Synthesis of 2,3-Dihydro-6*H*-1-oxa-3a-aza-phenalene and Its Benzo/Hetero-Fused Analog

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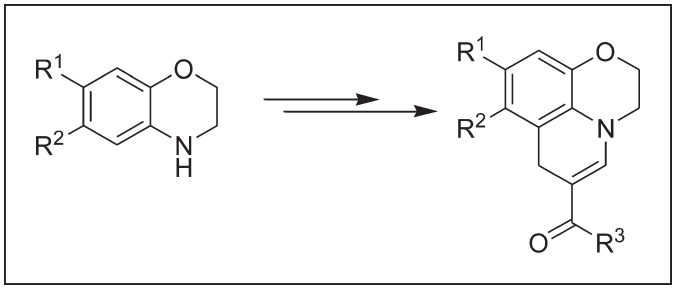

A simple and efficient method for the synthesis of highly substituted benzo- and hetero-fused analog of 2, 3-dihydro-6*H*-oxa-3a-aza-phenalene was developed using 2*H*-1, 4-benzoxazine and α-oxoketene dithio-acetals.

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INTRODUCTION

The 2*H*-1,4-benzoxazine derivatives have been extensively used as precursors for the synthesis of a variety of biologically active compounds. They have shown to be long-acting positive inotropes and peripheral vasodilator [1] with potential intracellular calcium activity [2]. Tricyclic analogs with a fused additional ring on the nitrogen atom of the benzoxazine moiety have been prepared and evaluated for their cardiovascular effects and as potential antihypertensive agents. Recently, Mérour and coworkers have used the benzoxazine framework for the synthesis of number of imidazolinic derivatives, which showed pronounced cardiovascular effects on both blood pressure and heart rate either after intraperitoneal (ip) or oral (po) administration. Among them, 6-fluoro-2-(4,5-dihydro-1*H*-imidazol-2-yl)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine was considered to be a potential antihypertensive agent [3]. Some tricylic benzoxazines are synthetic analogs of antibacterial fluoroquinolones, exemplified by norfloxacin and ciprofloxacin [4–8]. Although numerous methods for the synthesis of substituted 2*H*-1,4-benzoxazine and their corresponding benzo/hetero-fused derivatives have been developed, the search for new and efficient synthetic routes for these classes of compounds continues to attract a lot of attention.

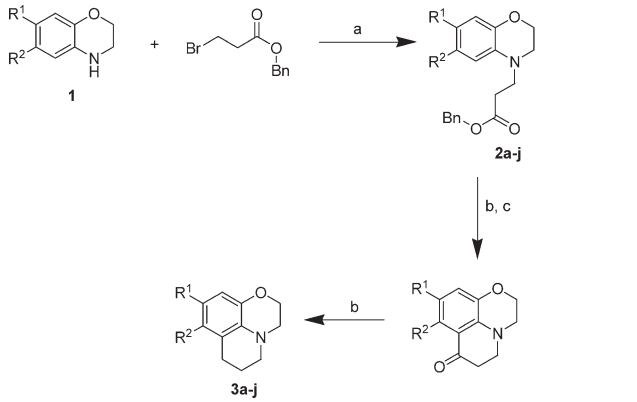
This work describes two general methods for the synthesis of 2,3-dihydro-6*H*-1-oxa-3a-aza-phenalene, one involving the general *N*-alkylation of the benzoxazines with benzyl propanoate and subsequent reduction and cyclization. The other by reaction of benzoxazine and α-oxoketene dithio-acetal to give the *S*,*N*-acetal, which when reacted with Vilsmeier reagent provides a versatile route to highly functionalized 2*H*-1,4-benzoxazine and their benzo- and hetero-fused analogs [9–11].

RESULTS AND DISCUSSION

As part of our earlier work aimed at synthesizing benzoxazine derivatives of biological interest,[14] we wanted to develop new and simpler routes for the synthesis of benzo/hetero-fused analogs. The first step employed was the *N*-alkylation of benzoxaxine **1** with 3-bromo-propionic acid benzyl ester in presence of K_2CO_3 to obtain 3-(6,7-Dialkyl-2,3-dihydro-benzo[1,4]oxazin-4-yl)-propionic acid benzyl ester **2a–j**. **2a–j** when subjected to reduction and subsequent cyclization using trifluoroacetic anhydride in dichloromethane at room temperature yielded the desired products **3a–j** (Scheme 1).

