Synthesis of tetracyclic 8-aza-naphthalen-9-ones and oxa-naphthalen-9-one

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Bromination of 1-methylbenzo[f]chromen-3-one with N-bromosuccinimide gives 2-bromo-1-methylbenzo[f]chromen-3-one which, on condensation with different primary aromatic amines, gives tetracyclic aza-naphthalen-9-ones. Condensation of 2-bromo-1-methylbenzo[f]chromen-3-one with different secondary cyclic amines also gives tetracyclic oxa-naphthalen-9-one. The formation of 8-aza-naphthalen-9-one and 7,8-dioxa-naphthalen-9-one is confirmed by their single crystal analyses.

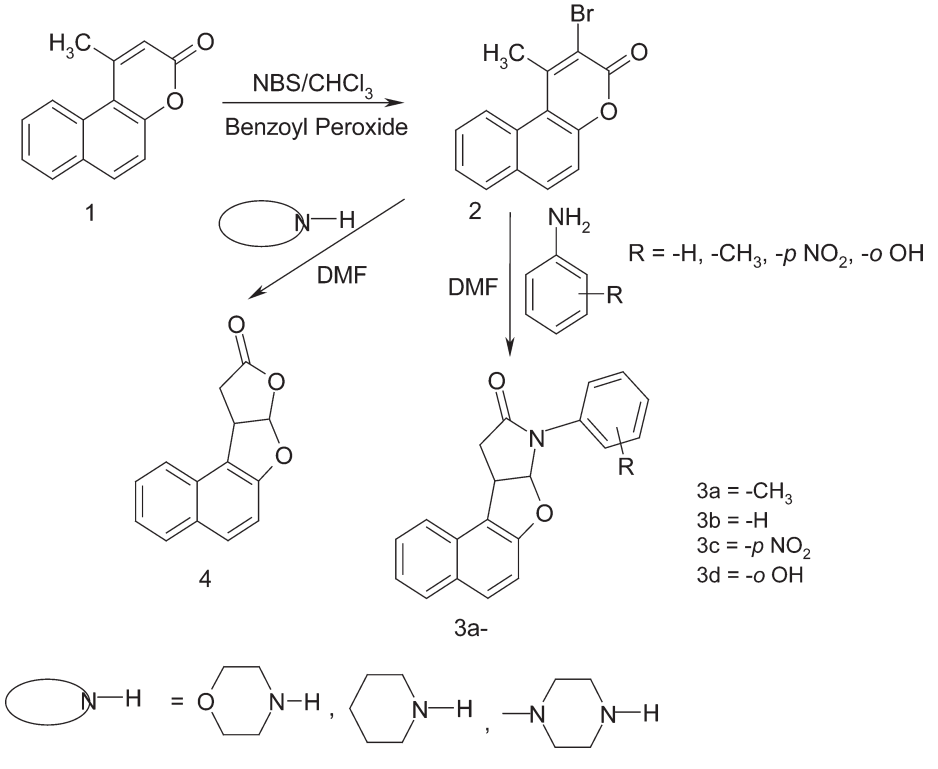
Keywords: bromonaphthochromen, azanaphthalen-ones, oxanaphthalen-one

Naphthopyrones possess various biological activities.[1–3] Naphthyl and coumarinyl biaryl piperazine derivatives are reported as highly potent human-β-secretase inhibitors,[4] $I_k\beta_\alpha$ kinase inhibitors[5] and antipsychotic agents.[6] In view of their biological activities and in continuation of our work on benzopyrone derivatives,[7,8] we describe here a synthesis of tetra cyclic 8-aza-naphthalen-9-ones and 7,8-dioxa-naphthalen-9-one.

Pechmann condensation[9] of β-naphthol with ethyl acetoacetate gave 1-methylbenzo[f]chromen-3-one **1**. Bromination of **1** with N-bromosuccinimide in the presence of benzoyl peroxide and light(100W bulb) in refluxing chloroform was expected to give 1-bromomethylbenzo[f]chromen-3-one,[8] but instead gave 2-bromo-1-methylbenzo[f]chromen-3-one **2**. The structure of **2** was confirmed by its ^{1}H NMR. In ^{1}H NMR of **1**, the presence of a sharp singlet at δ 6.4 integrating for one proton clearly indicated the C-2 proton, the singlet at δ 2.96 integrating for three protons indicated the methyl group at C-1. After bromination, in the ^{1}H NMR of **2**, **a** sharp singlet integrating for one proton at δ 6.4 has disappeared and the methyl signal for three protons at δ 2.96 is clearly observed, which indicated bromination with N-bromosuccinimide is observed to be at the 2-position of chromen-3-one. Literature reports[10–13] bromination of **1** with bromine in acetic acid to give 2-bromo-1-methylbenzo[f]chromen-3-one.

