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SYNTHESIS OF THE COMPLEX BRIDGED 1,5-OXAZABICYCLES *via* ONE-POT REACTIONS OF 4,5-DIAZAFLUOREN-9-ONE, ALKYL HALIDES, AND CYCLIC 1,3-DIKETONE

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An efficient and practical procedure for the preparation of the complex bridged 1,5-oxazabicycles was developed via a one-pot domino reaction of 4,5-diazafluoren-9-one, reactive alkyl halides, and cyclic 1,3-dicarbonyl compounds.

Keywords: 4,5-diazafluoren-9-one, dimedone, heterocycle, oxazabicycle, domino reactions, one-pot reaction.

The N,O-containing heterocycles are among the principal heterocyclic skeletons, which are widely found in natural alkaloids, biologically active compounds, and pharmaceutical agents [1–3]. Although versatile synthetic methods for obtaining N,O-containing normal-ring heterocycles such as oxazole, isoxazole, oxazine, and their benzo-annelated derivatives have been developed [4–9], the easy and efficient synthesis of medium-ring oxazabicycles from simple starting materials with milder reaction conditions and fewer preparative steps still remains an attractive goal [10–13]. Some examples on the synthesis of the bridged oxazabicycles from the tandem reactions involving reaction of bifunctionalized nucleophiles with *N*-alkylquinolinium and *N*-alkylisoquinolinium salts have been shown to be the very convenient methods [14–27]. Recently, we reported an efficient approach to bridged 1,3-oxazabicycles *via* the reactions of *N*-(*p*-nitrobenzyl)- or *N*-phenacylphenanthrolinium bromides with a series of cyclic 1,3-dicarbonyl compounds [28]. This successful experience prompted us to explore the scope and limitations of this reaction and to establish an oxazabicyclic library. Thus, the reactions of the quaternary ammonium salts of 4,5-diazafluoren-9-one with cyclic 1,3-dicarbonyl compounds were investigated, and we are pleased to find that a series of 1,5-oxazabicycles was obtained in satisfactory yields.

The quaternary ammonium salts [29, 30] can be easily obtained by the reactions of 4,5-diazafluoren-9-one with reactive halides, such as *p*-nitrobenzyl bromide, benzyl bromide, methyl iodide, phenacyl bromide, and ethyl bromoacetate, which were not separated from the solution and could be utilized in sequential reactions with cyclic 1,3-diketones. The reaction conditions were similar to those described in [28]: a mixture of the quaternary ammonium salt **1a**, dimedone, and triethylamine as base in acetonitrile was stirred at room

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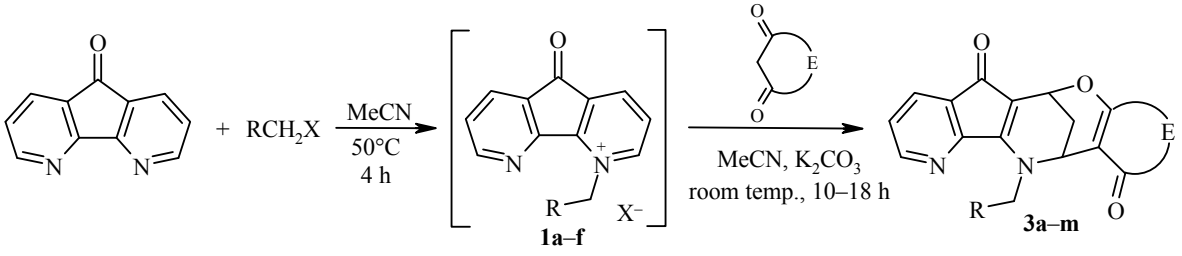
temperature for a long time or at elevated temperature overnight. TLC analysis showed that nearly no reaction took place. We suggested that triethylamine is relatively weak base, which could not deprotonate the quaternary ammonium salt **1a** to give the active pyridinium ylide intermediate. Thus K_2CO_3 was used to replace triethylamine in the reaction. A mixture of the quaternary ammonium salts **1a**, dimedone (**2a**), and potassium carbonate in acetonitrile was stirred at room temperature overnight. After workup, we found that the expected oxazabicycle **3a** was obtained in 78% yield. Under these conditions, the reactions of salt **1a,** 1,3-cyclohexanedione, and 4-hydroxycoumarin gave the corresponding products **3b,c** in good yields (Table, entries 1-3). These results indicated that a practical procedure for the preparation of oxazabicycles was established by using a one-pot domino reaction. We noticed that a C,O-dinucleophilic substitution reaction took place at the 2,4-position of the pyridine ring, not the benzyl position of the quaternary ammonium salt **1a**, which indicated that a stronger electron-withdrawing nitro group is not necessary for the reaction. Thus, the quaternary ammonium salts **1b,c**, which were obtained by the reaction of benzyl bromide or *p*-methylbenzyl bromide with 4,5-diazafluoren-9-one, reacted further with dimedone, 1,3-cyclohexanedione, and 4-hydroxycoumarin under similar conditions. The corresponding oxazabicycles **3d-g** were prepared in moderate yields (entries 4-7). The quaternary ammonium salt **1d** derived from methyl iodide also reacted smoothly with dimedone and 1,3-cyclohexanedione to give the expected 1,5-oxazabicycles **3h,i**, respectively. Lastly, the quaternary ammonium salts **1e**,**f**, which were prepared by the reaction of 4,5-diazafluoren-9-one with phenacyl bromide or ethyl bromoacetate, reacted similarly with cyclic 1,3-dicarbonyl compounds to give the desired products **3j**-**m** in good yields (entries 8-13). Due to the effect of stronger electron-withdrawing nitro and carbonyl groups, the reactions of quaternary ammonium salts **1a**,**e** gave relatively higher yields of products than those of other quaternary ammonium salts.