The use of α-oxoketene dithio-acetals in the synthesis of various heterocyclic molecules is well documented in the literature [12,13]. However, there is no report about its uses in the synthesis of tricyclic analogs of benzoxazines. We report here a simple procedure for the synthesis of this class of compounds starting from benzoxazine and α-oxoketene dithio-acetals. Benzoxaxine **1** when treated with aryl-oxoketene dithioacetal **4** in presence of *n*-BuLi in tetrahydofuran (THF) [14] gave the aryl-

Scheme 1. Synthesis of substituted 2,3-dihydro-6*H*-oxa-3a-aza-phenalene.



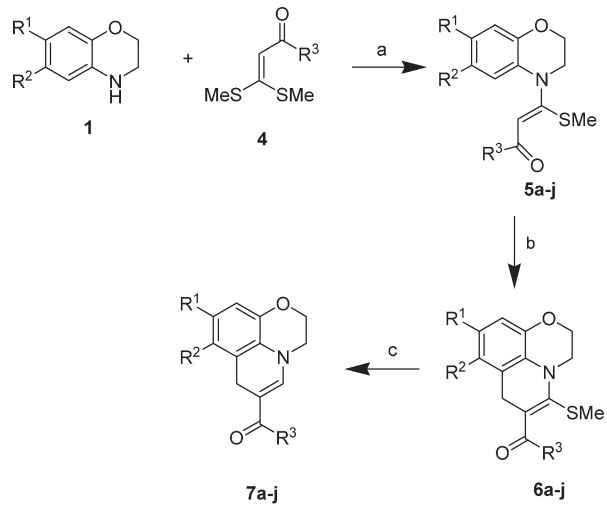
(a) K_2CO_3 DMF reflux; (b) H_2, Pd/C 10%, ethanol; (c) trifluoroacetic acid anhydride, CH_2Cl_2

oxoketene-*N*,*S*-2*H*-1,4 benzoxazinoacetal **5** by displacement of one of the methyl thiol groups of **4** (Scheme 2). Vilsmeier cyclization of **5a–j** afforded the tricyclic analog **6a–j**, which on subsequent reduction using Raney-Ni yielded the final products **7a–j** (Table 1).

It was observed that the yields of the products in the second method (**7**) varied significantly with the nature of the substituent. The presence of a methoxy or a hydroxyl group in the aromatic ring system significantly increases the yield as compared to an alkyl substituent. Thus, for obtaining an alkyl substituted product, the procedure shown in scheme 1 was preferred.

The 2-methylthiol group in 2,3-dihydro-6*H*-1-oxa-3a-aza-phenalene **6a** was oxidized with *m*-chloroperbenzoic acid to afford the corresponding 2-(methylsulfonyl) of 2,3-dihydro-6*H*-1-oxa-3a-aza-phenalene **8** (Scheme 3),

Scheme 2. Synthesis of substituted 2,3-dihydro-6*H*-oxa-3a-aza-phenalene.



(a) n BuLi / THF; (b) $POCl_3$, DMF, 80°C; (c) Raney Ni/ ethanol/ heat

which on further treatment with *n*-butylamine yielded the desired products **9a–j**. This process provided a simple and general route for the synthesis of highly functionalized tricyclic analogs of benzoxazine. The reaction proceeded under mild conditions, when an alkyl amine is used; however, for aryl amine groups more drastic conditions were necessary. Here, again the yield varied with the bulkiness of the substituent (Table 2).

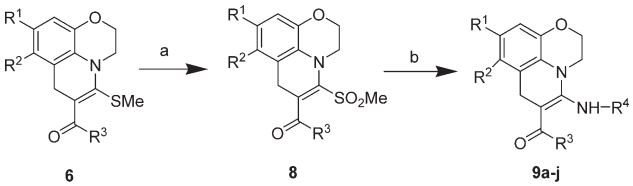
Interestingly, when **6j** was treated with ethyl amine in presence of Pd(dppf)Cl_2 and K_2CO_3 under microwave, the reaction did not undergo simple substitution but

Table 1

Substituted 2,3-dihydro-6*H*-1-oxa-3a-aza-phenalene.

