Syntheses of 3-[(Alkylamino)methylene]-6-methyl-1*H*-pyridine-2,4-diones, Fluorescence Probes 3-Substituted 7-Methyl-6*H*-pyrano[3,2-c]pyridine-2,5-diones, and Tetrahydro-6*H*-2,10-dioxa-9-azaanthracen-1-ones

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Syntheses of 3-[(Alkylamino)methylene]-6-methyl-1*H*-pyridine-2,4-diones, Fluorescence Probes 3-Substituted 7-Methyl-6*H*-pyrano[3,2-c]pyridine-2,5-diones, and Tetrahydro-6*H*-2,10-dioxa-9-azaanthracen-1-ones

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Abstract: Various condensation and ring closing reactions were used for the syntheses of 3-[(alkylamino)methylene]-6-methyl-1*H*-pyridine-2,4-diones, bicyclic pyridinones, and tricyclic morpholinopyrones. For instance, 3-(dialkylamino)methylene-6-methyl-1*H*-pyridine-2,4-diones were synthesized from the condensation of dialkylamines and 3-formyl-4-hydroxy-6-methyl-2-pyridinone (**17**). 3-Formyl-4-hydroxy-6-methyl-2-pyridinone (**19**), derived from **17**, was used to construct a number of bicyclic pyridinones via a one-pot Knoevenagal/intramolecular lactonization reaction. Tricyclic morpholinopyrones were assembled from a dialkylation reaction involving a dinucleophile, 3-amino-4-hydroxy-6-methyl-2-pyrone, and a dielectrophile, *trans*-3,6-dibromocyclohexene. Depending on the reaction conditions, isomers of the tricyclic molecules can be selectively produced, and their chemical structures were unequivocally determined using single-crystal X-ray analyses and 2D COSY spectroscopy. The fluorescently active bicyclic pyridinone compounds show longer absorption (368 - 430 nm; maximum) and emission wavelengths (450 ~ 467 nm) than those of 7-amino-4-methylcoumarin (AMC; $\lambda_{abs,max}$ = 350 nm; λ_{em} = 430 nm) suggesting these molecules, such as 3-(2-aminoacetyl)-7-methyl-6*H*-pyrano[3,2-c]pyridine-2,5-dione (**11**), can be employed as fluorescence activity-based probes for tracing biological pathways.

Key words: Dialkylation, fluorescence probes, heterocycles, 3-substituted 7-methyl-6*H*-pyrano[3,2-c]pyridine-2,5-diones, tetrahydro-6*H*-2,10-dioxa-9-azaanthracen-1-ones.

In an effort of finding new structures differed from the tricyclic pyrone pharmacophore,[1,2] we investigated various mono- and bicyclic pyridinone and tricyclic morpholinopyridinone molecules that may possess bioactivity.[1,2] Although several methods have been reported for the preparations of bicyclic pyridinones,[3-7] a method for the synthesis of tricyclic morpholinopyrones (such as **13** – **16**; Figure 1) is not available. Herein, we described a number of reactions including the coupling of 3-formyl-4-hydroxy-2-pyridinone (**19**) with secondary amines to produce exocyclic enamines and with α-sulfinyl, α-sulfonyl, and α-keto esters to afford bicyclic pyridinones, and ring closing reactions of 3-amino-4-hydroxy-2-pyrones with *trans*-3,6-dibromocyclohexene to give tricyclic morpholinopyrones. Bicyclic pyridinones possess strong fluorescence activity at wavelengths of 450 ~ 467 nm, which are suitable for activity-based probes[8] and activity-based proteomics studies.[9]

Synthesis of 3-(Alkylamino)methylene-6-methyl-1*H*-pyridine-2,4-diones

In search of new heterocyclic molecules possessing biological activity, monocyclic pyridinones **1** – **7**, bicyclic pyridinones **8** – **12**, and tricyclic morpholinopyrones **13** - **16** were synthesized (Figure 1). Since the synthesis of a monocyclic pyridinone, 6-methyl-3-phenylaminomethylidene-1*H*-pyridine-2,4-dione (**18**), has been reported through a coupling reaction of 4-hydroxy-6-methyl-2-pyridinone (**17**), triethyl orthoformate, and aniline,[4] we treated compound **17** with primary amines such as benzylamine and adenine separately under similar reaction conditions, and found that monocyclic pyridinones **1** and **3**, respectively, formed in 68% and 50% yields (Scheme 1). In the case of adenine, the C6-primary amino function appears to react faster than the C9-secondary amino group. In both cases a mixture of stereoisomers (*Z* and *E* at the enamine function) formed in an inseparable 1:4.5 ratio for compound **1** and a 1:2 ratio for compound **3**, based on NMR spectral data. The regiochemistry of compound **3** was determined from its 2D COSY NMR spectrum in which the enamine C7H of the major isomer at δ 9.55 (d, *J* = 12 Hz) correlates with C6'-NH at δ 13.95 (d, *J* = 12 Hz) and that of the minor isomer at δ 9.51 (d, *J* = 12.9 Hz) correlates with C6'-NH at δ 12.82 (d, *J* = 12.9 Hz). N1- and N9'-hydrogens of **3** appear as broad singlets. However this three-component coupling reaction appears to be applicable only with primary amines, when a secondary amine such as piperidine was used, under similar reaction conditions no condensation product, i.e., monocyclic pyridinone **4**, was found.

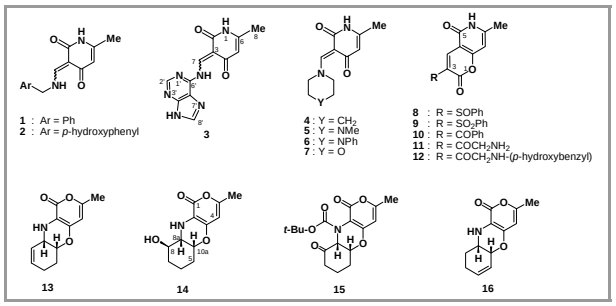
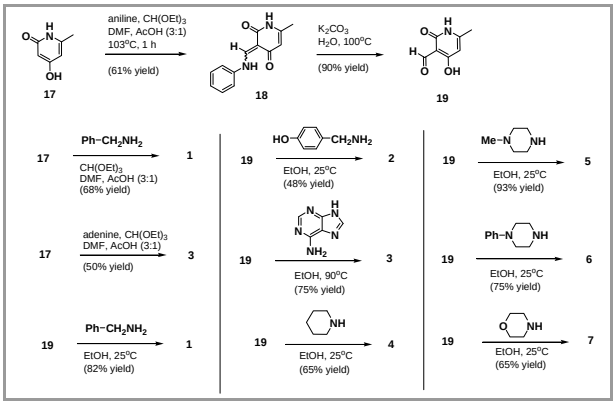


Figure 1 Synthesized monocyclic pyridinones **1** - **7**, bicyclic pyridinones **8** - **12**, and tricyclic morpholinopyrones **13** - **16**.

To overcome this problem, we utilized 3-formyl-4-hydroxy-6-methyl-2-pyridinone (**19**), which pre-installed with an aldehyde function at the C3 of the pyridinone as our starting material, in a two-component condensation reaction with various secondary amines (Scheme 1). Aldehyde **19** was prepared according to a previously established synthetic route starting from pyridinone **17**[4] as described in Scheme 1.



Scheme 1 Synthesis of monocyclic pyridinones **1** - **7**.

The enamine intermediate **18**, formed as a 4:1 mixture of *E*- and *Z*-isomers, was hydrolyzed using aqueous potassium carbonate at 100°C to provide aldehyde **19** (90% yield). The spectral data for aldehyde **19** are similar to those previously reported.[4] Various monocyclic pyridinone enamines, **1** – **7**, were synthesized in good to excellent yields by treating aldehyde **19** with primary and secondary amines in ethanol (Scheme 1). Compounds **1**, **2**, and **4** - **7** could be obtained at room temperature by treating aldehyde **19** with benzylamine, 4-hydroxybenzylamine, piperidine, *N*-methylpiperazine, *N*-phenylpiperazine, and morpholine, respectively, however, condensation with adenine to form compound **3** required an elevated temperature to achieve product formation. During the course of the reaction, compounds **1** – **6** precipitated out from the ethanolic reaction solvent, which facilitated product formation and isolation, however, compound **7** remained soluble and hence 2 - 3 equivalents of morpholine was necessary to drive product formation as well as a longer reaction time. The ^{1}H NMR spectral data of compounds **4** - **7** show the presence of single stereoisomers and that of compounds **1** - **3** indicate two stereoisomers. The stereochemistry of **4** – **7** was not determined. Single crystals of the major stereoisomer of **1** could be grown by slow cooling and evaporation in ethanol. An ORTEP diagram of compound **1** from a single-crystal X-ray analysis is shown in Figure 2, which unequivocally determined the *E* enamine double bond geometry of **1** (NMR spectrum of the single crystals confirms it to be the major stereoisomer). Selected bond lengths and bond angles of compounds **1**, **13**, and **16** derived from single-crystal X-ray analyses are listed in Table 1.

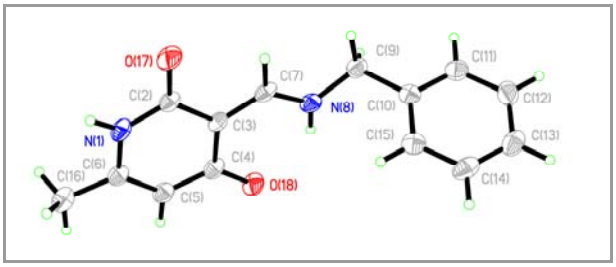
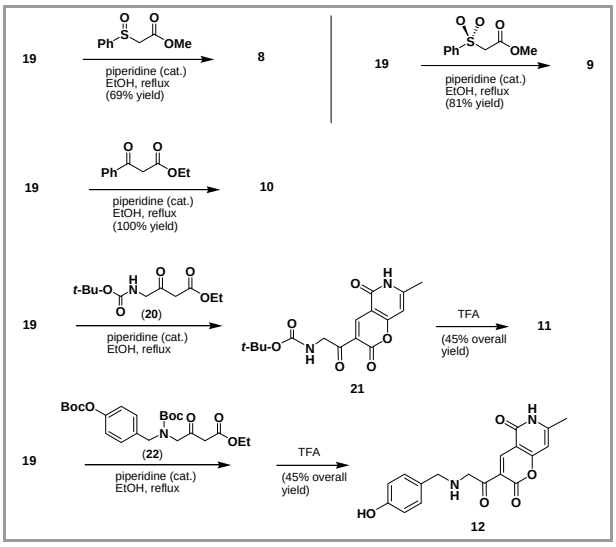


Figure 2 An ORTEP drawing of a single-crystal X-ray structure of *E*-3-(benzylamino-methylene)-6-methyl-1*H*-pyridine-2,4-dione (**1**), CCDC Reg. No. 989745, having a molecular formula of $C_{14}H_{14}N_2O_2$, triclinic, space group of $P\bar{1}$, Z=2, and R1 factor of 0.0702.

