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ARTICLE TYPE

Precursor directed regioselective synthesis of partially reduced benzo[*e*]indene through oxidative cyclization and benzo[*h*]quinolines

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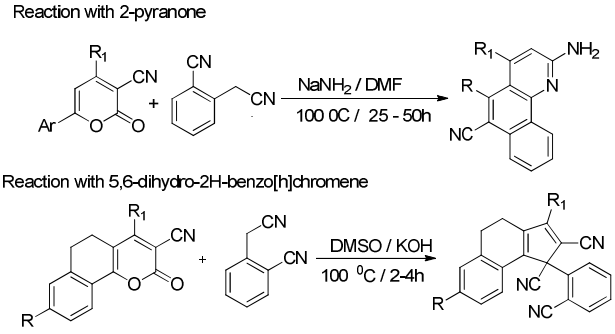
We have reported simple, unprecedented base promoted synthesis of 7-substituted-1-(2-cyano-phenyl/phenyl)-3-*sec.*amino-4,5-dihydro-1*H*-benz[*e*]indene-1,2-dicarbonitriles by reaction of 2-oxo-4-*sec.*amino-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles and 2-cyanomethyl-benzonitrile/phenyl-acetonitrile under basic condition at 100 °C. This reaction involves ring opening of 2-oxo-4-*sec.*amino-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitrile by carbanion generated in situ from 2-cyanomethylbenzonitrile/phenyl-acetonitrile followed by oxidative cyclization to afford the desired product. Alternatively, reaction of 6-aryl-4-*sec.*amino-2*H*-pyran-2-one-3-carbonitriles and 2-cyanomethyl-benzonitrile under basic conditions provides functionalized benzo[*h*]quinolines. Structure of the synthesized compound was confirmed by single crystal X-ray.

Benzo[*e*]indenes are widely present in nature and well known for their use as a building block in organic synthesis. Indene has broad use in medicine.[1] This skeleton is present as substructure in steroid,[2] hamigeran B[3] and polymers[4] in completely or partially reduced form. Various monosubstituted derivatives of 1*H*-benzo[*e*]indene-1,3-(2*H*)-dione exhibit antiviral activity.[5] Many approaches for the construction of benzo[*e*]indene as whole or substructure has been reported. Synthesis of indene derivatives has been carried out by reaction of alkynes and phenyl pyrrolidino or morpholino chromium carbene complexes[6] in DMF at 120-125 °C. Another approach used to build indene skeleton involves cyclization of substituted phenyl allylic cations.[7] Indene was also prepared by cycloalkylation procedure, such as; reaction of arylated alkene with phosphorus halide and dehydration of aryl substituted diols.[8-10] It was also synthesized by reaction of gem-dihalocyclopropane and benzene in presence of aluminium chloride.[11] Recently, indene was synthesized by metal catalyzed cycloisomerization of 1-alkyl-2-ethynylbenzenes.[12] This reaction can be performed by using $PtCl_2$ or $PtCl_4$ or $[RuCl_2(CO)_3]_2$ as a catalyst at 30-80 °C.[12] Au(l) catalyzed [3+3] cycloaddition,[13] and Pd-catalyzed carboannulation of propargyl carbonates[14] also provides functionalized indenes. Ru catalyzed hydroamination followed by Re catalyzed C-H bond activation approach using aryl alkyne as a precursor[15] was also reported for synthesis of indene. Bi et al have established electrocyclization approach for generation of indene.[16]

A careful literature survey confirms that various approach for the synthesis of indene skeleton requires various expensive metal catalyst and harsh reaction conditions. Recently, we have reported the synthesis of benzo[*h*]quinolines by reaction of 2-cyanomethylbenzonitrile and 2-pyranone under basic conditions.[17]

In this connection, we wish to report the use of 2-oxo-4-*sec.*amino-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles as a precursor, which changes the course of the reaction to give benzo[e]indenes (Scheme 1).

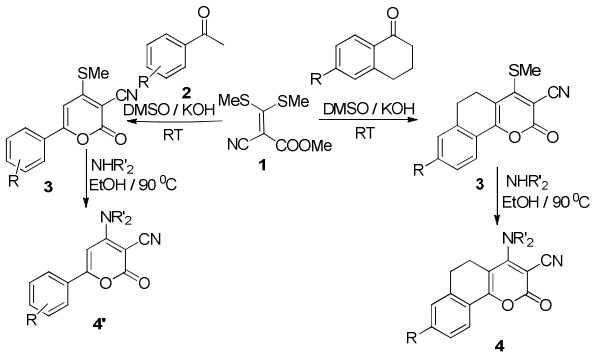
Scheme 1. Precursor dependent synthesis of functionalized benzo[h]quinoline and 4,5-dihydro-1*H*-benz[*e*]indene



Here, we have studied the comparison of two precursor 2-oxo-4-*sec.*amino-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles **4** and 6-aryl-4-*sec.*amino-2*H*-pyran-2-one-3-carbonitriles **4'** using 2-cyanomethylbenzonitrile as carbanion source. These precursors can be synthesized in two steps. First 8-substituted-4-methylsulfanyl-2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles **3** and 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carbonitriles were synthesized by reaction of 2-cyono-3,3-bis-methylthio-acrylic acid methyl ester **1** and 1-teteralone/6-methoxy-1-teteralone and functionalized acetophenones in DMSO in presence of KOH respectively. The compound **3** on amination with various secondary amine in refluxing ethanol provides 2-oxo-4-*sec.*amino-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitrile **4** and 6-aryl-4-*sec.*amino-2*H*-pyran-2-one-3-

carbonitriles **4'** in good yields (Scheme 2).[18]

