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Synthesis of 4-hydroxyindole fused isocoumarin derivatives and their fluorescence “Turn-off” sensing of Cu(II) and Fe(III) ions

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Abstract: A simple and efficient protocol has been developed for the synthesis of 4-hydroxyindole fused isocoumarins from easily available starting materials. Dihydroxy-
indenoindoles, the cyclic hemiaminals of the condensation products of ninhydrin and enamines of 1,3-cyclohexanedione, produced indole fused isocoumarins 11-(aryl/alkyl)-8,9,10,11-tetrahydro-6-oxa-11-aza-benzo[a]fluorene-5,7-diones through an acid catalyzed intramolecular rearrangement. The above isocoumarin derivatives furnished novel 4-hydroxyindole fused isocoumarins 11-(aryl or alkyl)-7-hydroxy-11H-6-oxa-11-aza-benzo[a]fluoren-5-ones through dehydrogenation with Pd/C. The synthesized 4-hydroxyindole fused isocoumarins show fluorescence property with good quantum yields and fluorescence "Turn-off" sensing of Cu$^{2+}$ and Fe$^{3+}$ ions. Importantly these molecules are found to be chemosensor only for Cu$^{2+}$ ion with respect to UV-Vis spectral change and naked eye colour change in presence and absence of UV radiation.

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Introduction

α-Pyranone (2H-pyran-2-one), a six-membered oxygen heterocycle, represents an important class of naturally occurring unsaturated lactones. Its benzo derivatives e.g. isocoumarins are found in many natural products and bioactive synthetic compounds.$^{1,2}$ This imperative class of naturally occurring lactones have attracted significance attention of chemists due to their varied biological activities.$^{3-8}$ Tricyclic isocoumarins A (Fig. 1) isolated from Microdochiumbolleyi have shown good antifungal, antibacterial and antialgal activities.$^9$ (-)-Cephalosol B is a potent naturally occurring antimicrobial metabolite (Fig. 1).$^{10}$ Polyheterocycles like isocoumarin C and isoquinolinone D framework also represent some privileged structures for the development of natural product-inspired compounds of potential biological interest (Fig. 1).$^{11,12}$ So development of new and efficient methodology for the synthesis of isocoumarins and their carbo/hetero annulated analogues have attracted great
attention of the synthetic as well as medicinal chemists. Various methodologies for the syntheses of isocoumarins have been reported such as the reaction of \( o \)-halobenzoic acids and 1,3-diketones via copper-catalyzed tandem sequential cyclization/addition/deacylation process,\(^{14}\) iridium-catalyzed oxidative lactonization or intramolecular cyclization reaction of \( \delta \)-ketoaldehydes,\(^{15}\) ruthenium-catalyzed aerobic oxidative cyclization of aromatic acids with alkynes,\(^{16}\) \( \text{FeCl}_3 \)-promoted regioselective annulation of \( o \)-(1-alkynyl)benzoates with disulfides,\(^{17}\) Heck-Matsuda cyclization reaction,\(^{18}\) 6-endo-dig cyclization of hetero arylesters to alkynes\(^{19}\) and Pd(II)-mediated cyclization.\(^{20}\)

Fig. 1 Some biologically active compounds and natural products containing an isocoumarin analogue.

In the present paper, we wish to report the synthesis of a new class of 4-hydroxyindole fused isocoumarins. These compounds also show diverse kinds of photophysical properties such as fluorescence “Turn-off” sensing of Cu(II) and Fe(III) ions, chemosensing of Cu\(^{2+}\) ion and differential fluorescence quantum yields and lifetimes depending upon the solvent polarity.
Copper is an essential trace element in the human body which plays a critical role in many biological processes and is also required by the human nervous system. However, the high levels of copper ion in living cell leads to neurodegenerative diseases. Thus, the sensing and recognition of divalent copper ion has attracted considerable attention in recent years and there is a need for development of new fluorescent sensors for detection of copper. To the best of our knowledge suitable isocoumarin based molecules have not been discovered to date for this purpose. In continuation of our research interest in the synthesis of various heterocyclic compounds from ninhydrin, we wish to report herein a novel class of potentially bioactive and fluorescence active 4-hydroxyindole fused isocoumarin systems.

Results and discussion

Recently a multicomponent reaction of N-heteroannulations involving enaminones, ninhydrin and acid anhydride or aromatic amines has been reported to produce fused pyrazole derivatives. In this reaction the acyclic hemiaminals of C-2 alkylated 1,3-indanediones (1) have been proposed to be an important intermediate (Scheme 1). We became interested to examine whether the above reaction would be fruitful starting from the proposed hemiaminals intermediate 1. Therefore initially a series of enamines of 1,3-cyclohexanedione and dimedone were reacted with ninhydrin in chloroform to isolate cyclic hemiaminals 1 according to the literature procedure. Subsequently the intermediate 5-benzyl-4b,9b-dihydroxy-4b,5,6,7,8,9b-hexahydroindeno[1,2-b]indole-9,10-dione 1a (R1=CH2Ph, R2=H) was heated in acetic anhydride or various acidic media like p-TSA, acetic acid, lactic acid, formic acid and citric acid under conventional refluxing as well as microwave irradiation. The reaction scarcely proceeded to give any fused pyrazole derivatives or any other products in these conditions even after prolong
refluxing (Table 1, entries 1-6). But when the same reaction was carried out in 8-11N aqueous H$_2$SO$_4$ solution at reflux, a white product was precipitated out from the reaction mixture in low yield after 10 hr. (Scheme 1, Table 1, entries 7-11). The NMR studies confirmed that the product was not the expected multifunctionalized tetracyclic indeno[1,2-$b$]indole derivatives$^{25}$ but a new rearranged product. Eventually, the structure elucidation of the product by single crystal X-ray diffraction study established that a novel indole fused isocoumarin $2a$ ($R_1^1$=CH$_2$Ph, $R_2^2$=H) has been formed (Fig. 2). The crystal structure of NaBH$_4$ reduced product of $2a$ was also determined (Fig. S12, See Supplementary Information). This significant result motivated us to carry out the above reaction at higher acidic condition to achieve better yields. Interestingly, when the acid strength of the reaction medium was increased to about 18N aqueous H$_2$SO$_4$, the yield of the product $2a$ was enhanced considerably (Table 1, entries 12, 13). Further the yield of the reaction was improved significantly when melamine sulfonic acid (Table 1, entry 14) and PEG-OSO$_3$H (Table 1, entry 15) were employed in water under reflux. After performing a series of experiments, we observed that the yield of the product $2a$ can reach maximum upto 87% without producing any by-product if the reaction was carried out in acetic acid at reflux for 15 min in presence of concentrated H$_2$SO$_4$ (Table 1, entry 16).

Having prepared $2a$ successfully, we decided to explore the scope and generality of the reaction in the synthesis of other analogues. Accordingly, a variety of cyclic hemiaminals $1$ derived from enamines of commercially available primary amines and 1,3-cyclohexanedione or dimidone were reacted under the optimized conditions (Table 1, Entry 16). As evident from Table 2, all the hemiaminals $1$ reacted well in the reaction affording the desired products $2a$-$k$ and $3a$-$k$ in good yields. All the structures of the products were determined by detailed study of the spectroscopic data.
Scheme 1 Synthesis of indole fused isocoumarin derivatives.