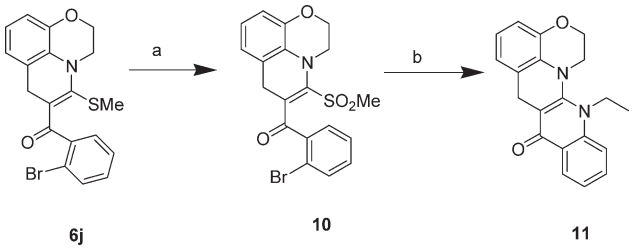
Entry	Product(**3**)	Yield (%) (**3**)	Product (**7**)	Yield (%) (**7**)
a	R^1=H, R^2=H	82	R^1=H, R^2=H, R^3=Ph	92
b	R^1=CH_3, R^2=H	84	R^1=H, R^2=OCH_3, R^3=Ph	80
c	R^1=CH_3, R^2=CH_3	86	R^1=OCH_3, R^2=H, R^3=Ph	86
d	R^1=OCH_3, R^2=H	56	R^1=CH_3, R^2=H, R^3=2-BrPh	66
e	R^1=H, R^2=OCH_3	49	R^1=CH_3, R^2=CH_3, R^3=Ph	52
f	R^1=OCF_3, R^2=H	41	R^1=CF_3, R^2=H, R^3=Ph	73
g	R^1=Cl, R^2=H	46	R^1=Cl, R^2=H, R^3=Ph	87
h	R^1=F, R^2=H	40	R^1=F, R^2=H, R^3=Ph	66
i	R^1=CH_2OH, R^2=H	42	R^1=OH, R^2=H, R^3=Ph	86
j	R^1=OCH_3, R^2=CH_3	50	R^1=H, R^2=H, R^3=2-BrPh	84

Scheme 3. Synthesis of highly substituted 2,3-dihydro-6*H*-oxa-3a-aza-phenalene.



further coupled to yield the cyclized product **11** (65%) as shown in Scheme 4.

Scheme 4. Microwave assisted synthesis of hetero-fused analog of 2,3-dihydro-6*H*-oxa-3a-aza-phenalene.



EXPERIMENTAL

Carbon, hydrogen, and nitrogen analysis were performed with a PerkinElmer 2400 series II instrument. IR spectra in BOMEM DA-8 Fourier transform infrared (FTIR) spectrophotometer. The ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AMX 400 spectrometer. Positive-ion and negative-ion electrospray ionization (ESI) mass spectra were measured on an ion trap analyzer Esquire 3000 (Bruker Daltonics).

2,3,4,6-Tetrahydro-6H-oxa-3a-aza-phenalene (3a). Amine **1** (7 mmol) and dry K_2CO_3 (15 mmol) were dissolved in dry dimethylformamide (DMF) (15 mL), then an alkyl halide (8.6 mmol) was added. The reaction mixture was stirred at room temperature overnight. After completion of the reaction (monitored by thin layer chromatography (TLC)), crushed ice was added and the product extracted with ethyl acetate. The combined organic extract was dried (Na_2SO_4), concentrated, and purified by passing over silica gel and eluting with ethyl acetate/hexane (1:15) to obtain the pure product. The *N*-substituted product (3.4 mmol) was then dissolved in ethanol (15 mL) containing Pd/C 10% (0.3 mmol) and the mixture stirred under 1 atm of H_2 for 4 h. It was then filtered under pressure, and the filtrate evaporated to give brownish oil. [IR (film) ν(cm^{-1}) 3540 (ν_{OH})]. This was dissolved in dichloroethane and cooled to 0°C. To this solution, trifluoroacetic anhydride (9 mmol) was added and the mixture stirred overnight at room temperature. The pH of the reaction mixture was adjusted to 9–10 by addition of 4N NaOH. Extraction with ethyl acetate, washing of the organic layer with water, drying over Na_2SO_4, and evaporation yield the crude product that was further purified by column chromatography using silica gel as the solid phase and dichloromethane (DCM) as the mobile phase. The product was further subjected to reduction following the method described above to yield the final product **3a**.

Table 2

Highly substituted 2, 3-dihydro-6*H*-1-oxa-3a-aza-phenalene.