When we have condensed **2** with different aromatic primary amines in dimethyl formamide (DMF), expecting to get the 1-amino methyl derivative of benzo[f]chromen-3-ones, as we have prepared furopsoralenamines,[8] the product obtained was tetracyclic **3a–d**. Carnduff[12,13] observed that alkaline hydrolysis of 2-bromo-1-methylbenzo[f]chromen-3-one gave two unusual products involving skeletal rearrangement but they have not reported the ^{1}H NMR in support of their structure. **2** on condensation with *p*-toluidine which gave 8-*p*-tolyl-7a,8,10,10a-tetrahydro-7-oxa-8-aza-pentaleno[1,2-a] naphthalene-9-one **3a**. The structure of this compound is confirmed by its IR, ^{1}H NMR, ^{13}C NMR and single crystal analysis. (Scheme 1).

In the ^{1}H NMR spectrum, the singlet at δ 2.38 integrated for three protons indicating a methyl group. Two double doublets integrating for one proton each at δ 2.90–2.96 with J = 3.7, 3.6Hz and δ 3.26–3.33 with J = 3.6, 3.7Hz clearly indicated



Scheme 1

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–CH_2 protons, one multiplet at δ 4.49–4.55 integrated for one proton indicated the proton at the ring junction while the doublet integrating for one proton at δ 6.61–6.63 indicated another proton at a ring junction, sandwiched between O and N. Other signals in the aromatic region indicated naphthalene ring protons. The IR spectrum showed a carbonyl band at 1715 cm^{-1} indicating a cyclic five-membered amide. ^{13}C NMR data also matches with a tetracyclic structure. Finally the structure of **3a** is confirmed by single crystal analysis (Fig. 1).

The single crystal structure of **3a** clearly indicated a tetracyclic ring structure in which three rings are in one plane and the fourth ring is out of plane. The furan ring and azalactone rings are *cis*-fused and the angle between these two rings is 110.72°. The azalactone ring and phenyl ring of the amine are in one plane. Similar compounds **3a–d** are obtained when different primary aromatic amines are condensed with **2**. The CCDC no. for **3a** is CCDC 766458**.**