Scheme 2 Synthesis of 8-OMe/H-2-Oxo-4- sec amino-1-yl-5,6-dihydro-2H-benzo[h]chromene-3-carbonitriles and 6-aryl-4-sec.amino-2H-pyran-2-one-3-carbonitriles



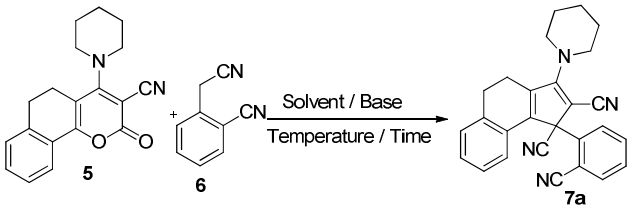
Recently, base promoted chemoselective synthesis of benzo[*h*]quinolines[17] was reported by reaction of 6-aryl-4-*sec.*amino-2-oxo-2*H*-pyran-3-carbonitriles **4'** and 2-cyanomethylbenzonitrile under basic conditions (Scheme 3). To expand the scope of reaction, we shifted to fused precursor 2-oxo-4-*sec.*amino-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles **4**. Interestingly, use of 2-oxo-4-*sec.*amino-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles **4** as a precursor did not followed the same course of reaction and 7-substituted-1-(2-cyano-phenyl)-3-*sec.*amino-1-yl-4,5-dihydro-1*H*-benz[*e*]indene-1,2-dicarbonitrile was obtained as a product.

To study the effect of base and solvents on reaction, we have chosen 2-oxo-4-piperidin-1-yl-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitrile and 2-cyanomethylbenzonitrile as model substrates. Initially, 4-methylsulfanyl-2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitrile **3** was used as substrate to perform the ring transformation reaction and complex mixture obtained, probably due to presence of methylthio group at position 4. To reduce the electrophilicity at C-4, methylthio group was replaced with secondary amine. We have started the study using sodamide as a base in DMF (entry 1) and DMSO (entry 2) at room temperature and observed complex mixture formation with major unreacted starting material. Then, we have performed the reaction **4** and **5** in DMF using sodamide as a base at 70 ^{o}C and 25% of desired product was isolated (entry 3), while at 100 ^{o}C, 40% of product formed in 2 h (entry 4). Use of sodamide in DMSO at 100 ^{o}C afforded 35 % of desired product (entry 5). Further optimization was carried out by using KOH as base in DMSO and DMF separately at 100 ^{o}C and 35% and 42% of the product isolated respectively (entry 6 and 7). In another experiment, reaction of **4** and **5** was carried out in DMF using KOH as a base at 120 ^{o}C and lowering in yield was observed (entry 8). Further reaction was also performed by using sodium hydride as base in DMSO and DMF separately at 100 ^{o}C and obtained the desired product in 32% and 37% of yield (entry 9 and 10).

Thus, stirring of a mixture of functionalized 5,6-dihydro-2H-benzo[*h*]chromene-3-carbonitrile **4** and 2-cyanomethylbenzonitrile in DMF using potassium hydroxide as a base at 100 ^{o}C for 2-4 h provides corresponding product in moderate yield (Scheme 3).

Efficiency of reaction condition as in entry 7 was tested for the synthesis of various 1-(2-cyano-phenyl/phenyl)-3-*sec.*amino-4,5-

Table 1: Effect of base and solvent on the synthesis of **7a**.[a]



Entry	Base	Solvent	Temp(^{o}C)	Time(h)	Yield(%)[b]
1	$NaNH_2$	DMF	RT[b]	5h	Complex mixture
2	$NaNH_2$	DMSO	RT	5h	Complex mixture
3	$NaNH_2$	DMF	70	4h	25
4	$NaNH_2$	DMF	100	2h	40
5	$NaNH_2$	DMSO	100	2h	35
6	KOH	DMSO	100	2h	35
7	**KOH**	**DMF**	100	**2h**	**42**
8	KOH	DMF	120	2h	35
9	NaH	DMSO	95	2h	32
10	NaH	DMF	95	2h	37

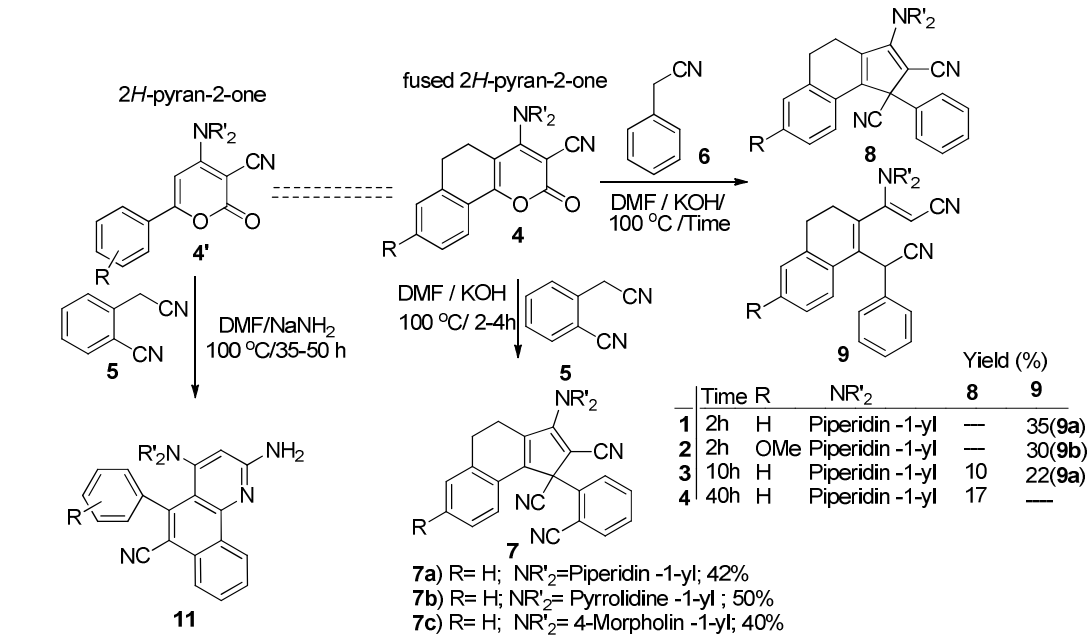
[a]Reactions were carried out by stirring 2-oxo-4-piperidin-1-yl-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitrile (0.5 mmol), 2-cyanomethylbenzonitrile (0.5 mmol), base (0.75 mmol) in solvent (4.0 mL); [b]RT = 25-35 ^{o}C

