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=175.9 (C2), 172.2 (CO_2Et), 168.0 (NH*C*O), 136.1 (C1′or C2′), 134.9 (C1′ or C2′), 131.1 (C5′), 128.8 (C3′), 127.9 (C4′), 127.2 (C6′), 60.8 (CH_3CH_2O), 51.8 (C5), 35.5 (CH_2NH), 34.0 (C3), 31.5 (CO_2CH_2), 18.9 (C4), 14.2 (CH_3CH_2O); IR (Nujol): ν_{max}=3341 (m) (OH), 2932 (m) (CH), 1732 (s) (C=O), 1601 (w), 1535 (w), 1490 (w), 1451 (w), 1409 (w), 1307 (m), 1188 (m) (C–O), 1073 (w), 1025 (w), 764 (m) (Ar–H) cm^{-1}; LRMS (ES$^+$): *m*/*z* (%) 327.04 (100) [M+Na]$^+$; HRMS (ES$^+$): *m*/*z* calcd for $C_{16}H_{20}N_2O_4Na$ [M+Na]$^+$: 327.1321; found: 327.1314.

*4.3.41. **5**(1,1,10) Methyl 5-bromo-2-[2-(2-oxo-pyrrolidin-1-yl)-benzoylamino]-benzoate*

Using the PyBroP procedure the title compound was afforded (0.156 g, 0.37 mmol, 37%) as a pale brown solid. Mp 187–188 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=11.38 (s, 1H, N*H*), 8.74 (d, ^3J=9.0 Hz, 1H, C3-*H*), 8.17 (d, ^4J=2.5 Hz, 1H, C6-*H*), 7.77 (dd, 1H, ^3J=8.0 Hz, ^4J=1.5 Hz, C6′-*H*), 7.66 (dd, ^3J=9.0 Hz, ^4J=2.5 Hz, 1H, C4-*H*), 7.54 (ddd, ^3J=8.0 Hz, ^3J=8.0 Hz, ^4J=1.5 Hz, 1H, C4′-*H*), 7.40 (ddd, ^3J=8.0 Hz, ^3J=8.0 Hz, ^4J=1.5 Hz, 1H, C5′-*H*), 7.34–7.29 (m, 1H, C3′-*H*), 3.94 (t, ^3J=7.0 Hz, 2H, CH_2N), 3.92 (s, 3H, CO_2CH_3), 2.49 (t, ^3J=8.5 Hz, 2H, CH_2CO), 2.25–2.13 (m, 2H, $CH_2CH_2CH_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=175.1 ($NCOCH_2$), 167.4 (CO_2CH_3), 166.3 (Ar*C*ONH), 140.7 (C2), 137.3 (C4), 136.9 (C2′), 133.5 (C1′), 133.4 (C6), 131.6 (C4′), 128.4 (C6′), 127.3 (C5′), 126.4 (C3′), 122.3 (C3), 117.0 (C5), 115.1 (C1), 52.7 (CO_2CH_3), 51.0 (NCH_2CH_2), 31.6 (CH_2CH_2CO), 18.8 ($CH_2CH_2CH_2$); IR (KBr): ν_{max}=3417 (s) (NH), 2959 (m) (CH_2) 1700 (s) (C=O), 1680 (s) (C=O), 1670 (s) (C=O), 1600 (m), 1576 (m), 1507 (s), 1439 (m), 1394 (m), 1310 (m), 1239 (m), 1120 (w) (C–O), 963 (w), 842 (s) (C–Br) cm^{-1}; LRMS (ES$^+$): *m*/*z* (%) 439.11 (100) [M^{79}Br+Na]$^+$, 441.11 (80) [M^{81}Br+Na]$^+$; HRMS (ES$^+$): *m*/*z* calcd for $C_{19}H_{17}N_2O_4Na^{79}Br$ [M^{79}Br+Na]$^+$: 439.0269; found: 439.0283.

4.4. Computational methods

Semi-empirical electronic structure calculations were carried out using the RM1 method[20] as implemented in MOPAC2007[21] (Version 8.148L) running on a Linux cluster. DFT calculations were carried out using GAMESS[22] running on a Linux cluster. The 64-bit Linux version dated 11 Apr 2008 (Revision 1) was used in all calculations. The transition states were located by generation of an initial guess using the results of the RM1 calculations. This model transition state was refined at the B3LYP/6-31G(d,p) level of theory to a transition state structure possessing single imaginary vibration that corresponded to the racemisation coordinate.

Acknowledgements

We would like to thank The Royal Society (University Research Fellowships to N.J.W. and T.v.M.), the BBSRC (A.M.J.), the Wellcome Trust (S.P.) and The University of St Andrews for funding. We would also like to thank Dr. Grace Vanier (CEM Labs, NC, USA) for photographic analysis of the microwave reactions. Mrs. M. H. Smith, Dr. C. Botting and Mrs. C. E. R. Horsburgh are kindly acknowledged for performing and assisting with NMR and MS analyses. We acknowledge EaStCHEM for computational support via the EaStCHEM Research Computing Facility (http://www.eastchem.ac.uk/rcf).

Supplementary data

Additional compound characterisation, LCMS data and a table of microwave optimisation reactions are provided. In addition, details of the methods used to calculation activation parameters and images from microwave reactions are included. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.10.049.