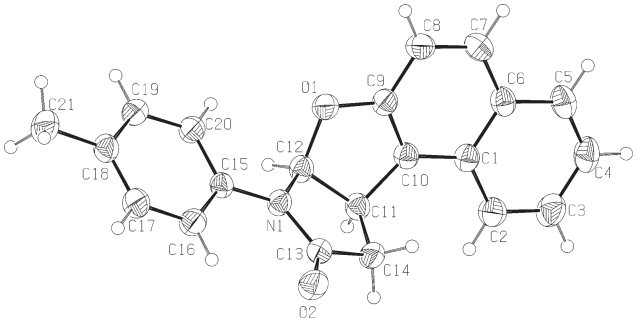
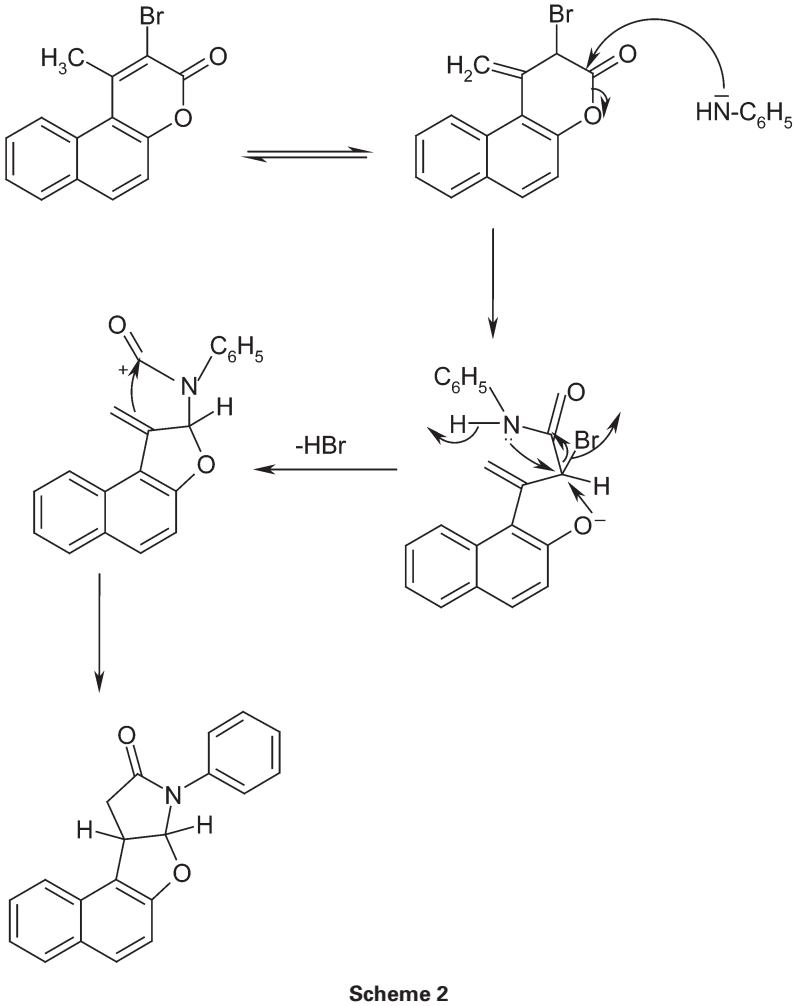


Fig. 1 ORTEP diagram of 8-*p*-tolyl-7a,8,10,10a-tetrahydro-7-oxa-8-aza-pentaleno[1,2-a] naphthalen-9-one (**3a**).

The formation of **3a–d** can be explained by lactone ring opening due to the attack of the base on the lactone carbonyl (more electron deficient due to bromine at second position) and then simultaneous attack by the lone pair of the oxygen, migration of the carbonyl carbon and then cyclisation. (Scheme 2) When we carried out the reaction in absolute ethanol, the starting material 2-bromo-1-methylbenzo[f]-chromen-3-one **2** was recovered. So the use of DMF as a solvent supports this mechanism which stabilises the intermediate.

When we condensed different cyclic secondary amines such as morpholine and piperidine with **2**, it gave only one product **4** which showed a ^1H NMR pattern almost the same as those of **3a–d.** Moreover the IR spectrum showed a carbonyl stretching frequency at 1774 $cm.^{-1}$ The Lassaigne's test and elemental analysis of product **4** indicated absence of nitrogen. The mass spectrum also indicated the absence of nitrogen (even at a molecular weight of M^+ 226). The ^1H NMR spectrum indicated the same ring pattern as in **3**. Since nitrogen is absent in the sample it indicated formation of a five membered lactone ring which is supported by the IR stretching frequency at 1774 $cm.^{-1}$ Finally the single crystal analysis indicated formation of 10,10a-dihydro-7aH-7,8-dioxa-pentaleno[1,2-a] naphthalene-9-one **4** (Fig. 2).

Here single crystal analysis of **4** clearly indicated a tetracyclic structure in which three rings are in one plane and the fourth lactone ring is out of plane. The furan ring and the oxalactone rings are *cis* fused and the angle between these two rings is 107.3. The CCDC no. for **4** is CCDC 766459. Mashelkar[14] reported formation of this product by oxidation of benzocoumarin-4-aceticacid with selenium dioxide and



