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Microwave assisted base dependent regioselective synthesis of partially reduced chromenes, isochromenes and phenanthrenes†‡

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We have reported a microwave assisted base directed regioselective synthesis of partially reduced chromenes, isochromenes and phenanthrenes. Functionalized 4-(piperidin-1-yl)-5,6-dihydro-2*H*-benzo[*h*]-chromen-2-one-3-carbonitriles have been used as precursors, which on reaction with functionalized acetophenones in the presence of KOH in DMF under microwave irradiation yield (*Z*)-2-(2-aryl-5,6-dihydro-4*H*-benzo[*f*]isochromen-4-ylidene)acetonitriles. The use of NaH in DMF provides 3-aryl-1-(piperidin-1-yl)-9,10-dihydro phenanthrene-2-carbonitriles in excellent yield regioselectively. The use of cyclohexanone as a nucleophile source yields (*Z*)-2-(3,4,7,8-tetrahydro-1*H*-naphtho[2,1-*c*]chromen-6(2*H*)-ylidene)acetonitriles. The structure and geometry of isochromene have been proved without any ambiguity by single crystal X-ray diffraction.

Introduction

The development of a new approach for the preparation of biologically active molecules constitutes a great challenge in modern organic chemistry. This challenge has led to growing interest in the field of microwave-enhanced procedures due to great reaction control and high reaction rates. Therefore, microwave-assisted organic synthesis (MAOS) is an invaluable technique for medicinal chemistry and drug discovery applications.[1,2]

Chromenes and isochromene are well known structural motifs that are frequently encountered in bioactive natural products.[3] They are also considered to be a venerable pharmacophore and exhibit a wide range of biological activities such as anti-HIV,[4] anticancer,[5] antihypertensive,[6] insecticidal,[7] and antifungal.[8] Seselin **i** and lonchocarpene **ii** are used as anticancer agents,[9,10] whereas acolbifene **iii**, LG120746 **iv** and **v** are a class of selective estrogen receptor modulators and progesterone receptor modulators, respectively (Fig. 1).[11,12] In addition, cannabinol **vi** has affinity towards CB1 and CB2 receptors, while moracin D **vii** is currently known as an antifungal agent (Fig. 1).[8,13] Apart from this, phenanthrenes have also drawn great attention because of their wide presence in natural products as well as their applications in medicinal chemistry and materials science.[14]

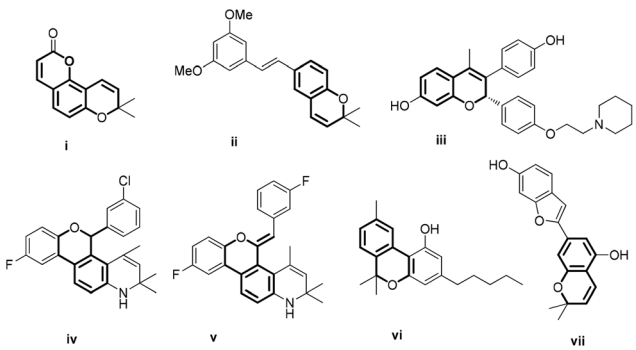

Fig. 1 Some natural products and biologically potent molecules containing chromene and isochromene skeletons.

Among the various functionalized chromenes, 2-ylidene-chromene is a very good progesterone receptor modulator.[12] Recently, Yanai *et al.* have reported a triple carbon acid (KSAs) catalysed synthesis of ylidene-isochromenes *via* reaction of lactones with ketene silyl acetals,[15] whereas Pal *et al.* used $AlCl_3$/Pd/C–Cu as a catalyst[16] (Scheme 1). Organolithium reagents[17] and Grignard reagents[18] were also used to construct this chromene skeleton. However, some protocols suffer from certain drawbacks, such as the use of moisture and air sensitive reagents, low yields and prolonged reaction time.[16–18]

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†This manuscript is dedicated to Dr Vishnu Ji Ram on his 72nd birthday.

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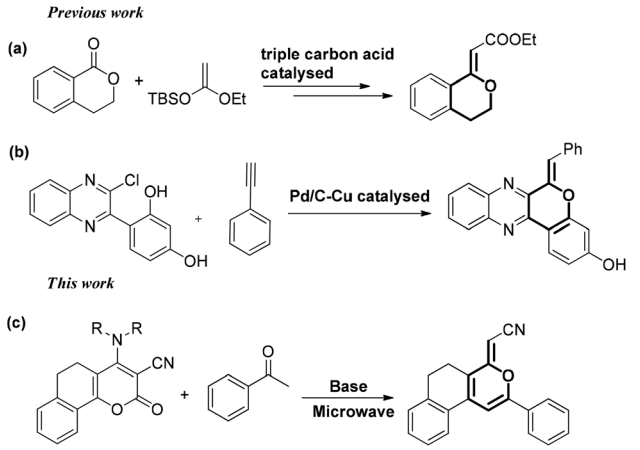
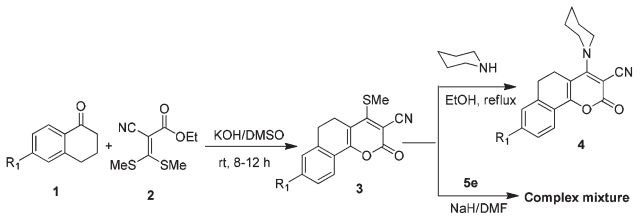


Scheme 1 Synthesis of 2-ylidene-chromenes and isochromenes using various catalysts.