Entry (**9**)	R^1	R^2	R^3	R^4	Yield %
a	H	H	Ph	Ph	82
b	H	H	2-Br Ph	Ph	75
c	H	H	Ph	n-Butyl	85
d	Cl	H	Ph	Ph	70
e	H	H	Ph	$PhCH_2$	72
f	H	H	2-BrPh	n-Butyl	70
g	Cl	H	2-Br Ph	Ph	80
h	OCH_3	H	2-Br Ph	Ph	68
i	OCH_3	H	Ph	Ph	65
j	H	CH_3	Ph	Ph	67

2,3,4,6-Tetrahydro-6H-oxa-3a-aza-phenalene (3a). Yield 82%; oil; IR (film) absence of ν_{NH} stretching. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 1.95 (m, 3H), 2.79 (t, 2H, J = 6.5 Hz), 3.08 (t, 2H, J = 6 Hz), 3.94 (t, 2H, J = 5 Hz), 4.31 (t, 2H, J = 4.5 Hz), 6.48–6.54 (m, 3H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) 30.1, 34.5, 58.7, 60.2 (NCH_2), 73.1 (OCH_2), 112.8, 116.8, 117.3, 119.5, 140.1, 130.2. MS (ESI) m/z = 176.21. Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99 found: C, 75.42; H, 7.49; N, 8.01.

8-Methyl-2,3,5,6-tetrahydro-4H-1-oxa-3a-aza-phenalene (3b). Yield 84%; oil IR (film) absence of ν_{NH} stretching. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 1.90 (m, 3H), 2.21 (s, 3H), 2.61 (t, 2H, J = 6.2 Hz), 3.25 (t, 2H, J = 6.4 Hz), 3.61 (t, 2H, J = 5.7 Hz), 4.24 (t, 2H, J = *4.9 Hz*), 6.41 (s, 1H, ArH), 6.55 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz); 20.1, 25.9, 30.6, 53.1, 61.1 (NCH_2), 73.6 (OCH_2), 112.3, 121.1, 123.2, 127.1, 129.1, 142.5. MS (ESI) m/z = 190.52. Calcd. for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40 found: C, 76.21; H, 8.09; N, 7.41.

8,9-Dimethyl-2,3,5,6-tetrahydro-4H-1-oxa-3a-aza-phenalene (3c). Yield 86%; oil IR (film) absence of ν_{NH} stretching. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 1.87 (m, 3H), 2.28 (s, 6H), 2.72 (t, 2H, J = 6.4 Hz), 3.17 (t, 2H, J = 6.7 Hz), 3.60 (t, 2H, J = 5.3 Hz), 4.21 (t, 2H, J = 4.7 Hz), 6.54 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) 12.4, 19.5, 21.1, 24.5, 46.6, 60.2 (NCH_2), 73.9 (OCH_2), 112.5, 121.9, 125.2, 127.1, 128.5, 140.1. MS (ESI) m/z = 204.12. Calcd. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89 found: C, 76.86; H, 8.48; N, 6.85.

8-Methoxy-2,3,5,6-tetrahydro-4H-1-oxa-3a-aza-phenalene (3d). Yield 56%; oil. IR (film) absence of ν_{NH} stretching. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 1.91 (m, 3H), 2.65 (t, 2H, J = 6.4 Hz), 3.26 (t, 2H, J = 6.2 Hz), 3.41 (s, 3H), 3.75 (t, 2H, J = 5.5 Hz), 4.19 (t, 2H, J = 4.5 Hz), 6.21 (s, 1H, ArH), 6.35 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz); 20.5, 31.1, 50.5, 56.5, 60.7 (NCH_2), 73.6 (OCH_2), 99.7, 105.8, 121.1, 126.1, 140.5, 149.3. MS (ESI) m/z = 206.1. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82; found: C, 70.21; H, 7.39; N, 6.76.

9-Methoxy-2,3,5,6-tetrahydro-4H-1-oxa-3a-aza-phenalene (3e). Yield 49%; oil. IR (film) absence of ν_{NH} stretching. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 1.96 (m, 3H), 2.72 (t, 2H, J = 6.8 Hz), 3.31 (t, 2H, J = 6.7 Hz), 3.54 (s, 3H), 3.79 (t, 2H, J = 6.5 Hz), 4.22 (t, 2H, J = 5.5 Hz), 6.25 (d, 1H, J = 7.1 Hz), 6.54 (d, 1H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz); 20.1, 26.1, 50.2, 56.9, 60.5 (NCH_2), 73.1 (OCH_2), 104.9, 110.1, 114.5, 131.1,

134.5, 149.9. MS (ESI) $m/z = 206.12$. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82; found: C, 70.26; H, 7.43; N, 6.78.