Synthesis of Bicyclic Pyridinones

Aldehyde **19** proved to be a versatile scaffold[4] through which to construct various bicyclic pyridinone structures by treating it with various doubly activated esters such as methyl α-(phenylsulfinyl)acetate, methyl α-(phenylsulfonyl)acetate, ethyl 3-oxo-3-phenylpropanoate, γ-(*N*-Boc-amino)-β-ketoester **20**,[10] and β-ketoester **22** in refluxing ethanol, employing piperidine as a catalyst (Scheme 2). The mechanism by which compounds **8** - **12** are formed is expected to proceed *via* Knoevenagel condensation[4] of the ester with aldehyde **19** followed by an intramolecular lactone formation. Notably, the ester function is required to orient at the *cis* configuration with the phenolic OH group for the lactonization. When one equivalent of piperidine was used, by-product, **4**, formed predominantly. The bicyclic pyridinones **8**, **9**, and **10** could be obtained in 69%, 81%, and 100% isolated yields, respectively, after filtration of the products out from the crude reaction mixtures or column chromatography on silica gel. The bicyclic pyridinone **11** containing an amino function in the side chain was obtained in 45% overall yield from the coupling of **19** and **20**[10] followed by removal of the Boc protecting group of **21** with trifluoroacetic acid (TFA).



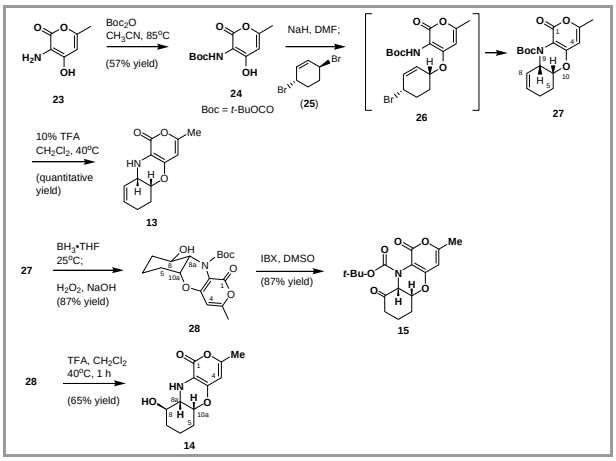
Scheme 2 Synthesis of bicyclic pyridinones **8** - **12**.

Similarly, coupling of **19** and β-ketoester **22** followed by Boc-deprotection gave compound **12**. Compound **22** was prepared by modifying the reported synthesis of compound **20**.[10] The amino function of **11** or **12** can condense with carboxylic acid group of various amino acids or peptides to generate fluorescence-active molecules.

Synthesis of Tricyclic Morpholinopyrones

Molecules containing tricyclic pyrone scaffolds have been synthesized in our laboratory and have been shown to possess strong cell protective action against oligomeric amyloid β peptide toxicity[1,11] and anti-viral activity.[2] To explore new structures, a tricyclic pyrone scaffold containing a nitrogen atom in the central ring (such as **13**) would provide an additional hydrogen bond donor (N-H) capacity. We therefore examined a two-component coupling reaction for the synthesis of tricyclic morpholinopyrones from dinucleophile, 3-aminopyrone **23**, and dielectrophile, *trans*-3,6-dibromocyclohexene (**25**).[12] The expeditious synthesis started from commercially available 4-hydroxy-6-methylpyran-2-one which was converted into 3-aminopyrone **23** *via* a two-step process[13] involving the nitration of 4-hydroxy-6-methylpyran-2-one at C-3 by nitric acid/sulfuric acid followed by reduction of the resulting nitro function to amine over hydrogen/palladium to provide **23** in 62% overall yield. To examine the two-component ring-closing reactions, we first study *N*-protected pyrone **24**. Aminopyrone **23** was capped with a *t*-butoxycarbonyl (Boc) protecting group to afford Boc-amino pyrone **24** in 57% yield (Scheme 3). Upon treatment of pyrone **24** with 1 equivalent of sodium hydride followed by dibromide **25**, Boc-tricyclic morpholinopyrone **27** resulted in a 25% yield, and no other isomers were found (Table 3, Entry 1). We envision that the initial step requires deprotonation of **24** with sodium hydride to form a pyrone oxy anion, which upon treatment with dibromide **25** supposedly forms *O*-alkylated intermediate **26**. This *O*-alkylated intermediate undergoes ring closing reaction to give **27**. The Boc protecting group of **27** was readily removed using 10% TFA in dichloromethane at 40°C to furnish tricyclic morpholinopyrone **13** in a quantitative yield. Only the *cis*-diastereomer, **13**, was detected from the cyclization reaction and the stereochemistry was unequivocally determined through a single-crystal X-ray analysis (Figure 3). Single crystals of tricyclic morpholinopyrone **13** were achieved by slow evaporation of a solution of **13** in ethanol. The crystal structure shows that the tricyclic scaffold forms a *cis*-fused ring junction upon cyclization and the double bond is situated between C7 and C8 implying a S_N2' reaction takes place from intermediate **26** with retention of configuration. The two synclinal bridge head protons have a torsion angle of 48.1°.

Dibromide **25** was prepared from a one-step double bromination of cyclohexene with 2 equiv. of *N*-bromosuccinimide (NBS)[14] and the *trans*-stereochemistry was verified by comparing its ^{1}H NMR spectral data with the literature values.[12] We have also obtained a single-crystal X-ray structure of this compound which agrees with that reported.[12] The presence of a double bond in the 6-membered carbocyclic ring of the tricyclic skeleton is significant because it allows for further modification of the tricyclic scaffold as demonstrated in Scheme 3. The double bond of **27** was regioselectively hydroxylated by employing standard hydroboration/oxidation conditions to give 8-hydroxy tricyclic morpholinopyrone **28** as a single stereoisomer. The stereochemistry at C8 was assumed in that borane approaches the C7,8 double bond from the least hindered face (same side of C8a and C10a Hs).



Scheme 3 Synthesis of tricyclic morpholinopyrones **13** - **15**.

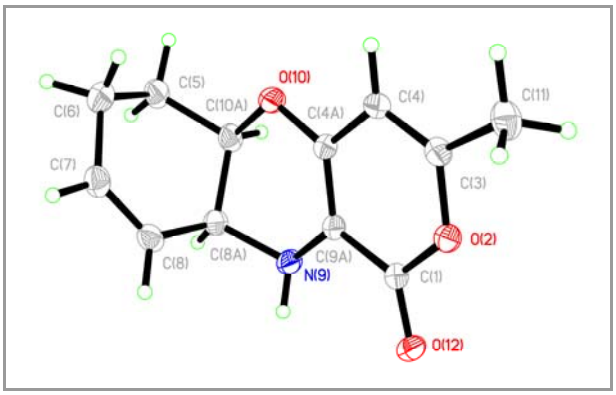
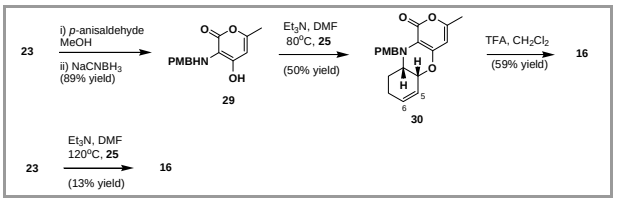


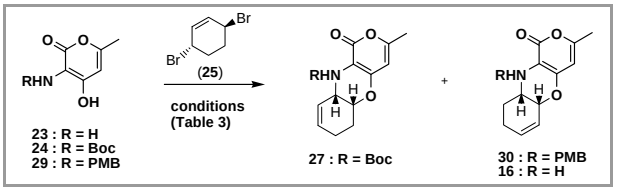
Figure 3 An ORTEP drawing of a single-crystal X-ray analysis of 3-methyl-5,8a,9,10a-tetrahydro-6*H*-2,10-dioxa-9-azaanthracen-1-one (**13**). CCDC Reg. No. 989746, having a molecular formula of $C_{12}H_{13}N_1O_3$, monoclinic, space group of $P2_1/c$, $Z = 4$, and R1 factor of 0.0538.

The regiochemistry of the C8 hydroxyl function was assigned from the appearances of C(8)H at δ 3.34 ppm showing a triplet of doublet with *J* values of 10.5 and 4.7 Hz, C(8a)H at δ 4.20 ppm showing a doublet of doublet with *J* values of 10.1 and 3.5 Hz, and C(10a)H at δ 4.40 ppm showing a quartet with *J* value of 3.1 Hz, suggesting C(8)H orients at the axial, C(8a)H at axial, and C(10a)H at equatorial position based on the *J* values. The chemical shift assignments and couplings were supported from the 2D COSY, HMBC, and HSQC spectra of **28**. The regiochemistry at C8 was further verified from the oxidation of **28** to ketone **15** using 2-iodoxybenzoic acid (IBX) in DMSO. Only two alkanyl down-field hydrogens at δ 5.20 (d, *J* = 4 Hz, C8aH) and 4.75 (q, *J* = 4 Hz, C10aH) ppm were found in the ^{1}H NMR spectrum of **15**. The Boc protecting group of **28** can be removed by 10% TFA in dichloromethane at 40°C to give 8-hydroxy tricyclic morpholinopyrone **14**. These results are encouraging because the alkene, hydroxyl and ketone functionalities provide a means for further structural modification of the tricyclic ring system making further synthesis of analogs possible.