Scheme 2

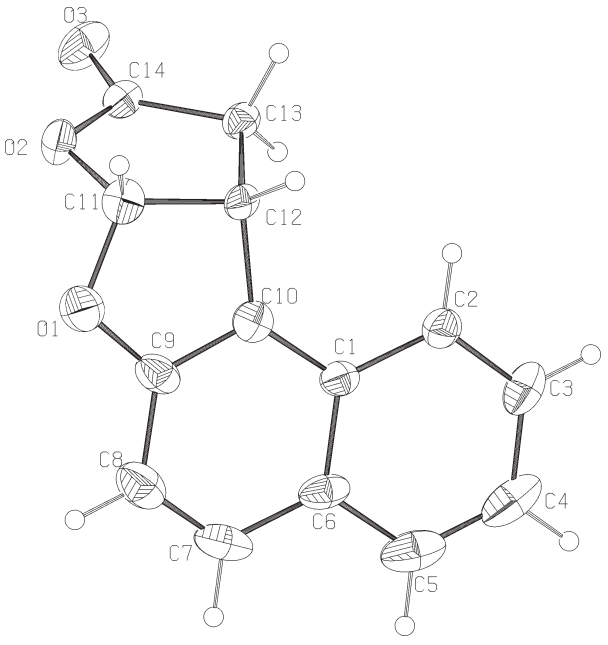


Fig. 2 ORTEP diagram of 10,10a-dihydro-7aH-7,8-dioxa-pentaleno[1,2-a]naphthalen-9-one (**4**).

further reactions but they have not supported their structure by single crystal analysis.

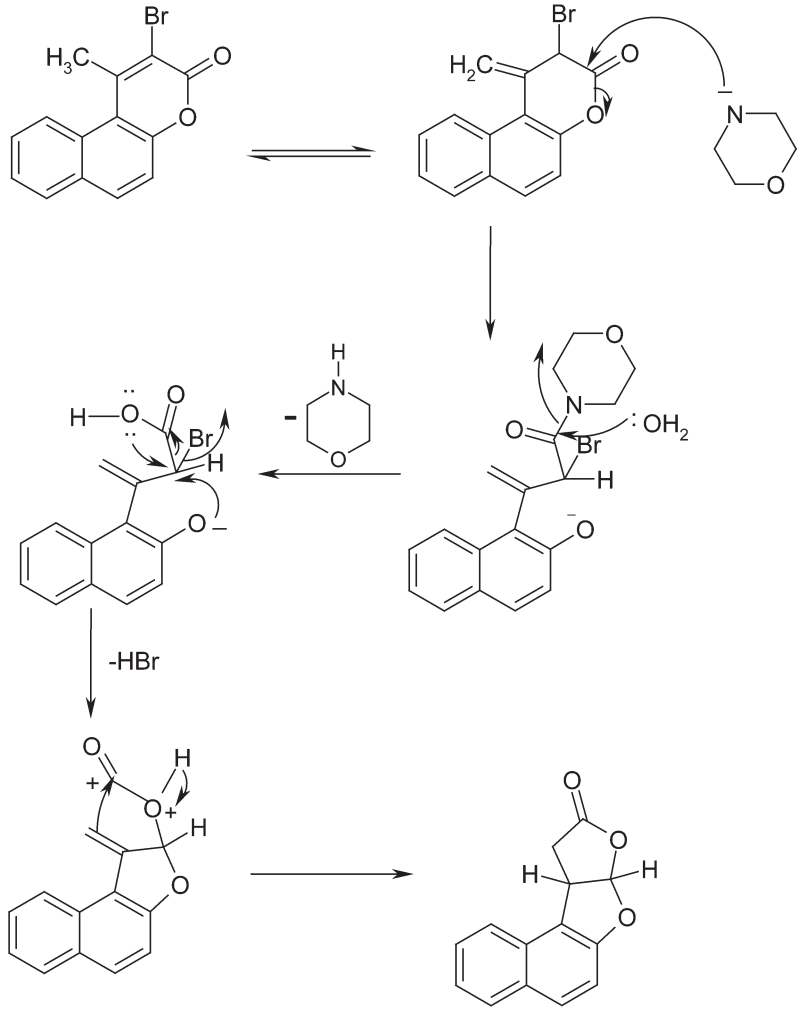
The formation **4** can be explained by the mechanism shown in Scheme-3. Thus we have observed formation of a tetracyclic ring during condensation of 2-bromo-1-methylbenzo[f] chromen-3-one with primary aromatic amines and secondary cyclic amines.