The structures of oxazabicycles **3a-m** were fully characterized by spectroscopy and were confirmed by single-crystal X-ray structural studies performed for two representative compounds **3i** (Fig. 1) and **3j** (Fig. 2). From the molecular structure, it is clearly seen that a 1,5-oxazabicyclic system was formed by the oxygen atom

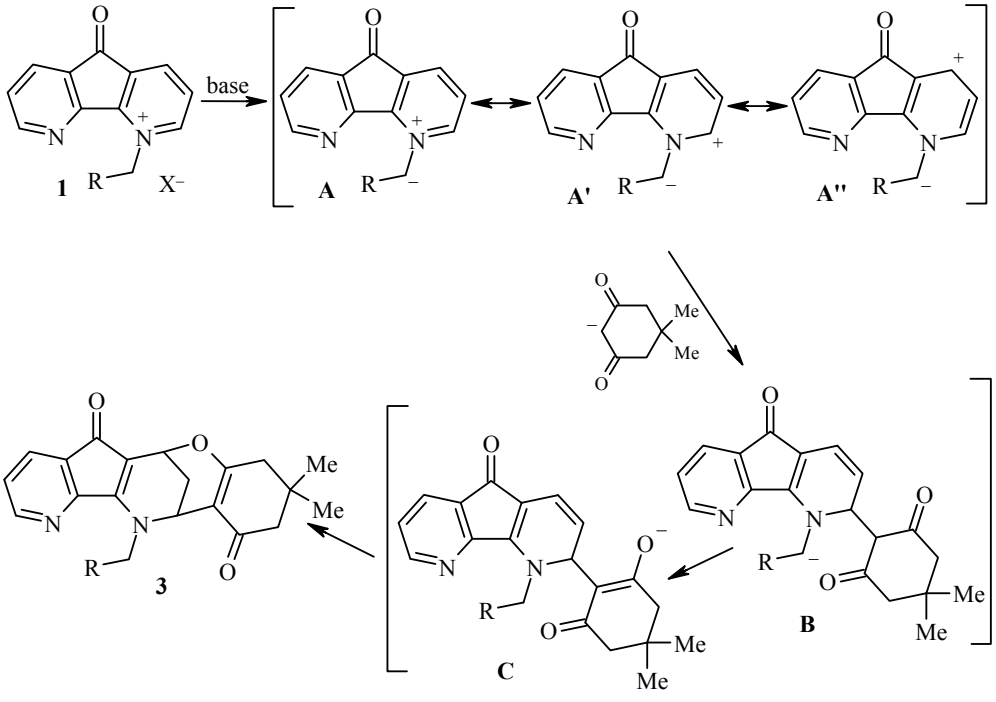
Synthesis of the bridged 1,5-oxazabicycles **3a-m**



Entry	Salt	R	Diketone	E	Product	Yield, %
1	**1a**	4-$O_2NC_6H_4$	Dimedone	$CH_2C(CH_3)_2CH_2$	**3a**	78
2	**1a**	4-$O_2NC_6H_4$	1,3-Cyclohexanedione	$CH_2CH_2CH_2$	**3b**	70
3	**1a**	4-$O_2NC_6H_4$	4-Hydroxycoumarin	*o*-OC_6H_4	**3c**	84
4	**1b**	Ph	Dimedone	$CH_2C(CH_3)_2CH_2$	**3d**	54
5	**1b**	Ph	1,3-Cyclohexanedione	$CH_2CH_2CH_2$	**3e**	49
6	**1c**	4-MeC_6H_4	Dimedone	$CH_2C(CH_3)_2CH_2$	**3f**	54
7	**1c**	4-MeC_6H_4	4-Hydroxycoumarin	*o*-OC_6H_4	**3g**	59
8	**1d**	H	Dimedone	$CH_2C(CH_3)_2CH_2$	**3h**	58
9	**1d**	H	1,3-Cyclohexanedione	$CH_2CH_2CH_2$	**3i**	50
10	**1e**	COPh	Dimedone	$CH_2C(CH_3)_2CH_2$	**3j**	80
11	**1e**	COPh	1,3-Cyclohexanedione	$CH_2CH_2CH_2$	**3k**	74
12	**1e**	COPh	4-Hydroxycoumarin	*o*-OC_6H_4	**3l**	76
13	**1f**	CO_2Et	Dimedone	$CH_2C(CH_3)_2CH_2$	**3m**	58

of the enolate unit connected to the 4-position of the pyridyl ring, which is different from the results of formation of 1,3-oxazabicyclic system in our previously reported reactions of *N*-alkylphenanthrolinium salts [28]. This difference is obviously due to the strong electron-withdrawing effect of the carbonyl group in 4,5-diazafluoren-9-one.

