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Synthesis and primary cytotoxicity evaluation of arylmethylenenaphthofuranones derivatives

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Abstract
New series of 2(or 3)-arylmethylenenaphtho[2,1-*b*]furan-3(or 2)-ones were synthesized, characterized and tested for anticancer properties *in vitro*. The target compounds were prepared by Knoevenagel coupling between the naphthofuranones **3**, **28**–**30** and formyl derivatives. 2-(4-Oxo-1-benzopyran-3-ylmethylene)naphtho[2,1-*b*]furan-3-one **36** was the most active compound (IC_{50} (L1210) = 1.6 μM). These compounds were also evaluated, in an independent manner, as inhibitors of Src protein tyrosine kinase, but only minor activity was observed.

Keywords: *3-(arylmethylene)naphtho[2,1-b]furan-2(3H)-ones, 2-(arylmethylene)naphtho[2,1-b]furan-3(2H)-ones, Knoevenagel coupling, Cytotoxicity evaluation*

Introduction

Angiogenesis, the growth of new blood vessels from existing host vasculature, plays a fundamental role in the development of solid tumors. During the last few years, development of small molecule tyrosine kinase inhibitors as anti-angiogenic and anti-tumor agents has generated great interest. Indeed, there are multiple tyrosine kinase receptors which appear to have key roles in the generation of new tumor blood vessels and, as such, represent valuable targets for cancer chemotherapy [1].

The former SUGEN organization (now part of Pharmacia) has initially focused its efforts to identify and develop inhibitors of tyrosine kinase incorporating an indolin-2-one pharmacophore (Figure 1). SU5416, one of the earliest compounds of this class, was found to be a potent inhibitor of both VEGFR and PDGFR kinases, by competing for ATP binding at the enzyme catalytic site [2].

In a previous work on the synthesis of potential inhibitors of angiogenesis, we reported a number of arylmethylenebenzofuranone derivatives and pointed out that the replacement of indolin-2-one in SU5416 by 2,3-dihydrobenzo[*b*]furan-2-one (Figure 1) induced a decrease in angiogenesis comparable to that observed with SU5416 [3].

These encouraging results prompted us to investigate novel oxygenated derivatives liable to exert anticancer activity. This study was aimed at exploring the effect of the replacement of the benzofuran-2-one

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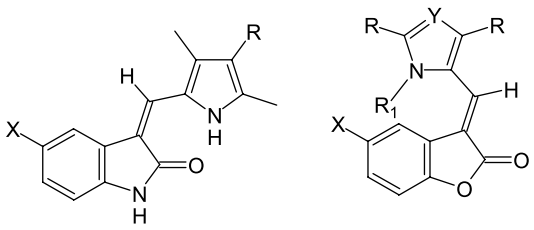


R = H: SU5416
R = $(CH_2)_2COOH$: SU6668

X = H, OH
Y = CH, N
R, R_1 = H, CH_3

Figure 1. Indolin-2-one and benzofuran-2-one structures.

moiety by a naphthofuran-2(or 3)-one core, substituted or unsubstituted on the homocycle.

Materials and methods

Chemistry

Instrumentation. Melting points were determined on an Electrothermal IA 9000 melting point apparatus in open capillary tubes and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 250 or AVANCE 400 spectrometer. Chemical shifts (δ) are reported in part per million (ppm) relative to tetramethylsilane as internal standard (in NMR description, s = singulet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad). Coupling constants J are given in Hz. IR spectra were recorded on a Perkin-Elmer Paragon 1000 PC spectrometer; only the most significant absorption bands have been reported. Electrospray ionization (ESI) mass spectra were recorded on a ESQUIRE-LC Ion Trap System. Reactions were monitored by TLC analysis using Merck silica gel 60F-254 thin-layer plates. Column chromatography was carried out on silica gel Merck 60 (70–230 mesh ASTM). Chemicals and solvents used were commercially available. 2-Formyl-3,5-dimethylpyrrole ***5*** was prepared by a Vilsmeier-Haack reaction [4]. *N*-Methylation of 4-formylimidazole was carried out using the couple NaH/DMF in presence of CH_3I as previously described [5]. 2-Hydroxyphenylacetic acid **51**, 2-naphthol **1**, 2-naphthoxyacetic acid **25**, benzofuran-3(2*H*)-one **54**, 3,5-dibromo-4-hydroxybenzaldehyde **4**, 4-formylimidazole **6** and 3-formylchromones **9**–**12** are commercially available (Figure 2).