Table 1 Optimization of reaction conditions for the synthesis of 2a from 1a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent (10 ml)</th>
<th>Acid</th>
<th>Time (hr)</th>
<th>Yield (%)</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>Acetic acid</td>
<td>_</td>
<td>10</td>
<td>_</td>
</tr>
<tr>
<td>2</td>
<td>H₂O</td>
<td>p-TSA</td>
<td>10</td>
<td>trace</td>
</tr>
<tr>
<td>3</td>
<td>H₂O</td>
<td>Acetic acid</td>
<td>10</td>
<td>_</td>
</tr>
<tr>
<td>4</td>
<td>H₂O</td>
<td>Lactic acid</td>
<td>10</td>
<td>_</td>
</tr>
<tr>
<td>5</td>
<td>H₂O</td>
<td>Formic acid</td>
<td>10</td>
<td>_</td>
</tr>
<tr>
<td>6</td>
<td>H₂O</td>
<td>Citric acid</td>
<td>10</td>
<td>_</td>
</tr>
<tr>
<td>7</td>
<td>H₂O</td>
<td>6.5(N) H₂SO₄</td>
<td>10</td>
<td>trace</td>
</tr>
<tr>
<td>8</td>
<td>H₂O</td>
<td>8.3(N) H₂SO₄</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>9</td>
<td>H₂O</td>
<td>9.3(N) H₂SO₄</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td>10</td>
<td>H₂O</td>
<td>10.3(N) H₂SO₄</td>
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<tr>
<td>11</td>
<td>H₂O</td>
<td>11.2(N) H₂SO₄</td>
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<td>24</td>
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<tr>
<td>12</td>
<td>H₂O</td>
<td>12.0(N) H₂SO₄</td>
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<td>26</td>
</tr>
<tr>
<td>13</td>
<td>H₂O</td>
<td>13.5(N) H₂SO₄</td>
<td>10</td>
<td>26</td>
</tr>
<tr>
<td>14</td>
<td>H₂O</td>
<td>20 mol % Melamine sulfonic acid (MSA)</td>
<td>5</td>
<td>40</td>
</tr>
<tr>
<td>15</td>
<td>H₂O</td>
<td>PEG₆₀₀₀-OH₃ (20 mol %)</td>
<td>4</td>
<td>50</td>
</tr>
<tr>
<td>16</td>
<td>Acetic acid</td>
<td>H₂SO₄ (0.5 mL)</td>
<td>0.25</td>
<td>87</td>
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</tbody>
</table>

![Chemical structure diagram](image-url)
Fig. 2 ORTEP diagram of X-ray crystal structure of isocoumarin 2a with atom numbering scheme (CCDC number 940456).

Table 2 Scope of isocoumarins synthesis using different amines and 1,3-cyclohexanones

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>Product</th>
<th>Time(min)</th>
<th>Yield(%)</th>
<th>Melting Point (ºC)</th>
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<tbody>
<tr>
<td>1</td>
<td></td>
<td>H</td>
<td>2a</td>
<td>15</td>
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<tr>
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<td>,,</td>
<td>2b</td>
<td>15</td>
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<td>295-297</td>
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<td>2c</td>
<td>20</td>
<td>83</td>
<td>298-300</td>
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<td>2d</td>
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<td>87</td>
<td>294-296</td>
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<td>80</td>
<td>292-294</td>
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<tr>
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<td></td>
<td>,,</td>
<td>2f</td>
<td>25</td>
<td>85</td>
<td>256-258</td>
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<tr>
<td>7</td>
<td></td>
<td>,,</td>
<td>2g</td>
<td>18</td>
<td>85</td>
<td>255-257</td>
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<tr>
<td>8</td>
<td></td>
<td>,,</td>
<td>2h</td>
<td>25</td>
<td>81</td>
<td>&gt;300</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>,,</td>
<td>2i</td>
<td>35</td>
<td>82</td>
<td>300-302</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>,,</td>
<td>2j</td>
<td>40</td>
<td>80</td>
<td>&gt;300</td>
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<tr>
<td>11</td>
<td></td>
<td>,,</td>
<td>2k</td>
<td>20</td>
<td>86</td>
<td>216-218</td>
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<tr>
<td>12</td>
<td>Me</td>
<td></td>
<td>3a</td>
<td>30</td>
<td>90</td>
<td>252-254</td>
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<tr>
<td>13</td>
<td></td>
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<td>294-296</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td>,,</td>
<td>3c</td>
<td>32</td>
<td>83</td>
<td>280-282</td>
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</table>
Formation of isocoumarin ring in products 2 or 3 from adducts 1 can be explained on the basis of the proposed mechanism depicted in Scheme 2. In strong acidic condition, protonation of the carbonyl oxygen in dihydroxy-indenopyrrole 1 generates the oxonium ion 5. Then hydroxyl group of 5 attacks the adjacent carbonyl carbon to generate a hydroxy epoxide intermediate 6 which is subsequently converted to intermediate 7 through protonation of the hydroxyl group. The intermediate 7 then loses water molecule to generate cationic intermediate 8 which provokes the ring expansion through the breaking of the central C-C bond affording an eight-membered lactum intermediate 2 with isocoumarin skeleton. It was not possible to isolate any of the intermediates 5-8 under the reaction conditions (Scheme 2).
Scheme 2 Plausible mechanism for the formation of isocoumarin derivatives 2 or 3.

Finally dehydrogenation of 2 with 10% Pd/C (10 mol % of Pd(0)) in the diphenyl ether at reflux produced 4-hydroxyindole fused isocoumarins 11-(aryl/alkyl)-7-hydroxy-11H-6-oxa-11-aza-benzo[a]fluoren-5-one 9a-f in good yields (Scheme 3, Table 3). All the structures of the aromatized products were determined by detailed analysis of the spectroscopic data. Furthermore, the formation of product 9c was unambiguously confirmed through X-ray crystallographic analysis (Fig. 3). Since palladium is electropositive, the high activity of the catalyst also led to dehalogenation reactions. In order to stop the dehalogenation, the reaction was carried out for shorter period of time at low temperature, but the reaction did not produce any satisfactory result. A plausible mechanism of dehalogenation is outlined in Scheme 4. When palladium (0) reacted with compound 2, dehydrogenation took place to produce 9 and palladium dihydride (“PdH$_2$”). This palladium dihydride (“PdH$_2$”) species might be responsible for dehalogenation reaction (Scheme 4). It should be noted that defluorination did not take place because of high carbon-fluorine (C-F) bond energy. Compounds 3, derived from dimidone, did
not aromatize in presence of 10% Pd/C due to the presence of two methyl groups at the same carbon atom of the cyclohexane ring.

\[
\begin{align*}
\text{No reaction} & \quad \text{10 mol % Pd/C} \\
& \quad \text{PhOPh} \\
& \quad \text{Reflux} \\
& \quad 1 \text{ hr.}
\end{align*}
\]

Here \( R^2 = \text{Me} \)

\[
\begin{align*}
\text{2 and 3} & \quad \text{10 mol % Pd/C} \\
& \quad \text{PhOPh} \\
& \quad \text{Reflux} \\
& \quad 1 \text{ hr.}
\end{align*}
\]

Here \( R^2 = \text{H} \)

6 examples

**Scheme 3** Synthesis of hydroxyindole fused isocoumarins 9.

**Fig. 3** ORTEP diagram of X-ray crystal structure of hydroxyindole fused isocoumarin 9c with atom numbering scheme (CCDC number 940458).
Table 3 Dehydrogenation using Pd/C to furnish hydroxylindole fused isocoumarin 9

| Entry | Isocoumarin (2) | Products (9) | Yield (%)
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>9a</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>9b</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>2c</td>
<td>9c</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>2d</td>
<td>9d</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>2e</td>
<td>9a</td>
<td>73</td>
</tr>
<tr>
<td>6</td>
<td>2f</td>
<td>9a</td>
<td>75</td>
</tr>
<tr>
<td>7</td>
<td>2g</td>
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<td>8</td>
<td>2h</td>
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<td>80</td>
</tr>
<tr>
<td>9</td>
<td>2i</td>
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<td>80</td>
</tr>
<tr>
<td>10</td>
<td>2j</td>
<td>9f</td>
<td>81</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Entry</th>
<th>Isocoumarin (2)</th>
<th>Products (9)</th>
<th>Yield (%)</th>
<th>Melting Point (°C)</th>
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<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>9a</td>
<td>79</td>
<td>260-262</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>9b</td>
<td>82</td>
<td>264-266</td>
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<tr>
<td>3</td>
<td>2c</td>
<td>9c</td>
<td>81</td>
<td>280-282</td>
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<tr>
<td>4</td>
<td>2d</td>
<td>9d</td>
<td>82</td>
<td>278-280</td>
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<td>2e</td>
<td>9a</td>
<td>73</td>
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<td>260-262</td>
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<td>9a</td>
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<td>10</td>
<td>2j</td>
<td>9f</td>
<td>81</td>
<td>282-284</td>
</tr>
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</table>