Intriguing differences were observed in the aforementioned double alkylation reaction for the formation of tricyclic morpholinopyrone scaffold. A regioisomer of **27**, **30**, was found when a different protecting group, *p*-methoxybenzyl (PMB), was used (Scheme 4). The PMB group was installed *via* a two-step reductive amination procedure[1] by treating 3-amino pyrone **23** with *p*-anisaldehyde in methanol followed by sodium cyanoborohydride and acetic acid in ethanol to give **29** in 89% yield. Various reaction conditions were examined for the dialkylation reactions and results are summarized in Scheme 5 and Table 3. A single diastereomer of the olefin regioisomer **30** was resulted when treating **29** with dibromide **25** and triethylamine in 50% isolated yield (Table 3, Entry 5) after column chromatographic purification. No other isomers were found. When sodium hydride was used in place of triethylamine in the above double alkylation reaction, only 7% yield of **30** was obtained (Entry 4). The PMB group was removed by 5% TFA in dichloromethane at 40°C to give tricyclic morpholinopyrone **16**, which structure was unequivocally determined from a single-crystal X-ray analysis (Figure 4).



Scheme 4 Synthesis of tricyclic morpholinopyrone **16**.



Scheme 5 Synthesis of tricyclic morpholinopyrones **27**, **30** and **16**.

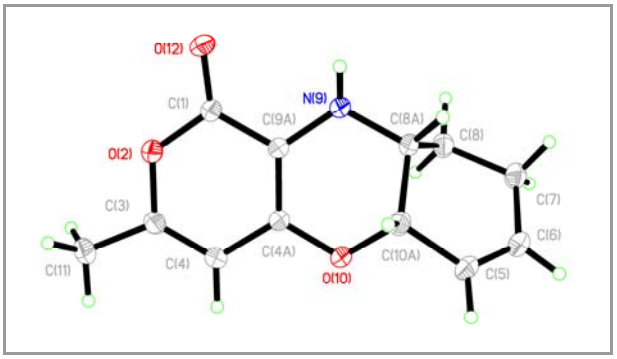


Figure 4 An ORTEP drawing of a single-crystal X-ray analysis of 3-methyl-7,8a,9,10a-tetrahydro-8*H*-2,10-dioxa-9-azaanthracen-1-one (**16**). CCDC Reg. No. 989747, having a molecular formula of $C_{12}H_{13}N_1O_3$, monoclinic, space group of $P2_1/c$, $Z = 4$, and R1 factor of 0.0595.

The tricyclic scaffold of **16** also formed a *cis*-fused ring junction upon cyclization and the two synclinal bridge head protons have a torsion angle of 44.2°. Of interest is the position of the double bond which is now found between C5 and C6. This suggests that the cyclization steps took place either *via* initial S_N2 *N*-alkylation of **29** with dibromide **25** followed by S_N2' nucleophilic substitution (with retention of configuration) by the hydroxyl function, or by initial S_N2' *O*-alkylation of **29** with dibromide **25** (with retention of configuration) followed by ring closing due to S_N2 nucleophilic substitution (inversion) by the amine function. We further discovered that pyrone **16** can be synthesized in a single step (in a lower yield; Table 3, Entry 7) by the direct treatment of amine **23** with dibromide **25** and triethylamine in DMF at 120°C

for 2 h without the PMB protection. Table 3 summarizes the reaction conditions that formed tricyclic morpholinopyrone scaffolds. The alkylation of Boc-protected pyrone **24** with **25** and potassium carbonate or triethylamine gave only 3% and 7% yield, respectively (Entries 2 and 3). The protecting groups appear to affect the regiochemistry of the olefinic moiety of the tricyclic products. The use of Boc as an amine protecting group resulted in C7,8 double bond isomer, while an amine substituent (with or without PMB protecting group) gave the C5,6-double bond isomer. The strengths of the N-H acidities appear to affect the initial alkylation step, which resulted in different regioisomers. Notably, no tricyclic product was found when amine **23** was treated with NaH or DBU and dibromide **25** (Entries 6 and 9), and the use of other bases such as pyridine only produced trace amounts of **16** (Entry 8).

One of our goals in the synthesis of bicyclic pyridinones is the construction of new fluorescence activity-based probes.[8,9] Based on the reported bicyclic heterocycles,[15] bicyclic pyridinones **8** – **12** should be fluorescently active. Indeed, Table 2 summarized photophysical data from the UV absorption and fluorescence emission spectra of **8** – **12** and **21** showing longer absorption and fluorescence emission wavelengths compare with those of commercially available 7-amino-4-methylcoumarin (AMC; λ_{ex} = 351 nm; λ_{em} = 430 nm; $\lambda_{abs,max}$ = 350 nm in ethanol), a widely used fluorescence probe.[15] All five compounds possess similar fluorescence emission wavelengths, λ_{em}, of 450 – 467 nm and quantum yields, Φ_F, ranging from 0.03 to 0.54. Perylene was used as a standard for the calculation of quantum yields.[16] The C3 electron-withdrawing group such as sulfoxide, sulfone, and ketone of the bicyclic pyridinone system contributes bathochromic and bathofluoric shifts in the absorption and fluorescence spectra, respectively. The extended conjugation contributed from the phenyl ring of ketone **10** leads to a longer emission wavelength of 467 nm than other measured compounds, and sulfone **9** possesses the highest quantum yield.

One-pot condensations of 3-formyl-4-hydroxy-6-methyl-2-pyridinone (**19**) with secondary amines afforded various 3-(dialkylamino)methylene-6-methyl-1*H*-pyridine-2,4-diones and with α-sulfinyl, α-sulfonyl, and β-keto esters gave bicyclic pyridinones, which can be used as fluorescence probes for biochemical research. Moreover, one-pot dialkylation reactions of 3-amino-4-hydroxy-6-methyl-2-pyrones with *trans*-3,6-dibromocyclohexene under various reaction conditions were investigated and different regioisomers can be selectively produced albeit in low yields. Bioactivity of the newly synthesized monocyclic, bicyclic and tricyclic molecules will be evaluated and reported in due course.

Table 1. Selected bond lengths and bond angles of compounds **1**, **13**, and **16** from single-crystal X-ray analyses.

Compound **1**		Compound **13**		Compound **16**	
Bond lengths, [Å]	Bond angles, [°]	Bond lengths, [Å]	Bond angles, [°]	Bond lengths, [Å]	Bond angles, [°]
N(1)-C(2), 1.362(3)	C(2)-N(1)-C(6), 124.60(19)	C(1)-O(12), 1.2236(15)	O(2)-C(1)-C(9A), 117.48(10)	C(1)-O(12), 1.2239(17)	O(12)-C(1)-O(2), 117.12(12)
N(1)-C(6), 1.386(3)	O(17)-C(2)-N(1), 119.57(19)	C(1)-O(2), 1.3749(15)	C(3)-O(2)-C(1), 122.73(10)	C(1)-O(2), 1.3757(17)	C(1)-O(2)-C(3), 122.99(11)
C(2)-O(17), 1.258(2)	O(17)-C(2)-C(3), 124.0(2)	C(1)-C(9A), 1.4283(16)	C(3)-C(4)-C(4A), 119.39(11)	C(1)-C(9A), 1.4395(18)	C(3)-C(4)-C(4A), 119.23(13)
C(2)-C(3), 1.446(3)	N(1)-C(2)-C(3), 116.38(19)	O(2)-C(3), 1.3686(15)	C(7)-C(8)-C(8A), 123.73(12)	O(2)-C(3), 1.3764(17)	C(6)-C(5)-C(10A), 123.20(14)
C(3)-C(7),	C(7)-C(3)-C(2),	C(3)-C(4),	N(9)-C(8A)-	C(3)-C(4),	C(5)-C(6)-C(7),

1.387(3)	116.65(19)	1.3446(17)	C(8), 113.59(11)	1.3476(19)	123.53(13)
C(3)-C(4), 1.448(3)	C(5)-C(4)-C(3), 116.64(19)	C(4)-C(4A), 1.4235(17)	N(9)-C(8A)-C(10A), 108.92(10)	C(4)-C(4A), 1.4269(19)	N(9)-C(8A)-C(8), 113.03(13)
C(4)-O(18), 1.257(3)	N(8)-C(7)-C(3), 127.3(2)	C(7)-C(8), 1.3314(19)	O(10)-C(10A)-C(8A), 111.68(10)	C(5)-C(6), 1.332(2)	N(9)-C(8A)-C(10A), 110.16(11)
C(7)-N(8), 1.303(3)	C(7)-N(8)-C(9), 123.29(19)	N(9)-C(9A), 1.3955(16)	C(5)-C(10A)-C(8A), 111.43(11)	C(8A)-C(10A), 1.533(2)	C(9A)-N(9)-C(8A), 119.03(12)

Table 2. Photophysical data for absorption (abs) and emission (em) of compounds **8** – **12** and **21** in methanol. [a] Wavelengths of maximum absorption. [b] Extinction coefficient. [c] Wavelengths of fluorescence excitation. [d] Wavelengths of maximum fluorescence emission. [e] Fluorescence quantum yields were calculated by following the reported method[16] from two independent experiments. [f] Data were obtained in cyclohexane due to solubility. [g] Literature quantum yield of perylene is 0.94 (in cyclohexane).[16]

Compounds	**8**	**9**	**10**	**11**	**12**	**21**	**Perylene**[f]
λ_{abs} (nm)[a]	368	385	381	427	430	393	436
log ε ($M^{-1}cm^{-1}$)[b]	4.16	4.26	4.18	3.85	3.67	4.18	4.40
λ_{ex} (nm)[c]	380	380	380	380	380	380	380
λ_{em} (nm)[d]	450	450	467	450	458	460	439
Φ_F[e]	0.03	0.54	0.03	0.14	0.06	0.22	0.94[g]

Table 3. Reaction conditions and yields of the formation of tricyclic morpholinopyrones **27**, **30**, and **16**.