Experimental

The melting points were determined in scientific open capillaries and are uncorrected. The IR spectra were determined as KBr pellets on a Shimadzu model IR-408 spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded using Bruker DRX 400 MHz in $CDCl_3$ or DMSO-d_6 with tetramethylsilane as internal standard. Mass spectra were recorded on a GC-MS spectrometer. Elemental analyses were performed on Carlo Erba-1108 elemental analyser. Acme's Silica gel (mesh size 60–120) was used for column chromatography. The single crystal X-ray analysis was done by using Bruker Smart Apex CCD diffractometer and the programme used to resolve the structure was SHELXS-97.

1-Methylbenzo[f]chromen-3-one (**1**): β-Naphthol (10 g, 0.0694 mol), ethyl acetoacetate (9.027 mL, 0.0694mol) and H_2SO_4 (20 mL) were mixed thoroughly in 100 mL beaker and kept overnight. The reaction mixture was poured into crushed ice (100 mL) with constant stirring. The crude product was filtered and recrystallised from ethanol as yellow crystals. M.p. 178–180°C. (Lit.[10] 182–183°C). Yield 7.85 g (53.8%) IR (cm^{-1}): 3079, 1713(>C=O), 1515. ^{1}H NMR δ: 2.96 (s, 3H, CH_3), 6.39 (s, 1H, H_2), 7.47–7.49 (d, 1H, H_6), 7.54–7.58 (m, 1H, H_8), 7.63–7.67 (m, 1H, H_9), 7.92–7.94 (d, 1H, H_7), 7.97–7.99 (d, 1H, H_5), 8.60–8.62 (d, 1H, H_{10}). Anal. Calcd for $C_{14}H_{10}O_2$: C, 80.00; H, 4.76. Found: C, 80.12; H, 4.54%.

2-Bromo-1-methylbenzo[f]chromen-3-one (**2**): 1-Methylbenzo[f] chromen-3-one (2 g, 0.0095 mol), N-bromosuccinimide (1.7 g, 0.0095 mol) and benzoyl peroxide (10mg) were taken in a 100 mL round bottom flask and dissolved in chloroform (25 mL) and placed in a photo reactor under reflux condition for 10h. The excess solvent was



Scheme 3

Table 1 Crystal data and structure refinement parameters for compound **3a** and **4**

	3a	4
Chemical formula	$C_{21}H_{17}NO_2$	$C_{14}H_{10}O_3$
Molecular weight	315.36	226.22
Crystal system	Monoclinic	Triclinic
Space group	P21/c	P-1
a (Å)	9.1559(13)	6.367(4)
b (Å)	12.5816(17)	9.908(6)
c (Å)	13.3441(18)	17.243(11)
α (°)	90	99.281(10)
β (°)	90.621(2)	93.737(9)
γ (°)	90	90.477(10)
V(Å^3)	1537.1(4)	1071.0(12)
Z	4	4
ρ(g cm^{-3})	1.363	1.403
Φ	2.22–28.29	2.08–23.00
h	–11–12	–6–6
k	–16–15	–10–10
l	–14–17	–18–18
Total reflections	9000	5726
independent reflections	3560	2857
Used no. of reflections	3028	2518
R[a]	0.0546	0.0692
Absorption coefficient (m Å^{-1})	0.088	**0.099**
R_{int}	0.0195	0.0429
Peak and hole	0.235 and –0.303 Å Å^3	0.832 and –0.535 Å Å^3

distilled off, crude product was filtered, washed with methanol, and recrystallised from toluene to give pure red coloured crystals. M.p. 143–145°C. (Lit.[10] M.p. 148°C, lit.[11] 145°C) Yield 2.24 g (81.7%) IR(cm^{-1}): 3081, 1721(>C=O), 1617,1529, 1373. ^{1}H NMR δ: 3.05 (s, 3H, –CH_3), 7.43–7.45 (d, 1H, H_6, *J* = 8.9 Hz), 7.56–7.59 (m, 1H, H_8), 7.65–7.68 (m, 1H, H_9), 7.92–7.94 (d, 1H, H_7, *J* = 8.0Hz), 7.98–8.01 (d, 1H, H_5, *J* = 8.0Hz), 8.44–8.46 (d, 1H, H_{10}, *J* = 8.7Hz). Mass: M+2: M+ (1:1) 291, 289(b), 262, 260, 211, 210, 180, 153, 152, 40, 39. Anal. Calcd for $C_{14}H_9O_2Br$: C, 58.23; H, 3.11. Found: C, 58.05; H, 3.41%.