$^a$Isolated yield

Scheme 4 The dehalogenation reactions in presence of Pd(0).
Steady state absorption and emission spectra of all the purified compounds 9a-f have been performed in solvents of different polarity. Probe concentration was maintained at 5x10^{-5} M. UV-vis absorption spectrum shows structured band with peaks around 380 nm, 339 nm and 311 nm. The emission spectrum shows a structure less band with maximum around 502 nm. The shape and band position of the emission spectra are same regardless of excitation wavelength. Noticeably the molecule displays large Stokes shifted emission of more than ~100 nm which indicates that the structure of the emitting species and the ground state species are considerably different. The emission maxima for all compounds have been found to shift to longer wavelength with increasing solvent polarity and hydrogen bonding ability (Fig. 4). The most bathochromic emission was found in methanol as solvents. This shifting of emission maxima in protic solvent clearly indicates more stabilization of the emissive species through intermolecular solute solvent intermolecular hydrogen bonding interaction. Concurrently, the measured fluorescence quantum yields (Φ_F) are found to decrease with increasing hydrogen bonding ability of the solvent (see Supporting Information Table S1). The high Φ_F values were observed in aprotic solvent, and the lowest were measured in protic polar methanol. The substantial fluorescence quenching of the compounds 9 in protic solvent methanol compared to that of in CH_3CN and DCM might be due to activation of some non-radiative decay channels of molecules 9 through intermolecular hydrogen bonding with the protic solvents.
Fig. 4 (a) UV-vis absorption spectra and (b) Fluorescence emission spectra ($\lambda_{ex}=\text{nm}$) of representative compound $9d$ in different solvents ($[9d]=\sim5\times10^{-5}\text{ M}$).

Ground state geometry of $9d$ has been optimized at B3LYP/6-31+G(d,p) level of theory in methanol solvent. The result shows that the 4-hydroxyindole fused isocoumarin moiety is planar in structure while the phenyl ring at N is perpendicular to the plane of the fused moiety. Further the UV-vis absorption and emission spectra of $9d$ have been simulated theoretically in methanol solvent. The calculated excited state energies match well with the experimental values of absorption band positions (Table 4, Supporting information Fig. S16).

Table 4 Excitation energies and oscillator strength calculated at B3LYP/6-31+G(d,p) level of theory in methanol solvent

<table>
<thead>
<tr>
<th>Excitation energy</th>
<th>Oscillator strength</th>
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<tr>
<td>390.74 nm</td>
<td>0.1734</td>
</tr>
<tr>
<td>339.00 nm</td>
<td>0.2633</td>
</tr>
<tr>
<td>317.43 nm</td>
<td>0.1345</td>
</tr>
<tr>
<td>310.70 nm</td>
<td>0.0149</td>
</tr>
<tr>
<td>306.43 nm</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

Photophysical properties of the ligand $9d$, in particular, have been performed in detail in presence of metal ions $\text{Ni}^{2+}$, $\text{Co}^{2+}$, $\text{Zn}^{2+}$, $\text{Cu}^{2+}$, $\text{Fe}^{3+}$, $\text{Cd}^{2+}$, $\text{Hg}^{2+}$ and $\text{Ca}^{2+}$. Complexation of the
ligand 9d with Cu$^{2+}$ and Fe$^{3+}$ ions was accompanied by the change of the colour of the solution from colourless to pink, which was easily observed by the naked-eye (Fig. 5a). This response was selective to Cu$^{2+}$ and Fe$^{3+}$ ions in solution, the colour being more intense in Cu$^{2+}$ than in Fe$^{3+}$. The addition of 10 equiv. of the other cations as their perchlorate salts resulted in no appreciable changes in colour under visible as well as UV-light (Fig. 5b). Interestingly, the molecule 9d in presence of Cu$^{2+}$ ion shows purple colour with UV radiation, but is found to be unchanged with all other metal ion including Fe$^{2+}$ (Fig. 5b).

![Fig. 5](image_url)

**Fig. 5** Change in color of solution of 9d in acetonitrile in presence of 10 equivalent of each metal ion (a) under visible light (b) under UV light.

UV-Vis spectra of the ligand 9d solution in acetonitrile show no significant change on increasing concentration of metal perchlorate salts of Ni$^{2+}$, Co$^{2+}$, Zn$^{2+}$, Fe$^{3+}$, Cd$^{2+}$, Hg$^{2+}$ and Ca$^{2+}$ (Supporting information Fig. S11(a)-(d)). However in presence of Cu$^{2+}$ the UV-Vis spectrum of 9d shows appreciable change compared to that in case of free ligand hence indicating ligand-
metal interaction. On gradual addition of Cu$^{2+}$ salt an absorption band develops near 500 nm with simultaneous appearance of two isobestic points at 308 nm and 419 nm (Fig. 6). The emission spectra of ligand 9d in acetonitrile shows no change in fluorescence intensity in presence of metal ions Ni$^{2+}$, Co$^{2+}$, Zn$^{2+}$, Cd$^{2+}$, Hg$^{2+}$ and Ca$^{2+}$. On the other hand fluorometric titration in presence of Fe$^{3+}$ and Cu$^{2+}$ shows substantial quenching of ligand emission. The extent of fluorescence quenching in Cu$^{2+}$ is significantly higher compared to that in case of Fe$^{3+}$ (Fig. 7). Detection limit of Cu$^{2+}$ by probe 9d has been estimated from fluorescence titration and has been found to be 7.07 x 10$^{-6}$ M (Supporting information Fig. S15). Selective complexation of an analyte coupled with the fluorescence properties of a bound chromophore resulted in the development of promising molecular fluorescent probes. Fe$^{3+}$ and Cu$^{2+}$ orientated probes have been developed widely with the use of highly selective copper and iron-chelating molecules such as naturally occurring fluorescent siderophores or synthetic siderophore analogs connected suitably to a light-emitting group. It is well known that d-block ions such as Fe$^{3+}$ or Cu$^{2+}$ often open excited state deexcitation pathways via electronic energy transfer (EET) and/or photoinduced electron transfer (PET) involving the metal centre. It is not surprising, therefore, that there are many more examples of “Turn-off” sensors than “Turn-on”. In the present case, quenching of fluorescence of the synthetic molecules 9 thus can be treated as fluorescence “Turn-off” sensor selective for Fe$^{3+}$ or Cu$^{2+}$ ions.
Fig. 6 Absorption spectra of 9d ([9d] = 5x 10^{-5} M) on increasing concentration of Cu^{2+} ions.
Fig. 7 (a) Emission spectra ($\lambda_{ex} = \text{nm}$) of 9d in acetonitrile in presence of various metal ions. Fluorescence quenching of 9d on gradual addition of (b) Cu$^{2+}$ and (c) Fe$^{3+}$ ions.

Additionally, $^1$H NMR titration was carried out by gradual addition of perchlorate salt of Cu$^{2+}$ ions to a DMSO-d$_6$ solution of 9f. The results show that the intensity of the proton signal corresponding to the hydroxyl group (-OH) at 10.25 ppm, which is the most probable binding site for Cu$^{2+}$ ions, decreases significantly relative to that of other protons upon exposure to Cu$^{2+}$ (Fig 8). This effect confirms the formation of weak complex between 9f and Cu$^{2+}$ ion. Moreover rapid broadening of the proton signal at 10.25 ppm with gradual addition of Cu$^{2+}$ ions further confirms the fast exchange of –OH protons due to complexation with Cu$^{2+}$ ion.
Fig. 8 Change in $^1$H NMR spectra of 9f upon addition of Cu$^{2+}$ ions, (a) 0.0 equiv., (b) 0.5 equiv., (c) 1.0 equiv., and (d) 2.0 equiv. in [D$_6$]-DMSO.