Benzo[b]furan-2(3H)-one ***(52)*** *[15]*. A solution of 2-hydroxyphenylacetic acid **51** (5.00 g, 32.86 mmol) in 60 mL of xylene, containing a catalytic amount of *p*-toluenesulfonic acid (0.30 g, 1.64 mmol) was refluxed for 2 h, under a Dean-Stark trap. After evaporation of the xylene, the residual oil was distilled under pressure. Yield: 89% as a yellow oil. Bp: 146°C (42 mmHg), lit[15]: 132–134°C (18 mmHg).

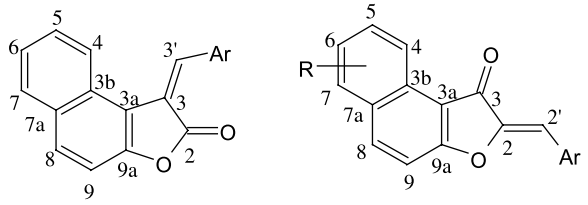


Figure 2. Structures of the studied 3-(arylmethylene)naphtho[2,1-*b*]furan-2(3*H*)-ones and 2-(arylmethylene)naphtho[2,1-*b*]furan-3(2*H*)-ones.

^{1}H NMR (DMSO-d_6): δ 3.95 (s, 2H, CH_2); 7.18 (ddd, 1H, H_5, J = 7.5, 1.2); 7.20 (d, 1H, H_7, J = 8.0); 7.33 (d, 1H, H_4, J = 8.0); 7.39 (ddd, 1H, H_6, J = 7.5, 1.2). IR: cm^{-1} 1702, 1614, 1462.

2,3-Dihydronaphtho[2,1-b]furan-2,3-diol ***(2)*** *[10]*. A solution of 2-naphthol **1** (2.00 g, 13.9 mmol) and KOH (0.78 g, 13.9 mmol) in 28 mL of water was added dropwise to a 40% aqueous glyoxal solution (12.00 g, 83.0 mmol). The mixture was stirred at 30°C for 3 h. The precipitate formed during the reaction was then filtered, washed with water and dried under vacuum. Yield: 80% as a beige solid. Mp: 61-62°C (H_2O), lit[10]: 60°C. ^{1}H NMR (DMSO-d_6): δ 5.26 (dd, 1H, C*H*, J = 6.8, 1.5); 5.73 (dd, 1H, C*H*, J = 6.4, 1.5); 5.89 (d, 1H, O*H*, J = 6.8); 7.20 (d, 1H, H_9, J = 8.8); 7.37 (dd, 1H, H_5, J = 7.6); 7.47 (d, 1H, O*H*, J = 6.4); 7.55 (dd, 1H, H_6, J = 7.6); 7.85–7.95 (m, 2H, H_4 and H_7); 7.91 (d, 1H, H_8, J = 8.8). IR: cm^{-1} 3400, 1589, 1445, 1140.

Naphtho[2,1-b]furan-2(3H)-one ***(3)*** *[10]*. A mixture of 2,3-dihydronaphtho[2,1-*b*]furan-2,3-diol **2** (1.06 g, 4.82 mmol) in 20 mL of chloroform and 25 mL of 3M aqueous HCl was heated at 50°C for 1 h. The organic layer was separated from the mixture, dried over Na_2SO_4 and concentrated. Recrystallization from diisopropyl ether gave the desired product as a pale yellow solid. Yield: 85%. Mp: 99–100°C (diisopropyl ether), lit[10]: 102-103°C. (Found M^+: 182.7, $C_{12}H_8O_2$ requires 184.19). ^{1}H NMR (DMSO-d_6): δ 4.20 (s, 2H, CH_2); 7.46 (d, 1H, H_9, J = 8.9); 7.47 (ddd, 1H, H_5, J = 7.6, 1.2); 7.59 (ddd, 1H, H_6, J = 7.6, 1.2); 7.74 (d, 1H, H_7, J = 8.4); 7.95 (d, 1H, H_8, J = 8.9); 7.98 (d, 1H, H_4, J = 8.4). ^{13}C NMR (DMSO-d_6): 111.56 (C9); 32.28 (C3); 129.31 (C3a); 129.08 (C4); 127.59 (C6); 118.22 (C3b); 129.31 (C8); 124.93 (C5); 129.17 (C7a); 123.74 (C7); 151.73 (C9a); 175.15 (C2). IR: cm^{-1} 1803, 1631, 1578, 1459.

