Substituent-Dependent Chemoselective Synthesis of Highly Functionalized Benzo[h]quinolines and 4-Benzylpyrans from 2-Methyl-5-nitro-benzonitrile

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Synthesis of fused and isolated quinolines, from Skraup, Doebner and von Miller syntheses, 16–19 through Diels–Alder reactions 20 and Friedlander condensations reactions. 21 Quinolines have also been synthesized by palladium, 22 copper, 23 nickel, 24 and zinc 25 catalyzed inter- and intramolecular cyclization reactions. The reaction of aryl isothiocyanates, alkynes, and alkyl triflates also provides quinolines and fused quinolines. 26 In another approach, partially reduced benzo[h]quinolines were obtained by reaction of arylidenedes, alkynes, and alkyl triflates also provides quinolines and fused quinolines. 26 In another approach, partially reduced benzo[h]quinolines were obtained by reaction of arylidenedes, alkynes, and alkyl triflates also provides quinolines and fused quinolines. 26 In another approach, partially reduced benzo[h]quinolines were obtained by reaction of arylidenedes, alkynes, and alkyl triflates also provides quinolines and fused quinolines. 26

Various synthetic methodologies have been reported for the synthesis of fused and isolated quinolines, from Skraup, Doebner and von Miller syntheses. 16–19 through Diels–Alder reactions. 20 and Friedlander condensations reactions. 21 Quinolines have also been synthesized by palladium, 22 copper, 23 nickel, 24 and zinc 25 catalyzed inter- and intramolecular cyclization reactions. The reaction of aryl isothiocyanates, alkynes, and alkyl triflates also provides quinolines and fused quinolines. 26 In another approach, partially reduced benzo[h]quinolines were obtained by reaction of arylidenedes, alkynes, and alkyl triflates also provides quinolines and fused quinolines. 26 In another approach, partially reduced benzo[h]quinolines were obtained by reaction of arylidenedes, alkynes, and alkyl triflates also provides quinolines and fused quinolines. 26

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Abstract A facile, efficient and atom-economic synthesis of highly substituted benzo[h]quinolines was established by reaction of 2-methyl-5-nitrobenzonitrile with suitably functionalized 2H-pyran-2-ones under basic conditions. We observed that the presence of a thiomethyl group at the C-4 position of pyran provides 6-aryl-4-(2-cyano-4-nitrobenzyl)-2-oxo-2H-pyran-3-carbonitrile exclusively without any trace of benzo[h]quinolines. Depending on the nature of the functional group at C-4 of the pyran ring, different products were achieved. To probe the mechanism, we performed control experiments and isolated 3-(1-ami- no-7-nitro-3-thiophen-2-yl-naphthalen-2-yl)-3-piperidin-1-yl-acrylonitrile, which, on further treatment with base, provided the benzo[h]quinolines. The structure of one the products was characterized by single crystal X-ray diffraction.

Key words 2H-pyran-2-one, 2-methyl-5-nitro-benzonitrile, benzo[h]quinoline, 4-benzylpyran, chemoselective

Polycyclic N- and O-heterocycles such as amsacrine, benzo[c]phenanthridines, ellipticines, intoplicine and coralyne exhibit excellent biological properties such as DNA topoisomerase inhibition and anticancer activity. 1–5 Among the N-heterocycles, fused and isolated quinolines are very important and exhibit a wide range of biological properties including antinaesthetic, 6a antiestrogenic, 6b-c antimalarial, 7 anti-HIV, 8 anticancer, 9 antitubercular, 10 and antimicrobial activities. 11 They have also been widely used in agrochemical areas 12 and in material chemistry. 13 Recently, our research group has reported the synthesis and anticancer activity of functionalized benzo[h]quinolines. 14 This class of compounds has also been used in the construction of nano and meso structures that exhibit novel electronic and photonic properties. 15

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amination of 6-aryl-4-methylthio-2-oxo-2H-pyran-3-carbonitriles with secondary amines in ethanol provided 6-aryl-4-amino-2-oxo-2H-pyran-3-carbonitriles 1,34a–e.