**Conclusions**

In summary, we have successfully developed a synthetic protocol for constructing novel tetracyclic skeleton of 4-hydroxyindole fused isocumarins. This methodology has the advantages of using easily available reactants and inexpensive catalyst and high yields of the product.
formation. To the best of our knowledge, this is the first report of synthesis of suitable isocoumarin based fluorescence active molecules with high quantum yields and ability to act as fluorescence "Turn-off" sensor for Cu$^{2+}$ and Fe$^{3+}$ ions. Most importantly the same molecules are found to be chemosensor for Cu$^{2+}$ ion only with respect to UV-Vis spectral change and naked eye colour change in presence and absence of UV radiation.

EXPERIMENTAL SECTION

General Procedure for the preparation of 2a-k or 3a-k: Concentrated H$_2$SO$_4$ (0.5 ml) was added to a solution of dihydroxy-indenopyrroles 1 (500 mg) in acetic acid (10 ml). The reaction mixture was heated at reflux for 15-45 min (as mentioned in Table 2). The initial colorless solution was intensified to red. Then it was poured into ice cold water to obtain solid products. The compounds were purified by crystallization technique using acetone and petroleum ether as mixed solvents.

General procedure for the preparation of 4a,b: The isocoumarin derivatives 2 (500 mg) were dissolved in 2.5 mL of methanol. NaBH$_4$ (0.3 eq) was added in one portion with stirring. A vigorous gas evolution occurs, together with a temperature rise. Stirring was continued for a few minutes (30 min) and then the pH was adjusted to neutrality with addition of dilute aqueous HCl, the mixture was extracted (ethyl acetate) and dried (Na$_2$SO$_4$), and the solvent was evaporated. The crude residue was then purified by column chromatography and crystallized by using petroleum ether and ethyl acetate.

General procedure for the preparation of 9a-f: 10% Pd/C (97 mg, 0.09 mmol) was added to a stirred solution of 2 (0.9 mmol) in Ph$_2$O (4 mL). The mixture was heated for 2 h at 250 °C under an inert atmosphere of N$_2$. After the mixture was cooled to room temperature, the catalyst was removed by filtration on Celite and the filter cake was rinsed several times with EtOAc. Volatiles
were removed under reduced pressure and the resulting mixture was loaded onto a silica gel column. Elution of the column with hexanes (for removal of Ph₂O) and then with 1:3 hexane-EtOAc provided yellow solid.

**11-Benzyl-8,9,10,11-tetrahydro-6-oxa-11-aza-benzo[a]fluorine-5,7-dione (2a):** White Solid (413 mg, 87%); m.p. 224-226 °C; \(^1\)H NMR (300 MHz, CDCl₃): \(\delta = 8.29\) (d, \(J = 8.7\) Hz, 1H), 7.48-7.42 (m, 1H), 7.38-7.22 (m, 5H), 7.03 (d, \(J = 6.9\) Hz, 2H), 5.53 (s, 2H), 2.83 (t, \(J = 6.3\) Hz, 2H), 2.53 (t, \(J = 6.0\) Hz, 2H), 2.23-2.15 (m, 2H); \(^{13}\)C NMR (75 MHz, CDCl₃): \(\delta = 191.8, 161.6, 145.4, 139.2, 135.2, 134.7, 131.6, 129.9, 129.3, 128.1, 125.7, 125.3, 118.8, 118.0, 112.8, 109.0, 49.2, 38.0, 22.8, 21.5\); IR (KBr): \(\tilde{\nu} = 1724\) cm\(^{-1}\); Anal calcd for C\(_{22}\)H\(_{17}\)NO\(_3\): C, 76.95; H, 4.99; N, 4.08 % Found C, 76.82; H, 4.93; N, 4.00 %.

**11-Phenyl-8,9,10,11-tetrahydro-6-oxa-11-aza-benzo[a]fluorine-5,7-dione (2b):** White Solid (408 mg, 86%); m.p. 295-297 °C; \(^1\)H NMR (300 MHz, CDCl₃): \(\delta = 8.13\) (d, \(J = 8.1\) Hz, 1H), 7.66-7.64 (m, 3H), 7.55-7.52 (m, 2H), 7.24 (t, \(J = 7.8\) Hz, 1H), 7.11 (t, \(J = 7.8\) Hz, 1H), 6.45 (d, \(J = 8.1\) Hz, 1H), 2.59 (t, \(J = 6.0\) Hz, 2H), 2.46 (t, \(J = 6.0\) Hz, 2H), 2.15-2.09 (m, 2H); \(^{13}\)C NMR (75 MHz, CDCl₃): \(\delta = 191.9, 161.5, 145.9, 138.9, 136.8, 134.1, 131.4, 130.2, 130.1, 128.2, 128.0, 125.7, 118.7, 118.0, 113.8, 109.2, 38.1, 22.9, 22.1\); IR (KBr): \(\tilde{\nu} = 1721\) cm\(^{-1}\); Anal calcd for C\(_{21}\)H\(_{15}\)NO\(_3\): C, 76.58; H, 4.59; N, 4.25 % Found C, 76.44; H, 4.52; N, 4.19 %.

**11-\(p\)-Tolyl-8,9,10,11-tetrahydro-6-oxa-11-aza-benzo[a]fluorine-5,7-dione (2c):** White Solid (394 mg, 83%); m.p. 298-300 °C; \(^1\)H NMR (300 MHz, CDCl₃): \(\delta = 8.14\) (d, \(J = 7.2\) Hz, 1H), 7.32 (d, \(J = 8.1\) Hz, 2H), 7.24-7.08 (m, 4H), 6.44 (d, \(J = 8.1\) Hz, 1H), 2.48 (t, \(J = 6.0\) Hz, 2H), 2.42-2.38 (m, 5H), 2.05-1.96 (m, 2H); \(^{13}\)C NMR (75 MHz, CDCl₃): \(\delta = 191.9, 161.7, 145.8, 140.3, 138.9, 134.2, 131.7, 130.8, 130.3, 127.7, 125.8, 125.6, 118.8, 118.3, 113.2, 109.3, 38.2, 22.8, 21.5\);
23.0, 22.2, 21.3; IR (KBr): $\nu$ 1722 cm$^{-1}$; Anal calcd for C$_{22}$H$_{17}$NO$_3$: C, 76.95; H, 4.99; N, 4.08 %; Found C, 76.80; H, 4.91; N, 4.03 %.

**11-(4-Fluorophenyl)-8,9,10,11-tetrahydro-6-oxa-11-aza-benzo[a]fluorine-5,7-dione** (2d):

White Solid (414 mg, 87%); m.p. 294-296 ºC; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 8.13$ (d, $J = 7.8$ Hz, 1H), 7.35-7.31 (m, 2H), 7.21-7.07 (m, 4H), 6.35 (d, $J = 8.1$ Hz, 1H), 2.44 (t, $J = 6.0$ Hz, 2H), 2.38 (t, $J = 6.0$ Hz, 2H), 2.03-1.97 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$, F coupled $^{13}$C spectra): $\delta = 191.7, 164.8, 161.6, 161.5, 145.7, 139.4, 135.4, 134.3, 134.2, 132.2, 131.9, 130.0, 129.9, 126.0, 118.5, 117.5, 117.2, 113.9, 109.4, 38.2, 23.0, 22.2; IR (KBr): $\nu$ 1716 cm$^{-1}$; Anal calcd for C$_{21}$H$_{14}$FNO$_3$: C, 72.62; H, 4.06; N, 3.80 %; Found C, 72.48; H, 3.98; N, 3.97 %.