Entry	R	Conditions	**27** (% yield)	**30** (% yield)	**16** (% yield)
1	Boc	(i) NaH, DMF; (ii) Et_3N, CH_3CN, 95°C, 8 h	25	-	-
2	Boc	K_2CO_3, DMF, 90°C, 8 h	3	-	-
3	Boc	Et_3N, DMF, 80°C, 3 h	7	-	-
4	PMB	NaH, DMF/CH_3CN (1:1), 80°C, 8 h	-	7	-
5	PMB	Et_3N, DMF, 80°C, 2.5 h	-	50	-
6	H	(i) NaH, DMF; (ii) Et_3N, CH_3CN, 80°C, 8 h	-	-	0
7	H	Et_3N, DMF, 120°C, 2 h	-	-	13
8	H	Pyridine, DMF, 120°C, 0.5 h	-	-	2

9	H	DBU, DMF, 120°C, 0.5 h	-	-	0

All melting points are uncorrected. ^{1}H NMR spectra (400 MHz) and ^{13}C NMR spectra (100 MHz) were measured from a solution in $CDCl_3$ or DMSO-d_6. The chemical shift data for each signal on ^{1}H NMR are given in units of δ relative to TMS (δ = 0) or $CHCl_3$ (δ = 7.26). For ^{13}C NMR spectra, the chemical shifts are recorded relative to $CDCl_3$ (δ = 77.0) or DMSO (δ = 39.5). The *E* and *Z* assignment in ^{13}C NMR spectral data are assumed and based on the signal intensities. Low-resolution mass spectra were taken from an API 2000-triple quadrupole ESI-MS/MS mass spectrometer. High-resolution Mass spectra were obtained using a LCT Premier time of flight mass spectrometer. IR spectra were measured directly in either solid or liquid form. UV-Vis absorption measurements were recorded on a Hewlett Packard 8453 UV-VIS spectrometer and fluorescence emission spectra were recorded on a Jobin Yvon-spec fluoromax-2 fluorescence spectrometer. The slits on the fluoromax-2 spectrometer were set at 2.5 nm and an integration time of 0.5 seconds was used throughout. An excitation wavelength of 380 nm was used in all compounds to record fluorescence emission spectra, and emissions were observed from 400 - 600 nm. The fluorescence quantum yields were determined by following a procedure reported by Brouwer[16] using perylene (Φ_F = 0.94 in cyclohexane) as the standard reference compound. Perylene was chosen as the reference because it has an emission wavelength similar to compounds **8** – **12** thus allowing the same excitation wavelength (380 nm) to be used for all molecules. Fluorescence emission spectra and UV-VIS absorption spectra for compounds **8** – **12**, and **21** were recorded at 2 μM and 20 μM, respectively, in methanol, and perylene recorded at 1 μM and 10 μM, respectively, in cyclohexane. Refractive indices for methanol and cyclohexane were incorporated when calculating relative fluorescence quantum yields.[16] X-ray crystal structure data sets were collected on a Bruker Kappa APEX II systems using MoKα radiation. Data were collected using APEX2 software (APEXII v2009, Bruker Analytical X-ray Systems, Madison, WI). Data collection strategies were determined using COSMO (v1.60, 1999-2009, Bruker Analytical X-ray System, Madison, WI). Scan speed and scan width were chosen based on scattering power and peak rocking curves. All datasets were collected at -153 °C using an Oxford Cryostream low-temperature device. Unit cell constants and orientation matrix were improved by least-squares refinement of reflections threshold from the entire dataset. Integration was performed with SAINT (v7.60a, 1997 – 2008, Bruker Analytical X-ray System, Madison, WI), using this improved unit cell as a starting point. Precise unit cell constants were calculated in SAINT from the final merged dataset. Lorenz and polarization corrections were applied. Multi-scan absorption corrections was performed with SADABS (v2008/1, Bruker Analytical X-ray System, Madison, WI). Data were reduced with SHELXTL (v2008/4, Bruker Analytical X-ray System, Madison, WI). The structures were solved in all cases by direct methods without incident. The molecules were fully ordered, no solvent was present, and no constraints or restraints were applied. Coordinates for N-H hydrogen atoms were allowed to refine. All other hydrogen atoms were located in idealized positions and were treated with a riding model. Refinement was continued to convergence using the recommended weighting scheme. 4-Hydroxy-6-methyl-2-pyridinone (**17**) and 4-hydroxy-6-methylpyran-2-one were purchased from Fisher Scientific and Sigma-Aldrich, respectively. All solvents were dried over appropriated drying chemical such as calcium hydride (for DMF), magnesium (for ethanol), or sodium and benzophenone (for THF) followed by distillation. All low molecular weight amines were purified by distillation.

3-Formyl-4-hydroxy-6-methyl-2-pyridinone (19).[4] A solution of 8.0 g (64 mmol) of 4-hydroxy-6-methyl-2-pyridinone (**17**), 53 mL (0.32 mol) of triethyl orthoformate, and 5.8 mL (64 mmol) of aniline in 60 mL of DMF and acetic acid (3:1) under argon was heated at 130 °C for 1 h. The solution was cooled to 25 °C, diluted with water (300 mL), and extracted four times with CH_2Cl_2 (100 mL each). The organic layers were washed with brine and concentrated to dryness. To it, diethyl ether (200 mL) was added, cooled to 0 °C, and the precipitated solid was collected by filtration, washed with diethyl ether, and dried under vacuum to give 8.9 g (61% yield) of 6-methyl-3-

[(phenylamino)methylene]pyridine-2,4(1*H*,3*H*)-dione (**18**)[4] as a 4:1 ratio of *E*- and *Z*-isomers. ^{1}H NMR δ 9.76 (bs, 1H, NH), 8.87 (d, *J* = 12.5 Hz, 1H, =CHN, minor isomer), 8.83 (d, *J* = 12.5 Hz, 1H, =CHN, major isomer), 7.45–7.25 (m, 5H), 5.67 (s, 1H, =CH, minor isomer), 5.64 (s, 1H, =CH, major isomer), 2.20 (s, 3H, major isomer), 2.18 (s, 3H, minor isomer). A solution of 2.0 g (8.7 mmol) of **18** and 40 g (0.29 mol) of K_2CO_3 in 800 mL of water was heated at 100°C for 4 h, cooled to 25 °C, acidified with conc. HCl to pH 2, and extracted twice with CH_2Cl_2. The combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated to give **19**.

19

Yield: 1.2 g (90%); yellow solids; mp 256°C (dec.).[4]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.71 (s, 1 H, NH), 11.50 (bs, 1 H, OH), 10.08 (s, 1 H, CHO), 5.86 (s, 1 H, =CH), 2.36 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d6): δ = 193.3, 174.7, 163.3, 157.1, 105.3, 97.7, 19.5.

MS (ESI, MeOH): *m/z* = 176.1 ([M + Na^+]).

3-[(Benzylamino)methylene]-6-methyl-1*H*-pyridine-2,4-dione (1); Typical procedure for the synthesis of compounds 1 – 7

To a solution of compound **19** (1.31 mmol) in distilled ethanol (4 mL) under argon was added benzylamine (1.44 mmol), stirred at 25 °C for 24 h, and the reaction solution was diluted with hexane:ether (1:1). The precipitated solid was collected by filtration, washed with hexane:ether (1:1), and dried under vacuum to yield pure compound **1**.

1

Yield: 0.26 g (82%); yellow solids (a mixture of *E* and *Z* isomers in a ratio of 4.5:1); mp 219-221°C.

^{1}H NMR (400 MHz. $CDCl_3$, major *E*-isomer): δ = 9.69 (bs, 1 H), 8.45 (d, *J* = 12 Hz, 1 H), 8.38 (s, 1 H), 7.23-7.45 (m, 5 H), 5.56 (s, 1 H), 4.65 (d, *J* = 4 Hz, 2 H), 2.13 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$, major *E*-isomer): δ = 185.0, 166.9, 160.7, 149.3, 135.5, 129,3, 128.7, 127.8, 107.0, 102.5, 54.5, 20.0.

MS (ESI, MeOH): m/z = 265.4 ([M + Na^+]).

HRMS-ESI: *m/z* [M + Na]$^+$ calcd for $C_{14}H_{14}N_2O_2Na$: 265.0953; found: 265.0946.

3-[(4-Hydroxybenzylamino)methylene]-6-methyl-1*H*-pyridine-2,4-dione (2)

From 1.7 mmol of aldehyde **19** and 1.7 mmol of 4-hydroxylbenzylamine in ethanol (2 mL), after stirring at 25 °C for 4 h, compound **2** was isolated.

2

Yield: 0.21 g (48%); yellow solids (a mixture of *E* and *Z* isomers in a ratio of 7:3); mp 222-225 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.07-12.19 (m, 0.7H, *E*-isomer), 10.91-11.01 (m, 0.3 H, *Z*-isomer), 10.27 (s, 1 H), 9.50 (s, 1 H), 8.29-8.36 (m, 1 H), 7.17 (d, *J* = 7.4 Hz, 2 H), 6.76 (d, *J* = 7.4 Hz, 2 H), 5.30 (s, 1 H), 4.54-4.61 (m, 2 H), 1.98 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 183.5 (*E*), 180.3 (*Z*), 166.9 (*Z*), 165.0 (*E*), 159.4 (*E*), 159.0 (*Z*), 157.1 (*E*&*Z*), 149.5 (*E*), 149.0 (*Z*), 129.5 (*E*&*Z*), 127.3 (*Z*), 127.1 (*E*), 115.5 (*E*&*Z*), 106.2 (*Z*), 105.1 (*E*), 101.5 (*E*), 101.4 (*Z*), 52.1 (*E*&*Z*), 19.1 (*E*&*Z*).

MS (ESI, MeOH): *m/z* = 281.3 ([M + $Na]^+$).

HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{14}H_{15}N_2O_3$: 259.1083; found: 259.1107.

6-Methyl-3-[(9*H*-purin-6-ylamino)methylene]-1*H*-pyridine-2,4-dione (3)

From 1.31 mmol of compound **19** and 1.31 mmol of adenine in ethanol (4 mL), after stirring at 90 °C for 14 h, compound **2** was isolated.