To study the optimization, 6-(4-chlorophenyl)-2-oxo-4-(piperidin-1-yl)-2H-pyran-3-carbonitrile (1) and 2-methyl-5-nitrobenzonitrile (2) were selected as a model substrates. Initially, we performed the reaction using triethylamine as base in dimethyl sulfoxide (DMSO) and DMF at 100 °C, but no reaction was observed (Table 1, entries 1 and 2). Similarly, the use of sodamide in DMF or DMSO at either room temperature or higher temperatures led mainly to starting material being recovered (entries 3–6); while use of sodium hydride afforded complex mixtures (entries 7–9) containing starting materials and desired product, along with unidentified decomposition products. When the reaction was performed in DMF using KOH as base at room temperature for 12 h, 45% yield of the desired product was isolated (entry 10) and when the same reaction mixture was heated at 100 °C for 6 h, 93% of the desired benzo[h]quinoline was isolated (entry 11). Use of DMSO instead of DMF, lowered the yield of product (entry 12). Use of potassium tert-butoxide as a base in DMF at 100 °C provided the desired product in 65% yield (entry 13); whereas using cesium carbonate as base was did not afford the desired product (entry 14). By using lithium hydroxide and sodium hydroxide under the same conditions noted in entry 11, a lower yield and complex reaction mixture were observed, respectively (entries 15 and 16). Use of KOH in water gave no reaction and starting materials were recovered (entry 17) and using KOH in DMSO for 6 hours provided only 40% yield of the desired product (entry 18). Thus, we chose the reaction of 2-pyranone and 2-methyl-5-nitrobenzonitrile with potassium tert-butoxide in DMF at 100 °C as the optimal reaction conditions.

The generality of the optimized protocol was then tested by the synthesis of a range of functionalized benzo[h]quinolines (Scheme 1). We have used pyrans functionalized with different secondary amine and aryl groups and the yield was generally not affected significantly by their nature, although the presence of a 2-thienyl group lowered the yield of product.

The structure of one of the products (3g) was confirmed by single-crystal X-ray analysis (Figure 1).35 It was found that benzo[h]quinoline ring is completely planar and one unit cell contains eight molecules. It is interesting to note that the C8–C7–C4 angle is 115.29° and not 120°, probably due to steric repulsion by the piperidine ring at C17. Bond angles for C12–C7–C4, C18–C17–N4 are 124.81° and 120.76°, respectively. This repulsion also leads to a higher torsion angle of 59° between the benzo[h]quinoline ring and the p-fluorophenyl ring.

### Table 1 Optimization of Reaction Conditions

| Entry | Base   | Solvent | Temp (°C) | t (h) | Yield 3 (%) |
|-------|--------|---------|-----------|-------|-------------|
| 1     | NEt₃   | DMSO    | 100       | 12    | –/d         |
| 2     | NEt₃   | DMF     | 100       | 12    | –/d         |
| 3     | NaNH₂  | DMSO    | r.t.⁵     | 12    | –/d         |
| 4     | NaNH₂  | DMSO    | 70        | 12    | –/d         |
| 5     | NaNH₂  | DMF     | 70        | 12    | –/d         |
| 6     | NaNH₂  | DMF     | 100       | 12    | –/d         |
| 7     | NaNH₂  | DMF     | r.t.⁵     | 12    | –/e         |
| 8     | NaNH₂  | DMF     | 100       | 12    | –/e         |
| 9     | NaNH₂  | DMF     | 100       | 12    | –/e         |
| 10    | KOH    | DMF     | r.t.⁵     | 12    | 45          |
| 11    | KOH    | DMF     | 100       | 6     | 93          |
| 12    | KOH    | DMSO    | 100       | 12    | 65          |
| 13    | t-BuOK | DMF     | 100       | 12    | 65          |
| 14    | CS₂CO₃ | DMF     | 100       | 12    | –/d         |
| 15    | LiOH   | DMF     | 100       | 8     | 55          |
| 16    | NaOH   | DMF     | 100       | 8     | –/e         |
| 17    | KOH    | H₂O     | 100       | 12    | –/d         |
| 18    | KOH    | DMSO    | 100       | 6     | 40          |

a All the reactions were performed by stirring 6-(4-chlorophenyl)-4-(piperidin-1-yl)-2H-pyran-2-one-3-carbonitrile (1; 0.5 mmol), 2-methyl-5-nitrobenzonitrile (2; 0.6 mmol), base (1.0 mmol) in solvent (5.0 mL).
b Room temperature (25–30 °C).
c Isolated yield reported.
d Starting materials recovered.
e Complex mixture formation.