**11-(2-Chlorophenyl)-8,9,10,11-tetrahydro-6-oxa-11-aza-benzo[a]fluorine-5,7-dione** (2e):

White Solid (381 mg, 80%); m.p. 292-294 ºC; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 8.22$ (d, $J = 8.1$ Hz, 1H), 7.77-7.73 (m, 1H), 7.70-7.58 (m, 3H), 7.34-7.29 (m, 1H), 7.26-7.17 (m, 1H), 6.37 (d, $J = 8.1$ Hz, 1H), 2.63-2.45 (m, 4H), 2.23-2.05 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 191.8, 161.5, 145.7, 139.0, 134.6, 134.5, 133.4, 131.7, 131.6, 130.9, 130.5, 130.0, 128.7, 125.9, 118.1, 117.8, 113.6, 109.7, 38.1, 22.9, 21.8; IR (KBr): $\nu$ 1726 cm$^{-1}$; Anal calcd for C$_{21}$H$_{14}$ClNO$_3$: C, 69.33; H, 3.88; N, 3.85 %; Found C, 69.21; H, 3.80; N, 3.78 %.

**11-(3-Chlorophenyl)-8,9,10,11-tetrahydro-6-oxa-11-aza-benzo[a]fluorine-5,7-dione** (2f):

White Solid (405 mg, 85%); m.p. 256-258 ºC; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 8.31$ (d, $J = 8.1$ Hz, 1H), 7.67-7.60 (m, 2H), 7.50 (s, 1H), 7.43-7.35 (m, 2H), 7.30-7.26 (m, 1H), 6.54 (d, $J = 8.1$ Hz, 1H), 2.63 (t, $J = 6$ Hz, 2H), 2.55 (t, $J = 6$ Hz, 2H), 2.20-2.11 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 191.6, 161.8, 145.4, 139.5, 136.9, 135.4, 134.8, 130.4, 130.2, 129.5, 128.8, 128.3, 127.6, 124.7, 118.5, 117.7, 113.6, 109.4, 38.1, 22.3, 21.8; IR (KBr): $\nu$ 1720 cm$^{-1}$; Anal calcd for C$_{21}$H$_{14}$ClNO$_3$: C, 69.33; H, 3.88; N, 3.85 %; Found C, 69.19; H, 3.81; N, 3.79 %.
11-(4-Chlorophenyl)-8,9,10,11-tetrahydro-6-oxa-11-aza-benzo[a]fluorine-5,7-dione (2g):
White Solid (405 mg, 85%); m.p. 255-257 °C; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 8.25 (d, $J$ = 7.8 Hz, 1H), 7.64 (d, $J$ = 8.1 Hz, 2H), 7.46 (d, $J$ = 9.3 Hz, 2H), 7.36 (t, $J$ = 7.2 Hz, 1H), 7.26-7.21 (m, 1H), 6.54 (d, $J$ = 7.8 Hz, 1H), 2.62-2.50 (m, 4H), 2.18-2.10 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 191.0, 160.8, 145.2, 138.5, 135.5, 134.6, 133.9, 131.0, 129.9, 129.3, 128.8, 125.5, 118.0, 117.5, 113.1, 108.9, 37.5, 22.3, 21.5; IR (KBr): $\tilde{\nu}$ 1718 cm$^{-1}$; Anal calcd for C$_{21}$H$_{14}$ClNO$_3$: C, 69.33; H, 3.88; N, 3.85%; Found C, 69.46; H, 3.79; N, 3.78%.

11-(4-Bromophenyl)-8,9,10,11-tetrahydro-6-oxa-11-aza-benzo[a]fluorine-5,7-dione (2h):
White Solid (388 mg, 81%); m.p. >300 °C; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 8.30 (d, $J$ = 6.6 Hz, 1H), 7.81-7.79 (m, 2H), 7.40-7.28 (m, 4H), 6.58 (d, $J$ = 7.8 Hz, 1H), 2.77-2.55 (m, 4H), 2.16-2.09 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 191.0, 160.7, 145.1, 138.9, 135.1, 133.9, 132.9, 131.0, 129.3, 129.0, 125.5, 123.6, 118.0, 117.4, 113.0, 108.7, 37.5, 22.3, 21.5; IR (KBr): $\tilde{\nu}$ 1723 cm$^{-1}$; Anal calcd for C$_{21}$H$_{14}$BrNO$_3$: C, 61.78; H, 3.46; N, 3.43%; Found C, 61.90; H, 3.37; N, 3.36%.

11-(3-Methoxyphenyl)-8,9,10,11-tetrahydro-6-oxa-11-aza-benzo[a]fluorine-5,7-dione (2i):
White Solid (390 mg, 82%); m.p. 300-302 °C; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 8.30 (d, $J$ = 8.4 Hz, 1H), 7.54 (t, $J$ = 8.7 Hz, 1H), 7.37-7.34 (m, 1H), 7.28-7.26 (m, 1H), 7.21-7.17 (m, 1H), 7.05-7.02 (m, 2H), 6.61 (d, $J$ = 8.1 Hz, 1H), 3.92 (s, 3H), 2.65 (t, $J$ = 6 Hz, 2H), 2.55 (t, $J$ = 6 Hz, 2H), 2.17-2.11 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 191.6, 161.4, 160.2, 145.6, 139.4, 137.9, 134.3, 131.8, 130.9, 130.1, 127.1, 125.9, 120.0, 118.8, 118.6, 116.0, 113.5, 109.2, 55.7, 38.2, 23.0, 22.2; IR (KBr): $\tilde{\nu}$ 1724 cm$^{-1}$; Anal calcd for C$_{22}$H$_{17}$NO$_4$: C, 73.53; H, 4.77; N, 3.90%; Found C, 73.40; H, 4.71; N, 3.82%.
11-(4-Methoxyphenyl)-8,9,10,11-tetrahydro-6-oxa-11-aza-benzo[a]fluorine-5,7-dione (2j):
White Solid (381 mg, 80%); m.p. >300 ºC; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 8.25$ (d, $J = 7.8$ Hz, 1H), 7.41 (d, $J = 9.0$ Hz, 2H), 7.37-7.18 (m, 2H), 7.13 (d, $J = 9.0$ Hz, 2H), 6.57 (d, $J = 7.8$ Hz, 1H), 3.95 (s, 3H), 2.60 (t, $J = 6.0$ Hz, 2H), 2.51 (t, $J = 6$ Hz, 2H), 2.16-2.08 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 191.7, 161.5, 160.4, 145.9, 139.4, 134.1, 131.5, 130.1, 129.2, 129.0, 125.9, 125.6, 118.6, 118.1, 115.1, 109.1, 55.5, 38.1, 22.9, 22.0; IR (KBr): $\delta = 1720$ cm$^{-1}$; Anal calcd for C$_{22}$H$_{17}$NO$_4$: C, 73.53; H, 4.77; N, 3.90 % Found C, 73.43; H, 4.70; N, 3.80 %.

11-(4-Nitrophenyl)-8,9,10,11-tetrahydro-6-oxa-11-aza-benzo[a]fluorine-5,7-dione (2k):
White Solid (410 mg, 86%); m.p. 216-218 ºC; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 8.53$ (d, $J = 6.9$ Hz, 2H), 8.31 (d, $J = 8.2$ Hz, 1H), 7.75-7.72 (m, 2H), 7.35-7.26 (m, 2H), 6.28 (d, $J = 8.1$ Hz, 1H), 2.63-2.55 (m, 4H), 2.17-2.12 (m, 2H); IR (KBr): $\delta = 1717$ cm$^{-1}$; Anal calcd for C$_{21}$H$_{14}$N$_2$O$_5$: C, 67.38; H, 3.77; N, 7.48 % Found C, 73.43; H, 3.69; N, 7.40 %.

