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DABCO-Catalyzed Efficient Synthesis of Naphthopyran Derivatives via One-Pot Three-Component Condensation Reaction at Room Temperature

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Abstract: Diazabicyclo[2.2.2]octane (DABCO) has been used as a mild and efficient catalyst for synthesis of 2-amino-3-cyano naphthopyran derivatives via a one-pot three-component reaction of aromatic aldehydes, naphthols, and malononitrile at room temperature. The short reaction times, easy workup, good to excellent yields, and mild reaction conditions make this domino Knoevenagel–Michael reaction both practical and attractive.

Keywords: 2-Amino-chromene, DABCO, domino Knoevenagel–Michael addition, one-pot three-component reaction, organocatalysis, naphthopyrans

INTRODUCTION

The rapid assembly of diverse molecular compounds is an important goal of synthetic organic chemistry and is one of the key paradigms of modern drug discovery.[1] One approach to address the challenge involves the development of atom-economical, single-pot, multicomponent coupling reactions and multicomponent processes. These processes additionally benefit from

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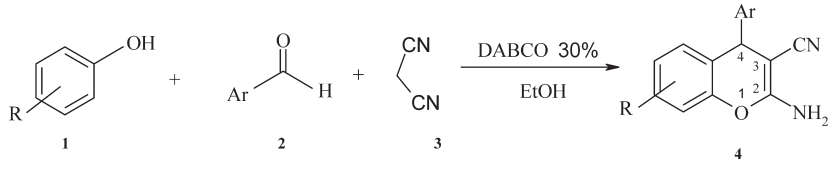
technically simple protocols, the use of common laboratory equipment, time and energy savings, and environmental advantages and have been of particular interest to both academic and industrial scientists.[2] When finding efficient new catalysts, mild reaction conditions are of particular interest. An example of such a reaction is the three-component synthesis of benzopyran derivatives.[3] Polyfunctionalized benzo[b]pyrans and their derivatives are important classes of oxygenated heterocycles, which have attracted much interest because of the biological activities of naturally occurring representatives.[4] Some of the reported biological activities of benzopyrans are anticoagulant, spasmolytic, diuretic, anti-anaphylactin, anticancer, and antidiabetic activities.[5] 4*H*-Benzo[*b*]pyrans and their derivatives are of considerable interest because of their wide range of biological activities as listed.[6] In addition, they can be used as cognitive enhancers for the treatment of neurodegenerative disease, including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's diseases, Parkinson's disease, AIDS-associated dementia, and Down syndrome as well as for the treatment of schizophrenia and myoclonus.[7] 4*H*-Pyrans also constitute the structural unit of a series of natural products.[8] A number of 2-amino-4*H*-pyrans are useful as photoactive materials.[9] Various methods for preparing these compounds have been reported.[10] Recently, tetra-*n*-butyl ammonium bromide was used as the catalyst for a three-component condensation to synthesize benzo[b]pyran derivatives in water at reflux condition.[11] Each of the methods mentioned has its own merit, with at least one of the limitations of low yield, long reaction times, effluent pollution, harsh reaction conditions, and tedious workup procedures. The development of an efficient, one-pot, chemoselective procedure is therefore of considerable interest. DABCO has been used recently as the most common catalyst in organic synthesis, for example, in the Baillys–Hillman reaction[12] and the selective cleavage of esters.[13] One of the remarkable features of DABCO is its efficient activity under neat conditions or high-concentration conditions. Thus, we considered DABCO to be an ideal base for effecting one-pot synthesis of naphthopyran derivatives. As a part of our work on one-pot multicomponent reactions (MCRs) for the synthesis of various heterocyclic compounds,[14] we describe herein the DABCO-mediated three-componenet coupling of naphthols, aromatic aldehydes and malononitrile in ethanol at room temperature to afford 2-amino-3-cyano-naphth[b]pyran derivatives in good to excellent yields (Scheme 1).



1 2 3 4

Scheme 1.

RESULTS AND DISCUSSION

DABCO is one of the most commonly used catalysts in organic synthesis. Thus, we considered this base to be ideal as a catalyst for three-component coupling of naphthols, aromatic aldehydes, and malononitrile in ethanol at room temperature to afford 2-amino-3-cyano-naphthopyrane derivatives **(4a–s)**. (see Scheme 1 and Table 1). The reaction of malononitrile, 1-naphthol, and 3-nitrobenzaldehyde was investigated in the presence of 0.1, 0.2, 0.3, and 0.5 equivalents of DABCO as catalyst. In all cases, the reaction times were 6 h, and the product was **4p** with 50, 75, 98, and 98% yields. Optimization of the reaction components afforded reasonable yields of **4**. The best yield was obtained with 0.3 equivalent of DABCO as catalyst. The reaction proceeded rapidly with the same yields when the amount of DABCO was increased from 0.3 equiv. to 1.0 equiv. for 6 h under similar conditions. Reactions were studied at 50 °C, but it was shown that the progress is