These interesting versatile pharmaceutical activities of 2-ylidene chromene have prompted us towards the improved synthesis of this skeleton. As a part of our continual work towards exploring the synthetic utility of functionalized 2-oxabenzochromene for the synthesis of various biologically important aromatic nucleuses, we wish to report herein a simple and efficient base catalysed microwave assisted regioselective synthesis of isochromene, chromenes and dihydrophenanthrene. The synthesized compounds contain both an exocyclic double bond and an aryl ring attached to the chromene ring, which were important for pharmaceutical activity.[12]

Results and discussion

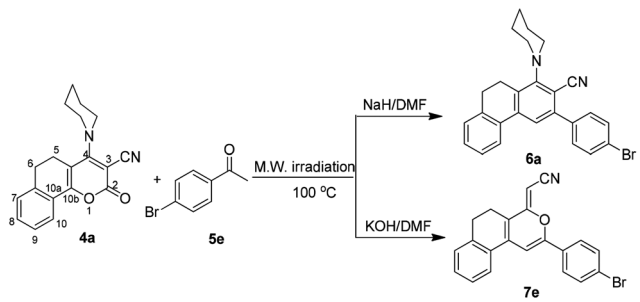
For the synthesis of chromene, isochromenes and dihydrophenanthrenes, 4-(piperidin-1-yl)-5,6-dihydro-2*H*-benzo[*h*]-chromen-2-one-3-carbonitrile **4a** has been taken as a precursor. This precursor was synthesized in three steps. The first step was synthesis of ethyl 2-cyano-3,3-dimethylthioacrylate **2**[19] by reaction of ethyl cyanoacetate, carbon disulphide and methyl iodide under basic conditions, which on reaction with various 1-tetralones gives 4-(methylthio)-2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles **3**.[20] We have tested compound **3** as a precursor for the synthesis of chromenes and dihydrophenanthrenes under various reaction conditions at different temperatures, but fail to achieve the desired product and end up with formation of a complex mixture. We assume that the presence of the SMe group at position 4 is the most probable reason for the formation of a complex mixture, as the SMe group acts as a good leaving group and is responsible for side reactions, and decomposed at high temperature.[20] Therefore in order to reduce the probability of side reactions, SMe has been replaced by piperidine, a secondary amine to reduce the electrophilicity of C-4. 4-(Piperidin-1-yl)-5,6-dihydro-2*H*-benzo[*h*]chromen-2-one-3-carbonitrile **4** was synthesised by amination of **3** with piperidine in boiling ethanol (Scheme 2).[20]



Scheme 2 Synthesis of 4-(piperidin-1-yl)-5,6-dihydro-2*H*-benzo[*h*]-chromen-2-ones **4**.

In search of better reaction conditions to achieve our goal, 4-(piperidin-1-yl)-5,6-dihydro-2*H*-benzo[*h*]chromen-2-one-3-carbonitrile **4a** and 4-bromoacetophenone **5e** were taken as model substrates. We have screened various base–solvent combinations at various temperatures using conventional heating as well as microwave mediated heating. The use of NaH–DMF at room temperature and 100 °C yields dihydrophenanthrene regioselectively, without the formation of **7e** (Table 1, entries 1 and 2). Previously, Ram *et al.* have already reported the regioselective synthesis of dihydrophenanthrenes using KOH–DMF at room temperature.[20] We checked the effect of temperature on the earlier reported reaction and surprisingly got the mixture of dihydrophenanthrene **6a** and isochromenes **7e** (Table 1, entry 3). We envisioned that **7e** might be synthesized regioselectively under appropriate reaction conditions. With the earlier results, we were encouraged to perform further

Table 1 Effect of base and solvent on the synthesis of **6a** and **7e**[a]



Entry	Base[b]	Solvent	Condition	Yield of **6a**[c] (%)	Yield of **7e**[c] (%)
1	NaH	DMF	rt[d]	75	—
2	NaH	DMF	100 °C[e]	78	—
3	KOH	DMF	100 °C[e]	35	43
4	$NaNH_2$	DMF	100 °C[e]	32	40
5	$KOBu^t$	DMF	100 °C[e]	73	Trace
6	KOH	DMF	M.W.[f]	—	82
7	$KOBu^t$	DMF	M.W.[f]	76	—
8	NaH	DMF	M.W.[f]	90	—
9	$NaNH_2$	DMF	M.W.[f]	Mixture	
10	NaH	THF	M.W.[f]	—	—
11	KOH	DMSO	M.W.[f]	Trace	48