To explain the formation of 1,5-oxazabicycles in the reaction of the quaternary ammonium salts of 4,5-diazafluoren-9-one, we outlined a plausible reaction mechanism based on the similar reaction of *N*-alkylphenanthrolinium salts [28], which is shown below. Firstly, the ammonium salt of 4,5-diazafluoren-9-one **1** was deprotonated to yield the expected pyridinium ylide **A**, in which the positive charge is spread to the C-1 and C-3 atoms in its resonance hybrid forms **A'** and **A"**. So C-1 and C-3 atoms become more susceptible to attack by nucleophilic reagent. Secondly, the *in situ* formed carbanion of cyclic 1,3-dicarbonyl compound, such as dimedone, attacks C-3 atom of ammonium salt **A'** to give the intermediate **B**. Due to the strong electron-withdrawing effect of two carbonyl groups in intermediate **B**, a new enolate **C** was formed by proton migration. Then the enolate, in turn, attacks the relatively positive C-1atom to give the final 1,5-oxazabicyclic compound **3**. In this reaction, the cyclic 1,3-dicarbonyl compounds acted as a C,O-bifunctionalized nucleophile to accomplish sequentially the *C*-alkylation and intramolecular *O*-alkylation. If the dimedone carbanion first attacks the resonance hybrid form **A"**, the sequential reaction would results in a 1,3-oxazabicyclic system. Here the relative stability of resonance hybrid forms **A'** and **A"** determines the direction of reaction. In the hybrid form **A',** the positive charge is far away from the electron-withdrawing carbonyl group, which makes the hybrid form **A'** more stable than hybrid form **A"**. Thus, only nucleophilic reaction to hybrid form **A'** and formation of 1,5-oxazabicycles were observed.



In summary, we have developed a practical method for preparation of the complex bridged 1,5-oxazabicycles *via* the reactions of quaternary ammonium salts of 4,5-diazafluoren-9-one with cyclic 1,3-dicarbonyl compounds. The reaction mechanism involves the domino *C*-alkylation and intramolecular *O*-alkylation of the enolate of cyclic 1,3-dicarbonyl compound. This protocol has the advantages of mild reaction conditions, easily accessible starting material, and easy purification of the products, which makes it a useful and attractive method for the synthesis of the complex N,O-containing heterocycles in synthetic and medicinal chemistry.

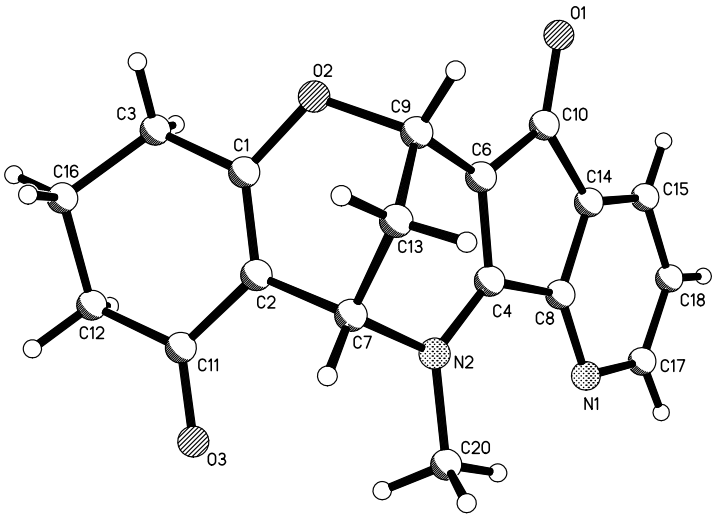


Fig. 1. Molecular structure of compound **3i**.

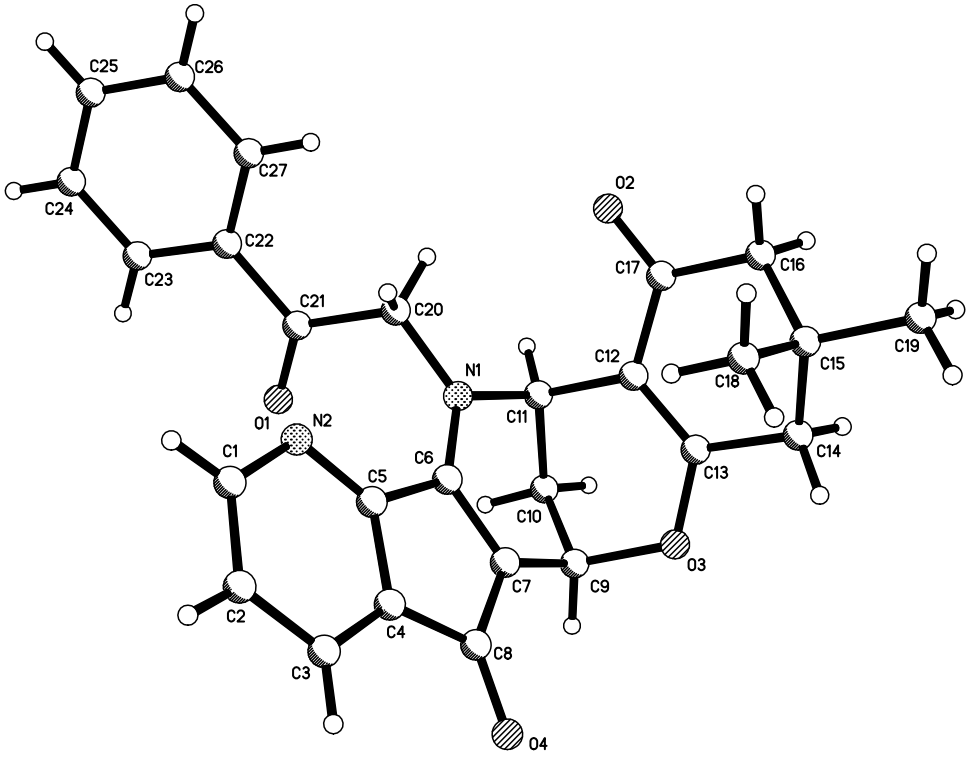


Fig. 2. Molecular structure of compound **3j**.