dihydro-1*H*-benz[*e*]indene-1,2-dicarbonitrile (**7**) derivatives. Surprisingly, When we have used benzyl cyanide in lieu of 2-cyanomethylbenonitrile as a carbanion source, under similar reaction condition cyclised product was not obtained after 2 h. Probably, 3-(1-(cyano(phenyl)methyl)-6-substituted-3,4-dihydronaphthalen-2-yl)-3-(piperidin-1-yl)acrylonitriles (**9**) is intermediate for the final product. In order to prove this we have performed the reaction for 10 h and obtained mixture of 3-(1-(cyano(phenyl)methyl)-6-substituted-3,4-dihydronaphthalen-2-yl)-3-(piperidin-1-yl)acrylonitriles (**9**) and proposed cyclized product 1-phenyl-3-(piperidin-1-yl)-4,5-dihydro-1*H*-cyclopenta[*a*]naphthalene-1,2-dicarbonitrile (**8**) in low yield (Scheme 3). Further increase in duration of reaction up to 40 h afforded regioselectively 1-phenyl-3-(piperidin-1-yl)-4,5-dihydro-1H-cyclopenta[a]naphthalene-1,2-dicarbonitrile (**8**) in 17% yield. This result concludes that presence of electron withdrawing group at ortho position of benzyl cyanide increase the rate of cyclization. To confirm **9a** as reaction intermediate, an independent reaction was performed and it was stirred in DMF in presence of KOH and 49% of desired product **8** was isolated (Scheme 4). We have further proved the role of aerial oxygen in cyclization by running the above mentioned reaction under nitrogen atmosphere. No desired product formation was observed except formation of complex reaction mixture and left starting material.

Recently, we have reported that use of 6-aryl-4-*sec.*amino-2*H*-pyran-2-one-3-carbonitriles as precursor afforded 2-amino-5-aryl-4-*sec.*amino-1-yl-benzo[*h*]quinoline-6-carbonitriles rather than cyclopentadiene. This reaction also requires longer duration for completion to afford good yield of benzo[*h*]quinoline. If we compare the structure of 6-aryl-4-*sec.*amino-2*H*-pyran-2-one-3-

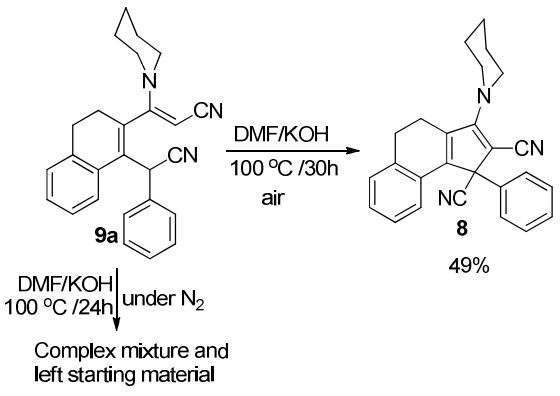
carbonitriles **4'** and 5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitrile **4**, only difference of substitution pattern at position 5 was observed, which change the course of reaction (Figure 1).

Scheme 3: Synthesis of 7-OMe/H-1-(2-cyano-phenyl/phenyl)-3-*sec*.amino-4,5-dihydro-1*H*-benz[*e*]indene-1,2-dicarbonitriles,[a] 3-[1-(cyano-phenyl-methyl)-6-OMe/H-3,4-dihydro-napthalen-2-yl]-3-piperidine-1-yl-acrylonitrile[b] and functionalized benzo[*h*]quinoline[18]



a) Reactions were performed by stirring 2-oxo-4-*sec*.amino-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles **4** (0.5 mmol) and 2-cynomethyl-benzonitrile **5** (0.5 mmol) using KOH (0.75 mmol) in DMF (4.0 mL) at 100 °C; b) Reactions were performed by stirring 2-oxo-4-*sec*.amino-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles **4** (0.5 mmol) and phenyl-acetonitrile **6** (0.5 mmol) using KOH (0.75mmol) as a base in DMF (4.0 mL) at 100 °C

Scheme 4: Scheme showing the proposed intermediate and role of aerial oxygen



Role of substitution at position 5 can be understood by intermediate involved in the mechanism itself. It is clear from topography of 6-aryl-4-*sec*.amino-2*H*-pyran-2-one-3-carbonitriles and 5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitrile **4**, that position C6 and C10b are more electrophilic in nature respectively and more vulnerable to nucleophilic attack. Mechanistically, if reaction follows path a, ring opening of pyran ring with carbanion generated by 2-cyanomethylbenzonitrile resulting in intermediate **A**.