[a] The reaction was conducted with 2-oxo-4-(piperidin-1-yl)-5,6-dihydro-2-benzo[*h*]chromene-3-carbonitrile **4a** (0.5 mmol) and 4-bromoacetophenone **5e** (0.5 mmol). [b] 0.75 mmol (1.5 eq.). [c] Yield of isolated product. [d] Reaction time 4 hours. [e] Reaction time 1 hour. [f] Under a microwave reactor at 100 °C at a maximum applied power of 200 W, 15 minutes.

optimization through various bases (KOH, $NaNH_2$, and $KOBu^t$) in different solvents (DMF, DMSO and THF). It was found that the use of KOH and $NaNH_2$ resulted in the desired product **7e** in 43% and 40% yield, whereas $KOBu^t$ did not give satisfactory results and only **6a** was obtained as a major product. In view of the previously reported organic synthesis to achieve high regioselectivity,[21] we turned our attention to a microwave assisted procedure. In order to elaborate our study, the previously used bases were further screened to synthesize **7e** under microwave irradiation.

Surprisingly, when we carried out the reaction under microwave conditions (100 °C, at a maximum applied power of 200 watts), interesting results were obtained. The use of KOH with DMF yielded **7e** as an exclusive product (Table 1, entry 6). Whereas $KOBu^t$ and NaH were found to be inefficient at producing the desired product, **6a** was obtained in 76% and 90% yield respectively. A complex mixture of **6a** and **7e** was found when we used $NaNH_2$ as a base. Furthermore, we performed the reaction in THF and DMSO with NaH and KOH to investigate the solvent effect under microwave conditions. The desired product **7e** was obtained in moderate yield in DMSO. However neither **6a** nor **7e** was observed in THF. Thus KOH and NaH were found to be the best bases in DMF for the regioselective synthesis of isochromene **7e** and dihydrophenanthrene **6a**, respectively.

Under these optimized reaction conditions, the generality of this procedure has been examined. Various functionalized isochromenes **7a–g** were synthesized in very good yields (Table 2).

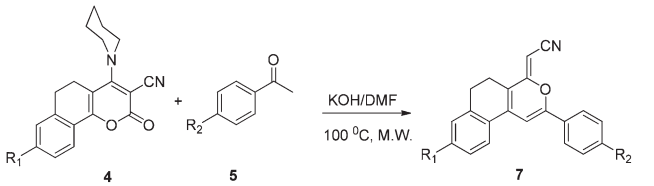
The structure and geometry of isochromene have been confirmed unambiguously by spectroscopic techniques and single crystal X-ray crystallography. The ^1H NMR spectrum of the desired product **7** exhibits a low δ value for proton (~4.40 ppm) at the carbon adjacent to the nitrile group due to the high shielding effect of pyran oxygen.[22] To assess the contribution of heteroaryl methyl ketone and aliphatic ketone as cyclohexanone to further expand the scope of the present methodology, isochromenes **9a–b** and chromenes **11a–b** were also synthesized and the results of this study are summarized in Tables 3 and 4.

All the ketone (aromatic and heteroaromatic) derivatives showed equal ease towards the product formation with 2-oxo-4-(piperidin-1-yl)-5,6-dihydro-2-benzo[*h*]chromene-3-carbonitriles **4**. It is noteworthy that the yield of chromenes **11a–b** was slightly lower.

Dihydrophenanthrenes **6a–c** were also synthesised using NaH and DMF under microwave conditions in good to excellent yields (Table 5). It has been observed that the yield of **6** is very high and the reaction requires much less time as compared to the conventional approach.

The molecular make up of precursor **4** reveals that it possesses three electrophilic centers C-2, C-4, and C-10b. Among them C-10b is highly susceptible to nucleophilic attack because of extended conjugation due to the presence of an electron withdrawing CN substituent at C-3 in the chromene

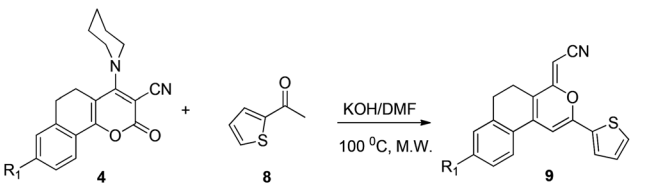
Table 2 Synthesis of (*Z*)-2-(2-aryl-5,6-dihydro-4*H*-benzo[*f*]isochromen-4-ylidene)acetonitriles **7**[a]



7	R_1	R_2	Yield (%)
a	H	H	77
b	H	OMe	79
c	H	F	84
d	H	Cl	80
e	H	Br	82
f	OMe	Br	85
g	OMe	OMe	78

[a] Reactions were performed under microwave irradiation at 100 °C and at a maximum applied power of 200 W for 15 minutes by use of **4** (0.5 mmol), **5** (0.5 mmol) and KOH (0.75 mmol) in 2.0 mL DMF.