*Preparation of azanaphthalen-9-ones (***3a–d***); general procedure*

2-Bromo-1-methylbenzo[f]chromen-3-one (2) (2.885 g, 0.01 mol), different aromatic amines (0.021 mol) and DMF (20 mL) were mixed in a 50 mL round bottom flask and refluxed for 6 h. The reaction mixture was cooled, poured into crushed ice (50 mL) and filtered. The crude product was purified by column chromatography using petroleum ether: ethyl acetate (9:1) as eluent.

8-p-Tolyl-7a,8,10,10a-tetrahydro-7-oxa-8-aza-pentaleno[1,2-a]naphthalen-9-one (**3a**): M.p. 169–171°C. Yield 1.64 g (52.0%) IR (cm^{-1}): 3054, 1715 (>C=O), 1628, 1599, 1515, 1465, 1344. ^{1}H NMR: δ 2.38 (s, 3H, CH_3), 2.90–2.96 (dd, 1H, H at –CH2, J_1 = 3.7, J_2 = 3.6Hz), 3.26–3.33 (dd, 1H, H at –CH2, J_1 = 3.6, J_2 = 3.7 Hz), 4.49–4.55 (m, 1H, H at ring junction), 6.61–6.63 (d, 1H, H at ring junction, *J* = 7.7Hz), 7.13–7.15 (d, 1H, H_5, *J* = 8.8Hz), 7.25–7.27 (m, 2H, $H_{3'}$, $H_{4'}$), 7.36–7.40 (m, 1H, H_3), 7.52–7.61 (m, 4H, $H_{1'}$, $H_{2'}$, H_2, H_4), 7.76–7.78 (d, 1H, H_6, *J* = 8.8Hz), 7.85–7.87 (d, 1H, H_1, *J* = 8.0Hz). ^{13}C NMR: δ 21.7, 37.5, 38.4, 98.3, 112.9, 120.6, 122.5, 124.1, 124.3, 128.1, 129.9, 130.4, 130.6, 131.2, 135.2, 137.1, 155.8, 173.6. Anal. Calcd for $C_{21}H_{17}NO_2$: C, 80.00; H, 5.39; N, 4.44. Found: C, 79.82; H, 5.43; N, 4.32%.

8-Phenyl-7a,8,10,10a-tetrahydro-7-oxa-8-aza-pentaleno[1,2-a]naphthalen-9-one (**3b**): M.p. 90–93°C. Yield 1.43 g (47.5%) IR (cm^{-1}): 3054, 1715 (>C=O), 1628, 1596, 1521, 1467. ^{1}H NMR: δ 2.92–2.97 (dd, 1H, H at –CH2, *J* = 3.7Hz), 3.28–3.35 (dd, 1H, H at –CH2, *J* = 3.8), 4.50–4.56 (m, 1H, H at ring junction, J_1 = 3.8, J_2 = 7.9), 6.66–6.68 (d, 1H, H at ring junction, *J* = 7.7Hz), 7.13–7.15 (d, 1H, H_5, *J* = 8.8Hz), 7.26–7.62 (m, 6H, H_2, H_3, H_4, $H_{2'}$, $H_{3'}$, $H_{4'}$), 7.71–7.73 (d, 2H, $H_{1'}$, H_5, *J* = 8.8Hz), 7.61–7.78 (d, 1H, H_6, *J* = 8.8Hz), 7.85–7.87 (d, 1H, H_1, *J* = 8.8Hz). Mass: (M+1) 302, (M+) 301, 181, 104, 88, 77, 41, 30. Anal. Calcd for $C_{20}H_{15}NO_2$: C, 79.73; H, 4.98; N, 4.80. Found: C, 79.91; H, 4.81; N, 4.65%.