Naphtho[2,1-b]furan-3(2H)-one ***(28)*** *[12]*. 2-Naphthoxyacetic acid **25** (8.00 g, 39.5 mmol) was heated

under reflux for 1 h with thionyl chloride in excess and a drop of dry DMF, in a round-bottomed flask equipped with a condenser. Thionyl chloride was distilled off; the acid chloride obtained was slowly added dropwise to $AlCl_3$ (5.35 g, 39.5 mmol) in 20 mL of CH_2Cl_2 cooled with ice water. The mixture was refluxed for 45 min. Then the cake was treated with cold water under a hood. The product was then extracted into ether (4 × 50 mL). The organic layer was dried with Na_2SO_4 and filtered. The solvent was evaporated in vacuum and the residue was purified by chromatography (CH_2Cl_2) to give naphtho [2,1-*b*]furan-3(2*H*)-one as a pale yellow solid. Yield: 80%. Mp: 129–130°C (CH_2Cl_2), lit[12]: 133°C. (Found M^+: 184.5, $C_{12}H_8O_2$ requires 184.19). ^{1}H NMR (DMSO-d_6): δ 4.77 (s, 2H, CH_2); 7.29 (d, 1H, H_9, J = 9.0); 7.38 (ddd, 1H, H_6, J = 7.0, 1.2); 7.57 (ddd, 1H, H_5, J = 7.0, 1.2); 7.86 (d, 1H, H_7, J = 8.1); 8.12 (d, 1H, H_8, J = 9.0); 8.47 (d, 1H, H_4, J = 8.1). ^{13}C NMR (DMSO-d_6): 75.81 (C2); 112.72 (C3a); 114.49 (C9); 122.09 (C4); 125.45 (C6); 128.59 (C3b); 128.92 (C7a); 129.06 (C7); 130.02 (C5); 140.08 (C8); 176.16 (C9a); 199.42 (C3). IR: cm^{-1} 1689, 1631, 1579, 1455.

5-Methoxynaphtho[2,1-b]furan-3(2H)-one ***30***. Yield: 90% as a pale yellow solid. Mp: 154-155°C (CH_2Cl_2). (Found M^+: 214.3, $C_{13}H_{10}O_3$ requires 214.22). ^{1}H NMR (DMSO-d_6): δ 4.95 (s, 2H, CH_2); 8.06 (d, 1H, H_4, J = 2.7); 3.94 (s, 3H, CH_3O); 7.97 (d, 1H, H_7, J = 8.8); 7.19 (dd, 1H, H_6, J = 8.8, 2.7); 7.30 (d, 1H, H_9, J = 8.8); 8.25 (d, 1H, H_8, J = 8.8). ^{13}C NMR (DMSO-d_6): 55.48 (CH_3O); 75.69 (C2); 101.90 (C4); 111.29 (C6); 112.13 (C3a); 116.70 (C9); 123.97 (C7a); 130.51 (C3b); 130.72 (C7); 139.77 (C8); 160.90 (C5); 176.44 (C9a); 199.29 (C3). IR: cm^{-1} 3412, 1671, 1610, 1585, 1455.

8-[(N-tert-butyloxycarbonyl)amino]naphth-2-ol ***23*** *[14]*. A solution of 8-amino-2-naphthol (5.00 g, 31.42 mmol) and di-*tert*-butyl dicarbonate (7.19 g, 32.99 mmol) in 140 mL of CH_2Cl_2 and 100 mL of THF was heated to reflux for 36 h. The mixture was allowed to cool to ambient temperature and then filtered to give a white powder. The filtrate was concentrated in vacuum and purified by chromatography (CH_2Cl_2) to give another fraction of the desired product. Yield: 93% as a white solid. Mp: 142–143°C (CH_2Cl_2). (Found M^+: 253.6, $C_{15}H_{17}NO_3$ requires 259.30). ^{1}H NMR (DMSO-d_6): δ 1.53 (s, 9H, 3 × CH_3); 7.13 (dd, 1H, H_3, J = 8.8, 2.4); 7.26 (dd, 1H, H_6, J = 7.6); 7.31 (d, 1H, H_1, J = 2.4); 7.43 (d, 1H, H_7, J = 7.6); 7.65 (d, 1H, H_5, J = 7.6); 7.80 (d, 1H, H_4, J = 8.8); 9.01 (s, 1H, N*H*); 9.79 (s, 1H, O*H*). IR: cm^{-1} 3304, 1690, 1630, 1529, 1455.