![Figure 1 ORTEP diagram of 3g](image)
To expand the scope of the reaction, 6-aryl-4-methyl-sulfanyl-2-oxo-2H-pyr-3-carbonitriles were reacted under similar reaction conditions with 2. The usual workup and purification afforded the 6-aryl-4-(2-cyano-4-nitrobenzyl)-2-oxo-2H-pyr-3-carbonitriles chemoselectively (Scheme 2). Interestingly, it was observed that the presence of a thiomethyl group at C-4 diverts the chemoselectivity and provides 6-aryl-4-(2-cyano-4-nitrobenzyl)-2-oxo-2H-pyr-3-carbonitriles exclusively, without formation of benzo[h]quinolines. The structures of these condensation products were confirmed unambiguously by NMR and IR spectroscopy and by HRMS.

Mechanistically, the reaction is probably initiated by the generation of the carbanion of 2-methyl-5-nitrobenzonitrile (Scheme 3), which reacts at C-4 or C-6 of the 2-pyranone, depending on the substrate selected. If 6-aryl-4-sec-amino-2-oxo-2H-pyr-3-carbonitriles are the substrate, the carbanion attacks at C-6 through Michael addition to afford intermediate A. The latter intermediate can then undergo ring opening and protonation to afford two possible intermediate regioisomers, B and D. If reaction proceeds via cis intermediate B, then, in the presence of excess base, the benzylcarbanion attacks the aromatic nitrile group to afford intermediate C. Intermediate C undergoes decarboxylation followed by cyclization onto the aliphatic nitrile group with tautomerization to afford the benzo[h]quinolines.

Alternatively, if intermediate D were to be formed, then benzylcarbanion generated by the excess base could cyclize by involvement of vinylc nitrile to provide intermediate E. Subsequently, the imine group of intermediate E can cyclize onto the aromatic nitrile followed by decarboxylation to afford F, which, on tautomerization, provides functionalized phenanthridines. However, the reaction provides benzo[h]quinolines chemoselectively without any trace of phenanthridine.
On the other hand, if 6-aryl-4-methylsulfanyl-2-oxo-2H-pyran-3-carbonitiles are used as precursors then the carbanion from 2-methyl-5-nitrobenzonitrile attacks at C-4 of the pyran ring via Michael addition with formation of intermediate \( G \). Loss of the methylsulfanyl group then affords the 6-aryl-4-(2-cyano-4-nitrobenzyl)-2-oxo-2H-pyran-3-carbonitiles \( 5 \) exclusively.

It is interesting to note that, if 6-aryl-4-methylsulfanyl-2-oxo-2H-pyran-3-carbonitiles were used as precursors, the carbanion generated from 2-methyl-5-nitrotoluene attacks at C-4 rather than C-6, possibly due to the greater electrophilicity at C-4 caused by the vacant d-orbitals of sulfur and the better leaving group ability of the SMean group compared with the secondary amine.

To probe the mechanism, we performed the reaction of 2-oxo-4-piperidin-1-yl-6-thiophen-2-yl-2H-pyran-3-carbonitrile and 2-methyl-5-nitrotoluene using a lower concentration of base and isolated the 3-(1-amino-7-nitro-3-thiophen-2-yl-naphthalen-2-yl)-3-(piperidin-1-yl)-acrylonitrile in 81% yield, which supports the intermediacy of C (Scheme 4). Furthermore, we used compound \( 7 \) and performed the cyclization under optimized reaction conditions and isolated the benzo[h]quinoline.
It is interesting to note that reaction of 2-pyranone with 2-cyanomethylbenzonitrile requires 35–50 hours for completion of the reaction, whereas the use of 2-methyl-5-nitrobenzonitrile as a carbanion source provides the benzo[h]quinoline in 4–6 hours. We propose that the presence of a nitrite group reduces the rate of reaction, probably by stabilizing the carbanion formed and slowing the cyclization step due to steric hindrance.