Table 1. DABCO-catalyzed synthesis of naphthopyrans (**4a–s**) at room temperature

Entry	Naphthol	Ar	Yield (%)[a]
4a	1-Naphthol	C_6H_5	75
4b	1-Naphthol	4-Br-C_6H_4	99
4c	1-Naphthol	3-Cl-C_6H_4	95
4d	2-Naphthol	3-Cl-C_6H_4	80
4e	1-Naphthol	4-Cl-C_6H_4	82
4f	2-Naphthol	4-Cl-C_6H_4	72
4g	1-Naphthol	4-CN-C_6H_4	87
4h	2-Naphthol	4-CN-C_6H_4	77
4i	1-Naphthol	2,3-Cl_2-C_6H_3	85
4j	2-Naphthol	2,3-Cl_2-C_6H_3	47
4k	1-Naphthol	2,4-Cl_2-C_6H_3	75
4l	1-Naphthol	3-OH-C_6H_4	85
4m	2-Naphthol	3-OH-C_6H_4	91
4n	1-Naphthol	3-OH-4-OMe-C_6H_3	75
4o	1-Naphthol	2-NO_2-C_6H_4	71
4p	1-Naphthol	3-NO_2-C_6H_4	98
4q	2-Naphthol	3-NO_2-C_6H_4	76
4r	1-Naphthol	4-CF_3-C_6H_4	91
4s	2-Naphthol	4-CF_3-C_6H_4	77

Notes. In all cases, the optimized amount of DABCO is 30% mol. Reaction conditions: Stirred at room temperature for 2–4 h.

[a]Yields refer to those of pure isolated products characterized by IR, ^{1}H NMR, and ^{13}C NMR spectroscopic data.

not sufficient, and unreacted alkene was recovered. The reactions of aldehydes containing electron-donating groups show only a slightly slower reaction rate and lower yields than those containing electron-withdrawing groups. The three-component reaction of α- and β-naphthols, malononitrile, and benzaldehyde derivatives was carried out by using catalytic amounts of triethylamine (0.3 equivalent), but the reaction proceeded slowly, and the only products were the alkenes. We observed reduced chemical yields for both *ortho*-substituted benzaldehyde derivatives regardless of the electronic nature of the substituent. This suggests that steric factors for *ortho*-substituted alkene intermediates can significantly reduce the reaction yield. When the three-component condensations of phenol, 4-chlorophenol, or 4-nitro phenol with anisaldehyde and malononitrile in the presence of 0.3 equiv. of DABCO was carried out, only the alkene from the reaction of anisaldehyde and malononitrile was produced. The same reaction conditions were employed with different phenols without success. This reaction goes well only with naphthols.

The structures of all products were determined on the basis of their analytical data. The ^{1}H NMR spectra of products **(4a–s)** show characteristic peaks at δ 4.90–5.90 ppm for H-4. The ^{13}C NMR spectra of **4a–s** exhibit a specific peak in the region of δ 54–60 ppm that is related to C-4.

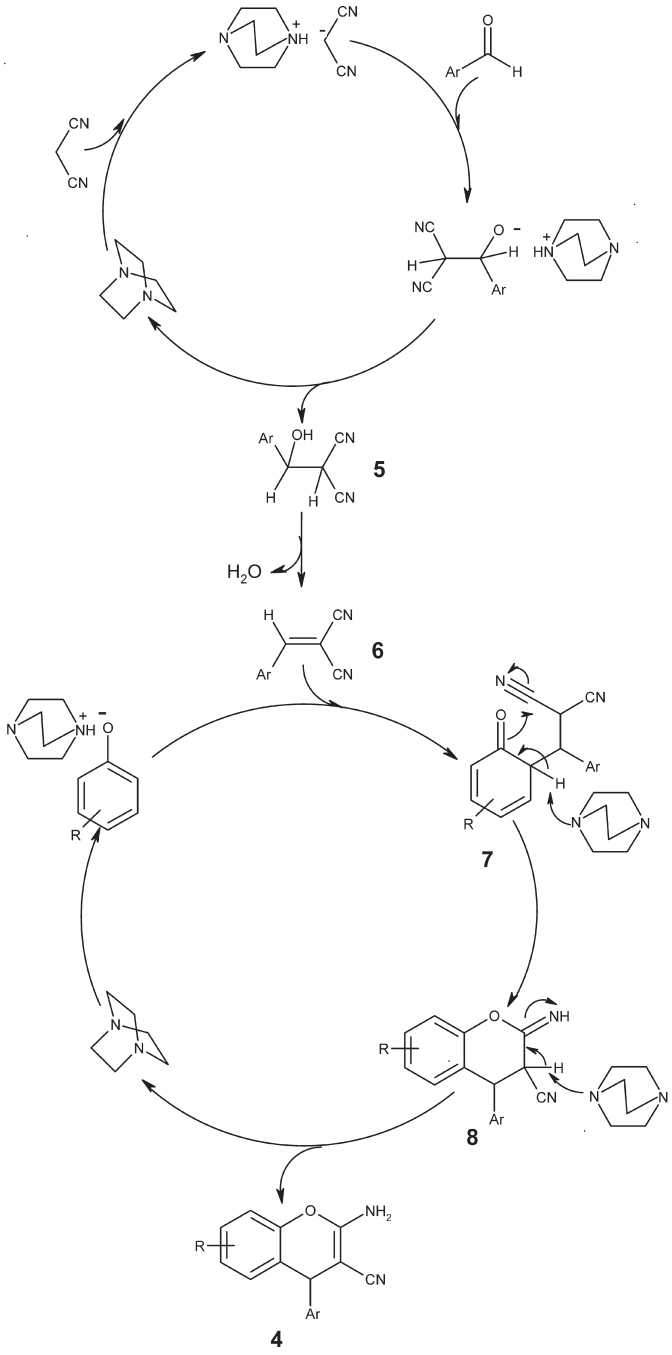
Although we have not yet established the mechanism of the one-pot reaction of naphthols, benzaldehyde derivatives, and malononitrile in the presence of DABCO in an experimental manner, a possible explanation is proposed in Scheme 2. Based on this proposed mechanism, DABCO is an effective catalyst for the formation of the olefin **6**. This is readily prepared in situ by Knoevenagel condensation of aryl aldehyde and the active methylene compound **3**, which proceeds via the intermediate **5**. After dehydration, the olefin **6** is produced. (Scheme 2).