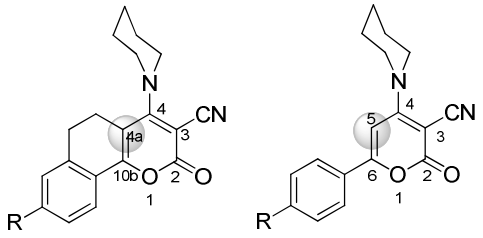
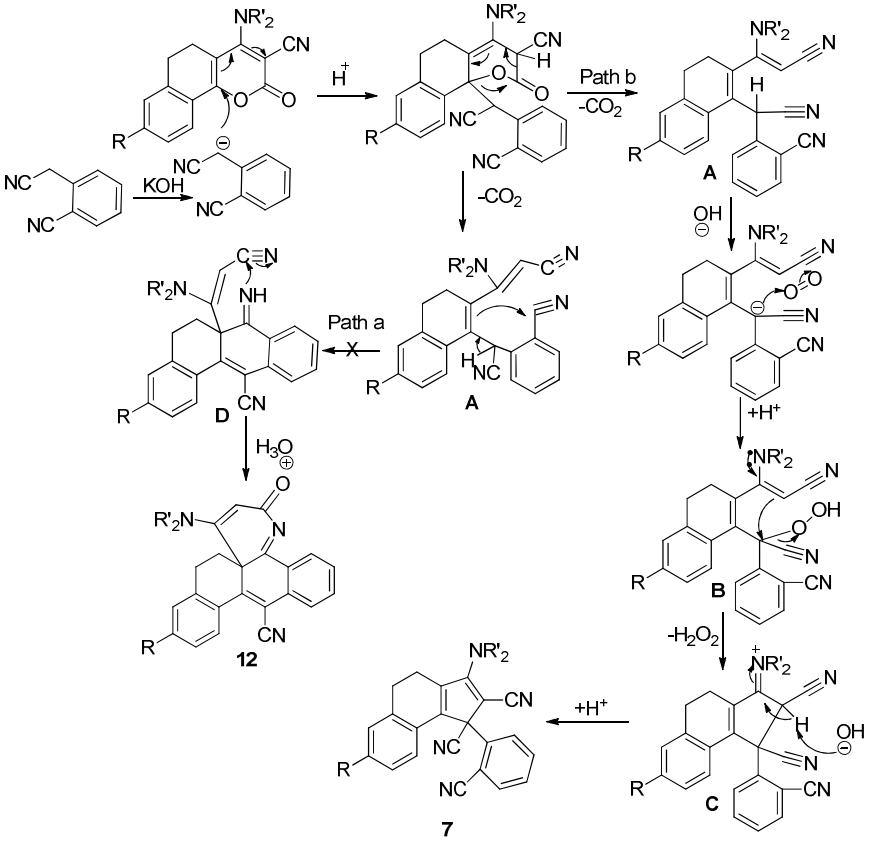


Figure 1: Structural comparison of precursors 6-aryl-4-*sec*.amino-2*H*-pyran-2-one-3-carbonitriles **4'** and 5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitrile **4**

If this intermediate followed the previous pathway seen with the pyrones, a cyclization involving the nitrile group of benzonitrile and C4a of chromone provide the formation of intermediate **D**, which can further cyclize by involving imine generated in situ with nitrile present in chromene to result the final product **12**. Product **12** was not formed probably due to involvement of sterically congested and rigid intermediate, which cannot undergo cyclization (path a). According to path **b**, 2-((2-(1-*sec*.amino-2-cyanovinyl)-3,4-dihydronaphthalen-1-yl)-

(cyano)methyl)benzonitriles formed by attack of carbanion generated from 2-cyanomethylbenzonitrile at C-10b position of 5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitrile **4** followed by decarboxylation. In presence of excess of base, carbanion generated at benzylic carbon of intermediate **A**, which reacts with molecular oxygen, resulting an intermediate **B**. Intermediate **B** undergoes cyclization involving C3 of 5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitrile **4** and benzylic carbon of 2-cyanomethylbenzonitrile involving loan pair of secondary amine

Scheme 5: Mechanistic approach for the synthesis of 1-(2-cyano-phenyl/phenyl)-3-*sec*.amino-4,5-dihydro-1*H*-benz[*e*]indene-1,2-dicarbonitriles **7**



present at C4 position leading the intermediate **C** with loss of peroxide. Intermediate **C** leads to the desired product **7** with loss of proton (Scheme 5). It is clear from the mechanistic discussion

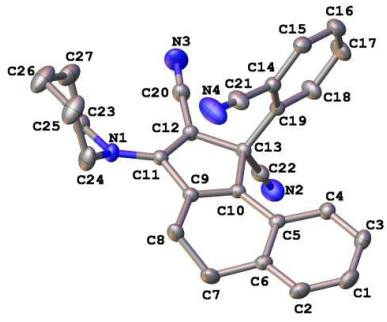


Figure 2: ORTEP image of 7a at 30% probability with atom numbering scheme

that presence of functional group at position 5 of pyran ring change the course of reaction possible due to involvement of steric factor.

Structure of one of the synthesized compound **7a** was confirmed by single crystal X-ray (Fig. 2).[19] From the structure of compound, it is clear that piperidine ring exhibit chair form. Cyclopentadiene and phenyl rings are planar and C7 and C8 push them in different plane due to puckered ring. There is no major interaction present in the molecule.

Conclusions

In summary, we have demonstrated the precursor directed synthesis of 1-(2-cyano-phenyl/phenyl)-3-*sec*.amino-4,5-dihydro-1*H*-benz[*e*]indene-1,2-dicarbonitriles in one pot under basic condition through aerial oxidation and functionalized benzo[*h*]quinolines. Intermediate involved in the synthesis of 1-(2-cyano-phenyl/phenyl)-3-*sec*.amino-4,5-dihydro-1*H*-benz[e]indene-1,2-dicarbonitriles was also isolated. Role of aerial oxygen was also demonstrated by independent reaction. This procedure is metal free and all the required precursors are easily accessible. These molecules could not be synthesized in single step by using available literature method. We have also tried to explain the role of structure of precursor for synthesis of corresponding product.