11-Benzyl-9,9-dimethyl-8,9,10,11-tetrahydro-6-oxa-11-aza-benzo[a]fluorine-5,7-dione (3a):
White Solid (429 mg, 90%); m.p. 252-254 ºC; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 8.15$ (d, $J = 8.1$ Hz, 1H), 7.35-7.13 (m, 6H), 6.94 (d, $J = 7.2$ Hz, 2H), 5.45 (s, 2H), 2.60 (s, 2H), 2.28 (s, 2H), 1.03 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 191.2, 161.6, 144.3, 139.1, 135.2, 134.8, 131.7, 129.9, 129.4, 128.1, 125.7, 125.1, 118.8, 118.0, 113.1, 107.9, 52.0, 49.1, 35.5, 35.0, 28.5; IR (KBr): $\delta = 1715$ cm$^{-1}$; Anal calcd for C$_{24}$H$_{21}$NO$_3$: C, 77.61; H, 5.70; N, 3.77 % Found C, 77.75; H, 5.63; N, 3.71 %.

9,9-Dimethyl-11-phenyl-8,9,10,11-tetrahydro-6-oxa-11-aza-benzo[a]fluorine-5,7-dione (3b):
White Solid (405 mg, 85%); m.p. 294-296 ºC; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 8.40$ (d, $J = 7.5$ Hz, 1H), 7.89-7.86 (m, 3H), 7.71-7.68 (m, 2H), 7.47 (t, $J = 7.8$ Hz, 1H), 7.38-7.35 (m, 1H), 6.66 (d, $J = 8.1$ Hz, 1H), 2.66 (s, 2H), 2.56 (s, 2H), 1.28 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta =
191.4, 161.5, 144.8, 138.9, 136.8, 134.2, 131.5, 130.3, 130.3, 130.2, 128.1, 125.7, 118.7, 118.1, 114.1, 108.2, 52.2, 36.0, 35.1, 28.4; IR (KBr): ν 1722 cm⁻¹; Anal calcd for C₂₃H₁₉NO₃: C, 77.29; H, 5.36; N, 3.92 %; Found C, 77.42; H, 5.28; N, 3.83 %.

9,9-Dimethyl-11-\(p\)-tolyl-8,9,10,11-tetrahydro-6-oxa-11-aza-benzo[\(a\)]fluorine-5,7-dione (3c): White Solid (396 mg, 83%); m.p. 280-282 ºC; \(^1\)H NMR (300 MHz, CDCl₃): δ = 8.34 (d, \(J = 6.3\) Hz, 1H), 7.45-7.26 (m, 6H), 6.55 (d, \(J = 7.8\) Hz, 1H), 2.65-2.41 (m, 7H), 1.09 (s, 6H); \(^{13}\)C NMR (75 MHz, CDCl₃): δ = 191.39, 161.6, 144.7, 140.4, 138.1, 134.2, 131.8, 130.9, 130.3, 127.7, 125.8, 125.6, 118.7, 118.3, 113.6, 108.3, 52.3, 36.1, 35.1, 28.4, 21.4; IR (KBr): ν 1725 cm⁻¹; Anal calcd for C₂₄H₂₁NO₃: C, 77.61; H, 5.70; N, 3.77 %; Found C, 77.47; H, 5.61; N, 3.69 %.

11-(4-Fluorophenyl)-9,9-dimethyl-8,9,10,11-tetrahydro-6-oxa-11-aza-benzo[\(a\)]fluorine-5,7-dione (3d): White Solid (410 mg, 86%); m.p. >300 ºC; \(^1\)H NMR (300 MHz, CDCl₃): δ = 8.2 (d, \(J = 7.8\) Hz, 1H), 7.53-7.49 (m, 2H), 7.39-7.17 (m, 4H), 6.49 (d, \(J = 8.1\) Hz, 1H), 2.45 (s, 2H), 2.37 (s, 2H), 1.09 (s, 6H); \(^{13}\)C NMR (75 MHz, CDCl₃, F coupled \(^{13}\)C spectra): δ = 191.4, 164.8, 161.6, 161.6, 144.9, 138.6, 134.3, 132.8, 131.7, 130.1, 130.0, 125.9, 124.7, 118.5, 118.1, 117.6, 117.3, 113.9, 108.4, 52.1, 36.0, 35.1, 28.4; IR (KBr): ν 1724 cm⁻¹; Anal calcd for C₂₃H₁₈FNO₃: C, 73.59; H, 4.83; N, 3.73 %; Found C, 73.70; H, 4.75; N, 3.66 %.

11-(2-Chlorophenyl)-9,9-dimethyl-8,9,10,11-tetrahydro-6-oxa-11-aza-benzo[\(a\)]fluorine-5,7-dione (3e): White Solid (373 mg, 78%); m.p. 255-257 ºC; \(^1\)H NMR (300 MHz, CDCl₃): δ = 8.30 (d, \(J = 6.9\) Hz, 1H), 7.72-7.59 (m, 3H), 7.37-7.23 (m, 3H), 6.36 (d, \(J = 7.8\) Hz, 1H), 2.45 (s, 2H), 2.33 (s, 2H), 1.11 (s, 3H), 1.09 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl₃): δ = 191.6, 161.6, 145.0, 138.8, 134.7, 134.5, 133.2, 131.9, 131.5, 130.9, 130.6, 130.1, 128.9, 126.0, 118.0, 117.9, 113.9, 108.5, 52.1, 35.7, 35.2, 29.3, 27.4; IR (KBr): ν 1721 cm⁻¹; Anal calcd for C₂₃H₁₈ClNO₃: C, 70.50; H, 4.63; N, 3.57 %; Found C, 70.36; H, 4.56; N, 3.51 %.
11-(3-Chlorophenyl)-9,9-dimethyl-8,9,10,11-tetrahydro-6-oxa-11-aza-benzo[a]fluorine-5,7-dione (3f): White Solid (397 mg, 83%); m.p. 282-284 °C; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 8.17$ (d, $J = 7.8$ Hz, 1H), 7.66-7.62 (m, 2H), 7.51-7.49 (m, 2H), 7.31 (t, $J = 7.5$ Hz, 1H), 7.15 (t, $J = 7.5$ Hz, 1H), 6.48 (d, $J = 8.1$ Hz, 1H), 2.47 (s, 2H), 2.35 (s, 2H), 1.09 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 191.4$, 161.3, 144.9, 138.8, 137.9, 135.8, 134.3, 131.5, 131.4, 130.5, 129.8, 128.3, 126.8, 125.8, 118.6, 117.8, 113.9, 108.3, 52.0, 35.9, 35.2, 28.3; IR (KBr): $\nu = 1719$ cm$^{-1}$; Anal calcd for C$_{23}$H$_{18}$ClNO$_3$: C, 70.50; H, 4.63; N, 3.57 % Found C, 70.39; H, 4.56; N, 3.51 %.

11-(4-Chlorophenyl)-9,9-dimethyl-8,9,10,11-tetrahydro-6-oxa-11-aza-benzo[a]fluorine-5,7-dione (3g): White Solid (392 mg, 82%); m.p. 285-287 °C; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 8.27$ (d, $J = 8.1$ Hz, 1H), 7.66 (d, $J = 8.4$ Hz, 2H), 7.46-7.33 (m, 3H), 7.27 (t, $J = 7.8$ Hz, 1H), 6.55 (d, $J = 8.1$ Hz, 1H), 2.46 (s, 2H), 2.40 (s, 2H), 1.10 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 191.3$, 161.4, 144.6, 138.9, 136.4, 136.2, 135.4, 131.9, 130.6, 130.0, 129.4, 126.0, 118.5, 118.4, 114.2, 108.3, 52.2, 36.1, 35.2, 28.4; IR (KBr): $\nu = 1722$ cm$^{-1}$; Anal calcd for C$_{23}$H$_{18}$ClNO$_3$: C, 70.50; H, 4.63; N, 3.57 % Found C, 70.64; H, 4.56; N, 3.51 %.