3

Yield: 0.27 g (75%); yellow solids (a mixture of *E*- and *Z*-isomers in a 2:1 ratio); mp >300°C (not melt).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.95 (d, *J* = 12.0 Hz, 0.7 H, *E* isomer), 13.75 (bs, 1 H, NH of two isomers), 12.82 (d, *J* = 12.9 Hz, 0.3 H, *Z* isomer), 10.80 (bs, 0.3 H, NH of *Z* isomer), 10.73 (bs, 0.7 H, NH of *E* isomer), 9.55 (d, *J* = 12.0 Hz, 0.7 H, *E* isomer), 9.51 (d, *J* = 12.9 Hz, 0.3 H, *Z* isomer), 8.69 (s, 1 H, two isomers), 8.59 (s, 1 H, two isomers), 5.51 (s, 0.7 H, *E* isomer), 5.48 (s, 0.3 H, *Z* isomer), 2.08 (s, 2.1 H, *E* isomer), 2.07 (bs, 0.9 H, *Z* isomer).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 193.3 (*E*&*Z*), 185.1 (*E*&*Z*), 180.8 (*E*&*Z*), 174.7 (*Z*), 167.6 (*E*), 153.5 (*E*), 152.4 (*Z*), 151.9 (*E*&*Z*), 150.4 (*E*), 149.7 (*Z*), 146.8 (*Z*), 144.4 (*E*), 122.3 (*Z*), 106.5 (*Z*), 106.4 (*E*), 105.1 (*E*&*Z*), 19.5 (*E*), 19.4 (*Z*).

MS (ESI, MeOH): *m/z* = 292.9 ([M + $Na]^+$).

HRMS-ESI: m/z [M + Na]$^+$ calcd for $C_{12}H_{10}N_6O_2Na$: 293.0763; found: 293.0749.

6-Methyl-3-piperidin-1-ylmethylene-1*H*-pyridine-2,4-dione (4)

From 1.31 mmol of compound **19** and 1.44 mmol of piperidine in ethanol (4 mL), after stirring at 25 °C for 12 h, compound **4** was isolated as a single stereoisomer.

4

Yield: 0.19 g (65%); yellow solids; mp 250-252 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.64 (bs, 1 H), 8.21 (s, 1 H), 5.52 (s, 1 H), 3.93 (bs, 2 H), 3.70 (bs, 2 H), 2.10 (s, 3 H), 1.84 (bs, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 182.0, 166.5, 161.3, 148.1, 107.8, 101.7, 59.2, 54.7, 27.0, 26.6, 23.4, 19.6.

MS (ESI, MeOH): *m/z* = 243.5 ([M + $Na]^+$).

HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{12}H_{17}N_2O_2$: 221.1290; found: 221.1262.

6-Methyl-3-(4-methylpiperazin-1-ylmethylene)-1*H*-pyridine-2,4-dione (5)

From 1.31 mmol of compound **19** and 1.44 mmol of 1-methylpiperazine in ethanol (4 mL), after stirring at 25 °C for 12 h, compound **5** was obtained.

5

Yield: 0.29 g (93%); yellow solids; mp 216 °C (dec.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.41 (bs, 1 H), 8.22 (s, 1 H), 5.53 (s, 1 H), 4.03-4.15 (m, 2 H), 3.71-3.82 (m, 2 H), 2.54-2.72 (m, 4 H), 2.35 (s, 3 H), 2.11 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.2, 161.2, 148.5, 107.9, 102.1, 100.0, 57.6, 55.4, 55.3, 53.6, 45.8, 19.7.

MS (ESI, MeOH): *m/z* = 258.4 ($[M + Na]^+$).

HRMS-ESI: *m/z* $[M + Na]^+$ calcd for $C_{12}H_{17}N_3O_2Na$: 258.1218; found: 258.1242.

6-Methyl-3-(4-phenylpiperazin-1-ylmethylene)-1*H*-pyridine-2,4-dione (6)

From 1.31 mmol of compound **19** and 1.60 mmol of 1-phenylpiperazine in ethanol (4 mL), after stirring at 25 °C for 12 h, compound **6** was obtained.

6

Yield: 0.29 g (75%); yellow solids; mp 201°C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.01 (s, 1 H, NH), 8.22 (s, 1 H, =CH), 7.25 (t, *J* = 8 Hz, 2 H), 7.00 (d, *J* = 8 Hz, 2 H), 6.84 (t, *J* = 8 Hz, 1 H), 5.20 (s, 1 H, =CH), 4.12-4.09 (m, 2 H), 3.85-3.92 (m, 2 H), 3.42-3.35 (m, 4 H), 1.95 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.8, 150.1, 148.4, 148.3, 129.0, 119.5, 115.9, 112.1, 106.1, 101.5, 56.0, 52.3, 49.1, 48.8, 18.8.

MS (ESI, MeOH): *m/z* = 320.2 ($[M + Na]^+$).

HRMS-ESI: *m/z* $[M + H]^+$ calcd for $C_{17}H_{20}N_3O_2$: 298.1556; found: 298.1570.

6-Methyl-3-morpholin-4-ylmethylene-1*H*-pyridine-2,4-dione (7)

From 1.31 mmol of compound **19** and 2.60 mmol of morpholine in ethanol (4 mL), after stirring at 25 °C for 24 h, and crystallization of the crude product from ethyl acetate and diethyl ether (1:1), compound **7** was obtained.

7

Yield: 0.19 g (65%); yellow solids; mp 180–182 °C (dec.).

^{1}H NMR (400 MHz, $CDCl_3$): δ =8.71, (bs, 1 H), 8.23 (s, 1 H), 5.53 (s, 1 H), 4.26-3.56 (m, 8 H), 2.11 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.0, 148.7, 130.2, 118.7, 107.8, 102.3, 67.4, 67.2, 57.6, 54.3, 19.7.

MS (ESI, MeOH): *m/z* = 223.2 ($[M + H]^+$).

HRMS-ESI: *m/z* $[M + Na]^+$ calcd for $C_{11}H_{14}N_2O_3Na$: 245.0902; found: 245.0892.

3-Benzenesulfinyl-7-methyl-6*H*-pyrano[3,2-c]pyridine-2,5-dione (8); Typical procedure for the synthesis of compounds 8 – 12

To a solution of compound **19** (0.16 mmol) and methyl α-(phenylsulfinyl)acetate (0.20 mmol) in dry ethanol (1 mL) under argon was added piperidine (0.01 mmol) and the mixture stirred at 80 °C for 48 h. The reaction mixture was cooled to 25 °C and concentrated on a rotary evaporator to give a solid which was washed with ether, suspended in CH_2Cl_2 (1 mL), and filtered. The resulting solid was washed with CH_2Cl_2 twice and dried under vacuum to give compound **8**.

8

Yield: 34 mg (69%); yellow solids; mp 281–283 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.43 (s, 1 H), 8.36 (s, 1 H), 7.75-7.70 (m, 2 H), 7.52–7.50 (m, 3 H), 6.30 (s, 1 H), 2.28 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.7, 160.1, 156.0, 153.0, 142.8, 137.4, 132.0, 129.5, 127.2, 125.6, 105.7, 96.7, 19.3.

MS (ESI, MeOH): *m/z* = 324.2 ($[M + Na]^+$).

HRMS-ESI: *m/z* $[M = Na]^+$ calcd for $C_{15}H_{11}NO_4SNa$: 324.0307; found: 324.0305.

3-Benzenesulfonyl-7-methyl-6*H*-pyrano[3,2-c]pyridine-2,5-dione (9)

From 0.20 mmol of compound **19**, 0.24 mmol of methyl α-(phenylsulfonyl)acetate (0.235 mmol) and 0.01 mmol of piperidine in ethanol (1 mL), after stirring at 80 °C for 48 h, compound **9** was obtained.

9

Yield: 50 mg (81%); yellow solids; mp >300 °C (not melt).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.41 (s, 1 H), 8.66 (s, 1 H), 8.00 (d, *J* = 7.5 Hz, 2 H), 7.70 (t, *J* = 7.5 Hz, 1 H), 7.60 (t, *J* = 7.5 Hz, 2 H), 6.33 (s, 1 H), 2.31 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.6, 160.8, 156.5, 155.1, 145.7, 139.5, 134.8, 129.9, 129.1, 121.6, 105.6, 97.5, 20.3.

MS (ESI, MeOH): *m/z* = 340.4 ($[M + Na]^+$).

HRMS-ESI: *m/z* $[M + Na]^+$ calcd for $C_{15}H_{11}NO_5SNa$: 340.0256; found: 340.0246.

3-Benzoyl-7-methyl-6*H*-pyrano[3,2-c]pyridine-2,5-dione (10)

From 0.65 mmol of compound **19**, 0.98 mmol of ethyl 3-oxo-3-phenylpropanoate, and 0.03 mmol of piperidine in ethanol (3 mL), after stirring at 80 °C for 48 h, compound **10** was obtained.

10

Yield: 0.18 g (100%); yellow solids; mp 312–314 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.23 (bs, 1 H), 8.15 (s, 1 H), 7.84 (d, *J* = 7.5 Hz, 2 H), 7.66 (t, *J* = 7.5 Hz, 1 H), 7.53 (t, *J* = 7.5 Hz, 2 H), 6.33 (s, 1 H), 2.32 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 191.3, 165.6, 160.3, 157.5, 153.4, 143.6, 136.7, 133.3, 129.3, 128.5, 120.5, 105.2, 96.8, 19.4.

MS (ESI, MeOH): *m/z* = 304.1 ([M + Na]$^+$).

HRMS-ESI: *m/z* [M = Na]$^+$ calcd for $C_{16}H_{11}NO_4Na$: 304.0586; found: 304.0586.

3-(2-Aminoacetyl)-7-methyl-6*H*-pyrano[3,2-c]pyridine-2,5-dione (11)

From 0.99 mmol of compound **19**, 1.5 mmol of 4-*tert*-butoxycarbonylamino-3-oxo-butyric acid ethyl ester (**20**),[10] and 0.05 mmol of piperidine in ethanol (3 mL), after stirring at 70 °C for 48 h, and column chromatographic purification on silica gel using CH_2Cl_2:MeOH (15:1) as eluent, **21** was obtained.