References and notes

1. Patterson, S.; Lorenz, C.; Slawin, A. M. Z.; Westwood, N. J. *QSAR Comb. Sci.* **2004**, *23*, 883–890.
2. Moehrle, H.; Seidel, C. *Chem. Ber.* **1973**, *106*, 1595–1600.
3. See Supplementary data.
4. Werner, S.; Kasi, D.; Brummond, K. M. *J. Comb. Chem.* **2007**, *9*, 677–683.
5. Hammett parameters suggest Br is more electron withdrawing than Cl. Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165–195.
6. Methyl 5-bromo anthranilate has been shown to be stable up to 160 °C under microwave irradiation. Carpenter, R. D.; Lam, K. S.; Kurth, M. J. *J. Org. Chem.* **2007**, *72*, 284–287.
7. It may be speculated from this outcome that a more reactive intermediate is formed that allows the desired reaction to occur through the chemodifferentiation of the three esters.
8. (a) Kalach, A. V. *Russ. Chem. Bull.* **2006**, *55*, 212–217; (b) Macdonald, S. J. F. *J. Chem. Soc., Chem. Commun.* **1987**, 1528–1530; (c) Saeki, S. *Chem. Pharm. Bull.* **1989**, *37*, 2207–2208; (d) Newman, M. S. *J. Org. Chem.* **1976**, *41*, 3356–3359; (e) Conversion of aromatic isocyanates and isothiocyanates with aluminum chloride. Dokunikhin, N. S. *Org. Poluprod I Krasiteli, Nauch. –Issledovatel. Inst. Org. Poluprod., Krasitelei* im. K. E., Voroshilova, CAPLUS: Shornik Statei, 1959; Vol. 1, pp 148–159; (f) Okulova, A. N. *Zh. Org. Khim.* **1975**, *11*, 1473–1476; (g) Singh, P. N. *J. Indian Chem. Soc.* **1981**, *58*, 874–876.
9. A possible reduction in the relative electrophilicity of the ester carbonyl group in **4** resulting from incorporation of the electron-donating methoxy group in **4** may explain these trends. To date no additional products have been isolated from these reactions with only significant decomposition being observed under the standard set of conditions used.
10. (a) Astill, B. D.; Boekelheide, V. *J. Am. Chem. Soc.* **1955**, *77*, 4079–4084; (b) Li, J. Faming Zhuanli Shenqing Gongkai Shuomingshu, CN1690040, 2005.
11. (a) Coste, J.; Frerot, E.; Jouin, P. *J. Org. Chem.* **1994**, *59*, 2437–2446; (b) Haque, T. S.; Tadesse, S.; Macinkeviciene, J.; Rodgers, M. J.; Sizemore, C.; Kopcho, L. M.; Amsler, K.; Ecret, L. D.; Zhan, D. L.; Hobbs, F.; Slee, A.; Trainor, G. L.; Stern, A. M.; Copeland, R. A.; Combs, A. P. *J. Med. Chem.* **2002**, *45*, 4669–4678; (c) Frerot, E.; Coste, J.; Pantaloni, A.; Dufour, M. N.; Jouin, P. *Tetrahedron* **1991**, *47*, 259–270.
12. This may be attributed to the conformation of the 9-membered ring, restricted rotation of the lactam unit observed in the ^{1}H NMR spectra and the suggestion that the amide bond can sit trans in this system. (a) Hemmi, K.; Nakai, H.; Naruto, S.; Yonemitsu, O. *J. Chem. Soc., Perkin Trans. 2* **1972**, 2252–2254; (b) Yamada, S.; Homma, A. *Chem. Commun.* **2002**, 2656–2657.
13. Taylor, E. C.; Shvo, Y. *J. Org. Chem.* **1968**, *33*, 1719–1727.
14. (a) Abraham, R. J.; Mobli, M.; Smith, R. J. *Magn. Reson. Chem.* **2003**, *41*, 26–36; (b) Martin, N. H.; Allen, N. W., III; Brown, J. D.; Kmiec, D. M., Jr.; Vo, L. *J. Mol. Graphics Modell.* **2003**, *22*, 127–131.
15. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652.
16. Ditchfield, R. *Mol. Phys.* **1974**, *27*, 789–807.
17. Wolinsky, K.; Hilton, J. F.; Pulay, P. *J. Am. Chem. Soc.* **1990**, *112*, 8251–8260.
18. Wilson, P. J.; Bradley, T. J.; Tozer, D. J. *J. Chem. Phys.* **2001**, *115*, 9233–9242.
19. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*; Gaussian: Pittsburgh, PA, 2003.
20. Rocha, G. B.; Freire, R. O.; Simas, A. M.; Stewart, J. J. P. *J. Comput. Chem.* **2006**, *27*, 1101–1111.
21. MOPAC2007, Stewart J. J. P. *Stewart Computational Chemistry*, Colorado Springs, CO, USA, http://openmopac.net, 2007.
22. (a) Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J. Comput. Chem.* **1993**, *14*, 1347–1363; (b) Gordon, M. S.; Schmidt, M. W. In *Theory and Applications of Computational Chemistry: the First Forty Years*; Dykstra, C. E., Frenking, G., Kim, K. S., Scuseria, G. E., Eds.; Elsevier: Amsterdam, 2005; p 1167.