Experimental Section

General remarks: Commercial available reagent and solvent

purchased by Sigma Aldrich and Alfa Aesar and used without further purification. IR spectra were recorded on a Perkin-Elmer AX-1 spectroscopy in wave number (cm^{-1}). The ^1H NMR (400MHz) and ^{13}C NMR (100MHz) spectra were recorded in $CDCl_3$ considering ($CDCl_3$) δ 7.24 ppm for ^1H NMR and δ 77.00 ppm for ^{13}C NMR as an internal standard. Coupling constant J is reported in Hz and internal signal patterns reported as m, multiplet; dd double doublet; t, triplet; d, doublet; s, singlet. HRMS were recorded ESIMS spectrometer.

Intensity data for the white crystal of **7a** was collected at 298(2) K on a OXFORD CrysAlis diffractometer system equipped with graphite monochromated Mo Kα radiation λ = 0.71073 Å. The final unit cell determination, scaling of the data, and corrections for Lorentz and polarization effects were performed with CrysAlis RED.[20] The structures were solved by direct methods (SHELXS-97)[21] and refined by a full-matrix least-squares procedure based on F2.[22] All the calculations were carried out using WinGX system Ver-1.64.[23]

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General procedure for the synthesis of 7-OMe/H-1-(2-cyanophenyl)-3-*sec*.amino-4,5-dihydro-1*H*-benz[*e*]indene-1,2-dicarbonitrile (7a-7f): A mixture of 8-OMe/H-2-oxo-4-*sec*.amino-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitrile (0.5 mmol), 2-cyanomethylbenzonitrile (0.5 mmol, 71.0 mg) and KOH (0.75 mmol,42.0 mg) in DMF (4.0 mL) was stirred at 100 ^oC for 2-4 h. Reaction was monitored by TLC. After completion, reaction mixture was poured onto ice-water with constant stirring and then neutralized with 10% HCl. The precipitate obtained was filtered, washed with water and dried over dry sodium sulphate. Crude product was purified on silica-gel column chromatography using 10 % ethyl acetate in hexane as an eluent.

1-(2-Cyano-phenyl)-3-piperidine-1-yl-4,5-dihydro-1*H*-benz[*e*]indene-1,2-dicarbonitrile 7a: Yield: 42%, 0.45 R_f (20% ethylacetate-hexane), orange solid; mp: 222-224 ^oC; IR (KBr): 2926, 2854, 2180 cm^{-1}; ^1H NMR (400 MHz , $CDCl_3$): δ 1.63-1.82 (m, 6H, -CH_2-), 2.64-2.75 (m, 1H, -CH_2-), 2.77-2.89 (m, 1H, -CH_2-), 2.90-3.01 (m, 1H, -CH_2-), 3.03-315 (m, 1H, -CH_2-), 3.46-3.62 (m, 4H, -CH_2-), 6.81 (d, *J* = 7.6 Hz, 1H, ArH), 6.94-7.02 (m, 1H, ArH), 7.13-7.19 (m, 2H, ArH), 7.43 (t, *J* = 7.6 Hz, 1H, ArH), 7.56-7.61 (dd, *J* = 1.5Hz, 1H, ArH), 7.72-7.78 (m, 1H, ArH), 8.24 (d, *J* = 7.6 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.1, 23.7, 26.0, 27.9, 51.0, 55.0, 83.6, 108.8, 116.2, 116.7, 117.6, 123.0, 126.9, 128.1, 128.3, 129.1, 129.3, 129.5, 133.7, 135.2, 136.4, 136.6, 142.3, 142.6, 165.0; HRMS (ESI) calculated for $C_{27}H_{22}N_4$, 403.1917 (MH^+); found for *m/z*, 403.1896.

1-(2-Cyano-phenyl)-3-pyrrolidin-1-yl-4,5-dihydro-1*H*-benz[*e*]indene-1,2-dicarbonitrile 7b: Yield: 50%, 0.46 R_f (20% ethylacetate-hexane), orange solid; mp: 172-174 ^oC; IR (KBr): 2924, 2854, 2174 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 190-2.03 (m, 4H, -CH_2-), 2.83-3.20 (m, 4H, -CH_2-), 3.72-3.97 (m, 4H, -CH_2-), 6.89 (d, *J* = 7.6 Hz, 1H, ArH), 6.95-7.02 (m, 1H, ArH), 7.12-7.18 (m, 2H, ArH), 7.41 (t, *J* = 7.6 Hz, 1H, ArH), 7.56 (d, *J* = 7.6 Hz, 1H, ArH), 7.68-7.77 (m, 1H, ArH), 8.23 (d, *J* = 7.6 Hz,1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.7, 25.5, 27.7, 51.3, 55.0, 78.1, 108.8, 116.4, 117.2, 119.4, 123.2, 126.8, 128.0, 128.1, 128.9, 129.3, 129.4, 133.6, 136.0, 136.1, 136.6, 140.9, 142.8, 159.8; HRMS (ESI) calculated for $C_{26}H_{19}N_4$, 389.1761 (MH^+); found for *m/z*, 389.1741.