EXPERIMENTAL

IR spectra were obtained on a Bruker Tensor 27 spectrometer (KBr disc). ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AV-600 (600 and 150 MHz, respectively) spectrometer with $CDCl_3$ as solvent and TMS as internal standard. HPLC/MS were recorded on a Finnigan LCQ Deca XP MAX instrument. Melting points were determined on a hot-plate microscope apparatus. All reactions were monitored by TLC, eluent light petroleum ether–EtOAc, 3:1. Silica gel GF254 (100 mesh) purchased from Qingdao Haiyang Chemical Co.,

Ltd. was used for column chromatography. 4,5-Diazafluoren-9-one, cyclic 1,3-dicarbonyl compounds, alkyl halides, and other reagents were commercial reagents and used without additional purification. Solvents were purified by standard techniques.

Crystallographic data for compounds **3i,j** have been deposited at the Cambridge Crystallographic Data Center (CCDC 827897 and 827898).

Reaction of 4,5-Diazafluoren-9-one, Alkyl Halides, and Cyclic 1,3-Dicarbonyl Compounds (General Method). A solution of 4,5-diazafluoren-9-one (0.364 g, 2 mmol) and f alkyl halide (2 mmol) in MeCN (20 ml) was heated at 50°C for 4 h. Then cyclic 1,3-dicarbonyl compounds (2 mmol) and K_2CO_3 (0.138 g, 1 mmol) were added to the system. The solution was stirred at room temperature for 10-18 h until completion of the reaction. After removing the solvent, the crude oily mixture was purified using column chromatography, eluent petroleum ether–EtOAc, 1:1, to give a pure product for analysis.

16,16-Dimethyl-2-(4-nitrobenzyl)-13-oxa-2,5-diazapentacyclo[10.7.1.0^{3,11}.0^{4,9}.0^{14,19}]icosa-4,6,8,14(19)-tetraene-10,18-dione (3a). Yield 78%; yellow solid, mp 162-164°C. IR spectrum, ν, cm^{-1}: 2960 (m), 1680 (s), 1643 (s), 1608 (vs), 1554 (s), 1522 (s), 1453 (w), 1426 (w), 1375 (s), 1343 (s), 1305 (w), 1260 (w), 1175 (m), 1112 (m), 1081 (w), 1044 (m), 951 (w), 893 (w). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.40 (1H, d, *J* = 5.4, H Ar); 8.23 (2H, d, *J* = 7.8, H Ar); 7.76 (1H, d, *J* = 7.2, H Ar); 7.65 (2H, d, *J* = 8.4, H Ar); 7.28-7.24 (1H, m, H Ar); 6.95 (1H, d, *J* = 15.0) and 5.10 (1H, d, *J* = 15.0, CH_2); 5.56 (1H, s, CH); 4.69 (1H, s, CH); 2.37 (1H, d, *J* = 17.4) and 2.32-2.23 (3H, m, 2 CH_2); 1.94 (1H, d, *J* = 13.2) and 1.71 (1H, d, *J* = 13.2, CH_2); 1.05 (3H, s, CH_3); 1.01 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 197.3; 185.1; 172.3; 160.3; 158.3; 149.7; 147.6; 144.9; 132.4; 129.2; 128.1; 124.7; 124.1; 111.0; 106.3; 63.7; 52.6; 50.5; 46.0; 42.0; 32.4; 29.5; 27.3; 27.0. Mass spectrum (ESI$^-$), *m*/*z*: 456.44 [M-1]$^-$. Found, %: C 67.97; H 5.44; N 8.84. $C_{26}H_{23}N_3O_5$. Calculated, %: C 68.26; H 5.07; N 9.18.

2-(4-Nitrobenzyl)-13-oxa-2,5-diazapentacyclo[10.7.1.0^{3,11}.0^{4,9}.0^{14,19}]icosa-4,6,8,14(19)-tetraene-10,18-dione (3b). Yield 70%; yellow solid, mp 184-186°C. IR spectrum, ν, cm^{-1}: 2945 (m), 1675 (s), 1640 (s), 1601 (vs), 1556 (s), 1523 (s), 1432 (w), 1384 (m), 1349 (s), 1301 (w), 1176 (m), 1117 (w), 1081 (w), 1028 (m), 963 (w), 893 (w). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.40 (1H, d, *J* = 4.8, H Ar); 8.23 (2H, d, *J* = 8.4, H Ar); 7.76 (1H, d, *J* = 7.2, H Ar); 7.65 (2H, d, *J* = 8.4, H Ar); 7.25 (1H, t, *J* = 6.0, H Ar); 6.94 (1H, d, *J* = 15.0) and 5.15 (1H, d, *J* = 15.0, CH_2); 5.56 (1H, s, CH); 4.68 (1H, s, CH); 2.47 (2H, t, *J* = 6.0, CH_2); 2.41 (2H, t, *J* = 6.0, CH_2); 1.99-1.94 (3H, m) and 1.71 (1H, d, *J* = 13.2, 2CH_2). ^{13}C NMR spectrum, δ, ppm: 197.5; 185.1; 174.1; 160.3; 158.3; 149.7; 147.7; 145.0; 132.4; 129.2; 128.1; 124.7; 124.0; 112.2; 106.3; 63.5; 52.6; 46.2; 36.5; 28.5; 27.2; 20.6. Mass spectrum (ESI$^-$), *m*/*z*: 428.62. Found, %: C 66.85; H 4.77; N 9.56. $C_{24}H_{19}N_3O_5$. Calculated, %: C 67.13; H 4.46; N 9.78.