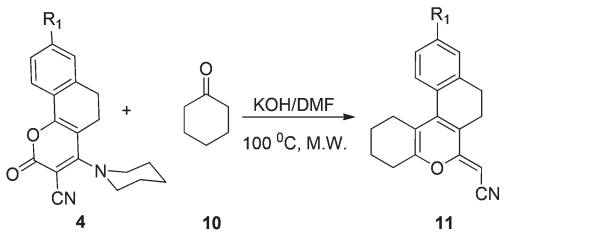
Table 3 Synthesis of (*Z*)-2-(2-(thiophen-2-yl)-5,6-dihydro-4*H*-benzo-[*f*]isochromen-4-ylidene)acetonitriles **9**[a]



9	R_1	Yield (%)
a	H	78
b	OMe	76

[a] Reactions were performed under microwave irradiation at 100 °C and at a maximum applied power of 200 W for 15 minutes by use of **4** (0.5 mmol), **8** (0.5 mmol), and KOH (0.75 mmol) in 2.0 mL DMF.

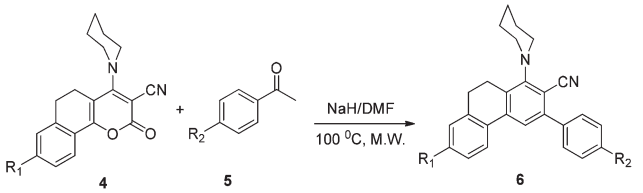
Table 4 Synthesis of (*Z*)-2-(3,4,7,8-tetrahydro-1*H*-naphtho [2,1-*c*]-chromen-6(2*H*)-ylidene)acetonitriles **9**[a]



11	R_1	Yield (%)
a	H	72
b	OMe	69

[a] Reactions were performed under microwave irradiation at 100 °C and at a maximum applied power of 200 W for 15 minutes by use of **4** (0.5 mmol), **10** (0.5 mmol), and KOH (0.75 mmol) in 2.0 mL DMF.

Table 5 Synthesis of 3-phenyl-1-(piperidin-1-yl)-9,10-dihydro phenanthrene-2-carbonitriles **6**[a]



6	R_1	R_2	Yield (%)
a	H	Br	90
b	H	OMe	86
c	OMe	Br	87

[a] Reactions were performed under microwave irradiation at 100 °C and at a maximum applied power of 200 W for 15 minutes by use of **4** (0.5 mmol), **5** (0.5 mmol), and NaH 0.75 mmol in 2.0 mL DMF.

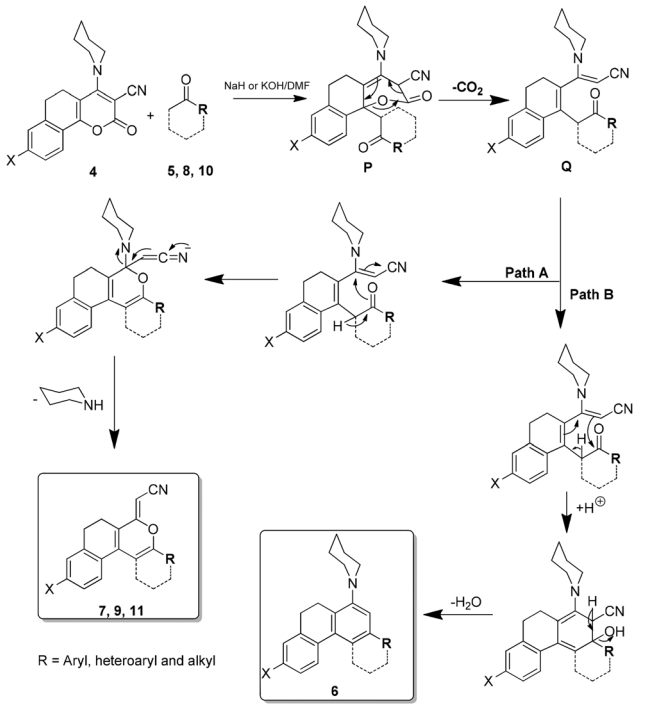
ring. Keeping this fact in mind we hypothesized the mechanism of our reaction as shown in Scheme 3. The reaction commences with the formation of intermediate **P** by a nucleophilic attack of carbanion generated *in situ* at the C-10b position of **4**. **P** undergoes decarboxylation to form **Q**. Thereafter the reaction may follow either path **A** for the formation of chromene or isochromene derivatives **7**, **9**, **11** *via* elimination of piperidine through SNi reaction of enolate formed in the presence of a base or path **B** to yield dihydrophenanthrene **10** *via* cyclization involving C-3 of chromene and the carbonyl group of ketone followed by aromatization *via* dehydration. One of the key differences between the conventional approach and the microwave assisted approach is regioselectivity for the product formation (Table 1, entries 3 and 6). We proposed that fast and uniform heating in microwave is responsible for regioselectivity, which is difficult through conventional heating. On the basis of the obtained regioselectivity, we propose that KOH stabilized the enolate form at high temperature, while NaH stabilized the keto form at both high and low temperatures.

X-ray structural analysis

X-ray diffraction studies[23] of (*Z*)-2-(2-(4-bromophenyl)-5,6-dihydro-4*H*-benzo[*f*]isochromen-4-ylidene)acetonitrile (**7e**) showed that the compound has a non-planarity induced chirality due to distortion in the aromatic rings. The conformation is shown as an ORTEP diagram in Fig. 2.