DABCO also catalyzes the generation of the naphtholate anion, which reacts with the dicyanoolefin **6**, followed by cyclization to give the iminium ion. Upon hydrolysis of this ion, the product **4** can be formed. Existence of DABCO is essential for both steps.

In summary, we have demonstrated a rapid and efficient DABCO-catalyzed one-pot, three-component synthesis of naphthopyran derivatives at room temperature. The direct use of commercially available and inexpensive reagents, easy workup, short reaction times, and mild reaction conditions at room temperature make this domino Knoevenagel–Michael reaction very attractive and practical.

EXPERIMENTAL SECTION

Melting points were determined with Electrothermal 9100 apparatus and were uncorrected. IR spectra were obtained on an ABB FT-IR (FTLA 2000) spectrometer. ^{1}H and ^{13}C NMR spectra were run on a Bruker DRX-300 instrument at 300 MHz and 75 MHz using TMS as internal standard and DMSO-d_6,



Scheme 2. Proposed mechanism for the synthesis of naphthopyranes **4a**–**s** catalyzed by DABCO (30%).

$CDCl_3$, or acetone-d_6 as solvent. Mass spectra were recorded on Jeol JMS-700 (HR-EI) and Bruker APEX QE (ESI) spectrometers.

General Procedure for the Preparation of Naphthopyrans (4a–s)

A mixture of an aromatic aldehyde (1 mmol), mononitrile (79 mg, 1.1 mmol), naphthol (172 mg, 1.2 mmol), and DABCO (30 mol%) in ethanol (5 mL) was stirred at room temperature for 2–4 h. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, the mixture was then concentrated under reduced pressure, and 0.5 ml of water was added. The remaining solid was collected by filtration. Further purification was done by recrystallization in EtOH.

Selected Data for Compounds 4a–s

Compound 4a: 4H-Naphtho[1,2-b]pyran-3-carbonitrile,2-amino-4-phenyl, mp = 215–217 °C [lit. 210 °C].[11] IR (KBr, cm^{-1}) 3447, 3301, 3187, 2201, 1657, 1600. ^{1}H NMR (300 MHz, acetone-d_6, ppm): δ 4.93 (s, 1H, H-4), 6.46 (brs, 2H, NH_2), 7.14 (d, 1H, J = 8.3 Hz, H-Ar), 7.21–7.37 (m, 5H, H-Ar), 7.54–7.64 (m, 3H, H-Ar), 7.89 (d, 1H, J = 8.3 Hz, H-Ar), 8.3 (d, 1H, J = 8.3 Hz, H-Ar). ^{13}C NMR (75 MHz, acetone-d_6, ppm) δ 58.75, 118.0, 119.33, 120.85, 123.38, 124.11, 126.33, 126.58, 126.70, 127.01, 127.70, 127.95, 128.67, 133.33, 143.27, 145.74, 160.04. MS (70 eV, EI): $C_{20}H_{14}N_2O$: 298 (45%, $M^{+\bullet}$), 222 (41%, $[M\text{-}C_6H_4]^{+\bullet}$), 221 (100%, $[M\text{-}C_6H_5]^{+}$).