8-Trifluoromethoxy-2,3,5,6-tetrahydro-4H-1-oxa-3a-aza-phenalene (3f). Yield 41%; oil IR (film) absence of ν_{NH} stretching. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 1.89 (m, 3H), 2.64 (t, 2H, $J = 6.0$ Hz), 3.29 (t, 2H, $J = 6.3$ Hz), 3.73 (t, 2H, $J = 5.7$ Hz), 4.26 (t, 2H, $J = 5.0$ Hz), 6.15 (s, 1H, ArH), 6.32 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz); 19.7, 29.6, 52.7, 60.7 (NCH_2), 72.9 (OCH_2), 98.7, 105.1, 121.7, 122.9, 126.1, 143.1, 151.2. MS (ESI) m/z = 260.02. Calcd. for $C_{12}H_{12}F_3NO_2$: C, 55.60; H, 4.67; N, 5.40; found: C, 55.65; H, 4. 73; N, 5.45.

8-Chloro-2,3,5,6-tetrahydro-4H-1-oxa-3a-aza-phenalene (3g). Yield 46%; oil. IR (film) absence of ν_{NH} stretching. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 2.01 (m, 3H), 2.61 (t, 2H, $J = 6.0$ Hz), 3.27 (t, 2H, $J = 6.2$ Hz), 3.86 (t, 2H, $J = 5.5$ Hz), 4.22 (t, 2H, $J = 4.5$ Hz), 7.11 (s, 1H, ArH), 7.36 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz); 23.0, 30.9, 53.2, 61.1 (NCH_2), 73.5 (OCH_2), 113.1, 119.9, 121.9, 124.1, 129.5, 141.2. MS (ESI) $m/z = 210.5$ Calcd. for $C_{11}H_{12}ClNO$: C, 63.01; H, 5.77; N, 6.68; found: C, 63.06; H, 5.82; N, 6.75.

8-Fluoro-2,3,5,6-tetrahydro-4H-1-oxa-3a-aza-phenalene (3h). Yield 40%; oil. IR (film) absence of ν_{NH} stretching. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 2.05 (m, 3H), 2.63 (t, 2H, $J = 6.4$ Hz), 3.32 (t, 2H, $J = 6.7$ Hz), 3.79 (t, 2H, $J = 6.0$ Hz), 4.27 (t, 2H, $J = 5.7$ Hz), 6.54 (s, 1H, ArH), 6.67 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz); 22.6, 31.2, 53.7, 61.4 (NCH_2), 73.5 (OCH_2), 101.3, 108.1, 123.9, 125.7, 143.7, 152.8. MS (ESI) $m/z = 194.05$ Calcd. for $C_{11}H_{12}FNO$: C, 68.38; H, 6.26; N, 7.25; found: C, 68.43; H, 6.20; N, 7.29.

(2,3,4,6-Tetrahydro-6H-oxa-3a-aza-phenalene) methanol (3i). Yield 42%; oil. IR (film) absence of ν_{NH} stretching. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 1.97 (m, 3H), 2.67 (t, 2H, $J = 6.8$ Hz), 3.39 (t, 2H, $J = 6.9$ Hz), 3.72 (t, 2H, $J = 6.2$ Hz), 4.23 (t, 2H, $J = 5.9$ Hz), 4.62 (s, 2H), 5.21 (s, OH), 6.59 (s, 1H, ArH), 6.72 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz); 21.9, 30.7, 50.1, 60.9 (NCH_2), 67.7, 72.8 (OCH_2), 110.7, 121.3, 123.5, 129.6, 132.5, 143.2. MS (ESI) $m/z = 206.10$. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82; found: C, 70.26; H, 7.42; N, 6.87.

8-Methoxy-9-methyl-2,3,5,6-tetrahydro-4H-1-oxa-3a-aza-phenalene (3j). Yield 50 %; oil. IR (film) absence of ν_{NH} stretching. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 1.88 (m, 3H), 2.28 (s,3H), 2.59 (t, 2H, $J = 6.7$ Hz), 3.39 (t, 2H, $J = 6.1$ Hz), 3.62 (s, 3H), 3.81 (t, 2H, $J = 5.9$ Hz), 4.23 (t, 2H, $J = 5.9$ Hz), 6.22 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz); 9.7, 20.7, 26.7, 51.2, 56.1, 60.1 (NCH_2), 73.0 (OCH_2), 98.9, 115.3, 122.8, 124.6, 140.9, 149.1. MS (ESI) $m/z = 206.1$. Calcd. for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39; found: C, 71.16; H, 7.87; N, 6.45.