The X-ray studies further showed that the terminal rings A and C are nearly planar, while the central ring B adopts a half chair conformation. The average mean plane angle (torsion angle) for the twist between the terminal rings A and C is 17.8°.

The X-ray studies further confirmed that the *Z* geometry of the molecule and the nitrile group is present at the *syn* position to oxygen in the ring C (Fig. 2a). Crystal packing of (*Z*)-2-(2-(4-bromophenyl)-5,6-dihydro-4*H*-benzo[*f*]isochromen-4-ylidene)acetonitrile (**7e**) has shown some significant intermolecular interactions. It has been observed that moderate hydrogen bonding interaction (C–H···Br = 2.991 Å) occurs between the bromo (Br1) group and *ortho* hydrogen (H3) of ring D with the neighbouring molecules (Fig. 2b). This molecule also



Scheme 3 A plausible mechanism for the synthesis of isochromenes **7** and **9**, chromenes **11** and dihydrophenanthrenes **6**.

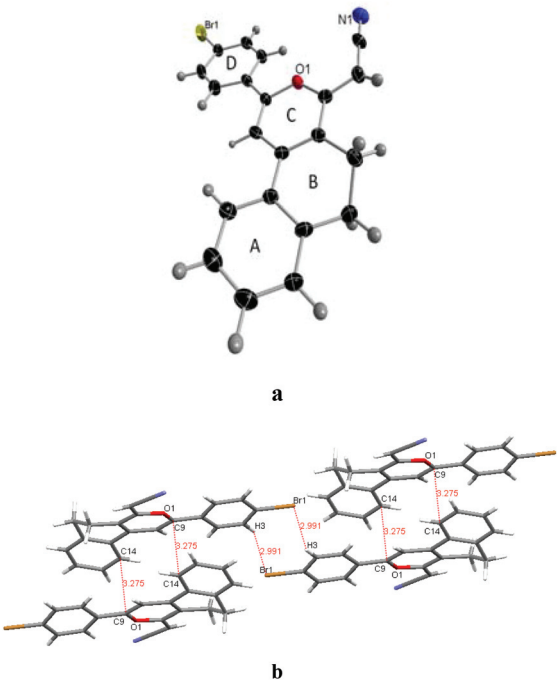


Fig. 2 (a) ORTEP diagram of (*Z*)-2-(2-(4-bromophenyl)-5,6-dihydro-4*H*-benzo[*f*]isochromen-4-ylidene)acetonitrile (**7e**); (b) capped stick model of **7e** showing intermolecular interactions.

exhibits weak pi interaction (C9···C14 = 3.275 Å) between rings C and A of neighbouring molecules.

Conclusion

In summary, we have developed a simple, efficient, non-catalytic regioselective synthesis of biologically important chromene, isochromene and dihydrophenanthrene derivatives from 2-oxabenzo[*h*]chromene under microwave irradiation. Our protocol avoids the use of expensive, moisture and air sensitive metal catalysts, organometallic reagents and ligands. Microwave irradiation played a major role in achieving regioselectivity and high yields. Thus, formation of two products from a single reaction can be performed in a regioselective manner *via* a cascade route using different bases. The structure of isochromene has also been confirmed unambiguously by spectroscopic analysis and X-ray diffraction study.

Experimental section

General remarks

Commercially available reagents were used without purification. ^{1}H and ^{13}C NMR spectra were taken on a 400 MHz NMR spectrometer and $CDCl_3$ was used as a solvent. Chemical shifts are reported in parts per million shift (δ-value) from ($CDCl_3$) (δ 7.24 ppm for ^{1}H) or based on the middle peak of the solvent ($CDCl_3$) (δ 77.00 ppm for ^{13}C NMR) as an internal standard. Signal patterns are indicated as s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet; bs, broad singlet; bm, broad multiplet. Coupling constants (J) are given in hertz (Hz). Infrared (IR) spectra were recorded on a Perkin-Elmer AX-1 spectrophotometer and reported in wave number (cm^{-1}). All the reactions were performed on a CEM microwave synthesizer. The reaction was performed at a constant temperature of 100 °C for 15 min with a maximum applied power of 200 W in a microwave synthesizer.

General procedure for the synthesis of (*Z*)-2-(2-aryl-5,6-dihydro-4*H*-benzo[*f*]isochromen-4-ylidene)acetonitriles (7a–k), (*Z*)-2-(2-(thiophen-2-yl)-5,6-dihydro-4*H*-benzo[*f*]isochromen-4-ylidene)-acetonitriles (9a–b), (*Z*)-2-(3,4,7,8-tetrahydro-1*H*-naphtho[2,1-*c*]-chromen-6(2*H*)-ylidene)acetonitrile (11a–b)

A dried microwave vial containing an equimolar mixture of 4-(piperidin-1-yl)-5,6-dihydro-2*H*-benzo[*h*]chromen-2-one-3-carbonitriles **4** (0.5 mmol) and functionalized acetophenones **5** or 2-acetylthiophene **8** or cyclohexanone **10** (0.5 mmol), potassium hydroxide (0.75 mmol) and DMF (2.0 mL) was placed in a microwave reactor for 15 minutes at 100 °C with a maximum applied power of 200 W. Completion of the reaction was monitored by TLC. After the completion, the reaction mixture was poured onto crushed ice with vigorous stirring followed by neutralization with 10% HCl. The precipitate obtained was filtered, dried and purified using 20% ethyl acetate in hexane as an eluent.