Compound 4b: 4H-Naphtho[1,2-b]pyran-3-carbonitrile,2-amino-4-(4-bromophenyl), mp = 241–243 °C (dec.). IR (KBr, cm^{-1}) 3417, 3326, 3071, 2195, 1625, 1593; ^{1}H NMR (300 MHz, acetone-d_6, ppm): δ 4.97 (s, 1H, H-4), 6.51 (brs, 2H, NH_2), 7.15 (d, 1H, J = 8.4 Hz, H-Ar), 7.30 (d, 2H, J = 8.3 Hz, H-Ar), 7.53 (d, 2H, J = 8.3 Hz, H-Ar), 7.58–7.65 (m, 3H, H-Ar), 7.90 (d, 1H, J = 8.5 Hz, H-Ar), 8.30 (d, 1H, J = 7.9 Hz, H-Ar). ^{13}C NMR (75 MHz, acetone-d_6, ppm) δ 58.2, 117.35, 119.13, 120.43, 120.87, 123.36, 124.27, 126.15, 126.66, 126.83, 127.72, 130.08, 131.70, 133.42, 143.31, 145.13, 160.07. HR-MS (70 eV, EI): $C_{20}H_{13}N_2O^{79}Br$: $[M]^{+\cdot}$ found 376.0211; calc. 376.0212; $C_{20}H_{13}N_2O^{81}Br$ $[M+2]^{+\bullet}$ found 378.0205; calc. 378.0219.

Compound 4c: 4H-Naphtho[1,2-b]pyran-3-carbonitrile,2-amino-4-(3-chlorophenyl), mp = 218–222 °C (dec.). IR (KBr, cm^{-1}) 3455, 3340, 2192, 1659, 1590. ^{1}H NMR (300 MHz, acetone-d_6, ppm): δ 5.00 (s, 1H, H-4), 6.54 (brs, 2H, NH_2), 7.17 (d, 1H, J = 8.3 Hz, H-Ar), 7.30 (d, 2H, J = 8.3 Hz, H-Ar), 7.27–7.40 (m, 4H, H-Ar), 7.56–7.65 (m, 3H, H-Ar), 7.90 (d, 1H, J = 8.5 Hz, H-Ar), 8.31 (d, 1H, J = 7.8 Hz, H-Ar). ^{13}C NMR (75 MHz,

acetone-d_6, ppm) δ 58.10, 117.21, 119.14, 120.90, 123.37, 124.33, 126.10, 126.60, 126.69, 126.87, 127.15, 127.73, 127.87, 130.43, 133.45, 134.04, 143.36, 148.15, 160.20. HR-MS (70 eV, EI): $C_{20}H_{13}N_2O^{35}Cl$ $[M]^{+\bullet}$ found: 332.0705; calc. 332.0716; $C_{20}H_{13}N_2O^{37}Cl$ $[M^+ + 2]^{+\bullet}$ found: 334.0695; calc. 334.0703.

Compound 4d: 1H-Naphtho[2,1-b]pyran-2-carbonitrile,3-amino-1-(3-chlorophenyl), mp = 235–238 °C (dec.). IR (KBr, cm^{-1}) 3431, 3328, 2182, 1646, 1588. ^{1}H NMR (300 MHz, acetone-d_6, ppm): δ 5.40 (s, 1H, H-4), 6.34 (brs, 2H, NH_2), 7.23–7.38 (m, 5H, H-Ar), 7.44–7.48 (m, 2H, H-Ar), 7.87–7.98 (m, 2H, H-Ar). ^{13}C NMR (75 MHz, acetone-d_6, ppm) δ 59.08, 111.50, 115.09, 118.33, 119.49, 120.66, 120.86, 123.38, 123.93, 126.44, 126.48, 126.59, 127.67, 133.27, 137.20, 143.06, 145.77, 147.60, 159.89. HR-MS (70 eV, EI): $C_{20}H_{13}N_2O^{35}Cl$ $[M]^{+\bullet}$ found: 332.0705; calc. 332.0716; $C_{20}H_{13}N_2O^{37}Cl$ $[M + 2]^{+\bullet}$ found: 334.0695; calc. 334.0703.

Compound 4e: 4H-Naphtho[1,2-b]pyran-3-carbonitrile,2-amino-4-(4-chlorophenyl): mp = 245–248 °C [lit. 231–232 °C][11] (dec.). IR (KBr, cm^{-1}) 3451, 3338, 2192, 1664, 1588. ^{1}H NMR (300 MHz, acetone-d_6, ppm): δ 4.95 (s, 1H, H-4), 7.10 (d, 1H, J = 8.2 Hz, H-Ar), 7.20 (brs, 2H, NH_2), 7.27 (d, 2H, J = 7.0 Hz, H-Ar), 7.38 (d, 2H, J = 7.0 Hz, H-Ar), 7.54–7.66 (m, 3H, H-Ar), 7.88 (d, 1H, J = 7.7 Hz, H-Ar), 8.22 (d, 1H, J = 8.2 Hz, H-Ar). ^{13}C NMR (75 MHz, acetone-d_6, ppm) δ 56.31, 117.84, 120.86, 121.18, 123.20, 124.46, 126.52, 127.18, 127.32, 128.14, 129.15, 130.03, 132.02, 133.21, 143.22, 145.11, 160.63. HR-MS (70 eV, EI): $C_{20}H_{13}N_2O^{35}Cl$ $[M]^{+\bullet}$ found: 332.0705; calc. 332.0716; $C_{20}H_{13}N_2O^{37}Cl$ $[M + 2]^{+\bullet}$ found: 334.0695; calc. 334.0703.