In summary, we have developed a simple and efficient approach for the chemoselective synthesis of 5-ary1-4-sec-amino-benzo[h]quinoline-6-carbonitriles and 6-ary1-4-(2-cyano-4-nitrobenzyl)-2-oxo-2H-pyrany1-3-carbonitriles by reaction of 2-oxo-4-carbonitrile with 6-aryl-4-(methylthio)-2-oxo-2H-pyrany1-3-carbonitrile, respectively, under basic conditions. We also investigated mechanistic aspects of the reaction and found that the reaction can be stopped at the functionalized naphthalene stage. We confirmed the structure of compound by single-crystal X-ray analysis and found that the aryl group present at position 5 is distorted from the usual sp² angle of 120°.

Commercially available reagents were used directly. NMR spectra were recorded at 400 MHz for ¹H and 100 MHz for ¹³C and chemical shifts (δ) are given as parts per million. Spectra were referenced to the residual ¹H signal of CDCl₃ at δ = 7.24 ppm, ¹³C of CDCl₃ at δ = 77.00 ppm, the residual ¹H of DMSO-d₆ at δ = 2.49 ppm and the ¹³C of DMSO-d₆ at δ = 39.50 ppm as the internal standards. Splitting patterns in ¹H NMR data are described as s, singlet; d, doublet; dd, doublet-doublet; t, triplet; bs, broad singlet; m, multiplet and coupling constants given in hertz (Hz). HRMS was recorded using an Agilent LCMS with Quadrupole time of flight using the ESI mode of ionization. All the required starting materials were synthesized by following reported procedures.

Synthesis of Benzo[h]quinolines (3a–p); General Procedure

A mixture of 6-ary1-2-oxo-4-sec-amino-2H-pyrany1-3-carbonitrile (0.5 mmol), 2-ary1-5-nitrobenzonitrile (0.6 mmol) and KOH (1.0 mmol) in DMF (5.0 mL) was stirred at 100–110 °C for 6 h. After completion of reaction, the reaction mixture was poured onto crushed ice and neutralized with 10% HCl to pH ~6–7. The solid product was filtered, washed with cold water, dried and purified by silica gel column chromatography, eluting with hexane–EtOAc (70:30).

Synthesis of 6-Ary1-4-(2-cyano-4-nitrobenzyl)-2-oxo-2H-pyrany1-3-carbonitriles (5a–d); General Procedure

A mixture of 6-ary1-4-(methylthio)-2-oxo-2H-pyrany1-3-carbonitrile (0.5 mmol), 2-ary1-5-nitrobenzonitrile (0.6 mmol) and KOH (0.6 mmol) in DMF (5.0 mL) was stirred at 100–110 °C for 2–3 h. After completion of reaction, the reaction mixture was poured onto crushed ice followed by neutralization with 10% HCl to pH ~6–7. The solid product was filtered, washed with water, dried, and purified by silica gel column chromatography eluting with hexane–EtOAc (70:30).

9-Nitro-5-phenyl-4-(piperidin-1-yl)benzo[h]quinolin-2-amine (3a)

Yield: 88% (175 mg); red solid; mp 190–192 °C.

IR (KBr): 3356, 1334 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 0.75–0.85 (m, 2 H), 0.92–1.00 (m, 2 H), 1.26–1.28 (s, 2 H), 1.52–1.54 (s, 2 H), 1.91–1.93 (s, 2 H), 2.01–2.03 (s, 2 H), 2.33–2.39 (m, 2 H), 2.97 (d, J = 12 Hz, 2 H), 3.22–3.24 (m, 2 H), 3.60–3.62 (m, 2 H), 4.76 (d, J = 12 Hz, 2 H), 7.25–7.32 (m, 3 H, ArH), 7.36 (s, 1 H, ArH), 7.41 (d, J = 8 Hz, 1 H, ArH), 7.76 (d, J = 8 Hz, 1 H, ArH), 8.24 (dd, d = 8 Hz, 1 H, ArH), 9.96 (s, 1 H, ArH).