(*Z*)-2-(2-Phenyl-5,6-dihydro-4*H*-benzo[*f*]isochromen-4-ylidene)-acetonitrile (7a). Red solid; yield: 84%; melting point: 155–157 °C; IR (film): 2926 (CH), 2195 (CN) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.41 (t, J = 8.0 Hz, 2H), 2.90 (t, J = 8.0 Hz, 2H), 4.40 (s, 1H), 6.84 (s, 1H), 7.31–7.34 (m, 2H), 7.39–7.49 (m, 4H), 7.57–7.59 (m, 1H), 7.83–7.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 27.2, 63.9, 97.6, 118.7, 121.2, 123.9, 124.9, 125.1, 127.2, 128.3, 128.9, 129.8, 130.3, 131.4, 134.9, 137.0, 155.2, 166.0; *m*/*z* (CI) 320 (M + 23, 100%); HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{21}H_{16}NO$: 298.1232; found: 298.1226.

(*Z*)-2-(2-(4-Methoxyphenyl)-5,6-dihydro-4*H*-benzo[*f*]isochromen-4-ylidene)acetonitrile (7b). Red solid; yield: 79%; melting point: 190–192 °C; IR (film): 2933 (CH), 2192 (CN) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.39 (t, J = 8.0 Hz, 2H), 2.88 (t, J = 8.0 Hz, 2H), 3.84 (s, 1H), 4.35 (s, 1H), 6.71 (s, 1H), 6.95 (d, J = 6.4 Hz, 2H), 7.22–7.32 (m, 4H), 7.83 (d, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7, 27.2, 55.4, 63.2, 96.0, 114.3, 119.0, 120.0, 123.8, 123.9, 126.6, 127.1, 128.2, 129.7, 130.5, 135.2, 137.0, 155.2, 161.3, 166.2; HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{22}H_{18}NO_2$: 328.1338; found: 328.1330.

(*Z*)-2-(2-(4-Fluorophenyl)-5,6-dihydro-4*H*-benzo[*f*]isochromen-4-ylidene)acetonitrile (7c). Red solid; yield: 84%; melting point: 188–190 °C; IR (film): 2927 (CH), 2193 (CN) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 (t, J = 7.7 Hz, 2H), 2.90 (t, J = 7.7 Hz, 2H), 4.41 (s, 1H), 6.78 (s, 1H), 7.12–7.17 (m, 2H), 7.26–7.34 (m, 3H), 7.56–59 (m, 1H), 7.86–7.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 27.2, 64.1, 97.3, 116.1 (d, J = 20 Hz, 2C), 118.7, 121.0, 123.9, 127.0, 127.1 (d, J = 10 Hz, 2C), 127.6, 128.3, 129.9, 130.3, 134.9, 137.0, 154.2, 164.0 (d, J = 250 Hz, 1C), 166.0; *m*/*z* (CI) 316 (M + 1, 100%); HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{21}H_{15}FNO$: 316.1138; found: 316.1132.

(*Z*)-2-(2-(4-Chlorophenyl)-5,6-dihydro-4*H*-benzo[*f*]isochromen-4-ylidene)acetonitrile (7d). Red solid; yield: 80%; melting point: 192–194 °C; IR (film): 2924 (CH), 2194 (CN) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (t, J = 7.6 Hz, 2H), 2.85 (t, J = 7.6 Hz, 2H), 4.37 (s, 1H), 6.77 (s, 1H), 7.18–7.29 (m, 3H), 7.36 (d, J = 8.0 Hz, 2H), 7.51–7.53 (m, 1H), 7.76–7.78 (d, J = 8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 27.1, 29.7, 64.4, 97.9, 118.6, 121.5, 123.9, 126.2, 127.2, 128.3, 129.2, 129.8, 130.0, 130.2, 136.3, 136.9, 154.0, 165.8; *m*/*z* (CI) 332 (M + 1, 100%); HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{21}H_{15}ClNO$: 332.0842; found: 332.0835.

(*Z*)-2-(2-(4-Bromophenyl)-5,6-dihydro-4*H*-benzo[*f*]isochromen-4-ylidene)acetonitrile (7e). Red solid; yield: 82%; melting point: 190–192 °C; IR (film): 2929 (CH), 2195 (CN) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.39 (t, J = 7.6 Hz, 2H), 2.90 (t, J = 7.6 Hz, 2H), 4.41 (s, 1H), 6.81 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 27.1, 64.4, 97.9, 118.6, 121.5, 123.8, 124.6, 126.3, 126.5, 127.2, 128.3, 130.0, 130.2, 132.1, 134.7, 136.9, 154.0, 165.8; *m*/*z* (CI) 376 (M + 1, 100%); HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{21}H_{15}BrNO$: 376.0337; found: 376.0323.