21

Yield: 0.15 g (45%); colorless oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.29 (s, 1 H), 8.50 (s, 1 H), 7.69–7.70 (bs, 1 H), 6.34 (s, 1 H), 4.32 (d, *J* = 5.9 Hz, 2 H), 2.32 (s, 3 H), 1.39 (s, 9 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 192.3, 166.4, 160.4, 158.3, 155.8, 155.0, 144.6, 117.1, 105.5, 96.7, 78.0, 49.8, 28.2, 19.5.

MS (ESI, MeOH): *m/z* = 357.3 ([M + Na]$^+$).

HRMS-ESI: *m/z* [M + Na]$^+$ calcd for $C_{16}H_{18}N_2O_6Na$: 357.1057; found: 357.1066.

A solution of **21** (0.024 mmol) in 1 mL of 10% TFA/CH_2Cl_2 was stirred at 25 °C for 8 h. The solvent was removed under *vacuo* and the remaining solid kept under high vacuum to yield compound **11**.

11

Yield: 8 mg (100%); yellow solids; mp 310 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.39 (bs, 1 H), 8.58 (s, 1 H), 8.10–8.20 (bs, 2 H), 6.35 (s, 1 H), 4.32 (s, 2 H), 2.30 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 187.9, 165.7, 159.2, 157.1, 155.1, 144.2, 114.5, 104.5, 95.7, 46.4, 18.5.

MS (ESI, MeOH): *m/z* = 235.2 ([M + H]$^+$).

HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{11}H_{11}N_2O_4$: 235.0719; found: 235.0728.

Ethyl 4-[*N*-(*tert*-butoxycarbonyl)-*N*-(4-(*tert*-butoxycarbonyloxybenzyl)amino-3-oxobutanoate (22)

To a cold (0 °C) solution of 4-(aminomethyl)phenol (40.6 mmol) and triethylamine (40.6 mmole) in THF (50 mL) under argon was added methyl 2-bromoacetate (28.4 mmol) dropwise, and the solution was stirred at 25 °C for 12 h, concentrated, and column chromatographed on silica gel using a mixture of CH_2Cl_2 and MeOH (9:1) as eluant to give methyl *N*-(4-hydroxybenzylamino)acetate.[17]

Yield: 3.6 g (45% yield); off-white solids; mp 105-107 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.25 (bs, 1 H, OH), 8.30 (s, 1 H, NH), 7.10 (d, *J* = 7.5 Hz, 2 H), 6.70 (d, *J* = 7.5 Hz, 2 H), 3.60 (s, 3 H), 3.55 (s, 2 H), 3.24 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7, 155.4, 130.2, 129.8, 115.5, 52.7, 51.9, 49.5.

MS (ESI, MeOH): *m/z* = 218.1 ([M + Na]$^+$).

To a solution of methyl *N*-(4-hydroxybenzylamino)acetate (5.31 mmol) in 5 mL of *p*-dioxane and H_2O (9:1), $NaHCO_3$ (11.6 mmol) was added and the mixture was stirred at 25 °C for 5 minutes. To it, di-*tert*-butyl dicarbonate (11.6 mmol) was added, and the solution was stirred for 12 h, diluted with brine (40 mL), and extracted four times with CH_2Cl_2 (100 mL each). The combined organic layer was washed with water and brine, dried (anhydrous Na_2SO_4), concentrated, and column chromatographed on silica gel using a mixture of CH_2Cl_2 and MeOH (20:1) as eluant to give methyl *N*-(4-hydroxybenzyl)-*N*-(*tert*-butoxycarbonyl)amino-acetate.

Yield: 1.19 g (76%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) (indicating two rotamers): δ = 7.07-7.05 (m, 2 H), 6.82-6.77 (m, 2 H), 6.47-6.45 (bs, 1 H), 4.45 & 4.42 (2 s, 2 H), 3.90 & 3.78 (2 s, 2 H), 3.71 & 3.68 (2 s, 3 H), 1.49 & 1.47 (2 s, 9 H).

MS (ESI, MeOH): *m/z* = 318.3 ([M + Na]$^+$).

To a solution of methyl *N*-(4-hydroxybenzyl)-*N*-(*tert*-butoxycarbonyl)aminoacetate (4.03 mmol) in 2 mL of dioxane and H_2O (1:1), NaOH (12.1 mmol) was added. The solution was stirred at 25 °C for 2h, neutralized with 1 N HCl to pH 6, and concentrated to dryness leaving a white solid. The solid was dissolved in 5 mL of dry DMF under argon, and NaH (8.11 mmol) and di-*tert*-butyl dicarbonate (4.87 mmol) were added. The solution was stirred at 25 °C for 12 h, diluted with water, and extracted with ethyl acetate twice (100 mL each). The combined organic layer was washed with brine, dried (anhydrous Na_2SO_4), concentrated to give *N*-(4-*tert*-butoxycarbonylbenzyl)-*N*-(*tert*-butoxycarbonyl)-aminoacetic acid.

Yield: 1.56 g (84%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) (2 rotamers): δ = 7.28-7.22 (m, 2 H), 7.14-7.11 (m, 2 H), 4.53-4.49 (m, 2 H), 3.94-3.80 (m, 2 H), 1.55-1.52 (m, 9 H), 1.48-1.47 (m, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$) (2 rotamers): δ = 174.58, 174.57, 155.5, 155.4, 151.6, 150.3, 134.5, 134.4, 128.9, 128.2, 121.2, 83.3, 81.0, 80.8, 50.8, 50.2, 47.5, 28.1, 28.0, 27.4.

MS (ESI, MeOH; negative ion mode): *m/z* = 380.5 ($[M - H]^-$).

To a solution of *N*-(4-*tert*-butoxycarbonylbenzyl)-*N*-(*tert*-butoxycarbonyl)aminoacetic acid (4.09 mmol) in dry THF (4 mL) under argon was added 1,1'-carbonyldiimidazole (4.44 mmol). The solution was stirred at 25 °C for 4 h to give the corresponding acyl imidazole. To a mixture of 0.54 g (5.65 mmol) of $MgCl_2$ and 0.71 g (5.36 mmol) of monoethyl malonate potassium salt under argon, 0.85 mL (6.14 mmol) of triethylamine and 2 mL of THF were added. The solution was stirred at 25 °C for 4 h, and the above acyl imidazole solution was added via cannula. The resulting reaction mixture was stirred at 25 °C for 18 h, diluted with H_2O and 0.1 M HCl to pH = 5, and extracted three times with ethyl acetate. The combined organic layer was washed with aqueous $NaHCO_3$, and brine, dried (anhydrous Na_2SO_4), concentrated, and column chromatographed on silica gel using a mixture of hexane and EtOAc (15:1) as eluant to give compound **22**.

22

Yield: 0.66 g (36%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) (2 rotamers): δ = 7.28-7.20 (m, 2 H), 7.14–7.12 (m, 2 H), 4.49–4.45 (m, 2 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 4.07 & 3.93 (2 s, 2 H; 2 rotamers), 3.42 & 3.35 (2 s, 2 H; 2 rotamers), 1.56 (s, 9 H), 1.47 (s, 9 H), 1.26 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) (2 rotamers): δ = 198.8, 198.6, 166.8, 166.6, 155.6, 155.3, 151.8, 150.5, 150.4, 134.9, 134.8, 129.2, 128.5, 121.4, 83.6, 80.9, 61.5, 55.8, 55.4, 51.0, 50.5, 46.4, 46.2, 28.3, 28.1, 27.64, 27.59, 14.0.

MS (ESI, MeOH): *m/z* = 474.5 ($[M + Na]^+$).

HRMS-ESI: *m/z* $[M + Na]^+$ calcd for $C_{23}H_{33}NO_8Na$: 474.2098; found: 474.2087.

3-[2-(4-Hydroxybenzylamino)acetyl]-7-methyl-6*H*-pyrano[3,2-c]pyridine-2,5-dione (12)

To a solution of compound **19** (1.22 mmol) and **22** (1.22 mmol) in ethanol (8 mL) under argon was added piperidine (0.05 mmol), and the reaction mixture was stirred at 70 °C for 48 h. It was cooled to 25 °C, diluted with ether (10 mL), and the solid was collected by filtration and purified by column chromatography on silica gel using CH_2Cl_2:MeOH (15:1) as an eluant to give the *N*-Boc derivative of **12**.

Yield: 0.26 g (41%); yellow solids; mp 188-190 °C.

^{1}H NMR (400 MHz, $CDCl_3$) (2 rotamers): δ = 12.87 & 12.80 (2 bs, 1 H NH, for two rotamers), 8.85 & 8.83 (2 s, 1 H, =CH), 7.27-7.25 (m, 2 H, Ar), 7.13-7.09 (m, 2 H, Ar), 6.16 & 6.14 (2 s, 1 H, =CH), 4.62 (s, 1 H, CH_2N of one rotamer), 4.53 (bs, 2 H, CH_2N), 4.50 (s, 1 H, CH_2N of one rotamer), 2.47 and 2.45 (2 s, 3 H, two rotamers), 1.54 and 1.53 (2 s, 9 H, *t*-Bu, two rotamers), 1.45 and 1.41 (2 s, 9 H, two rotamers).

^{13}C NMR (100 MHz, $CDCl_3$) (2 rotamers): δ = 191.7, 191.6, 166.7, 162.6, 158.2, 155.8, 153.6, 153.5, 151.8, 150.2, 145.6, 135.4, 135.2, 128.9, 128.3, 121.2, 118.5, 118.3, 105.8, 98.3, 83.5, 80.5, 80.2, 56.3, 56.2, 51.5, 50.6, 28.3, 28.2, 27.6, 20.0.

MS (ESI, MeOH): *m/z* = 563.7 ($[M + Na]^+$).

The above solid (0.10 mmol) was dissolved in 20% TFA/CH_2Cl_2 (1 mL) and stirred at 25 °C for 30 min. The solvent was removed under a rotary evaporator and the remaining solid kept under high vacuum to yield compound **12**.