11-(4-Bromophenyl)-9,9-dimethyl-8,9,10,11-tetrahydro-6-oxa-11-aza-benzo[a]fluorine-5,7-dione (3h): White Solid (379 mg, 79%); m.p. 280-282 °C; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 8.24$ (d, $J = 8.1$ Hz, 1H), 7.81-7.78 (dd, $J_1 = 2.1$ Hz, $J_2 = 6.6$ Hz, 2H), 7.39-7.32 (m, 3H), 7.24 (t, $J = 8.2$ Hz, 1H), 6.53 (d, $J = 8.1$ Hz, 1H), 2.44 (s, 2H), 2.36 (s, 2H), 1.08 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 190.8$, 161.4, 144.2, 138.7, 135.5, 133.9, 133.2, 131.3, 129.5, 129.3, 125.5, 123.9, 118.1, 117.9, 113.8, 108.4, 51.7, 35.7, 34.7, 28.0; IR (KBr): $\nu = 1720$ cm$^{-1}$; Anal calcd for C$_{23}$H$_{18}$BrNO$_3$: C, 63.32; H, 4.16; N, 3.21 % Found C, 63.47; H, 4.07; N, 3.16 %.

11-(3-Methoxyphenyl)-9,9-dimethyl-8,9,10,11-tetrahydro-6-oxa-11-aza-benzo[a]fluorine-5,7-dione (3i): White Solid (387 mg, 81%); m.p. 278-280 °C; $^1$H NMR (300 MHz, CDCl$_3$): $\delta =
8.10 (d, J = 7.8 Hz, 1H), 7.49 (t, J = 8.1 Hz, 1H), 7.26 (t, J = 7.8 Hz, 1H), 7.17-7.08 (m, 3H), 6.97 (d, J = 7.8 Hz, 1H), 6.51 (d, J = 8.1 Hz, 1H), 3.92 (s, 3H), 2.42 (d, J = 6.3 Hz, 2H), 2.23 (d, J = 2.7 Hz, 2H), 1.03 (s, 3H), 1.00 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 191.3, 161.5, 160.9, 144.7, 138.7, 137.7, 134.2, 131.4, 131.3, 130.9, 125.6, 119.9, 118.8, 117.9, 116.2, 113.9, 113.5, 108.0, 55.7, 52.0, 35.8, 35.0, 28.6, 28.0; IR (KBr): ν 1721 cm⁻¹; Anal calcd for C₂₄H₂₁NO₄: C, 74.40; H, 5.46; N, 3.62 % Found C, 74.52; H, 5.38; N, 3.55 %.

11-(4-Methoxyphenyl)-9,9-dimethyl-8,9,10,11-tetrahydro-6-oxa-11-aza-benzo[a]fluorine-5,7-dione (3j): White Solid (373 mg, 78%); m.p. 286-288 ºC; ¹H NMR (300 MHz, CDCl₃): δ = 8.22 (d, J = 8.1 Hz, 1H), 7.40-7.28 (m, 3H), 7.21-7.12 (m, 3H), 6.55 (d, J = 7.8 Hz, 1H), 3.97 (s, 3H), 2.45 (s, 2H), 2.35 (s, 2H), 1.07 (s, 6H); ¹³C NMR (75 MHz, CDCl₃): δ = 191.4, 161.6, 160.6, 145.1, 138.8, 134.3, 131.6, 130.6, 130.3, 129.2, 129.2, 125.7, 118.7, 118.1, 115.4, 108.1, 55.7, 52.2, 36.0, 35.1, 28.4; IR (KBr): ν 1726 cm⁻¹; Anal calcd for C₂₄H₂₁NO₄: C, 74.40; H, 5.46; N, 3.62 % Found C, 74.27; H, 5.37; N, 3.55 %.

9,9-Dimethyl-11-(4-nitrophenyl)-8,9,10,11-tetrahydro-6-oxa-11-aza-benzo[a]fluorine-5,7-dione (3k): White Solid (407 mg, 85%); m.p. 270-272 ºC; ¹H NMR (300 MHz, CDCl₃): δ = 8.54 (d, J = 8.7 Hz, 2H), 8.31 (d, J = 8.1 Hz, 1H), 7.34 (d, J = 6.3 Hz, 2H), 7.26 (t, J = 4.8 Hz, 1H), 7.26-7.24 (m, 1H), 6.48 (d, J = 7.8 Hz, 1H), 2.47 (s, 2H), 2.42 (s, 2H), 1.10 (s, 6H); ¹³C NMR (75 MHz, CDCl₃): δ = 191.4, 161.6, 152.5, 144.5, 135.2, 134.4, 131.9, 129.2, 126.2, 125.5, 124.8, 123.1, 118.3, 118.2, 113.3, 108.5, 51.8, 36.1, 35.2, 28.2; IR (KBr): ν 1727 cm⁻¹; Anal calcd for C₂₃H₁₈N₂O₅: C, 68.65; H, 4.51; N, 6.96 % Found C, 68.76; H, 4.44; N, 6.91 %.

11-Benzyl-7-hydroxy-8,9,10,11-tetrahydro-7H-6-oxa-11-aza-benzo[a]fluoren-5-one (4a): White Solid (377 mg, 75%); m.p. 150-152 ºC; ¹H NMR (300 MHz, CDCl₃): δ = 8.33 (d, J = 8.4 Hz, 1H), 7.50-7.44 (m, 1H), 7.38 (m, 5H), 7.02 (d, J = 6.9 Hz, 2H), 5.42 (s, 2H), 5.13 (t, J = 4.2
2.70-2.48 (m, 2H), 2.13-1.85 (m, 4H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ = 162.6, 140.4, 136.5, 134.7, 134.2, 131.1, 129.1, 127.7, 125.4, 124.6, 118.4, 117.6, 111.6, 108.7, 61.1, 48.5, 31.4, 21.6, 18.5; IR (KBr): $\delta$ 3491, 1695 cm$^{-1}$; Anal calcd for C$_{22}$H$_{19}$NO$_3$: C, 76.50; H, 5.54; N, 4.06 % Found C, 76.37; H, 5.49; N, 3.99%.

7-Hydroxy-11-p-tolyl-8,9,10,11-tetrahydro-7H-6-oxa-11-aza-benzo[a]fluoren-5-one (4b): White Solid (362 mg, 72%); m.p. 170-172 ºC; $^1$H NMR (300 MHz, CDCl$_3$): δ = 8.32-8.29 (dd, $J_1$ = 3.0 Hz, $J_2$ = 8.1 Hz, 1H), 7.36-7.20 (m, 6H), 6.61 (d, $J$ = 8.1 Hz, 1H), 5.14 (t, $J$ = 4.2 Hz, 1H), 2.50 (s, 3H), 2.69-2.44 (m, 2H), 2.11-1.84 (m, 4H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ = 162.5, 139.3, 135.2, 135.0, 134.2, 131.8, 131.3, 130.5, 130.4, 128.0, 127.9, 124.6, 118.5, 117.5, 108.8, 61.2, 31.6, 22.3, 21.3, 18.5; IR (KBr): $\delta$ 3499, 1700 cm$^{-1}$; Anal calcd for C$_{22}$H$_{19}$NO$_3$: C, 76.50; H, 5.54; N, 4.06 % Found C, 76.35; H, 5.48; N, 3.99%.