(*Z*)-2-(2-(4-Bromophenyl)-8-methoxy-5,6-dihydro-4*H*-benzo[*f*]-isochromen-4-ylidene)acetonitrile (7f). Red solid; yield: 80%; melting point: 228–230 °C; IR (film): 2923 (CH), 2188 (CN) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.39 (t, J = 7.8 Hz, 2H), 2.87 (t, J = 7.8 Hz, 2H), 3.84 (s, 3H), 4.35 (s, 1H), 6.77–6.78 (m,

1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 27.6, 55.4, 63.2, 97.9, 112.3, 114.0, 118.9, 119.4, 123.1, 124.6, 125.5, 126.4, 130.4, 132.1, 134.7, 139.1, 153.9, 161.0, 165.9; *m*/*z* (CI) 428 (M + 23, 100%); HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{22}H_{17}BrNO_2$: 406.0437; found: 406.0443.

(*Z*)-2-(8-Methoxy-2-(4-methoxyphenyl)-5,6-dihydro-4*H*-benzo[*f*]-isochromen-4-ylidene)acetonitrile (7g). Red solid; yield: 78%; melting point: 156–158 °C; IR (film): 2935 (CH), 2192 (CN) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.32 (t, *J* = 8.0 Hz, 2H), 2.81 (t, *J* = 8.0 Hz, 2H), 3.78–3.79 (m, 6H), 4.24 (s, 1H), 6.62 (s, 1H), 6.71 (d, *J* = 2.8 Hz, 1H), 6.77 (dd, *J* = 8.8 Hz, *J* = 2.8 Hz, 1H), 6.90 (d, *J* = 7.2 Hz, 2H), 7.45 (d, *J* = 8.8 Hz, 1H), 7.77 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7, 27.7, 55.4, 62.1, 94.0, 112.2, 113.9, 114.3, 117.9, 119.4, 123.4, 124.0, 125.6, 126.6, 135.3, 139.2, 155.1, 160.8, 161.3, 166.3; HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{23}H_{20}NO_3$: 358.1443; found: 358.1438.

(*Z*)-2-(2-(Thiophen-2-yl)-5,6-dihydro-4*H*-benzo[*f*]isochromen-4-ylidene)acetonitrile (9a). Red solid; yield: 78%; melting point: 162–164 °C; IR (film): 2925 (CH), 2197 (CN) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (t, *J* = 8.0 Hz, 2H), 2.84 (t, *J* = 8.0 Hz, 2H), 4.34 (s, 1H), 6.58 (s, 1H), 7.04 (t, *J* = 4.8 Hz, 1H), 7.16–7.18 (m, 1H), 7.25–7.29 (m, 2H), 7.34 (d, *J* = 4.8 Hz, 1H), 7.48–7.50 (m, 1H), 7.59 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 27.2, 64.3, 96.9, 118.5, 120.7, 123.9, 126.8, 127.2, 127.7, 128.3, 129.9, 130.2, 134.9, 135.1, 136.9, 151.1, 165.6; *m*/*z* (CI) 326 (M + 23, 100%); HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{19}H_{13}NOS$: 304.0796; found: 304.0786.

(*Z*)-2-(8-Methoxy-2-(thiophen-2-yl)-5,6-dihydro-4*H*-benzo[*f*]-isochromen-4-ylidene)acetonitrile (9b). Red solid; yield: 76%; melting point: 180–182 °C; IR (film): 2924 (CH), 2192 (CN) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (t, *J* = 7.8 Hz, 2H), 2.86 (t, *J* = 7.8 Hz, 2H), 3.83 (s, 3H), 4.32 (s, 1H), 6.59 (s, 1H), 6.76 (d, *J* = 2.0 Hz, 1H), 6.82 (dd, *J* = 8.8 Hz, *J* = 2.0 Hz, 1H), 7.08–7.10 (m, 1H), 7.37–7.38 (m, 1H), 7.47 (d, *J* = 8.8 Hz, 1H), 7.62–7.63 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 27.6, 55.4, 63.0, 96.9, 112.3, 114.0, 118.5, 118.7, 123.1, 125.6, 126.7, 127.6, 128.2, 134.9, 135.2, 139.1, 151.0, 160.9, 165.7; HRMS (*m*/*z*): [M]+ calcd for $C_{20}H_{15}NO_2S$: 333.0823; found: 333.0879.

(*Z*)-2-(3,4,7,8-Tetrahydro-1*H*-naphtho[2,1-*c*]chromen-6(2*H*)-ylidene)acetonitrile (11a). Viscous red liquid; yield: 72%; IR (film): 2928 (CH), 2194 (CN) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.60–1.66 (m, 2H), 1.83–1.87 (m, 2H), 2.25 (t, *J* = 7.4 Hz, 2H), 2.57 (t, *J* = 6.4 Hz, 4H), 2.73 (t, *J* = 7.4 Hz, 2H), 4.28 (s, 1H), 7.21–7.28 (m, 3H), 7.49–7.51 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 22.8, 23.2, 27.5, 27.8, 28.1, 61.8, 110.4, 119.3, 123.2, 126.2, 127.4, 127.8, 128.8, 131.1, 138.1, 138.9, 155.0, 165.8; HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{19}H_{18}NO$: 276.1388; found: 276.1383.