Compound 4f: 1H-Naphtho[2,1-b]pyran-2-carbonitrile,3-amino-1-(4-chlorophenyl), mp = 217–220 °C [lit. 206–208 °C][11] (dec.). IR (KBr, cm^{-1}) 3409, 3322, 3029, 2223, 1630, 1586. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.36 (s, 1H, H-4), 7.11 (brs, 2H, NH_2), 7.25 (d, 1H, J = 8.4 Hz, H-Ar), 7.29 (d, 1H, J = 8.4 Hz, H-Ar), 7.35 (d, 1H, J = 8.9 Hz, H-Ar), 7.38–7.45 (m, 3H, H-Ar), 7.80 (d, 1H, J = 8.2 Hz, H-Ar), 7.88 (d, 1H, J = 7.8 Hz, H-Ar), 7.92 (d, 1H, J = 9.0 Hz, H-Ar). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 61.18, 112.37, 113.48, 114.40, 116.68, 123.58, 125.28, 127.40, 128.56, 128.63, 129.13, 129.27, 129.92, 130.08, 131.43, 131.86, 147.10, 158.34, 158.68. HR-MS (70 eV, EI): $C_{20}H_{13}N_2O^{35}Cl$ $[M]^{+\bullet}$ found: 332.0705; calc. 332.0716; $C_{20}H_{13}N_2O^{37}Cl$ $[M + 2]^{+\bullet}$, found: 334.0695; calc. 334.0703.

Compound 4g: 4H-Naphtho[1,2-b]pyran-3-carbonitrile,2-amino-4-(4-cyanophenyl), mp = 258–260 °C (dec.). IR (KBr, cm^{-1}) 3436, 3325, 3053, 2230, 2190, 1655, 1630. ^{1}H NMR (300 MHz, acetone-d_6, ppm): δ 5.10 (s, 1H, H-4), 6.60 (brs, 2H, NH_2), 7.15 (d, 1H, J = 8.5 Hz, H-Ar), 7.56 (d, 2H, J = 8.3 Hz, H-Ar), 7.59–7.67 (m, 3H, H-Ar), 7.77 (d, 2H, J = 8.3 Hz, H-Ar), 7.90 (d, 1H, J = 7.9 Hz, H-Ar), 8.31 (d, 1H, J = 7.8 Hz, H-Ar). ^{13}C NMR (75 MHz, acetone-d_6, ppm) δ 58.49, 111.75, 117.63, 119.24, 119.91,

121.80, 124.26, 125.35, 126.88, 127.66, 127.88, 128.65, 129.94, 133.54, 134.42, 144.37, 151.81, 161.20. HR-MS (70 eV, EI): $C_{21}H_{13}N_3O$: $[M]^{+\bullet}$ found 323.1058; calc. 323.1058.

Compound 4h: 1H-Naphtho[2,1-b]pyran-2-carbonitrile,3-amino-1-(4-cyanophenyl), mp = 285–287 °C (dec.). IR (KBr, cm^{-1}) 3440, 3301, 2223, 2182, 1653, 1591. ^1H NMR (300 MHz, acetone-d_6, ppm): δ 5.49 (s, 1H, H-4), 6.41 (brs, 2H, NH_2), 7.37 (d, 1H, $J = 8.9$ Hz, H-Ar), 7.44–7.49 (m, 2H, H-Ar), 7.48 (d, 2H, $J = 8.9$ Hz, H-Ar), 7.70 (d, 2H, $J = 7.5$ Hz, H-Ar), 7.82–7.85 (m, 1H, H-Ar), 7.92–7.95 (m, 1H, H-Ar), 7.98 (d, 1H, $J = 8.9$ Hz, H-Ar). ^{13}C NMR (75 MHz, acetone-d_6, ppm) δ 58.93, 110.55, 114.49, 116.83, 118.28, 119.00, 123.51, 125.18, 127.30, 128.26, 128.66, 130.08, 130.55, 131.49, 132.66, 147.44, 150.73, 159.84. HR-MS (70 eV, EI): $C_{21}H_{13}N_3O$: $[M]^{+\bullet}$ found 323.1058; calc. 323.1058.