23-(4-Nitrobenzyl)-4,12-dioxa-20,23-diazahexacyclo[11.10.1.0^{2,11}.0^{5,10}.0^{14,22}.0^{16,21}]tetracosa-2(11),5(10),6,8,16,18,20-heptaene-3,15-dione (3c). Yield 84%; yellow solid, mp 146-148°C. IR spectrum, ν, cm^{-1}: 2969 (w), 1697 (s), 1617 (vs), 1556 (s), 1517 (s), 1491 (w), 1456 (w), 1427 (w), 1401 (s), 1378 (m), 1343 (s), 1289 (w), 1204 (m), 1174 (m), 1105 (m), 1085 (w), 1041 (m), 951 (w), 881 (w). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.41 (1H, d, *J* = 4.8, H Ar); 8.26 (2H, d, *J* = 8.4, H Ar); 7.88 (1H, d, *J* = 7.8, H Ar); 7.76 (1H, d, *J* = 7.2, H Ar); 7.69 (2H, d, *J* = 8.4, H Ar); 7.56 (1H, t, *J* = 7.8, H Ar); 7.30 (1H, d, *J* = 9.0, H Ar); 7.27-7.25 (2H, m, H Ar); 7.10 (1H, d, *J* = 15.0) and 5.30 (1H, d, *J* = 15.0, CH_2); 5.87 (1H, s, CH); 4.87 (1H, s, CH); 2.21 (1H, d, *J* = 13.8, CH_2); 1.95 (1H, d, *J* = 13.8, CH_2). ^{13}C NMR spectrum, δ, ppm: 185.3; 163.3; 161.8; 160.6; 158.1; 152.8; 149.9; 147.7; 144.6; 133.0; 132.1; 129.2; 128.3; 124.8; 124.3; 124.2; 123.9; 116.7; 115.1; 106.0; 100.8; 64.2; 63.1; 48.0; 27.1. Mass spectrum (ESI$^-$), *m*/*z*: 478.41. Found, %: C 67.57; H 3.84; N 8.67. $C_{27}H_{17}N_3O_6$. Calculated, %: C 67.64; H 3.57; N 8.76.

2-Benzyl-16,16-dimethyl-13-oxa-2,5-diazapentacyclo[10.7.1.0^{3,11}.0^{4,9}.0^{14,19}]icosa-4,6,8,14(19)-tetraene-10,18-dione (3d). Yield 54%; yellow solid, mp 172-174°C. IR spectrum, ν, cm^{-1}: 2959 (w), 1681 (s), 1650 (s), 1615 (vs), 1555 (s), 1489 (w), 1455 (w), 1378 (s), 1314 (w), 1279 (w), 1253 (w), 1205 (w), 1174 (m), 1154 (m), 1118 (m), 1079 (m), 1046 (m), 1024 (w), 983 (w), 896 (w). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.41 (1H, d, *J* = 3.6, H Ar); 7.75 (1H, d, *J* = 6.0, H Ar); 7.45 (2H, d, *J* = 7.8, H Ar); 7.36 (2H, t, *J* = 7.2, H Ar); 7.31 (1H, t, *J* = 7.2, H Ar); 7.24-7.22 (1H, m, H Ar); 6.93 (1H, d, *J* = 14.4) and 4.92 (1H, d, *J* = 14.4, CH_2); 5.53 (1H, d,

J = 1.8, CH); 4.77 (1H, s, CH); 2.36 (1H, d, *J* = 17.4), 2.29 (1H, d, *J* = 16.2) and 2.25-2.22 (2H, m, $2CH_2$); 1.88-1.85 (1H, m) and 1.63 (1H, d, *J* = 13.8, CH_2); 1.04 (3H, s, CH_3); 1.00 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 197.1; 184.8; 172.3; 160.5; 158.4; 149.6; 137.3; 132.9; 128.8; 128.5; 127.9; 127.8; 124.5; 111.2; 105.8; 64.0; 53.4; 50.2; 45.7; 42.1; 32.3; 29.5; 27.3; 27.0. Mass spectrum (ESI^-), *m*/*z*: 411.31. Found, %: C 75.52; H 6.13; N 6.47. $C_{26}H_{24}N_2O_3$. Calculated, %: C 75.71; H 5.86; N 6.79.

2-Benzyl-13-oxa-2,5-diazapentacyclo[10.7.1.0^{3,11}.0^{4,9}.0^{14,19}]icosa-4,6,8,14(19)-tetraene-10,18-dione (3e). Yield 49%; yellow solid, mp 170–172°C. IR spectrum, ν, cm^{-1}: 2952 (w), 1675 (s), 1638 (s), 1605 (vs), 1553 (s), 1492 (s), 1454 (w), 1434 (w), 1380 (w), 1301 (s), 1279 (w), 1261 (w), 1177 (m), 1156 (w), 1124 (m), 1085 (w), 1063 (w), 1046 (w), 1030 (m), 993 (w), 894 (w). ^1H NMR spectrum, δ, ppm (*J*, Hz): 8.41 (1H, d, *J* = 4.2, H Ar); 7.75 (1H, d, *J* = 6.6, H Ar); 7.44 (2H, d, *J* = 7.2, H Ar); 7.36 (2H, t, *J* = 7.2, H Ar); 7.31 (1H, t, *J* = 7.2, H Ar); 7.23 (1H, t, *J* = 6.0, H Ar); 6.92 (1H, d, *J* = 14.4) and 4.96 (1H, d, *J* = 14.4, CH_2); 5.53 (1H, s, CH); 4.75 (1H, s, CH); 2.42 (2H, d, *J* = 5.4, CH_2); 2.40 (2H, d, *J* = 6.0, CH_2); 1.99–1.90 (3H, m) and 1.62 (1H, d, *J* = 13.2, $2CH_2$). ^{13}C NMR spectrum, δ, ppm: 197.4; 184.9; 173.9; 160.6; 158.5; 149.6; 137.4; 132.9; 128.8; 128.5; 127.8; 124.4; 112.4; 106.0; 63.8; 53.4; 45.9; 36.6; 28.5; 27.3; 20.7. Mass spectrum (ESI^-), *m*/*z:* 383.49. Found, %: C 74.62; H 5.47; N 7.02. $C_{24}H_{20}N_2O_3$. Calculated, %: C 74.98; H 5.24; N 7.29.