12

Yield: 34 mg (100% yield); yellow solids (a TFA salt); mp 180–181 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.42 (bs, 1 H), 9.69 (bs, 1 H), 9.15 (bs, 1 H), 8.61 (s, 1 H), 7.31 (d, *J* = 8.6 Hz, 2 H), 6.80 (d, *J* = 8.6 Hz, 2 H), 6.40 (s, 1 H), 4.46 (s, 2 H), 4.10 (s, 2 H), 2.34 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d6): δ = 188.3, 169.5, 165.0, 158.2, 157.0, 154.1, 137.3, 129.6, 121.5, 115.5, 114.5, 105.5, 96.9, 53.7, 45.6, 18.9.

MS (ESI, MeOH): *m/z* = 341.4 ($[M + H]^+$).

HRMS-ESI: *m/z* $[M + Na]^+$ calcd for $C_{18}H_{16}N_2O_5Na$: 363.0957; found: 363.0981.

3-Amino-4-hydroxy-6-methylpyran-2-one (23)[13]

To a cold (0 °C) solution of 4-hydroxy-6-methyl-2*H*-pyrone (79.3 mmol) in H_2SO_4 (25 mL) was added drop wise a mixture of H_2SO_4 (4.23 mL) and HNO_3 (119 mmol) over 10 min. After stirring for 30 min, the reaction mixture was poured into ice water, and the precipitate was collected by filtration, washed with cold water (3 times) and dried under vacuum to give 4-hydroxy-6-methyl-3-nitropyran-2-one.

Yield: 10.7 g (79%); white solids; mp 163-166 °C (lit.[18] 165 °C).

IR (solid form): 1748, 1639, 1530, 1215, 1194, 1086, 996, 827, 783 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.21 (bs, 1 H, OH), 6.14 (s, 1 H, =CH), 2.37 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d6): δ = 166.4, 165.4, 156.6, 119.5, 100.7, 19.8.

MS (ESI, MeOH, negative ion mode): *m/z* = 170.4 ($[M - H]^-$).

A solution of 4-hydroxy-6-methyl-3-nitropyran-2-one (2.0 g, 11.7 mmol) and 10% palladium on carbon (0.2 g) in MeOH (30 mL) was stirred under 1 atmosphere of hydrogen at 25 °C for 18 h. The reaction mixture was filtered and concentrated to give compound **23**.[13]

23

Yield: 1.33 g (80%); brown solids; mp 198–200 °C.

^{1}H NMR (400 MHz, DMSO-d6): δ = 6.31 (s, 1 H, ═CH), 3.80 (bs, 3 H, NH_2, OH), 2.22 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d6): δ = 161.7, 153.5, 119.6, 104.4, 103.3, 18.9.

MS (ESI, MeOH): *m/z* = 164.1 ($[M + Na]^+$).

tert-Butyl (4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)carbamate (24)

To a hot (85 °C) solution of 3-amino-4-hydroxy-6-methyl-pyran-2-one (**23**, 1.28 mmol) in 5 mL of acetonitrile under argon was added di-*tert*-butyl dicarbonate (2.46 mmol) in portion wise over a period of 6 h. The reaction solution was cooled and concentrated on a rotary evaporator to give an oil, which was purified by flash chromatography on silica gel eluting with hexane/ethyl acetate (gradient elution) to yield compound **24**.

24

Yield: 0.18 g (57%); white solids; mp 87–89 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.08 (s, 1 H, OH), 7.05 (s, 1 H, NH), 5.88 (s, 1 H, ═CH), 2.21 (s, 3 H, CH_3), 1.50 (s, 9 H, *tert*-butyl).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.3, 156.7, 156.6, 155.1, 103.6, 102.8, 83.7, 28.2, 19.4.

MS (ESI, MeOH): *m/z* = 264.0 ($[M + Na]^+$).

HRMS-ESI: *m/z* $[M + Na]^+$ calcd for $C_{11}H_{15}NO_5Na$: 264.0848; found: 264.0831.

tert-Butyl (8a*S,10a*R**)-3-methyl-1-oxo-5,6,8a,10a-tetrahydro-1*H*-2,10-dioxa-9-azaanthracene-9-carboxylate (27)**

To a cold (0 °C) mixture of sodium hydride (0.25 mmol) in dry DMF (1 mL) under argon was added compound **24** (0.25 mmol), and stirred at 25 °C for 30 min. The reaction solution was again cooled to 0 °C and a solution of *trans*-3,6-dibromocyclohexene (**25**; 0.3 mmol) in dry DMF (1 mL) was added via cannula, and stirred at 25 °C for 18 h. To it, were added dry acetonitrile (10 mL) and triethylamine (0.25 mmol), and the solution was heated at 95 °C for 8 h. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (50 mL), and the organic layer was washed with brine (20 mL), dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a mixture of hexane:ethyl acetate (1:1) as eluant to give compound **27**.

27

Yield: 20 mg (25%); white solids; mp 129–130 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.78-5.71 (m, 1 H, C8H), 5.72 (s, 1 H, C4H), 5.35–5.25 (m, 1 H, C7H), 5.05–4.9 (m, 1 H, C8aH), 4.55–4.50 (m, 1 H C10aH), 2.25-1.85 (m, 4 H), 2.19 (s, 3 H, CH_3), 1.50 (s, 9 H, *t*-Bu).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.5, 159.1, 157.3, 153.4, 131.6, 123.9, 102.5, 99.4, 82.2, 74.5, 48.6, 28.4, 25.9, 19.9, 19.5.

2D-COSY NMR (acetone-d_6, the use of acetone d_6 as a solvent has changed the chemical shifts slightly from that of $CDCl_3$): signal C10aH (δ 4.57) correlates with signal C8aH (δ 5.04), signal C8aH (δ 5.04) correlates with signal C8H (δ 5.78-5.71), and signal C8H correlates with signal C7H (δ 5.29).

MS (ESI, MeOH): *m/z* = 342.3 ($[M + Na]^+$).

HRMS-ESI: *m/z* $[M + Na]^+$ calcd for $C_{17}H_{21}NO_5Na$: 342.1317; found: 342.1299.

(8a*S,10a*R**)-3-Methyl-5,8a,9,10a-tetrahydro-6*H*-2,10-dioxa-9-azaanthracen-1-one (13)**

A solution of compound **27** (0.04 mmol) in CH_2Cl_2 containing 10 % trifluoroacetic acid was stirred at 40 °C for 1 h. The reaction solution was diluted with 20 mL of water, basified with 10% aqueous ammonium hydroxide, and extracted with CH_2Cl_2 three times (10 mL each). The combined organic layers were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a 1:1 mixture of ethyl acetate and hexane as an eluant to give compound **13**.

13

Yield: 9 mg (100%); white solids; mp 131–133 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.86-5.80 (m, 1 H, ═CH), 5.82 (s, 1 H, ═CH), 5.53–5.50 (m, 1 H, CH═), 4.48–4.40 (m, 1 H, CH-O), 3.87 (s, 1 H, CH-N), 3.78 (bs, 1 H, NH), 2.06-2.34 (m, 3 H, CH_2-CH_2), 2.17 (s, 3 H, CH_3), 1.91-1.81 (m, 1 H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.9, 152.0, 148.3, 130.7, 126.7, 110.3, 100.6, 73.3, 47.4, 25.7, 22.1, 19.5.

MS (ESI, MeOH): *m/z* = 242.5 ($[M + H]^+$).

HRMS-ESI: *m/z* $[M = Na]^+$ calcd for $C_{12}H_{13}NO_3Na$: 242.0793; found: 242.0775.

(8*R,8a*S**,10a*R**)-8-Hydroxy-3-methyl-1-oxo-5,6,7,8,8a,10a-hexahydro-1*H*-2,10-dioxa-9-azaanthracene-9-carboxylic acid *tert*-butyl ester (28)**

To a solution of compound **27** (0.11 mmol) in dry THF (0.5 mL) at 0 °C under argon was added BH_3•THF in tetrahydrofuran (1 M, 0.109 mmol) and the resulting solution was stirred at 25 °C for 18 h, cooled to 0 °C, and added with 30% hydrogen peroxide (1 mL) and 0.1% aqueous sodium hydroxide (1 mL). The mixture was stirred for 10 min. at 0 °C followed by 3 h at 25 °C, diluted with water, and extracted four times with CH_2Cl_2 (10 mL each). The combined organic layers were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluant to give compound **28**. TLC and NMR spectral data indicate it

to be a single stereoisomer and 2D COSY and NOESY spectra show the hydroxyl function is *cis* to the angular hydrogens (C8a and C10a H's).

28

Yield: 32 mg (87%); white solids; mp 162–163 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.82 (s, 1 H, C4H), 4.40 (q, *J* = 3 Hz, 1 H, C10aH), 4.22 (dd, *J* = 10.1, 3.5 Hz, 1 H, C8aH), 3.33 (td, *J* = 10.5, 4.7 Hz, 1 H, C8H), 2.90 (bs, 1 H, OH), 2.23 (s, 3 H), 2.18-2.06 (m, 2 H), 1.72-1.63 (m, 2 H), 1.50 (s, 9 H), 1.50-1.38 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.7, 159.1, 156.0, 153.9, 102.9, 99.4, 82.8, 76.6, 65.5, 57.4, 32.2, 29.9, 28.2, 19.9, 18.4.

2D-NOESY NMR (400 MHz, $CDCl_3$): signal C4H (δ 5.82) correlates with signal C3-Me (δ 2.23), signal C10aH (δ 4.40) correlates with signal C8aH (δ 4.22), and signal C8aH (δ 4.22) correlates with signal C8H (δ 3.33). No correlation is found between signals C8H and C10aH.

MS (ESI, MeOH): *m/z* = 360.5 ([M + Na]$^+$).

HRMS-ESI: *m/z* [M + Na]$^+$ calcd for $C_{17}H_{23}NO_6Na$: 360.1423; found: 360.1411.