¹³C NMR (100 MHz, CDCl₃): δ = 23.5, 24.3, 52.5, 98.5, 113.1, 121.2, 122.0, 124.5, 127.0, 127.2, 128.3, 129.1, 129.4, 136.3, 141.5, 141.6, 145.2, 145.8, 157.7, 160.2.

HRMS (ESI): m/z [MH⁺] calcd. for C₂₄H₂₃N₄O₂: 399.1816; found: 399.1819.

4-Morpholino-9-nitro-5-phenylbenzo[h]quinolin-2-amine (3b)

Yield: 85% (170 mg); red solid; mp >250 °C.

IR (KBr): 3449, 1334 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 2.52 (t, J = 20 Hz, 2 H), 2.66 (t, J = 20 Hz, 2 H), 7.28 (d, J = 12 Hz, 2 H), 3.49 (d, J = 12 Hz, 2 H), 4.91 (s, 2 H, –N₂H₂), 6.34 (s, 1 H, ArH), 7.04–7.42 (m, 2 H, ArH), 7.45 (d, J = 1 H, ArH), 7.48–7.50 (m, 3 H, ArH), 7.86 (d, J = 8 Hz, 1 H, ArH), 8.34 (dd, d = 12 Hz, 1 H, ArH), 10.0–10.0 (m, 1 H, ArH).

¹³C NMR (100 MHz, DMSO-d₆): δ = 51.1, 64.6, 99.2, 111.4, 120.8, 121.0, 123.3, 127.0, 127.1, 128.6, 129.1, 129.3, 136.0, 141.0, 141.7, 144.4, 144.8, 157.8, 159.3.

HRMS (ESI): m/z [MH⁺] calcd. for C₂₅H₂₄N₅O₂: 401.1608; found: 401.1609.
9-Nitro-4-[(piperidin-1-yl)-5-(p-toly)benzol][h]quinolin-2-amine (3c)
Yield: 86% (180 mg); red solid; mp 150–152 °C.
IR (KBr): 3480, 1337 cm⁻¹.
1H NMR (400 MHz, CDCl₃); δ = 1.18–1.26 (m, 3 H), 1.39–1.40 (m, 4 H), 2.33 (s, 3 H, -CH₃), 2.78–2.90 (m, 3 H, CH₂-N(CH₃)₂), 3.01–3.09 (m, 1 H, CH₂-N(CH₃)₂), 3.84 (s, 2 H, -NH₂), 6.25 (d, J = 8 Hz, 2 H, ArH), 7.10 (s, 1 H, ArH), 9.73 (d, J = 8 Hz, 1 H, ArH).
13C NMR (100 MHz, CDCl₃); δ = 31.5, 46.4, 56.9, 114.4, 124.3, 128.2, 128.4, 129.0, 129.5, 129.9, 131.1, 160.1, 167.3.
HRMS (ESI): m/z [MH⁺] calcld. for C₂₃H₂₂N₄O₄: 431.1714; found: 431.1715.

(5-Fluorophenyl)-9-nitro-4-(piperidin-1-yl)benzol][h]quinolin-2-amine (3g)
Yield: 81% (168 mg); red solid; mp 200–202 °C.
IR (KBr): 3353, 1334 cm⁻¹.
1H NMR (400 MHz, CDCl₃); δ = 1.19–1.23 (m, 3 H), 1.30–1.34 (m, 3 H), 2.37–2.43 (m, 2 H, CH₂-N(CH₃)₂), 3.01–3.04 (m, 2 H, CH₂-N(CH₃)₂), 4.83 (s, 2 H, -NH₂), 6.33 (s, 1 H, ArH), 7.04–7.09 (m, 2 H, ArH), 7.37 (s, 1 H, ArH), 7.43–7.46 (m, 2 H, ArH), 7.82 (d, J = 12 Hz, 1 H), 8.31 (dd, J = 8 Hz, 1 H), 7.98 (d, J = 4 Hz, 1 H).
13C NMR (100 MHz, CDCl₃); δ = 24.6, 29.7, 52.7, 98.8, 114.1 (d, J = 20 Hz), 121.7 (d, J = 80 Hz), 124.5, 128.3, 129.8, 131.0 (d, J = 10 Hz), 136.3, 138.0, 140.4, 145.3, 149.4, 158.0, 160.1.
HRMS (ESI): m/z [MH⁺] calcld. for C₂₃H₂₁FN₂O₄: 417.1721; found: 417.1724.