3-(2,3-Dihydro-benzo[1,4]oxazin-4-yl)-3-methylsulfanyl-1-phenyl-propenone (5a). To a solution of 3,4-dihydro-2*H*-1,4-benzoxazines (7 mmol) in dry THF (30 mL) was added *n*-BuLi (9 mmol) drop wise under nitrogen atmosphere at −78°C, it was then allowed to attain room temperature and further stirred for 30 min. To the reaction mixture a solution of the phenyl oxoketene-*S*,*S*-acetal (**4**) (8 mmol) in dry THF (25 mL) was added at 0°C, stirred at room temperature for 1 h, and refluxed. The reaction mixture was then cooled, quenched with saturated NH_4Cl solution, evaporated in vacuum, and extracted with $CHCl_3$. The combined organic extract was dried over Na_2SO_4 and evaporated to give a solid mass, which was purified by column chromatography over silica gel using hexanes-EtOAc (6:1) as eluent to yield the pure product of 82%.

IR (KBr), ν (cm^{-1}). 2925, 1614. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 2.45 (s, 3H), 3.25(t, 2H, $J = 7.7$ Hz), 4.07 (t, 2H, $J = 8.6$ Hz), 5.89 (s, 1H), 6.46–6.65 (m, 4H, ArH), 7.42–7.54 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz); 12.6 (SCH_3), 60.2 (NCH_2), 73.1 (OCH_2), 87.1, 112.8, 116.8, 117.3, 119.5, 129.1, 130.2, 130.2, 134.3, 137.0, 140.1, 166.7, 187.8. MS (ESI) $m/z = 310.41$. Calcd. for $C_{18}H_{17}NO_2S$: C, 69.43; H, 5.50; N, 4.50; found: C, 69.52; H, 5.49; N, 4.51.

3-(6-Methoxy-2,3-dihydro-benzo[1,4]oxazin-4-yl)-3-methylsulfanyl-1-phenyl-propenone (5b). Yellowish solid. Yield 78%; IR (KBr), ν (cm^{-1}). 1627 ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 2.41 (s, 3H), 3.31(t, 2H, $J = 7.5$ Hz), 3.51 (s, 3H), 4.05 (t, 2H, $J = 6.7$ Hz), 5.75 (s, 1H), 5.92(s, H), 6.15 (d, 1H, $J = 8.5$ Hz), 6.56 (d, 1H, $J = 8.5$Hz) 7.62–7.84 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz); 12.7 (SCH_3), 59.9 (NCH_2), 61.5, 73.6 (OCH_2), 89.2, 96.5, 102.7, 116.5, 128.7, 130.4, 132.7, 133.5, 134.1, 137.3, 152.1, 165.9, 188.2. MS (ESI) $m/z = 342.32$. Calcd. for $C_{19}H_{19}NO_3S$: C, 66.84; H, 5.61; N, 4.10; found: C, 66.82; H, 5.59; N, 4.12.

1-(2-Bromo-phenyl)-3-(2,3-dihydro-benzo[1,4]oxazin-4-yl)-3-methylsulfanyl-propenone (5j). Solid. Yield 77%; IR (KBr), ν (cm^{-1}). 1645 ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 2.46 (s, 3H), 3.2(t, 2H, $J = 7.2$ Hz), 4.11 (t, 2H, $J = 7.1$ Hz), 5.95 (s, 1H), 5.92(s, H), 6.51–6.67 (m, 4H, ArH) 7.32–7.41 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz); 12.9 (SCH_3), 60.4 (NCH_2), 73.8 (OCH_2), 90.2, 114.7, 116.1, 118.2, 120.6, 121.9, 128.1, 130.1, 131.4, 132.5, 136.9, 139.4, 141.1, 164.9, 188.6. MS (ESI) $m/z = 389.15$. Calcd. for $C_{18}H_{16}BrNO_2S$: C, 55.39; H, 4.13; N, 3.59; found: C, 55.42; H, 4.15; N, 3.56.

(4-Methylsulfanyl-2,3-dihydro-6*H*-1-oxa-3a-aza-phenalen-5-yl)-phenyl-methanone (6a). To a solution of **5a** (3 mmol) in DMF was added drop wise a solution of Vilsmeier reagent at 0°C [prepared from $POCl_3$ (5 mmol) and DMF (5 mmol) at 0–5°C] under nitrogen atmosphere and stirred for 4 h at room temperature. The reaction mixture was then heated at 90°C for 3 h. The reaction mixture was poured into ice cold saturated $NaHCO_3$ solution (20 mL) and extracted with chloroform (2 × 25 mL). The combined organic extract was dried over Na_2SO_4 and then evaporated under reduced pressure. The pure product was obtained by column chromatography over silica gel using hexane-EtOAc as eluent (4.1).