1-(2-Cyano-phenyl)-3-morpholin-1-yl-4,5-dihydro-1*H*-benz[*e*]indene-1,2-dicarbonitrile 7c: Yield: 40%, 0.40 R_f (30% ethylacetate-hexane), orange solid; mp: 188-190 ^oC; IR (KBr): 2923, 2853, 2182 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.63-2.74 (m, 1H, -CH_2-), 2.76-2.87 (m, 1H, -CH_2-), 2.92-3.03 (m, 1H, -CH_2-), 3.03-315 (m, 1H, -CH_2-), 3.54-3.69 (m, 4H, -CH_2-), 3.81-3.88 (m, 4H, -CH_2-), 6.79 (d, *J* = 7.3 Hz, 1H, ArH), 6.95-7.03 (m, 1H, ArH), 7.19 (d, *J* = 4.4 Hz, 2H, ArH), 7.44-7.51 (m, 1H, ArH), 7.58-7.63 (m, 1H, ArH), 7.74-7.81 (m, 1H, ArH), 8.25 (d, *J* = 8.0 Hz,1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.0, 27.8, 50.0, 55.1, 66.5, 85.0, 108.7, 116.2, 116.3, 117.0, 123.0, 127.0, 128.1, 128.2, 129.3, 129.6, 129.6, 133.9, 134.6, 136.3, 136.7, 141.7, 143.1, 164.5; HRMS (ESI) calculated for $C_{26}H_{20}N_4O$, 405.1710 (MH^+); found for *m/z*, 405.1717.

1-(2-Cyano-phenyl)-3-(4-benzyl-piperazin)-1-yl-4,5-dihydro-1*H*-benz[*e*]indene-1,2-dicarbonitrile 7d: Yield: 38%, 0.42 R_f (30% ethylacetate-hexane), orange solid; mp: 186-188 ^oC; IR (KBr): 2924, 2853, 2183 cm^{-1}; ^1H NMR (400 MHz , $CDCl_3$): δ 2.58-2.63 (m, 4H, -CH_2-), 2.63-2.73 (m, 1H, -CH_2-), 2.76-2.86 (m, 1H, -CH_2-), 2.90-3.00 (m, 1H, -CH_2-), 3.03-313 (m, 1H, -CH_2-), 3.55 (s, 2H, -CH_2-), 3.58-3.66 (m, 4H, -CH_2-), 6.79 (d, *J* = 7.3 Hz, 1H, ArH), 6.95-7.01 (m, 1H, ArH), 7.16 (d, *J* = 4.4 Hz, 2H, ArH), 7.39-7.35 (m, 5H, ArH), 7.42-7.48 (m, 1H, ArH), 7.57-7.62 (m, 1H, ArH), 7.72-7.79 (m, 1H, ArH), 8.24 (d, *J* = 8.0 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.1, 27.9, 49.7, 52.7, 55.0, 62.6, 84.3, 108.7, 116.2, 116.6, 117.3, 123.0, 126.9, 127.3, 128.1, 128.2, 128.3, 129.0, 129.2, 129.4, 129.5, 133.8, 134.9, 136.3, 136.7, 137.4, 142.0, 142.9, 164.5; HRMS (ESI) calculated for $C_{33}H_{27}N_5$, 494.2339 (MH^+); found for *m/z*, 494.2343.

1-(2-Cyano-phenyl)-7-methoxy-3-piperidine-1-yl-4,5-dihydro-1*H*-benz[*e*]indene-1,2-dicarbonitrile 7e: Yield: 40%, 0.47 R_f (30% ethylacetate-hexane), orange solid; mp: 119-121^oC; IR (KBr): 2939, 2855, 2179 cm^{-1}; ^1H NMR (400 MHz , $CDCl_3$): δ 1.60-1.80 (m, 6H, -CH_2-), 2.60-2.73 (m, 1H, -CH_2-), 2.74-2.86 (m, 1H, -CH_2-), 2.87-299 (m, 1H, -CH_2-), 3.00-312 (m, 1H, -CH_2-), 3.49-3.60 (m, 4H, -CH_2-), 3.72 (s, 3H, -O-CH_3), 6.47-6.53 (d,d, *J* = 2.2 Hz, 1H, ArH), 6.69-6.79 (m, 2H, ArH), 7.39-7.46 (m, 1H, ArH), 7.55-7.60 (m, 1H, ArH), 7.70-7.77 (m, 1H, ArH), 8.22 (d, *J* = 8.0 Hz, 1H, ArH); ^{13}C NMR (100 MH, $CDCl_3$): δ 23.0, 23.7, 26.0, 28.4, 50.9, 54.9, 55.1, 82.5, 108.8, 111.5, 114.4, 116.2, 116.9, 117.9, 121.4, 124.4, 129.0, 129.4, 133.6, 135.5, 136.6, 138.6, 139.3, 142.8, 160.4, 165.3; HRMS (ESI) calculated for $C_{28}H_{24}N_4O$, 433.2023 (MH^+); found for *m/z*, 433.2023.

1-(2-Cyano-phenyl)-7-methoxy-3-morpholine-1-yl-4,5-dihydro-1*H*-benz[*e*]indene-1,2-dicarbonitrile 7f: Yield: 37%, 0.38 R_f (30% ethylacetate-hexane), orange solid; mp: 131-133 ^oC; IR (KBr): 2941, 2859, 2185 cm-^{1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.60-2.71 (m, 1H, -CH_2-), 2.73-2.84 (m, 1H, -CH_2-), 2.89-3.00 (m, 1H, -CH_2-), 3.01-3.12 (m, 1H, -CH_2-), 3.54-3.69 (m, 4H, -CH_2-), 3.73 (s, 3H, -O-CH_3), 3.79-3.88 (m, 4H, -CH_2-), 6.48-6.53 (dd, *J* = 2.4 Hz, 1H, ArH), 6.71-6.75 (m, 2H, ArH), 7.42-7.50 (m, 1H, ArH), 7.60 (d, *J* = 7.9 Hz,1H, ArH), 7.72-7.80 (m, 1H, ArH), 8.23 (d, *J* = 7.93 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.0, 28.3, 49.9, 55.2, 66.5, 84.0, 108.6, 111.6, 114.6, 116.2, 116.5, 117.3, 121.2, 124.5, 129.2, 129.5, 133.8, 135.0, 136.7, 138.5, 138.7, 143.3, 160.6, 165.0; HRMS (ESI) calculated

for $C_{27}H_{22}N_4O_2$, 435.1816 (MH^+); found for *m/z*, 435.1808.