{8-[(tert-Butyloxycarbonylamino)naphth-2-yl]oxy}acetic acid ***(26)***. To a solution of **23** (5.00 g, 19.28 mmol) in 15 mL of THF at 40°C was added bromoacetic acid (2.95 g, 21.21 mmol) in 30 mL of water. Then, a solution of sodium hydroxide (1.62 g, 40.49 mmol) in 7 mL of water was added dropwise at 40°C. The mixture was heated to gentle reflux for 21 h. After cooling to room temperature, the THF was evaporated, the pH of the aqueous phase adjusted to 8 with a saturated solution of sodium hydrogen carbonate. The product was then extracted into ethyl acetate. The aqueous phase was acidified to pH 3 with concentrated hydrochloric acid. The mixture was stirred at 20°C for 1 h. The precipitate formed was then filtered, washed with water and dried under vacuum. Yield: 82% as a beige solid. Mp: 154–155°C (CH_2Cl_2). (Found M^+: 317.1, $C_{17}H_{19}NO_5$ requires 317.34). ^{1}H NMR (DMSO-d_6): δ 1.55 (s, 9H, 3 × CH_3); 4.85 (s, 2H, CH_2); 7.24 (dd, 1H, H_3, J = 8.8, 2.4); 7.35 (dd, 1H, H_6, J = 7.9); 7.43 (d, 1H, H_1, J = 2.4); 7.64 (d, 1H, H_7, J = 7.9); 7.67 (d, 1H, H_5, J = 7.9); 7.88 (d, 1H, H_4, J = 8.8); 9.22 (s, 1H, N*H*). IR: cm^{-1} 3400, 1735, 1687, 1601, 1480.

[(7-Methoxynaphth-2-yl)oxy]acetic acid ***(27)***. Yield: 90% as a white solid. Mp: 159-160°C (CH_2Cl_2). (Found M^+: 232.4, $C_{13}H_{12}O_4$ requires 232.24). ^{1}H NMR (DMSO-d_6): δ 3.88 (s, 3H, CH_3O); 4.78 (s, 2H, CH_2); 7.02 (dd, 1H, H_3, J = 8.9, 2.5); 7.06 (dd, 1H, H_6, J = 8.9, 2.5); 7.19 (d, 1H, H_8, J = 2.5); 7.24 (d, 1H, H_1, J = 2.5); 7.76 (d, 1H, H_5, J = 8.9); 7.78 (d, 1H, H_4, J = 8.9). IR: cm^{-1} 1745, 1627, 1513, 1466.

4-Aminonaphtho[2,1-b]furan-3(2H)-one ***(29)***. A mixture of **26** (1.00 g, 3.15 mmol) and polyphosphoric acid (10.00 g) was heated at 90° for 16 h under nitrogen. After cooling to ambient temperature, iced water was added and the product was extracted into diethyl ether (3 × 100 mL). Organic phases were then washed with 2.5M aqueous NaOH and water. The organic layer was dried with Na_2SO_4, filtered, and the solvent was evaporated in vacuum. Recrystallization from diisopropyl ether gave the desired product as an ochre solid. Yield: 45%. Mp: 156–157°C (diisopropyl ether). (Found M^+: 199.4, $C_{12}H_9NO_2$ requires 199.21). ^{1}H NMR (DMSO-d_6): δ 5.03 (s, 2H, CH_2); 6.82 (d, 1H, H_5, J = 7.6); 6.94 (br, 2H, NH_2); 7.11 (d, 1H, H_7, J = 7.6); 7.24 (dd, 1H, H_6, J = 7.6); 7.35 (d, 1H, H_9, J = 9.1); 8.18 (d, 1H, H_8, J = 9.1). ^{13}C NMR (DMSO-d_6): 76.11 (C2); 111.21 (C5); 112.80 (C3a); 115.11 (C9); 115.85 (C7); 117.15 (C3b); 127.04 (C6); 135.80 (C7a); 142.27 (C8); 146.50 (C4); 175.83 (C9a); 199.78 (C3). IR: cm^{-1} 3412, 1671, 1610, 1585, 1455.