16,16-Dimethyl-2-(4-methylbenzyl)-13-oxa-2,5-diazapentacyclo[10.7.1.0^{3,11}.0^{4,9}.0^{14,19}]icosa-4,6,8,14(19)-tetraene-10,18-dione (3f). Yield 54%; yellow solid, mp 194-198°C. IR spectrum, ν, cm^{-1}: 2962 (w), 1677 (s), 1643 (s), 1610 (vs), 1555 (s), 1454 (w), 1378 (m), 1311 (w), 1176 (m), 1118 (m), 1084 (m), 1045 (m), 954 (w), 895 (w). ^1H NMR spectrum, δ, ppm (*J*, Hz): 8.41 (1H, d, *J* = 4.8, H Ar); 7.74 (1H, d, *J* = 7.2, H Ar); 7.33 (2H, d, *J* = 7.8, H Ar); 7.23-7.21 (1H, m, H Ar); 7.16 (2H, d, *J* = 7.8, H Ar); 6.88 (1H, d, *J* = 13.8) and 4.87 (1H, d, *J* = 13.8, CH_2); 5.52 (1H, d, *J* = 2.4, CH); 4.77 (1H, s, CH); 2.37 (1H, m) and 2.31-2.28 (1H, m, CH_2); 2.34 (3H, s, $C_6H_4C\underline{H}_3$); 2.25-2.21 (2H, m, CH_2); 1.87-1.84 (1H, m) and 1.63-1.60 (1H, m, CH_2); 1.03 (3H, s, CH_3); 1.00 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 197.1; 184.9; 172.3; 160.5; 158.4; 149.6; 137.6; 134.2; 132.9; 129.5; 128.5; 127.7; 124.4; 110.2; 105.7; 64.0; 53.1; 55.5; 45.6; 42.1; 32.3; 29.4; 27.3; 27.0; 21.2. Mass spectrum (ESI^-), *m*/*z*: 425.23. Found, %: C 75.86; H 6.40; N 6.74. $C_{27}H_{26}N_2O_3$. Calculated, %: C 76.03; H 6.14; N 6.57.

23-(4-Methylbenzyl)-4,12-dioxa-20,23-diazahexacyclo[11.10.1.0^{2,11}.0^{5,10}.0^{14,22}.0^{16,21}]tetracosa-2(11),5(10),6,8,16,18,20-heptaene-3,15-dione (3g). Yield 59%; yellow solid, mp 168-175°C. IR spectrum, ν, cm^{-1}: 2980 (w), 1710 (s), 1672 (m), 1616 (vs), 1549 (s), 1488 (m), 1456 (w), 1455 (s), 1380 (m), 1175 (m), 1105 (m), 1084 (m), 1040 (m), 968 (w), 879 (w). ^1H NMR spectrum, δ, ppm (*J*, Hz): 8.43 (1H, d, *J* = 4.8, H Ar); 7.87 (1H, d, *J* = 7.8, H Ar); 7.74 (1H, d, *J* = 7.2, H Ar); 7.53 (1H, t, *J* = 7.2, H Ar); 7.37 (2H, d, *J* = 7.8, H Ar); 7.29 (1H, d, *J* = 8.4, H Ar); 7.27-7.25 (1H, m, H Ar); 7.22 (1H, t, *J* = 6.6, H Ar); 7.19 (2H, d, *J* = 7.8, H Ar); 7.03 (1H, d, *J* = 14.4) and 5.05 (1H, d, *J* = 14.4, CH_2); 5.82 (1H, s, CH); 4.94 (1H, s, CH); 2.37 (3H, s, $C_6H_4C\underline{H}_3$); 2.10 (1H, d, *J* = 13.8, CH_2); 1.82 (1H, d, *J* = 13.8, CH_2). ^{13}C NMR spectrum, δ, ppm: 185.1; 163.1; 161.7; 160.8; 158.3; 152.8; 149.8; 137.8; 134.0; 132.7; 132.6; 129.6; 128.5; 128.0; 124.6; 124.1; 123.9; 116.6; 115.2; 105.4; 101.1; 64.5; 53.7; 47.6; 27.2; 21.2. Mass spectrum (ESI^-), *m*/*z*: 447.47. Found, %: C 74.72; H 4.81; N 5.89. $C_{28}H_{20}N_2O_4$. Calculated, %: C 74.99; H 4.50; N 6.25.