Yield 90% (0.849 g). ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 2.34 (s, 3H), 3.21 (s, 2H), 3.35(t, 2H, $J = 6.1$ Hz), 4.07 (t, 2H, $J = 5.6$ Hz), 6.46–6.65 (m, 3H, ArH), 7.42–7.54 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz); 12.1 (SCH_3), 27.9, 60.1 (NCH_2), 73.5 (OCH_2), 96.1, 112.5, 116.3, 117.1, 119.2, 129.8, 130.5, 130.2, 134.3, 137.0, 140.1, 156.7, 186.8. MS (ESI) $m/z = 322.21$. Calcd. for $C_{19}H_{17}NO_2S$: C, 70.56; H, 5.30; N, 4.33; found: C, 70.60; H, 5.35; N, 4.31.

(8-Methoxy-4-methylsulfanyl-2,3-dihydro-6*H*-1-oxa-3a-aza-phenalen-5-yl)-phenyl-methanone (6c). Dirty yellow solid. Yield 82%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 2.35 (s, 3H), 3.19(s, 2H), 3.41(t, 2H, $J = 6.2$ Hz), 3.56 (s, 3H), 4.16 (t, 2H, $J = 5.9$ Hz), 5.76 (s, 1H, ArH), 6.03 (s, 1H, ArH), 7.42–7.51 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz); 12.5 (SCH_3), 28.7, 54.9, 60.1 (NCH_2), 73.5 (OCH_2), 95.9, 98.1, 104.8, 122.7, 128.4, 129.1, 132.9, 134.8, 138.1, 141.4, 149.1, 158.9, 180.6. MS (ESI) $m/z = 354.1$. Calcd. for $C_{20}H_{19}NO_3S$: C, 67.97; H, 5.42; N, 3.96; found: C, 67.94; H, 5.40; N, 3.98.

(8-Fluoro-4-methylsulfanyl-2,3-dihydro-6*H*-1-oxa-3a-aza-phenalen-5-yl)-phenyl-methanone (6h). Solid. Yield 68%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 2.31 (s, 3H), 3.26(s, 2H), 3.45(t, 2H, J = 6.5 Hz), 4.21 (t, 2H, J =7.1 Hz), 6.15 (s, 1H, ArH), 6.21 (s, 1H, ArH), 7.21–7.42 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz); 12.8 (SCH_3), 28.9, 60.3 (NCH_2), 73.8 (OCH_2), 96.7, 100.9, 107.8, 124.7, 128.9, 129.2, 134.1, 136.9, 138.2, 142.1, 150.1, 158.6, 189.8. MS (ESI) m/z = 340.52. Calcd. for $C_{19}H_{16}FNO_2S$: C, 66.84; H, 4.72; N, 4.10; found: C, 66.87; H, 4.73; N, 4.13.

(8-Chloro-2,3-dihydro-6*H*-1-oxa-3a-aza-phenalen-5-yl)-phenyl-methanone (7g). ***Reduction using Raney-Ni.*** To a solution of **6g** (6.4 mmol) in ethanol was added Raney-Ni (three times by weight) and the suspension refluxed for 2 h. The reaction mixture was then cooled and filtered through sintered funnel. The residue washed with ethanol (3 × 10 mL) and the filtrate evaporated to give **7g** which was further purified by column chromatography over silica gel using EtOAc–Hexane (1:10) as eluent.

Yield 87% (1.99 g); ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 3.15 (s, 3H), 3.41 (t, 2H, J = 6 Hz), 4.03 (t, 2H, J = 7.1 Hz), 3.41(s, 3H), 4.05 (t, 2H, J = 5.5 Hz), 6.15 (s, 1H, ArH), 6.21 (s, 1H, ArH). 6.54 (s, 1H), 7.32–7.45 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) 31.5, 61.7 (NCH_2), 73.8 (OCH_2), 111.9, 113.6, 119.5, 120.1, 127.3, 127.8, 128.1, 129.1, 132.1, 135.2, 136.3, 141.1, 165.3. MS (ESI) m/z = 312.82. Calcd. for $C_{18}H_{14}ClNO_2$: C, 69.35; H, 4.53; N, 4.49; found: C, 69.41; H, 4.59; N, 4.42.