Method A

A mixture of naphtho[2,1-*b*]furan-2(3*H*)-one **3** (0.30 g, 1.63 mmol), an aldehyde (1.63 mmol) and *para*-toluenesulfonic acid (0.15 g, 0.82 mmol), in anhydrous toluene (8 mL), under nitrogen, was stirred at 100°C for 20 h (in the case of products **13–17**) or 3 h (in the case of products **18–21**). After cooling to room temperature, the resulting precipitate was collected by filtration, washed with water and recrystallized from ethanol.

(3Z)-3-(3,5-Dibromo-4-hydroxybenzylidene) naphtho[2,1-b]furan-2(3H)-one ***(13)***. Yield: 76% as a red solid. Mp > 400°C (H_2O). (Found M^+: 444.8, $C_{19}H_{10}Br_2O_3$ requires 446.09). ^{1}H NMR (DMSO-d_6): δ 7.44 (d, 1H, H_9, $J = 8.7$); 7.50 (dd, 1H, H_6, $J = 7.2$); 7.65 (dd, 1H, H_5, $J = 7.2$); 7.81 (d, 1H, H_8, $J = 8.7$); 8.00 (d, 1H, H_7, $J = 8.1$); 8.15 (s, 1H, $H_{3'}$); 8.67 (d, 1H, H_4, $J = 8.1$); 8.80 (s, 2H, Ph-*H*). ^{13}C NMR (DMSO-d_6): 111.48 (C9); 116.29 (C3); 121.70 (C3a); 122.98 (C4); 124.97 (C6); 127.49 (C3b); 128.85 (C8); 130.13 (C5); 130.84 (C7a); 132.17 (C7); 139.66 (C3'); 151.83 (C9a); 165.92 (C2); 111.00, 128.15, 136.25, 153.01 (C Ph). IR: cm^{-1} 3424, 1739, 1544, 1467, 806.

(3Z)-3-[(3,5-Dimethyl-1H-pyrrol-2-yl) methylene]naphtho[2,1-b]furan-2(3H)-one ***(14)***. Yield: 20% as a red solid. Mp: 165–166°C (EtOH). (Found M^+: 289.3, $C_{19}H_{15}NO_2$ requires 289.33). ^{1}H NMR (DMSO-d_6): δ 2.43 and 2.44 (2s, 6H, 2 × CH_3); 6.08 (d, 1H, pyr-*H*, $J = 2.5$); 7.37 (d, 1H, H_9, $J = 8.8$); 7.46 (ddd, 1H, H_6, $J = 7.0, 1.2$); 7.63 (ddd, 1H, H_5, $J = 7.0, 1.2$); 7.72 (d, 1H, H_8, $J = 8.8$); 7.92 (d, 1H, H_7, $J = 8.0$); 8.06 (s, 1H, $H_{3'}$); 8.33 (d, 1H, H_4, $J = 8.0$); 12.51 (s, 1H, N*H*). ^{13}C NMR (DMSO-d_6): 11.81, 13.83 (2 × CH_3); 111.43 (C9); 106.83 (C3); 117.98 (C3a); 122.40 (C4); 124.66 (C6); 127.14 (C3b); 127.11 (C8); 128.12 (C5); 131.05 (C7a); 128.17 (C7); 130.15 (C3'); 148.89 (C9a); 170.10 (C2); 114.00, 126.96, 136.03, 139.64 (C pyr). IR: cm^{-1} 3450, 1715, 1561, 1448.