4-Morpholino-9-nitro-5-(p-toly)benzol][h]quinolin-2-amine (3d)
Yield: 82% (170 mg); red solid; mp 240–242 °C.
IR (KBr): 3354, 1332 cm⁻¹.
1H NMR (400 MHz, CDCl₃); δ = 2.44 (s, 3 H, -CH₃), 2.54–2.62 (m, 2 H), 2.65–2.69 (m, 2 H), 2.93 (d, J = 8 Hz, 2 H, CH₂-N(CH₃)₂), 3.5 (d, J = 8 Hz, 2 H, CH₂-N(CH₃)₂), 4.88 (s, 2 H, -NH₂), 6.32 (s, 1 H, ArH), 7.22 (d, J = 8 Hz, 2 H, ArH), 7.37 (d, J = 4 Hz, 2 H, ArH), 7.43 (s, 1 H, ArH), 7.84 (d, J = 8 Hz, 1 H, ArH).
13C NMR (100 MHz, CDCl₃); δ = 21.7, 52.1, 70.0, 114.6, 116.0, 121.0, 122.5, 125.2, 127.0, 127.1, 127.4, 127.5, 128.4, 129.7, 130.1, 130.2, 130.8, 130.9, 133.1, 156.4.
HRMS (ESI): m/z [MH⁺] calcld. for C₂₃H₂₁N₄O₄: 415.1765; found: 415.1762.

5-(4-Fluorophenyl)-9-nitro-4-(piperidin-1-yl)benzol][h]quinolin-2-amine (3e)
Yield: 80% (167 mg); red solid; mp >250 °C.
IR (KBr): 3484, 1332 cm⁻¹.
1H NMR (400 MHz, CDCl₃); δ = 2.53–2.69 (m, 4 H), 2.89 (d, J = 8 Hz, 2 H, CH₂-N(CH₃)₂), 3.52 (d, J = 12 Hz, 2 H, CH₂-N(CH₃)₂), 4.90 (s, 2 H, -NH₂), 6.32 (s, 1 H, ArH), 7.40 (t, J = 12 Hz, 2 H, ArH), 7.38 (s, 1 H, ArH), 7.74–7.76 (m, 2 H, ArH), 7.84 (d, J = 8 Hz, 1 H, ArH), 8.31 (dd, J = 4 Hz, 1 H, ArH), 9.98 (d, J = 4 Hz, 1 H).
13C NMR (100 MHz, CDCl₃); δ = 51.3, 65.4, 98.5, 112.5, 114.2 (d, J = 30 Hz), 121.6 (d, J = 20 Hz), 125.0, 128.5, 130.8, 130.8, 136.3, 145.4, 157.7, 159.0, 161.1, 163.5.
HRMS (ESI): m/z [MH⁺] calcld. for C₂₃H₁₉FN₂O₄: 419.1514; found: 419.1513.

(5-Fluorophenyl)-4-morpholino-9-nitrobenzo[h]quinolin-2-amine (3h)
Yield: 93% (201 mg); red solid; mp 215–217 °C.
IR (KBr): 3489, 1328 cm⁻¹.
1H NMR (400 MHz, CDCl₃); δ = 0.94–1.02 (m, 1 H), 1.17–1.20 (m, 1 H), 1.26–1.29 (m, 3 H), 1.38–1.41 (m, 1 H), 2.35 (t, J = 24 Hz, 2 H, CH₂-N(CH₃)₂), 2.95 (d, J = 12 Hz, 2 H, CH₂-N(CH₃)₂), 4.81 (s, 2 H, -NH₂), 6.28 (s, 1 H, ArH), 7.28–7.30 (m, 3 H, ArH), 7.36 (d, J = 8 Hz, 2 H, ArH), 7.76 (d, J = 8 Hz, 1 H, ArH), 8.25 (dd, J = 8 Hz, 1 H, ArH), 9.92–9.93 (m, 1 H, ArH).
13C NMR (100 MHz, CDCl₃); δ = 24.1, 26.2, 53.7, 104.5, 115.6, 115.8, 116.1, 121.2, 128.6, 129.2, 130.7, 130.8, 134.8, 135.2, 138.3, 145.0, 147.0, 158.8, 162.0, 164.3.
HRMS (ESI): m/z [MH⁺] calcld. for C₂₄H₂₁ClN₂O₄: 433.1426; found: 433.1435.