General procedure for the synthesis of 1-(phenyl)-3-piperidine-1-yl-4,5-dihydro-1*H*-benz[*e*]indene-1,2-dicarbonitrile 8: A mixture of 2-oxo-4-piperidine-1-yl-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitrile (0.5 mmol, 153.0 mg), phenylacetonitrile (0.5 mmol, 0.057 mL) and KOH (0.75 mmol, 42.0 mg) in DMF (4.0 mL) was stirred at 100°C for 40 h. After completion, reaction mixture was poured onto ice-water with vigorous stirring followed by neutralization with 10% HCl. The precipitate obtained was filtered, washed with water and dried over dry sodium sulphate. Crude mixture was purified by silica-gel column chromatography using 10 % ethyl acetate in hexane as an eluent: yield: 17%, 0.48 R_f (20% ethylacetate-hexane), orange solid; mp: 207-209 °C; IR (KBr): 2924, 2853, 2182 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.60-1.75 (m, 6H, -CH_2-), 2.65-2.80 (m, 2H, -CH_2-), 2.90-3.07 (m, 2H, -CH_2-), 3.38-3.50 (m, 4H, -CH_2-), 6.95-7.07 (m, 2H, ArH), 7.13-7.19 (m, 2H, ArH), 7.27-7.38 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ; 23.0, 23.7, 25.9, 28.4, 50.8, 54.7, 88.9, 117.6, 117.7, 124.2, 125.6, 127.0, 127.8, 128.6, 128.7, 129.1, 129.4, 133.6, 135.9, 139.3, 144.9, 162.9; HRMS (ESI) calculated for $C_{26}H_{23}N_3$, 378.1965 (MH^+); found for *m/z*, 378.1953.

General processor synthesis of 3-(1-(cyano(phenyl)methyl)-6-OMe/H-3,4-dihydronaphthalen-2-yl)-3-(piperidin-1-yl)acrylonitrile (9a-9b): A mixture of 2-oxo-4-piperidine-1-yl-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitrile (0.5 mmol, 153.0 mg), phenylacetonitrile (0.5 mmol, 0.057 mL) and KOH (0.75 mmol, 42.0 mg) in DMF (4.0 mL) was stirred at 100°C for 2 h. After completion, reaction mixture was poured onto ice-water with vigorous stirring followed by neutralization with 10% HCl. The precipitate obtained was filtered, washed with water and dried over dry sodium sulphate. Crude mixture was purified by silica-gel column chromatography using 8 % ethyl acetate in hexane as an eluent:

3-(1-(Cyano(phenyl)methyl)-3,4-dihydronaphthalen-2-yl)-3-(piperidin-1-yl)acrylonitrile 9a: Yield: 35%, 0.50 R_f (20% ethylacetate-hexane), orange solid; mp: 135-137 °C; IR (KBr): 2925, 2853, 2192 cm-^{1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.50-1.84 (m, 6H, -CH_2-), 2.50-2.62 (m, 2H, -CH_2-), 2.70-2.81 (m, 1H, -CH_2-), 2.82-2.91 (m, 1H, -CH_2-), 3.20-3.32 (m, 4H, -CH_2-), 4.13 (s, 1H, -CH-), 5.41 (s, 1H, -CH-), 6.97 (t, *J* = 7.96 Hz, 1H, ArH), 7.05-7.20 (m, 3H, ArH), 7.21-7.26 (m, 1H, ArH), 7.30-7.40 (m, 2H, ArH), 7.58 (d, *J* = 7.5 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.8, 27.9, 28.9, 29.6, 36.9, 63.6, 118.7, 121.4, 125.8, 126.2, 127.0, 127.7, 128.1, 128.8, 129.0, 129.9, 130.4, 132.8, 136.9, 137.0, 164.8 ; HRMS (ESI) calculated for $C_{26}H_{25}N_3$, 380.2121 ($M+H^+$); found for *m/z*, 380.2118.

3-(1-(Cyano(phenyl)methyl)-6-methoxy-3,4-dihydronaphthalen-2-yl)-3-(piperidin-1-yl)acrylonitrile 9b: Yield: 30%, 0.41 R_f (20% ethylacetate-hexane), orange solid; mp: 141-143 °C; IR (KBr): 2925, 2853, 2192 cm^{-1}; ^1H NMR (400 MHz , $CDCl_3$): δ 1.40-1.80 (m, 6H, -CH_2-), 2.45-2.58 (m, 2H, -CH_2-), 2.67-2.85 (m, 2H, -CH_2-), 3.12-3.30 (m, 4H, -CH_2-), 3.71 (s, 3H, -O-CH_3), 4.11 (s, 1H, -CH-), 5.37 (s, 1H, -CH-), 6.45-6,52 (dd, *J* = 2.4 Hz, 1H, ArH), 6.68 (d, *J* = 2.4 Hz, 1H, ArH),7.08 (d, *J* = 8.5 Hz, 1H, ArH) 7.20-7.27 (m, 1H, ArH), 7.30-7.38 (m, 2H, ArH), 7.57 (d, *J* = 7.93 Hz, 2H, ArH); ^{13}C NMR (100 MH, $CDCl_3$): δ 23.8, 28.3, 28.8, 36.9, 51.1, 63.6, 110.8, 113.9, 118.8, 121.6, 122.8, 126.9, 127.2, 127.7, 128.8, 129.0, 129.9, 129.9, 132.9, 134.1, 139.0, 159.1, 165.0; HRMS (ESI) calculated for $C_{27}H_{27}N_3O$, 410.2227 (MH^+); found for *m/z*, 410.2222.