2-(Methylsulfonyl) of 2,3-dihydro-6*H*-1-oxa-3a-aza-phenalene (8). To a solution of **6j** (2.5 mmol) in dry DCM (30 mL) was added a solution of meta-chloroperbenzoic acid (*m*CPBA) (5.0 mmol) dropwise over a period of 15 min and stirred at room temperature for 3 h. The reaction mixture was then neutralized with saturated $NaHCO_3$ (2 × 25 mL) and washed with brine, dried over anhydrous $NaSO_4$, and evaporated to yield the crude product, which was purified by column chromatography using EtOAc–Hexane (1:20) as eluent.

Yield 80% (0.892 g); ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 3.21 (s, 2H), 3.34 (s, 3H), 3.45(t, 2H, J = 6.3 Hz), 4.14 (t, 2H, J = 6.7 Hz), 6.56–6.65 (m, 3H, ArH), 7.39–7.64 (m, 5H, ArH).. ^{13}C NMR ($CDCl_3$, 100 MHz); 27.9, 38.5, 59.1 (NCH_2), 74.9 (OCH_2), 95.9, 112.8, 118.3, 120.6, 121.9, 122.8, 128.7, 131.2, 132.6, 136.5, 138.9, 140.1, 141.5, 160.3, 191.1. MS (ESI) m/z = 435.31. Calcd. for $C_{19}H_{16}BrNO_4S$: C, 52.54; H, 3.71; N, 3.23; found: C, 52.57; H, 3.73; N, 3.21.

Synthesis of 4-phenylamino-2,3-dihydro-6*H*-1-oxa-3a-aza-phenalene (9a). A solution of **8a** (3 mmol) and *n*-butyl amine (15 mmol) was refluxed for 6 h in dry THF (toluene for aryl amine). The reaction mixture was cooled and THF evaporated off to yield a yellow solid, which was further purified by column chromatography on silica gel using EtOAc–Hexane (1:2) as an eluent.

Yield 82% (0.87 g). IR (KBr), ν (cm^{-1}), 3316, 1342. ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm 3.16 (s, 2H), 3.54 (t, 2H, J = 6.5 Hz), 4.21 (t, 2H, J = 6.4 Hz), 6.35–6.42 (m, 3H, ArH), 6.62 (b, 1H), 6.98–7.14 (m, 4H, ArH), 7.42–7.54 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz); 26.1, 58.6 (NCH_2), 75.4 (OCH_2), 82.9, 111.5, 115.9, 117.3, 119.3, 121.3, 123.1, 128.9, 129.2, 130.1, 135.2, 138.7, 140.9, 141.8, 144.8, 156.3, 190.5. MS (ESI) m/z = 367.41. Calcd. for $C_{24}H_{20}N_2O_2$: C, 78.24; H, 5.47; N, 7.60; found: C, 78.21; H, 5.50; N, 7.61.

Synthesis of 13-ethyl-1,2,7,13-tetrahydro-3-oxa-13,13b-diaza-benzo-naphthacen-8-one (11). (2-Bromo-phenyl)-(4-methanesulfonyl-2,3-dihydro-6*H*-1-oxa-3a-aza-phenalen-5-yl)-methanone (**10**) (2.3 mmol) was taken in a 25 mL container, which was then sealed with septum and purged with N_2. K_2CO_3 (5.75 mmol) and Pd(dppf)Cl_2 (0.23 mmol) were introduced and the reaction mixture was again purged with N_2. It was then heated in the microwave synthesizer for 10 min at 100°C and allowed to cool to room temperature. The content of the vessel was filtered through celite and washed with CH_2Cl_2 (3 × 5 mL). The combined organic extracts was further washed with saturated aqueous $NaHCO_3$ and evaporated to yield the crude product (**11**), which was purified by column chromatography using EtOAc–Hexane (1:5) as an eluent.

Yield 65% (0.65 g); IR (KBr) 1712 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 1.09 (t, 3H, J = 3.6 Hz), 2.98 (q, 2H, J = 3.5 Hz), 3.18 (s, 2H), 3.54 (t, 2H, J = 6.5 Hz), 4.21 (t, 2H, J = 6.4 Hz), 6.48–6.54 (m, 3H, ArH), 7.12–7.34 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) 13.1, 26.2, 44.5, 55.2 (NCH_2), 74.1 (OCH_2), 84.1, 111.4, 112.4, 117.1, 117.9, 120.5, 121.3, 122.4, 129.2, 130.4, 135.6, 142.1, 144.6, 155.2, 179.6. MS (ESI) m/z = 317.41. Calcd. for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80; found: C, 75.42; H, 5.69; N, 8.81.

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