Compound 4i: 4H-Naphtho[1,2-b]pyran-3-carbonitrile,2-amino-4-(2,3-dichlorophenyl), mp = 260–263 °C (dec.). IR (KBr, cm^{-1}) 3424, 3316, 2187, 1658, 1620. ^1H NMR (300 MHz, DMSO-d_6, ppm): δ 5.50 (s, 1H, H-4), 6.99 (d, 1H, $J = 8.5$ Hz, H-Ar), 7.27 (brs, 2H, NH_2), 7.23–7.35 (m, 2H, H-Ar), 7.53–7.67 (m, 4H, H-Ar), 7.84 (d, 1H, $J = 8.0$ Hz, H-Ar), 8.24 (d, 1H, $J = 8.0$ Hz, H-Ar). ^{13}C NMR (75 MHz, acetone-d_6, ppm) δ 54.47, 116.04, 120.07, 120.77, 122.65, 124.19, 125.26, 126.80, 126.98, 127.70, 129.42, 129.95, 130.20, 132.31, 132.92, 143.07, 144.76, 160.44. HR-MS (70 eV, EI): $C_{20}H_{12}N_2O^{35}Cl_2$ $[M]^{+\bullet}$ found 366.0319; calc. 366.0327; $C_{20}H_{12}N_2O^{35}Cl^{37}Cl$ $[M+2]^{+\bullet}$ found 368.0282; calc. 368.0297; $C_{20}H_{12}N_2O^{37}Cl_2$ $[M+4]^{+\bullet}$ found 370.0261; calc. 370.0267.

Compound 4j: 1H-Naphtho[2,1-b]pyran-2-carbonitrile,3-amino-1-(2,3-dichlorophenyl), mp = 319–322 °C (dec.). IR (KBr, cm^{-1}) 3439, 3322, 2135, 1630, 1589. ^1H NMR (300 MHz, acetone-d_6, ppm): δ 5.94 (s, 1H, H-4), 6.38 (brs, 2H, NH_2), 7.03 (d, 1H, $J = 7.8$ Hz, H-Ar), 7.21 (t, 1H, $J = 7.8$ Hz, H-Ar), 7.35 (d, 1H, $J = 8.9$ Hz, H-Ar), 7.41–7.54 (m, 3H, H-Ar), 7.70 (d, 1H, $J = 8.3$ Hz, H-Ar), 7.94 (d, 1H, $J = 7.9$ Hz, H-Ar), 7.98 (d, 1H, $J = 9.0$ Hz, H-Ar). HR-MS (70 eV, EI): $C_{20}H_{12}N_2O^{35}Cl_2$ $[M]^{+\bullet}$ found 366.0319; calc. 366.0327; $C_{20}H_{12}N_2O^{35}Cl_2$ $[M]^{+\bullet}$ found 366.0319; calc. 366.0327; $C_{20}H_{12}N_2O^{35}Cl^{37}Cl$ $[M+2]^{+\bullet}$ found 368.0282; calc. 368.0297; $C_{20}H_{12}N_2O^{37}Cl_2$ $[M+4]^{+\bullet}$ found 370.0261; calc. 370.0267.

Compound 4k: 4H-Naphtho[1,2-b]pyran-3-carbonitrile,2-amino-4-(2,4-dichlorophenyl), mp = 214–216 °C [lit. 213–215 °C][11] (dec.). IR (KBr, cm^{-1}) 3455, 3332, 2188, 1667, 1604. ^1H NMR (300 MHz, DMSO-d_6, ppm): δ 5.40 (s, 1H, H-4), 6.98 (d, 1H, $J = 8.0$ Hz, H-Ar), 7.26 (brs, 2H, NH_2), 7.36–7.39 (m, 1H, H-Ar), 7.57–7.63 (m, 4H, H-Ar), 7.88 (d, 1H, $J = 6.2$ Hz, H-Ar), 8.23 (d, 1H, $J = 6.7$ Hz, H-Ar). ^{13}C NMR (75 MHz, acetone-d_6, ppm) δ 56.85, 116.37, 118.84, 120.89, 123.27, 124.44, 125.45, 126.73, 126.9, 127.73, 128.08, 129.22, 132.64, 133.08, 133.47, 133.54, 141.55, 143.53, 160.46. HR-MS (70 eV, EI): $C_{20}H_{12}N_2O^{35}Cl_2$ $[M]^{+\bullet}$ found

366.0319; calc. 366.0327; $C_{20}H_{12}N_2O^{35}Cl^{37}Cl$ $[M+2]^{+\bullet}$ found 368.0282; calc. 368.0297; $C_{20}H_{12}N_2O^{37}Cl_2$ $[M+4]^{+\bullet}$ found 370.0261; calc. 370.0267.

Compound 4l: 4H-Naphtho[1,2-b]pyran-3-carbonitrile,2-amino-4-(3-hydroxyphenyl), mp = 250–253 °C (dec.). IR (KBr, cm^{-1}) 3445, 3337, 2182, 1658, 1610. ^{1}H NMR (300 MHz, acetone-d_6, ppm): δ 5.40 (s, 1H, H-4), 6.44 (brs, 2H, NH_2), 6.70–6.76 (m, 2H, H-Ar), 6.82 (d, 1H, $J = 7.7$ Hz, H-Ar), 7.16 (t, 2H, $J = 8.5$ Hz, H-Ar), 7.54–7.65 (m, 3H, H-Ar), 7.88 (d, 1H, $J = 8.0$ Hz, H-Ar), 8.29 (d, 1H, $J = 8.0$ Hz, H-Ar). 8.33 (brs, 1H, OH). ^{13}C NMR (75 MHz, acetone-d_6, ppm) δ 58.80, 114.13, 114.79, 118.05, 119.07, 119.43, 120.82, 123.36, 124.08, 126.34, 126.56, 126.67, 127.70, 129.67, 133.33, 143.25, 147.30, 157.79, 160.06. ESI: $C_{20}H_{15}N_2O_2$ $[M+1]^+$ found 315.11280; calc. 314.1129, $C_{20}H_{14}N_2O_2Na$ $[M+Na]^+$ found 337.09475; calc. 337.09493, $C_{40}H_{28}N_4O_4Na$ $[2M+Na]$ found 651.20028; calc. 651.20047.