(*Z*)-2-(10-Methoxy-3,4,7,8-tetrahydro-1*H*-naphtho[2,1-*c*]-chromen-6(2*H*)-ylidene)acetonitrile (11b). Viscous red liquid; yield: 69%; IR (film): 2927 (CH), 2192 (CN) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.61–1.63 (m, 2H), 1.81 (t, *J* = 6.0 Hz, 2H), 2.21 (t, *J* = 7.4 Hz, 2H), 2.54 (t, *J* = 6.0 Hz, 4H), 2.69 (t, *J* = 7.4 Hz, 2H), 3.81 (s, 3H), 4.19 (s, 1H), 6.73–6.76 (m, 2H), 7.43 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 22.6, 23.2, 27.5, 27.9, 28.6, 55.3, 60.7, 110.4, 111.2, 113.6, 119.6, 121.3, 123.9, 130.0, 138.1, 141.1, 155.0, 159.8, 165.9; *m*/*z* (CI) 306 (M + 1, 100%); HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{20}H_{20}NO_2$: 306.1489; found: 306.1496.

General procedure for the synthesis of 3-aryl-1-(piperidin-1-yl)-9,10-dihydrophenanthrene-2-carbonitriles (6a–c)

A dried microwave vial containing an equimolar mixture of 4-(piperidin-1-yl)-5,6-dihydro-2*H*-benzo[*h*]chromen-2-ones **4** (0.5 mmol) and different acetophenones **5** (0.5 mmol) with NaH (0.75 mmol) and DMF (2 mL) was placed in a microwave reactor for 15 minutes at 100 °C. The reaction was monitored by TLC and after completion the reaction mixture was poured onto crushed ice and neutralized by 10% HCl with vigorous stirring. The precipitate was filtered, dried and purified using 20% ethyl acetate in hexane as an eluent. Compounds **6a** and **6b** have been reported in earlier literature.[20]

3-(4-Bromophenyl)-7-methoxy-1-(piperidin-1-yl)phenanthrene-2-carbonitrile (6c). Off white solid; yield: 87%; melting point: 168–170 °C; IR (film): 2924 (CH), 2213 (CN) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.73 (br, 6H), 2.81 (t, *J* = 8.0 Hz, 2H), 2.91 (t, *J* = 8.0 Hz, 2H), 3.26 (br, 4H), 3.84 (s, 3H), 6.79–6.84 (m, 2H), 7.41 (d, *J* = 8.8 Hz, 2H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.4, 24.1, 26.8, 28.9, 52.0, 55.4, 105.8, 112.7, 113.3, 118.7, 120.5, 122.7, 126.1, 126.5, 130.6, 131.7, 133.9, 138.0, 139.8, 140.1, 144.2, 154.8, 160.2; HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{27}H_{25}BrN_2O$: 473.1229; found: 473.1223.

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23 Crystal data for $C_{21}H_{14}BrNO$: a red crystal (0.11 × 0.10 × 0.03 mm) was mounted on a capillary tube for indexing and intensity data collection at 293(2) K on an Oxford Xcalibur Sapphire3 CCD single-crystal diffractometer (Mo Kα radiation, λ = 0.71073 Å). Routine Lorentz and polarization corrections were applied, and an absorption correction was performed using the ABSCALE 3 program [CrysAlis Pro software system, Version 171.34; Oxford Diffraction Ltd, Oxford, UK, 2011]. Patterson methods were used to locate the heavy metal atoms (SHELXS-86), and the remaining atoms were located from successive Fourier maps (SHELXL-97). All the non-hydrogen atoms were refined anisotropically; hydrogen atoms were located at calculated positions using a riding model. All hydrogen atoms were calculated after each cycle of refinement using a riding model, with C–H = 0.93 Å + U_{iso}(H) = 1.2 U_{eq}(C) for aromatic H atoms, and with C–H = 0.97 Å + U_{iso}(H) = 1.2 U_{eq}(C) for methylene H atoms. Crystal data: $C_{21}H_{14}BrNO$; M_r = 376.25, crystal system: triclinic; space group $P\bar{1}$, a = 7.3715(4) Å, b = 9.3781(7) Å, c = 12.8371(12) Å, α = 96.360(7)°, β = 99.202(7)°, γ = 111.905(6)°, V = 798.57(10) Å^3, Z = 2, ρ_{calcd} = 1.565 g cm^{-3}, μ = 2.580 mm^{-1}, F(000) = 380, R_1 = 0.0759 and wR_2 = 0.2085 for $I > 2\sigma(I)$ and 226 parameters, R_1 = 0.0892 and wR_2 = 0.2198, gof = 1.097 for all data. CCDC (Deposit no. 959771) contains the supplementary crystallographic data.