2,16,16-Trimethyl-13-oxa-2,5-diazapentacyclo[10.7.1.0^{3,11}.0^{4,9}.0^{14,19}]icosa-4,6,8,14(19)-tetraene-10,18-dione (3h). Yield 58%; yellow solid, mp 148-150°C. IR spectrum, ν, cm^{-1}: 2962 (w), 1660 (s), 1606 (vs), 1555 (s), 1484 (w), 1457 (w), 1398 (s), 1372 (s), 1321 (w), 1302 (w), 1286 (w), 1247 (w), 1217 (w), 1183 (m), 1150 (w), 1121 (m), 1094 (w), 1069 (w), 1045 (m), 955 (w), 851 (w). ^1H NMR spectrum, δ, ppm (*J*, Hz): 8.40 (1H, d, *J* = 3.6, H Ar); 7.69 (1H, d, *J* = 6.0, H Ar); 7.20-7.18 (1H, m, H Ar); 5.55 (1H, d, *J* = 2.4, CH); 4.71 (1H, s, CH); 4.06 (3H, s, NCH_3); 2.34 (1H, d, *J* = 17.4) and 2.28-2.20 (3H, m, $2CH_2$); 2.01-1.94 (2H, m, CH_2); 1.02 (6H, s, $2CH_3$). ^{13}C NMR spectrum, δ, ppm: 198.2; 186.0; 173.5; 162.6; 159.6; 150.6; 134.3; 129.1; 125.7; 112.5; 106.9; 65.2; 51.8; 50.8; 43.4; 40.9; 33.7; 30.8; 28.5; 28.3. Mass spectrum (ESI^-), *m*/*z*: 335.36. Found, %: C 71.20; H 6.37; N 8.16. $C_{20}H_{20}N_2O_3$. Calculated, %: C 71.41; H 5.99; N 8.33.

2-Methyl-13-oxa-2,5-diazapentacyclo[10.7.1.0^{3,11}.0^{4,9}.0^{14,19}]icosa-4,6,8,14(19)-tetraene-10,18-dione (3i). Yield 50%, yellow solid, mp 150-152°C. IR spectrum, ν, cm^{-1}: 2937 (w), 1669 (s), 1642 (s), 1612 (vs),

1560 (s), 1490 (w), 1453 (w), 1416 (m), 1392 (s), 1372 (s), 1342 (w), 1313 (w), 1277 (w), 1179 (m), 1147 (w), 1125 (m), 1088 (w), 1069 (m), 1045 (m), 1029 (m), 966 (w), 897 (w). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.40 (1H, d, *J* = 5.4, H Ar); 7.70 (1H, d, *J* = 7.2, H Ar); 7.21-7.19 (1H, m, H Ar), 5.55 (1H, d, *J* = 1.8, CH); 4.70 (1H, s, CH); 4.08 (3H, s, NCH_3); 2.44 (2H, t, *J* = 6.0, CH_2); 2.39-2.37 (2H, m, CH_2); 2.02-1.99 (1H, m) and 1.97-1.94 (3H, m, $2CH_2$). ^{13}C NMR spectrum, δ, ppm: 197.1; 184.7; 173.7; 161.2; 158.3; 149.3; 132.9; 127.7; 124.3; 112.3; 105.5; 63.8; 49.6; 39.6; 36.6; 28.5; 26.8; 20.6. Mass spectrum (ESI$^-$), *m*/*z*: 307.53. Found, %: C 69.75; H 5.50; N 8.67. $C_{18}H_{16}N_2O_3$. Calculated, %: C 70.12; H 5.23; N 9.09.

16,16-Dimethyl-2-(2-oxo-2-phenylethyl)-13-oxa-2,5-diazapentacyclo[10.7.1.0^{3,11}.0^{4,9}.0^{14,19}]icosa-4,6,8,14(19)-tetraene-10,18-dione (3j). Yield 80%; yellow solid, mp 168-170°C. IR spectrum, ν, cm^{-1}: 2959 (w), 1703 (s), 1678 (s), 1611 (vs), 1556 (s), 1492 (w), 1452 (w), 1427 (w), 1391 (s), 1371 (s), 1344 (w), 1316 (w), 1221 (m), 1182 (m), 1111 (m), 1081 (m), 1047 (m), 1020 (w), 979 (w), 894 (w). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.19 (1H, d, *J* = 7.8, H Ar); 8.01 (2H, d, *J* = 7.8, H Ar); 7.67 (1H, d, *J* = 7.2, H Ar); 7.64 (1H, t, *J* = 7.2, H Ar); 7.53 (2H, t, *J* = 7.8, H Ar); 7.11 (1H, t, *J* = 7.2, H Ar); 6.72 (1H, m) and 5.74 (1H, d, *J* = 8.4, CH_2); 5.63 (1H, s, CH); 4.63 (1H, s, CH); 2.38-2.27 (3H, m), 2.25-2.17 (2H, m) and 2.07-2.04 (1H, m, $3CH_2$); 1.03 (3H, s, CH_3); 1.02 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 197.3; 195.1; 185.4; 172.0; 161.5; 158.2; 149.3; 135.0; 133.8; 132.3; 128.9; 128.1; 127.9; 124.2; 111.5; 106.6; 64.2; 58.6; 50.2; 49.3; 41.9; 32.2; 29.3; 27.3; 26.9. Mass spectrum (ESI$^-$), *m*/*z*: 439.53. Found, %: C 73.71; H 5.75; N 6.29. $C_{27}H_{24}N_2O_4$. Calculated, %: C 73.62; H 5.49; N 6.36.