8-p-Nitrophenyl-7a,8,10,10a-tetrahydro-7-oxa-8-aza-pentaleno [1,2-a]naphthalen-9-one (**3c**): M.p. 258–260°C. Yield 1.34 g (38.7%) IR (cm^{-1}): 3050, 1722 (>C=O), 1630, 1594, 1507, 1464. ^{1}H NMR: δ 2.95–3.02 (dd, 1H, H at –CH2, *J* = 3.4Hz), 3.38–3.45 (dd, 1H, H at –CH2, *J* = 10.2Hz), 4.62–4.67 (m, 1H, H at ring junction, J_1 = 3.5, J_2 = 10.4Hz), 6.86–6.88 (d, 1H, H at ring junction), 7.13–7.15 (d, 1H, H_5, *J* = 8.8Hz), 7.39–7.66 (m, 3H, H_2, H_3, H_4), 7.79–7.81 (d, 1H, H_6, *J* = 8.8Hz), 7.87–7.89 (d, 1H, H_1, *J* = 8.3Hz), 8.12–8.14 (d, 2H, $H_{1'}$, $H_{2'}$, *J* = 9.2Hz), 8.30–8.32 (d, 2H, $H_{4'}$, $H_{5'}$, *J* = 9.4Hz). Anal. Calcd for $C_{20}H_{14}N2O_4$: C, 69.36; H, 4.04; N, 8.09. Found: C, 69.12; H, 4.33; N, 7.88%.

8-o-Hydroxyphenyl-7a,8,10,10a-tetrahydro-7-oxa-8-aza-pentaleno [1,2-a]naphthalen-9-one (**3d**): M.p. 277–280°C. 1.81 g (57.1%) IR (cm^{-1}): 3422–2832 (OH), 3058, 1668 (>C=O), 1632, 1591, 1517, 1463. ^{1}H NMR: δ 2.83–2.87 (dd, 1H, H at –CH2), 3.26–3.33 (dd, 1H, H at –CH2), 4.57–4.61 (m, 1H, H at ring junction), 6.65–6.66 (d, 1H, H at ring junction), 6.88–7.66 (m, 8H, all aromatic protons, H_2, H_3, H_4, H_5, $H_{2'}$, $H_{3'}$, $H_{4'}$, $H_{5'}$), 7.76–7.78 (d, 1H, H_6, *J* = 8.8Hz), 7.86–7.87 (d, 1H, H_1, *J* = 8.2Hz), 9.14 (s, 1H, –OH). Mass (*m/z*) M$^+$:- 317(b), 209, 181, 170, 120, 65. Anal. Calcd for $C_{20}H_{15}NO_3$: C, 75.71; H, 4.73; N, 4.41. Found: C, 75.43; H, 4.93; N, 4.72%.

10,10a-Dihydro-7aH-7,8-dioxa-pentaleno[1,2-a]naphthalen-9-one (**4**): 2-Bromo-1-methylbenzo[f]chromen-3-one(**2**) (2.885 g, 0.01 mol), different secondary amines (0.021 mol) and DMF (20 mL) were mixed in a 50 mL round bottom flask and refluxed for 6h. The reaction mixture was cooled, poured into crushed ice (50 mL) and filtered. The crude product was purified by column chromatography using petroleum ether: ethyl acetate (9:1) as eluent. M.p. 96–98°C. Yield 1.14 g (50.4%) IR(cm^{-1}): 3050,1774(>C=O), 1631,1578,1520,1464. ^{1}H NMR: δ 2.91–2.98 (dd, 1H, H at –CH2, *J* = 6.5Hz), 3.27–3.34 (dd, 1H, H at –CH2, *J* = 9.9Hz), 4.59–4.64(m, 1H, H at ring junction, J_1 = 6.5, J_2 = 9.2Hz), 6.75–6.77 (d, 1H, H at ring junction, *J* = 6.5Hz), 7.20–7.22 (d, 1H, H_5, *J* = 8.8Hz), 7.40–7.61 (m, 3H, H_2, H_3, H_4), 7.81–7.84 (d, 1H, H_6, *J* = 8.8Hz), 7.88–7.90 (d, 1H, H_1, *J* = 8.3Hz). ^{13}C NMR: δ 33.9, 42.4, 108.9, 112.8, 118.8, 122.2, 124.7, 128.4, 130.0, 130.1, 131.0, 131.8, 155.4, 174.6. Mass (*m/z*): (M+) 226(b), 197, 181, 169, 153, 141, 115, 89, 63. Anal. Calcd for $C_{14}H_{10}O_3$: C, 74.33; H, 4.42. Found: C, 74.11; H, 4.68%.

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