(3Z)-3-(1H-Imidazol-4-ylmethylene)naphtho[2,1-b] furan-2(3H)-one ***(15)***. Yield: 40% as a yellow solid. Mp: 273-274°C (EtOH). (Found M^+: 263.0, $C_{16}H_{10}N_2O_2$ requires 262.27). ^{1}H NMR (DMSO-d_6): δ 7.57 (d, 1H, H_9, $J = 9.0$); 7.60 (dd, 1H, H_6, $J = 7.2$); 7.79 (dd, 1H, H_5, $J = 7.2$); 8.04 (d, 1H, H_8, $J = 9.0$); 8.08 (s, 1H, $H_{3'}$); 8.10 (d, 1H, H_7, $J = 8.2$); 8.48 (s, 2H, imid-*H*); 8.50 (d, 1H, H_4, $J = 8.2$); 12.8 (s, 1H, N*H*). ^{13}C NMR (DMSO-d_6): 111.64 (C9); 115.71 (C3); 116.44 (C3a); 122.43 (C4); 124.97 (C6); 127.31 (C3b); 128.71 (C8); 130.23 (C5); 130.94 (C7a); 130.91 (C7); 130.94 (C3'); 150.84 (C9a); 167.42 (C2); 126.23, 131.94, 139.43 (C imid). IR: cm^{-1} 3449, 1740, 1571, 1457.

(3Z)-3-[(1-Methyl-1H-imidazol-4-yl)methylene]naphtho [2,1-b]furan-2(3H)-one ***(16)***. Yield: 80% as a yellow solid. Mp: 249–250°C (EtOH). (Found M^+: 276.9, $C_{17}H_{12}N_2O_2$ requires 276.29). ^{1}H NMR (DMSO-d_6): δ 3.87 (s, 3H, CH_3); 7.56 (d, 1H, H_9, $J = 8.8$); 7.58 (dd, 1H, H_6, $J = 7.2$); 7.78 (dd, 1H, H_5, $J = 7.2$); 7.96 (s, 1H, $H_{3'}$); 8.04 (d, 1H, H_8, $J = 8.8$); 8.10 (d, 1H, H_7, $J = 8.2$); 8.36 and 8.82 (2s, 2H, imid-*H*); 8.47 (d, 1H, H_4, $J = 8.2$). ^{13}C NMR (DMSO-d_6): 33.85 (CH_3); 111.69 (C9); 116.31 (C3); 116.55 (C3a); 122.23 (C4); 124.98 (C6); 127.38 (C3b); 128.91 (C8); 130.30 (C5); 131.01 (C7a); 130.89 (C7); 135.69 (C3'); 150.80 (C9a); 166.65 (C2); 129.05, 136.18, 139.96 (C imid). IR: cm^{-1} 1755, 1583, 1460.

(3Z)-3-[(1-Methyl-1H-imidazol-5-yl)methylene] naphtho[2,1-b]furan-2(3H)-one ***(17)***. Yield: 40% as an orange solid. Mp: 213–214°C (EtOH). (Found M^+: 277.0, $C_{17}H_{12}N_2O_2$ requires 276.29). ^{1}H NMR (DMSO-d_6): δ 4.01 (s, 3H, CH_3); 7.56 (d, 1H, H_9, $J = 8.8$); 7.59 (ddd, 1H, H_6, $J = 7.0, 1.2$); 7.77 (ddd, 1H, H_5, $J = 7.0, 1.2$); 8.05 (d, 1H, H_8, $J = 8.8$); 8.13 (s, 1H, $H_{3'}$); 8.13 (d, 1H, H_7, $J = 8.2$); 8.15 and 8.69 (2s, 2H, imid-*H*); 8.55 (d, 1H, H_4, $J = 8.2$). ^{13}C NMR (DMSO-d_6): 32.04 (CH_3); 111.86 (C9); 116.80 (C3); 116.98 (C3a); 122.98 (C4); 125.22 (C6); 127.55 (C3b); 129.10 (C8); 130.45 (C5); 131.11 (C7a); 131.48 (C7); 139.47 (C3'); 151.14 (C9a); 166.42 (C2); 126.17, 133.10, 143.52 (C imid). IR: cm^{-1} 1762, 1581, 1458.