(5-Fluorophenyl)-4-morpholino-9-nitrobenzo[h]quinolin-2-amine (3i)
Yield: 91% (197 mg); red solid; mp 150–152 °C.
IR (KBr): 3353, 1329 cm⁻¹.
1H NMR (400 MHz, CDCl₃); δ = 2.60–2.71 (m, 4 H), 2.90 (d, J = 12 Hz, 2 H, CH₂-N(CH₃)₂), 3.55 (d, J = 12 Hz, 2 H, CH₂-N(CH₃)₂), 4.97 (s, 2 H, -NH₂), 6.35 (s, 1 H, ArH), 7.38–7.44 (m, 5 H, ArH), 7.85 (d, J = 8 Hz, 1 H, ArH), 8.34 (dd, J = 8 Hz, 1 H, ArH), 9.99 (d, J = 4 Hz, 1 H).

13C NMR (100 MHz, DMSO-d$_6$): $\delta = 55.4, 67.6, 112.6, 116.4, 120.4, 120.7, 121.3, 121.3, 128.3, 130.4, 130.6, 133.0, 137.3, 139.5, 139.6, 142.7, 144.4, 145.5, 160.6.

HRMS (ESI): $m/z$ [MH$^+$] calcd. for C$_{23}$H$_{22}$ClN$_4$O$_2$: 435.1219; found: 435.1219.

5-(4-Bromophenyl)-9-nitro-4-(piperidin-1-yl)benzo[h]quinolin-2-amine (3k)

Yield: 82% (195 mg); red solid; mp 150–152 °C.

IR (KBr): 3360, 1333 cm$^{-1}$.

HRMS (ESI): $m/z$ [MH$^+$] calcd. for C$_{23}$H$_{21}$ClN$_4$O$_2$: 467.1034; found: 467.1034.

5-(4-Bromophenyl)-9-nitro-4-(2-morpholino-4-piperidin-1-yl)benzo[h]quinolin-2-amine (3l)

Yield: 83% (199 mg); red solid; mp 210–212 °C.

IR (KBr): 3351, 1338 cm$^{-1}$.

HRMS (ESI): $m/z$ [MH$^+$] calcd. for C$_{23}$H$_{21}$BrN$_4$O$_2$: 479.0829; found: 479.0829.

5-(2,4-Dichlorophenyl)-5-(thiophen-2-yl)benzo[h]quinolin-2-amine (3m)

Yield: 84% (171 mg); red solid; mp 180–182 °C.

IR (KBr): 3356, 1362 cm$^{-1}$.

HRMS (ESI): $m/z$ [MH$^+$] calcd. for C$_{31}$H$_{32}$N$_5$O$_3$: 522.2500; found: 522.2500.

5-(2,4-Dichlorophenyl)-4-morpholino-9-nitrobenzo[h]quinolin-2-amine (3n)

Yield: 72% (168 mg); red solid; mp 240–242 °C.

IR (KBr): 3493, 1338 cm$^{-1}$.

HRMS (ESI): $m/z$ [MH$^+$] calcd. for C$_{23}$H$_{22}$BrN$_4$O$_2$: 481.0689; found: 481.0689.
Yield: 72% (161 mg); red solid; mp 210–212 °C.

1H NMR (400 MHz, CDCl3): δ = 1.23 (s, 2 H), 1.67 (s, 3 H), 2.16 (s, 3 H, N-CH3), 2.98–3.00 (m, 3 H, J=4 Hz, 2 H, ArH), 7.28–7.39 (m, 3 H, ArH), 7.83 (d, J = 8 Hz, 1 H, ArH), 8.22 (dd, J = 8 Hz, 1 H, ArH), 8.85–8.85 (m, 1 H, ArH).