(8*R,8a*S**,10a*R**)-8-Hydroxy-3-methyl-5,7,8,8a,9,10a-hexahydro-6*H*-2,10-dioxa-9-azaanthracen-1-one (14)**

A solution of compound **28** (0.065 mmol) in 2 mL of 10% TFA in CH_2Cl_2 was stirred at 40 °C for 1 h, partitioned between CH_2Cl_2 (10 mL) and water (20 mL), and basified using 10% aqueous NH_4OH. The organic layer was removed and the aqueous layer extracted three times with CH_2Cl_2 (10 mL each). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated on a rotary evaporator to give a solid which was purified by column chromatography on silica gel (8:1 of ethyl acetate:hexane) to afford compound **14**.

14

Yield: 10 mg (65%); white solids; mp 92–94 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.81 (s, 1 H), 4.33 (s, 1 H), 4.15 (bs, 1 H), 3.60-3.54 (m, 1 H), 3.21-3.19 (m, 1 H), 2.19 (s, 3 H), 2.18-2.02 (m, 4 H), 1.43-1.32 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.1, 152.1, 148.7, 110.7, 100.7, 74.5, 67.6, 57.4, 32.6, 29.9, 19.4, 18.8.

MS (ESI, MeOH): *m/z* = 260.3 ([M + Na]$^+$).

HRMS-ESI: *m/z* [M + Na]$^+$ calcd for $C_{12}H_{15}NO_4Na$: 260.0899; found: 260.0884.

(8a*R,10a*R**)-3-Methyl-1,8-dioxo-5,6,7,8,8a,10a-hexahydro-1*H*-2,10-dioxa-9-azaanthracene-9-carboxylic acid *tert*-butyl ester (15)**

To a solution of compound **28** (0.024 mmol) in DMSO (0.5 mL) under argon was added 2-iodoxybenzoic acid (IBX; 0.034 mmol), and the solution was stirred at 25 °C for 2 h. Additional IBX (0.034 mmol) was added and the reaction mixture was stirred for 12 h after which the mixture was diluted with water (5 mL) and extracted three times with diethyl ether (10 mL each). The combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated to give compound **15**.

15

Yield: 7 mg (87%); white solids; mp 90–92 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.69 (s, 1 H, C4H), 5.20 (d, *J* = 4 Hz, 1 H, CHN), 4.75 (q, *J* = 4 Hz, 1 H, CHO), 2.54-1.85 (m, 6 H), 2.17 (s, 3 H), 1.50 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.1, 159.4, 158.8, 155.0, 152.4, 104.5, 98.9, 83.2, 79.7, 60.4, 41.3, 29.5, 28.2, 21.6, 19.8.

MS (ESI, MeOH): *m/z* = 358.3 ([M + Na]$^+$).

HRMS-ESI: *m/z* [M + Na]$^+$ calcd for $C_{17}H_{21}NO_6Na$: 358.1267; found: 358.1257.

4-Hydroxy-3-(4-methoxybenzylamino)-6-methyl-2*H*-pyran-2-one (29)

A solution of compound **23** (1.42 mmol) and *p*-anisaldehyde (1.42 mmol) in methanol (10 mL) was stirred at 25 °C for 12 h. The reaction solution was concentrated to give intermediate compound 4-hydroxy-3-(4-methoxybenzylideneamino)-6-methyl-2*H*-pyran-2-one (0.37 g, 100% yield) as a yellow solid, which was used for the next step without further purification. To a solution the aforementioned imine (1.04 mmol) in ethanol (15 mL) was added sodium cyanoborohydride (1.25 mmol) and acetic acid (1.25 mmol) at 25 °C. After stirring for 30 min the solution was diluted with aqueous $NaHCO_3$ (1.5 mmol) and concentrated to give a crude oil that was purified by column chromatography on silica gel using a 5% methanol in CH_2Cl_2 as an eluant to give compound **29**.

29

Yield: 0.24 g (89%); yellow solids; mp 179–181 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.80 (bs, 2 H, NH, OH), 7.25 (d, *J* = 8.8 Hz, 2 H, Ar-H), 6.84 (d, *J* = 8.8 Hz, 2 H, Ar-H), 5.61 (s, 1 H, =CH), 4.17 (s, 2 H, CH_2N), 3.71 (s, 3 H, OCH_3), 2.00 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d6): δ = 165.8, 161.6, 158.9, 156.8, 130.6, 127.1, 113.5, 104.9, 101.5, 55.0, 48.7, 19.1.

MS (ESI, MeOH): *m/z* = 284.2 ([M + Na]$^+$).

HRMS-ESI: *m/z* [M + Na]$^+$ calcd for $C_{14}H_{15}NO_4Na$: 284.0899; found: 284.0895.

(8a*S,10a*R**)-9-(4-Methoxybenzyl)-3-methyl-7,8a,9,10a-tetrahydro-8*H*-2,10-dioxa-9-azaanthracen-1-one (30)**

A solution of 20 mg (76 μmol) of **29**, 31 mg (0.13 mmol) of *trans*-3,6-dibromocyclohexene (**25**), and 39 μL (0.28 mmol) of triethylamine in DMF (1 mL) was stirred at 80 °C under argon for 2.5 h. The reaction

mixture was diluted with 50 mL of ethyl acetate and washed three times with water (10 mL each), and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a mixture of 30% ethyl acetate in hexane as eluant to give compound **30**.

30

Yield: 13 mg (50%); pale yellow solids; mp 300°C (not melt).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (d, *J* = 8.0 Hz, 2 H, Ar-H), 6.86 (d, *J* = 8.0 Hz, 2 H, Ar-H), 6.04-5.97 (m, 1 H, CH=), 5.96-5.90 (m, 1 H, CH=), 5.78 (s, 1 H, CH=), 4.49 (d, *J* = 12 Hz, 1 H, Ar-CH_2N), 4.01 (d, *J* = 12 Hz, 1 H, Ar-CH_2N), 3.87 (t, *J* = 4 Hz, 1 H, CHO), 3.81 (s, 3 H, Ar-OCH_3), 3.02 (dt, *J* = 12, 4 Hz, 1 H, CHN), 2.21 (s, 3 H, CH_3), 2.18-2.03 (m, 2 H, CH_2), 1.52-1.32 (m, 2 H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.6, 159.1, 155.0, 152.4, 135.5, 130.5, 130.4, 123.8, 113.9, 111.1, 100.4, 66.3, 56.5, 55.4, 53.4, 26.4, 22.6, 19.6.

2D COSY NMR (400 MHz, $CDCl_3$): signal (δ 6.04-5.97 ppm; =CH) correlates with signal (δ 5.96-5.90 ppm; =CH), signal (δ 6.04-5.97 ppm; =CH) correlates with signal (δ 2.18-2.03 ppm), signal (δ 2.18-2.03 ppm) correlates with signal (δ 1.52-1.32 ppm), signal (δ 1.52-1.32 ppm) correlates with signal (δ 3.02 ppm, CHN), and signal (δ 3.02 ppm) correlates with signal (δ 3.87 ppm, CHO).

MS (ESI, MeOH): *m/z* = 362.2 ($[M + Na]^+$).

HRMS-ESI: *m/z* $[M + Na]^+$ calcd for $C_{20}H_{21}NO_4Na$: 362.1368; found 362.1360.

(8a*S,10a*R**)-3-Methyl-7,8,8a,9,10a-tetrahydro-8*H*-2,10-dioxa-9-azaanthracen-1-one (16)**

A solution of **30** (17.7 μmol) and TFA (1 drop) in CH_2Cl_2 (1 mL) was heated at refluxed for 12 h under argon, cooled to 25 °C, diluted with saturated aqueous $NaHCO_3$, and extracted three times with CH_2Cl_2. The combined organic layer was washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using 20% ethyl acetate in hexane as an eluant to afford compound **16**.

Yield: 2.3 mg (59%); white solids; mp 134–136 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.97 (dt, *J* = 10.0, 3.6 Hz, 1 H, CH=), 5.82 (s, 1 H, =CH), 5.81-5.70 (m, 1 H, CH=), 4.61 (s, 1 H, CHO), 3.76 (s, 1 H, NH), 3.63-3.50 (m, 1 H, CHN), 2.40-2.27 (m, 1 H, CH_2), 2.18 (s, 3 H, CH_3), 2.18-2.10 (m, 1 H, CH_2), 1.94-1.68 (m, 2 H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.8, 151.1, 145.7, 133.3, 124.4, 111.8, 100.7, 71.3, 47.5, 25.4, 23.5, 19.3.

MS (ESI, MeOH): *m/z* = 242.6 ($[M + Na]^+$).

HRMS-ESI: *m/z* $[M + Na]^+$ calcd for $C_{12}H_{13}NO_3Na$: 242.0793; found: 242.0776.

(8a*S,10a*R**)-3-Methyl-7,8,8a,9,10a-tetrahydro-8*H*-2,10-dioxa-9-azaanthracen-1-one (16)**. **From a one-step method**

A solution of **23** (3.54 mmol), *trans*-3,6-dibromocyclohexene (**25**; 4.25 mmol), and triethylamine (8.85 mmol) in DMF (35 mL) was stirred at 120 °C under argon for 2 h, cooled to 25 °C, diluted with saturated aqueous $NaHCO_3$, and extracted three times with CH_2Cl_2. The combined organic layer was dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using 10% ethyl acetate in hexane as an eluant to give compound **16**.

Yield: 99 mg (13%) white solids.

The spectral data are identical to that described in the previous experiment. Slow evaporation of a solution of **16** in ethanol provided single crystals which were used for X-ray analysis.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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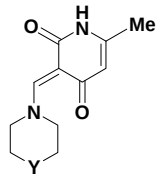
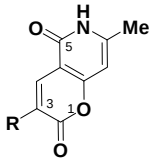
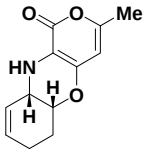


4 : Y = CH_2
5 : Y = NMe
6 : Y = NPh
7 : Y = O



8 : R = SOPh
9 : R = SO_2Ph
10 : R = COPh
11 : R = $COCH_2NH_2$
12 : R = $COCH_2NH$-(*p*-hydroxybenzyl)



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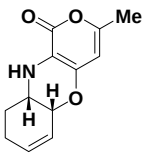

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Short title: Syntheses of Monocyclic and Bicyclic pyridinones and Tricyclic Morpholinopyrones