General procedure for the synthesis of 2-amino-5-aryl-4-*sec.*amino-benzo[*h*]quinoline-6-carbonitrile (11a-11d): A mixture of 6-aryl-2-oxo-4-*sec.*amino-2*H*-pyran-3-carbonitriles (0.5 mmol), 2-cynomethyl-benzonitrile (0.5 mmol; 142.0 mg) and $NaNH_2$ (1.0 mmol; 78.0 mg) in dry DMF (5.0 mL) was stirred at 100 °C for 35-50 h. After completion of reaction, mixture was poured onto crushed ice followed by neutralization with 10% HCl. The obtained solid material was filtered, washed with water, dried and purified by silica gel column chromatography using hexane: ethyl acetate (7:3) as eluent. Compound 11a and 11b is reported earlier.[18]

2-Amino-5-(2-fluoro-phenyl)-4-piperidin-1-yl-benzo[*h*]quinoline-6-carbonitrile 11c: Yield: 60%; 0.21 R_f (30% ethylacetate-hexane), grey solid, mp: 187-189 °C; IR (KBr): 3399, 2938, 2208 cm^{-1}; ^1H NMR (400 MH_Z , $CDCl_3$): δ 0.31-0.46 (m, 1H, -CH_2-), 0.80-1.06 (m, 2H, -CH_2-), 1.13-1.27 (m, 1H, -CH_2-), 1.33-1.50 (m, 2H, -CH_2-), 2.12-2.27 (m, 1H, -CH_2-), 2.45-2.57 (m, 1H, -CH_2-), 2.73-2.85 (m, 1H, -CH_2-), 2.95-3.06 (m, 1H, -CH_2-), 4.91 (s, 2H, -NH_2), 6.35 (s, 1H, ArH), 7.07-7.15 (m, 1H, ArH), 7.25-7.30 (m, 1H, ArH), 7.36-7.45 (m, 1H, ArH), 7.55-7.62 (m, 1H, ArH), 7.63-7.75 (m, 2H, ArH), 8.23 (d, *J* = 7.9 Hz,1H, ArH), 9.12-9.14 (dd, *J* = 1,83 Hz, 1H, ArH); ^{13}C NMR (100 MH_Z, $CDCl_3$): δ 23.3, 24.4, 24.7, 52.2, 54.6, 99.8, 106.7, 113.7, 114.9 (d, $J_{C\text{-}F}$ = 22.0 Hz), 118.1, 123.4, 125.2, 127.2, 127.4, 129.2, 129.8 (d, $J_{C\text{-}F}$ = 8.6 Hz), 130.3, 131.4, 131.7, 131.8, 138.4, 150.1, 158.9, 160.3 (d, $J_{C\text{-}F}$ = 247.2 Hz), 162.0; HRMS (ESI) calculated for $C_{25}H_{21}FN_4$, 397.1823 (MH^+); found for m/z, 397.1822.

2-amino-4-(4-benzylpiperazin-1-yl)-5-(4-methoxyphenyl)benzo[h]quinoline-6-carbonitrile 11d: Yield: 74%; 0.20 R_f (30% ethylacetate-hexane), yellow solid, mp: 216-218°C; IR (KBr): 3352, 2928, 2195 cm^{-1}; ^1H NMR (400 MH_Z , $CDCl_3$): δ 2.00-2.33 (m, 4H, -CH_2-), 2.80-3.15 (m, 4H, -CH_2-), 3.40 (s, 2H, -CH_2-), 3.84 (s, 3H, -OCH_3), 5.09 (s, 2H, -NH_2), 6.93 (d, *J* = 8.0 Hz, 2H, ArH), 7.15-7.35 (m, 7H, ArH), 7.48-7.58 (m, 2H, ArH), 7.64-7.72 (m, 1H, ArH), 7.82 (d, *J* = 8.8 Hz,1H, ArH), 8.20 (d, *J* = 8.0 Hz, 1H, ArH); ^{13}C NMR (100 MH_Z, $CDCl_3$): δ 55.2, 62.5, 67.6, 99.7, 112.5, 113.3, 118.1, 120.9, 121.1, 121.8, 126.1, 126.3, 127.3, 128.2, 129.0, 129.3, 129.6, 130.2, 133.7, 136.8, 144.7, 145.6, 159.7, 159.8; HRMS (ESI) calculated for $C_{32}H_{29}N_5O$, 500.2445 (MH^+); found for m/z, 500.2446.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [This material includes characterization data and ^{1}H and ^{13}C NMR spectra for all the reported compounds.]. See DOI: 10.1039/b000000x/

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Graphical Abstract

Precursor directed regioselective synthesis of partially reduced benzo[*e*]indene through oxidative cyclization and benzo[*h*]quinolines

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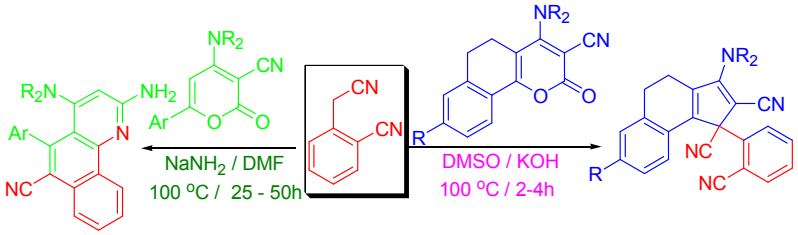

Precursor directed synthesis of various benzo[*h*]quinolines and 4,5-dihydro-1*H*-benz[*e*]indene has been reported.