2-(2-Oxo-2-phenylethyl)-13-oxa-2,5-diazapentacyclo[10.7.1.0^{3,11}.0^{4,9}.0^{14,19}]icosa-4,6,8,14(19)-tetraene-10,18-dione (3k). Yield 74%; yellow solid, mp 156–158°C. IR spectrum, ν, cm^{-1}: 2945 (w), 1678 (s), 1641 (s), 1607 (vs), 1556 (s), 1491 (w), 1430 (w), 1386 (s), 1314 (w), 1228 (m), 1177 (m), 1156 (w), 1120 (m), 1084 (w), 1053 (w), 1029 (w), 994 (w), 896 (w). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.19 (1H, d, *J* = 4.2, H Ar); 8.02 (2H, d, *J* = 7.8, H Ar); 7.67-7.66 (1H, m, H Ar); 7.64 (1H, t, *J* = 7.2, H Ar); 7.53 (2H, t, *J* = 7.2, H Ar); 7.12-7.10 (1H, m, H Ar); 6.80 (1H, m) and 5.73 (1H, d, *J* = 17.4, CH_2); 5.63 (1H, s, CH); 4.60 (1H, s, CH); 2.46 (2H, t, *J* = 6.0, CH_2); 2.40-2.30 (3H, m) and 2.08-2.04 (1H, m, 2 CH_2); 2.00-1.89 (2H, m, CH_2). ^{13}C NMR spectrum, δ, ppm: 197.0; 195.2; 185.4; 173.6; 161.4; 158.3; 149.3; 135.0; 133.8; 132.3; 128.9; 128.1; 127.8; 124.2; 112.8; 106.5; 64.2; 58.6; 49.4; 36.4; 28.4; 26.8; 20.6. Mass spectrum (ESI$^-$), *m*/*z*: 411.37. Found, %: C 72.62; H 5.17; N 6.53. $C_{25}H_{20}N_2O_4$. Calculated, %: C 72.80; H 4.89; N 6.79.

23-(2-Oxo-2-phenylethyl)-4,12-dioxa-20,23-diazahexacyclo[11.10.1.0^{2,11}.0^{5,10}.0^{14,22}.0^{16,21}]tetracosa-2(11),5(10),6,8,16,18,20-heptaene-3,15-dione (3l). Yield 76%; yellow solid, mp 184-186°C. IR spectrum, ν, cm^{-1}: 2934 (w), 1696 (vs), 1621 (s), 1556 (s), 1491 (w), 1451 (w), 1403 (m), 1375 (m), 1347 (w), 1324 (w), 1295 (w), 1273 (w), 1228 (m), 1207 (w), 1177 (m), 1160 (m), 1107 (w), 1085 (w), 1042 (m), 976 (w), 882 (w). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.22 (1H, d, *J* = 4.8, H Ar); 8.05 (2H, d, *J* = 7.8, H Ar); 7.90 (1H, d, *J* = 7.2, H Ar); 7.66 (2H, d, *J* = 7.2, H Ar); 7.56-7.52 (3H, m, H Ar); 7.27 (2H, d, *J* = 5.4, H Ar); 7.12 (1H, d, *J* = 6.0, H Ar); 7.05 (1H, m) and 5.78 (1H, d, *J* = 15.0, CH_2); 5.93 (1H, s, CH); 4.81 (1H, s, CH); 2.60 (1H, d, *J* = 13.8) and 2.30 (1H, d, *J* = 13.8, CH_2). ^{13}C NMR spectrum, δ, ppm: 195.2; 185.6; 163.3; 161.6; 161.4; 158.1; 152.7; 146.6; 134.9; 133.9; 132.7; 132.0; 129.3; 128.9; 128.2; 128.1; 124.4; 124.2; 124.0; 116.6; 106.3; 101.4; 64.8; 59.0; 51.1; 26.8. Mass spectrum (ESI$^-$), *m*/*z*: 461.37. Found, %: C 72.53; H 4.34; N 5.79. $C_{28}H_{18}N_2O_5$. Calculated, %: C 72.72; H 3.92; N 6.06.

Ethyl {16,16-Dimethyl-10,18-dioxo-13-oxa-2,5-diazapentacyclo[10.7.1.03,11.04,9.014,19]icosa-4,6,8,14(19)-tetraene-2-yl}acetate (3m). Yield 58%; yellow solid, mp 108–110°C. IR spectrum, ν, cm^{-1}: 2961 (w), 1745 (s), 1676 (m), 1643 (m), 1607 (vs), 1552 (s), 1490 (w), 1463 (w), 1396 (m), 1371 (m), 1321 (w), 1279 (w), 1208 (s), 1179 (m), 1115 (w), 1084 (w), 1048 (w), 954 (w), 892 (w). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.33 (1H, d, *J* = 4.2, H Ar); 7.68 (1H, d, *J* = 7.2, H Ar); 7.17-7.15 (1H, m, H Ar); 5.86 (1H, d, *J* = 17.4) and 5.03 (1H, d, *J* = 17.4, CH_2); 5.56 (1H, s, CH); 4.67 (1H, s, CH); 4.22-4.18 (2H, m, CH_2); 2.34 (1H, m) and 2.27 (1H, d, *J* = 13.8, CH_2); 2.24-2.20 (2H, m, CH_2); 2.16 (1H, d, *J* = 13.8) and 2.04-2.01 (1H, m, CH_2); 1.29 (3H, t, *J* = 7.2, CH_3); 1.02 (6H, s, $2CH_3$). ^{13}C NMR spectrum, δ, ppm: 197.1; 185.7; 171.7; 169.9; 161.1; 158.4; 149.5; 132.1; 127.9; 124.3; 114.4; 106.7; 63.9; 61.5; 53.0; 50.2; 49.1; 41.9; 32.2; 29.3; 27.2; 27.0; 14.2.

Mass spectrum (ESI^+), *m*/*z*: 407.38. Found, %: C 67.70; H 6.38; N 6.65. $C_{23}H_{24}N_2O_5$. Calculated, %: C 67.63; H 5.92; N 6.86.

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