11-Benzyl-7-hydroxy-11H-6-oxa-11-aza-benzo[a]fluoren-5-one (9a): Yellow Solid (242 mg, 79 %); m.p. 260-262 ºC; $^1$H NMR (300 MHz, DMSO-d$_6$): δ = 10.18 (bs, 1H), 8.29 (d, $J$ = 7.2 Hz, 1H), 7.93 (d, $J$ = 6.9 Hz, 1H), 7.77 (t, $J$ = 7.8 Hz, 1H), 7.50 (t, $J$ = 8.1 Hz, 1H), 7.27-7.04 (m, 7H), 6.57 (d, $J$ = 5.7 Hz, 1H), 5.90 (s, 2H); $^{13}$C NMR (75 MHz, DMSO-d$_6$): δ = 161.6, 151.5, 139.5, 137.9, 135.4, 131.4, 130.5, 129.0, 127.4, 126.9, 126.6, 125.9, 125.9, 120.9, 118.7, 115.3, 106.1, 105.0, 101.4, 48.1; IR (KBr): $\delta$ 3297, 1686 cm$^{-1}$; Anal calcd for C$_{22}$H$_{15}$NO$_3$: C, 77.41; H, 4.43; N, 4.10 % Found C, 77.54; H, 4.36; N, 4.05 %; HRMS (ESI-TOF) m/z calcd: 342.1130 [M+H]; found: 342.1124.

7-Hydroxy-11-phenyl-11H-6-oxa-11-aza-benzo[a]fluoren-5-one (9b): Yellow Solid (329 mg, 82%); m.p. 264-266 ºC; $^1$H NMR (300 MHz, DMSO-d$_6$): δ = 10.26 (bs, 1H), 8.28 (d, $J$ = 7.8 Hz, 1H), 7.67-7.44 (m, 7H), 7.11-7.05 (m, 1H), 6.77 (d, $J$ = 8.1 Hz, 1H), 6.59 (t, $J$ = 4.2 Hz, 1H), 6.46 (t, $J$ = 4.8 Hz, 1H); $^{13}$C NMR (75 MHz, DMSO-d$_6$): δ = 161.4, 151.4, 140.1, 137.7, 135.7,
134.8, 131.3, 130.3, 130.2, 129.4, 128.6, 126.9, 126.7, 119.9, 118.6, 115.9, 106.4, 105.4, 101.4;
IR (KBr): $\tilde{\nu}$ 3285, 1680 cm$^{-1}$; Anal calcd for C$_{21}$H$_{13}$NO$_3$: C, 77.05; H, 4.00; N, 4.28 %; Found C, 77.20; H, 3.93; N, 4.22 %; HRMS (ESI-TOF) m/z calcd: 328.0974 [M+H]; found: 328.1272.

7-Hydroxy-11-$p$-tolyl-11H-6-oxa-11-aza-benzo[a]fluoren-5-one (9c): Yellow Solid (249 mg, 81%); m.p. 280-282 ºC; $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta = 10.18$ (bs, 1H), 8.21 (d, $J = 7.8$ Hz, 1H), 7.55-7.53 (m, 1H), 7.48-7.35 (m, 5H), 7.00 (t, $J = 8.1$ Hz, 1H), 6.77 (d, $J = 8.1$ Hz, 1H), 6.52 (d, $J = 7.8$ Hz, 1H), 6.39 (d, $J = 8.4$ Hz, 1H), 3.26 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-d$_6$): $\delta =$ 161.4, 151.3, 140.2, 138.9, 135.5, 135.0, 134.8, 131.2, 130.7, 130.3, 128.3, 126.8, 126.6, 119.9, 118.6, 115.8, 106.2, 105.2, 101.4, 20.9; IR (KBr): $\tilde{\nu}$ 3290, 1682 cm$^{-1}$; Anal calcd for C$_{22}$H$_{15}$NO$_3$: C, 77.41; H, 4.43; N, 4.10 %; Found C, 77.30; H, 4.37; N, 4.05 %; HRMS (ESI-TOF) m/z calcd: 342.1130 [M+H]; found: 342.1246.

11-(4-Fluorophenyl)-7-hydroxy-11H-6-oxa-11-aza-benzo[a]fluoren-5-one (9d): Yellow Solid (255 mg, 82%); m.p. 278-280 ºC; $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta = 10.43$ (bs, 1H), 8.27 (d, $J = 7.8$ Hz, 1H), 7.66-7.38 (m, 6H), 7.14 (t, $J = 8.1$ Hz, 1H), 6.80 (d, $J = 8.1$ Hz, 1H), 6.60 (d, $J = 7.8$ Hz, 1H), 6.45 (d, $J = 8.4$ Hz, 1H); $^{13}$C NMR (75 MHz, DMSO-d$_6$), F coupled $^{13}$C spectra): $\delta =$ 163.7, 161.4, 160.4, 151.4, 140.3, 135.7, 134.9, 134.0, 131.0, 130.9, 130.8, 130.1, 126.9, 126.8, 119.8, 118.6, 117.3, 117.0, 115.9, 106.3, 105.5, 101.2; IR (KBr): $\tilde{\nu}$ 3296, 1686 cm$^{-1}$; Anal calcd for C$_{21}$H$_{12}$FNO$_3$: C, 73.04; H, 3.50; N, 4.06 %; Found C, 72.90; H, 3.44; N, 4.00 %.

7-Hydroxy-11-(3-methoxyphenyl)-11H-6-oxa-11-aza-benzo[a]fluoren-5-one (9e): Yellow Solid (257 mg, 80%); m.p. 262-264 ºC; $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta = 10.24$ (bs, 1H), 8.28 (d, $J = 7.8$ Hz, 1H), 7.66-7.45 (m, 3H), 7.23-7.05 (m, 4H), 6.87 (d, $J = 8.1$ Hz, 1H), 6.59 (d, $J = 7.5$ Hz, 1H), 6.52 (d, $J = 8.1$ Hz, 1H), 3.80 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-d$_6$): $\delta =$ 161.4, 160.5, 151.3, 140.1, 138.8, 135.7, 134.9, 131.2, 131.0, 130.2, 126.9, 126.7, 120.5, 120.0, 118.6,
115.8, 115.3, 114.0, 106.3, 105.4, 101.5, 55.6; IR (KBr): ν 3293, 1687 cm⁻¹; Anal calcd for C₂₂H₁₅NO₄: C, 73.94; H, 4.23; N, 3.92 %; Found C, 73.85; H, 4.16; N, 3.86 %.

7-Hydroxy-11-(4-methoxyphenyl)-11H-6-oxa-11-aza-benzo[a]fluoren-5-one (9f): Yellow Solid (260 mg, 81%); m.p. 282-284 ºC; ¹H NMR (300 MHz, CDCl₃): δ = 8.43-8.40 (dd, J₁ = 1.2 Hz, J₂ = 8.1 Hz, 1H), 7.49-7.37 (m, 4H), 7.17-7.10 (m, 3H), 6.92 (d, J = 8.1 Hz, 1H), 6.68-6.61 (m, 2H), 6.04 (s, 1H), 3.95 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 161.9, 159.9, 149.1, 140.0, 138.7, 134.4, 131.9, 130.6, 130.2, 129.7, 126.5, 126.5, 120.1, 119.0, 116.4, 115.0, 105.8, 105.7, 102.8, 55.5; IR (KBr): ν 3289, 1681 cm⁻¹; Anal calcd for C₂₂H₁₅NO₄: C, 73.94; H, 4.23; N, 3.92 %; Found C, 73.83; H, 4.17; N, 3.85 %; HRMS (ESI-TOF) m/z calcd: 358.1079 [M+H]; found: 358.1073.

ASSOCIATED CONTENT
Supporting Information
Supplementary data (¹H, ¹³C data of compounds 2, 3, 4 and 9 and crystallographic data for 9a, 9f) is available free of charge via the Internet at--------

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REFERENCES


Graphical Abstract

AcOH  
H₂SO₄  
15-45 min Reflux

NaBH₄
MeOH
22 Examples

Pd/C
PhOPh
Reflux
6 Examples

[9d] : [Cu²⁺]
1:0  
1:0.5  
1:1  
1:1.5  
1:2  
1:2.5  
1:3

Fluorescence Intensity (arb. unit)
Wavelength (nm)

(a)
(b)