Compound 4m: 1H-Naphtho[2,1-b]pyran-2-carbonitrile,3-amino-1-(3-hydroxyphenyl), mp = 280–282 °C (dec.). IR (KBr, cm^{-1}) 3419, 3327, 2187, 1642, 1586. ^{1}H NMR (300 MHz, acetone-d_6, ppm): δ 5.40 (s, 1H, H-4), 6.23 (brs, 2H, NH_2), 6.63–6.67 (m, 2H, H-Ar), 6.77 (d, 1H, $J = 7.6$ Hz, H-Ar), 7.10 (t, 1H, $J = 7.6$ Hz, H-Ar), 7.34 (d, 1H, $J = 8.9$ Hz, H-Ar), 7.40–7.49 (m, 2H, H-Ar), 7.92 (t, 3H, $J = 8.9$ Hz, H-Ar), 8.35 (brs, 1H, OH). ^{13}C NMR (75 MHz, acetone-d_6, ppm) δ 60.18, 113.82, 114.10, 115.81, 116.73, 118.36, 119.44, 123.84, 124.96, 126.99, 128.46, 129.47, 129.65, 130.89, 131.43, 147.12, 147.30, 157.78, 159.60. ESI: $C_{20}H_{15}N_2O_2$ $[M+1]^+$ found 315.11280; calc. 314.1129; $C_{20}H_{14}N_2O_2Na$ $[M+Na]^+$ found 337.09475; calc. 337.09493; $C_{40}H_{28}N_4O_4Na$ $[2M+Na]^+$ found 651.20028; calc. 651.20047.

Compound 4n: 4H-Naphtho[1,2-b]pyran-3-carbonitrile,2-amino-4-(3-hydroxy-4-methoxyphenyl), mp = 174–177 °C (dec.). IR (KBr, cm^{-1}) 3337, 3195, 2193, 1665, 1610. ^{1}H NMR (300 MHz, acetone-d_6, ppm): δ 3.80 (s, 3H, OMe), 4.85 (s, 1H, H-4), 6.39 (brs, 2H, NH_2), 6.76–6.81 (m, 2H, H-Ar), 6.96 (d, 1H, $J = 1.50$ Hz, H-Ar), 7.18 (d, 1H, $J = 8.5$ Hz, H-Ar), 7.55–7.61 (m, 3H, H-Ar), 7.87 (d, 1H, $J = 7.8$ Hz, H-Ar), 8.28 (d, 1H, $J = 7.8$ Hz, H-Ar). ^{13}C NMR (75 MHz, acetone-d_6, ppm) δ 55.38, 59.05, 111.49, 115.08, 118.33, 119.50, 120.65, 123.38, 123.93, 126.45, 126.48, 126.59, 127.67, 133.27, 137.20, 143.05, 145.76, 147.59, 159.89. HR-MS (70 eV, EI): $C_{11}H_8N_2O_2$ $[M\text{-}C_{10}H_6\text{-}H_2O]^+$ found 200.0588; calc. 200.0586.

Compound 4o: 4H-Naphtho[1,2-b]pyran-3-carbonitrile,2-amino-4-(2-nitrophenyl), mp = 241–242 °C (dec.). IR (KBr, cm^{-1}) 3471, 3332, 2192, 1663, 1610, 1596, 1550, 1374. ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 5.45 (s, 1H, H-4), 7.06 (d, 1H, $J = 8.5$ Hz, H-Ar), 7.29 (brs, 2H, NH_2), 7.36 (d, 1H, $J = 7.8$ Hz, H-Ar), 7.49 (t, 1H, $J = 7.6$ Hz, H-Ar), 7.60–7.69 (m, 4H, H-Ar), 7.90 (d, 2H, $J = 7.2$ Hz, H-Ar), 8.50 (d, 1H, $J = 8.0$ Hz,

H-Ar). ^{13}C NMR (75 MHz, acetone-d_6, ppm) δ 55.70, 116.58, 120.39, 121.27, 123.15, 124.34, 124.73, 126.03, 127.32, 127.55, 128.17, 128.96, 132.32, 133.40, 134.08, 139.17, 143.58, 149.28, 160.69. HR-MS (70 eV, EI): $C_{20}H_{13}N_3O_3$ $[M]^{+\bullet}$ found 343.0977; calc. 343.0957.