HRMS (EI): m/z [MH]+ calcd. for C19H16N4O6: 432.0582; found: 432.0535.

4-(2-Cyano-4-nitrobenzyl)-6-oxo-2-phenyl-2H-pyran-3-carbonitrile (5b)

Yield: 71% (127 mg); red solid; mp 220–222 °C.

IR (KBr): 2226, 1730, 1528 cm–1.

1H NMR (400 MHz, DMSO-d6): δ = 4.34 (s, 2 H, -CH2), 6.95–7.04 (m, 3 H, ArH), 7.75–7.79 (m, 2 H, ArH), 7.82 (d, J = 8 Hz, 1 H, ArH), 8.46 (dd, J = 8 Hz, 1 H, ArH), 8.58 (d, J = 4 Hz, 1 H, ArH).

HRMS (ESI): m/z [MH]+ calcd. for C20H17N3O6: 380.1147; found: 380.1113.

5-(4-Methoxyphenyl)-4-(4-methylpiperazin-1-yl)-9-nitro-4a,10b-dihydronaphthalen-2-amine (3r)

Yield: 80% (162 mg); red solid; mp 170–172 °C.

IR (KBr): 3360, 2214, 1334 cm–1.

1H NMR (400 MHz, CDCl3): δ = 1.14–1.23 (m, 2 H), 1.37–1.48 (m, 2 H), 2.88–2.93 (m, 2 H, CH2–N–CH3), 3.16–3.22 (m, 2 H, CH2–N–CH3), 4.33 (s, 1 H, =CH-CN), 4.88 (s, 2 H, -NH2), 7.05–7.07 (m, 1 H, ArH), 7.33–7.36 (m, 3 H, ArH), 7.48 (s, 1 H, ArH), 7.83 (d, J = 8 Hz, 1 H, ArH), 8.21 (dd, J = 8 Hz, 1 H, ArH), 8.82 (s, 1 H, ArH).

HRMS (ESI): m/z [MH]+ calcd. for C25H21N3O5S: 405.1380; found: 405.1379.
Crystal data for C$_{24}$H$_{23}$FN$_{4}$O$_{2}$: A red crystal (0.220 × 0.200 × 0.180 mm$^{3}$) was mounted on a capillary tube for indexing and intensity data collection at 298 K with an Oxford Xcalibur Sapphire3 CCD single-crystal diffractometer (Mo Ka radiation, $\lambda = 0.71073$ Å). Routine Lorentz and polarization corrections were applied, and an absorption correction was performed using the ABSCALE 3 program [CrysAlis Pro software system, Version 1.1744.3; Oxford Diffraction Ltd., Oxford U. K., 2011]. Patterson methods were used to locate the heavy atoms (SHELXS-86), and the remaining atoms were located from successive Fourier maps (SHELXL-97). All the non-hydrogen atoms were refined anisotropically. All hydrogen atoms were calculated after each cycle of refinement using a Riding model, with C–H = 0.93 Å + Uiso(H) = 1.2Ueq(C) for methylene H atoms. Crystal data: CCDC No 1862527 for C$_{24}$H$_{23}$FN$_{4}$O$_{2}$; Mr = 416.45, crystal system: monoclinic; space group C2/c; $a = 16.9960(14)$ Å, $b = 8.9323(6)$ Å, $c = 26.3854(19)$ Å, $\alpha = 90$, $\beta = 101.583$, $\gamma = 90$; $V = 3924.1(5)$ Å$^3$; $Z = 8$, $\rho_{\text{calc}} = 1.410$ Mg/m$^3$; $g$ cm$^{-3}$; $\mu = 0.999$ mm$^{-1}$; $F(000) = 1744.0$, $R1 = 0.0558$ (3860) and wR2 = 0.1420 for I > 2σ(I) and 226 parameters, R1 = 0.0558 (3860) and wR2 = 0.1420 (5075), gof = 0.904 for all data.