Compound 4p: 4H-Naphtho[1,2-b]pyran-3-carbonitrile,2-amino-4-(3-nitrophenyl), mp = 217–1219 °C (dec.). [lit. 214–216 °C].[11] IR (KBr, cm^{-1}) 3460, 3363, 2183, 1650, 1603, 1596. ^{1}H NMR (300 MHz, acetone-d_6, ppm): δ 5.22 (s, 1H, H-4), 6.65 (brs, 2H, NH_2), 7.20 (d, 1H, J = 8.5 Hz, H-Ar), 7.58–7.70 (m, 4H, H-Ar), 7.82 (d, 1H, J = 7.7 Hz, H-Ar), 7.91 (d, 1H, J = 7.7 Hz, H-Ar), 8.15 (d, 1H, J = 8.5 Hz, H-Ar), 8.33 (d, 1H, J = 8.5 Hz, H-Ar). ^{13}C NMR (75 MHz, acetone-d_6, ppm) δ 57.68, 116.72, 119.03, 120.94, 122.11, 122.48, 123.37, 124.52, 125.98, 126.80, 127.02, 127.76, 130.20, 133.54, 134.52, 143.47, 147.95, 148.63, 160.35. HR-MS (70 eV, EI): $C_{20}H_{13}N_3O_3$ $[M]^{+\bullet}$ found 343.0977; calc. 343.0957.

Compound 4q: 1H-Naphtho[2,1-b]pyran-2-carbonitrile,3-amino-1-(3-nitrophenyl), mp = 239–241 °C (dec.). IR (KBr, cm^{-1}) 3464, 3357, 2192, 1657, 1590. ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 5.61 (s, 1H, H-4), 7.15 (brs, 2H, NH_2), 7.38 (d, 1H, J = 8.9 Hz, H-Ar), 7.42–7.48 (m, 2H, H-Ar), 7.57 (t, 1H, J = 7.8 Hz, H-Ar), 7.65 (m, 1H, H-Ar), 7.85 (d, 1H, J = 7.5 Hz, H-Ar), 7.91–7.96 (m, 2H, H-Ar), 8.00 (d, 1H, J = 6.3 Hz, H-Ar), 8.05 (m, 1H, H-Ar). ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ 57.42, 115.04, 117.32, 120.66, 121.78, 122.29, 123.93, 125.60, 127.85, 129.05, 130.37, 130.52, 130.89, 131.31, 134.17, 147.43, 148.33, 148.44, 160.44. HR-MS (70 eV, EI): $C_{20}H_{13}N_3O_3$ $[M]^{+\bullet}$ found 343.0977; calc. 343.0957.

Compound 4r: 4H-Naphtho[1,2-b]pyran-3-carbonitrile,2-amino-4-(4-triflouromethylphenyl), mp = 243–46 °C (dec.). IR (KBr, cm^{-1}) 3481, 3334, 2187, 1670, 1639, 1602. ^{1}H NMR (300 MHz, acetone-d_6, ppm): δ 5.09 (s, 1H, H-4), 6.58 (brs, 2H, NH_2), 7.15 (d, 1H, J = 8.5 Hz, H-Ar), 7.55–7.72 (m, 7H, H-Ar), 7.91 (d, 1H, J = 7.60 Hz, H-Ar), 8.32 (d, 1H, J = 8.1 Hz, H-Ar). ^{13}C NMR (75 MHz, acetone-d_6, ppm) δ 57.93, 117.02, 119.08, 120.89, 123.37, 124.39, 125.57, 125.63, 125.68, 125.73 (CF_3), 126.06, 126.72, 126.91, 127.74, 128.47, 128.76, 133.49, 143.44, 150.13, 160.23. HR-MS (70 eV, EI): $C_{21}H_{13}N_2OF_3$ $[M]^{+\bullet}$ found 366.0980; calc. 366.0967.

Compound 4s: 1H-Naphtho[2,1-b]pyran-2-carbonitrile,3-amino-1-(4-trifluoromethylphenyl), mp = 215–217 °C (dec.). IR (KBr, cm^{-1}): 3470, 3358, 2193, 1739, 1576. ^{1}H NMR (300 MHz, acetone-d_6, ppm): δ 5.48 (s, 1H, H-4), 6.37 (brs, 2H, NH_2), 7.37 (d, 1H, J = 8.9 Hz, H-Ar), 7.41–7.50 (m, 4H, H-Ar), 7.64 (d, 2H, J = 8.2 Hz, H-Ar), 7.84–7.94 (m, 4H, H-Ar), 7.98 (d, 1H, J = 8.9 Hz, H-Ar). ^{13}C NMR (75 MHz, acetone-d_6, ppm) δ 58.93, 114.75, 116.82, 119.16, 122.59, 123.55, 125.12, 125.73, 127.25, 127.96, 128.15, 128.60, 130.00, 130.59, 131.48, 147.40, 149.96, 159.79. HR-MS (70 eV, EI) $C_{21}H_{13}N_2OF_3$ $[M]^{+\bullet}$ found 366.0980; calc. 366.0967.

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