(3Z)-3-(4-Oxo-1-benzopyran-3-ylmethylene) naphtho[2,1-b]furan-2(3H)-one ***(18)***. Yield: 72% as an orange solid. Mp: 222–223°C (EtOH). (Found M^+: 338.9, $C_{22}H_{12}O_4$ requires 340.33). ^{1}H NMR ($CDCl_3$): δ 7.33 (d, 1H, H_9, $J = 8.9$); 7.50 (dd, 1H, H_6, $J = 7.6$); 7.53 (dd, 1H, benzopy-*H*, $J = 7.0$); 7.57 (d, 1H, benzopy-*H*, $J = 8.5$); 7.70 (dd, 1H, H_5, $J = 7.6$); 7.76 (dd, 1H, benzopy-*H*, $J = 7.0$); 7.88 (d, 1H, H_8, $J = 8.9$); 7.91 (d, 1H, H_7, $J = 8.5$); 8.33 (d, 1H, benzopy-*H*, $J = 8.5$); 8.47 (d, 1H, H_4, $J = 8.5$); 8.63 (s, 1H, $H_{3'}$); 9.81 (s, 1H, benzopy-*H*). ^{13}C NMR (DMSO-d_6): 111.58 (C9); 115.52 (C3); 118.75 (C3a); 122.10 (C4); 125.14 (C6); 127.40 (C3b); 129.25 (C8); 130.22 (C5); 130.71 (C7a); 131.80 (C7); 132.75 (C3'); 152.02 (C9a); 165.95 (C2); 117.88, 123.14, 124.02, 125.45, 126.31, 134.82, 155.49, 159.37, 174.69 (C benzopy). IR: cm^{-1} 1767, 1661, 1620, 1575, 1461.

(3Z)-3-(6-Methyl-4-oxo-1-benzopyran-3-ylmethylene)naphtho[2,1-b]furan-2(3H)-one ***(19)***. Yield: 67% as a yellow solid. Mp: 262–263°C (CH_2Cl_2). (Found M^+: 354.0, $C_{23}H_{15}O_4$ requires 355.37). ^{1}H NMR ($CDCl_3$): δ 2.52 (s, 3H, C*H*$_3$); 7.34 (d, 1H, H_9, $J = 8.9$); 7.47 (d, 1H, benzopy-*H*, $J = 8.8$); 7.51 (dd, 1H, H_6, $J = 7.2$); 7.56 (d, 1H, benzopy-*H*, $J = 8.8$); 7.71 (dd, 1H, H_5, $J = 7.2$); 7.89 (d, 1H, H_8, $J = 8.9$); 7.92 (d, 1H, H_7, $J = 8.5$); 8.11 (br, 1H, benzopy-*H*); 8.49 (d, 1H, H_4, $J = 8.5$); 8.65 (s, 1H, $H_{3'}$); 9.78 (s, 1H, benzopy-*H*). ^{13}C NMR (DMSO-d_6): 21.06 (CH_3); 111.42 (C9); 116.73 (C3); 118.23 (C3a); 122.50 (C4); 125.01 (C6); 128.18 (C3b); 129.02 (C8); 130.08 (C5); 131.20 (C7a); 131.82 (C7); 132.21 (C3'); 152.37 (C9a); 167.38 (C2); 118.29, 123.37, 123.47, 125.70, 135.54, 136.11, 154.31, 160.07, 176.01 (C chrom). IR: cm^{-1} 1759, 1658, 1620, 1576, 1481.

(3Z)-3-(6-Chloro-4-oxo-1-benzopyran-3-ylmethylene)naphtho[2,1-b]furan-2(3H)-one ***(20)***. Yield: 71% as an orange solid. Mp: 286–287°C (CH_2Cl_2). (Found M^+: 374.0, $C_{22}H_{12}ClO_4$ requires 375.83). ^{1}H NMR ($CDCl_3$): δ 7.36 (d, 1H, H_9, $J = 8.8$); 7.56 (d, 1H, benzopy-*H*, $J = 8.8$); 7.53 (dd, 1H, H_6, $J = 7.4$); 7.71 (dd, 1H, benzopy-*H*, $J = 8.8$, 2.7); 7.73 (dd, 1H, H_5, $J = 7.4$); 7.91 (d, 1H, H_8, $J = 8.8$); 7.94 (d, 1H, H_7, $J = 8.5$); 8.28 (br, 1H, benzopy-*H*); 8.47 (d, 1H, H_4, $J = 8.5$); 8.56 (s, 1H, $H_{3'}$); 9.75 (s, 1H, benzopy-*H*). ^{13}C NMR (DMSO-d_6): 110.43 (C9); 115.48 (C3); 117.46 (C3a); 121.41 (C4); 124.11 (C6); 127.16 (C3b); 128.15 (C8); 129.14 (C5); 131.00 (C7a); 129.72 (C7); 131.59 (C3'); 151.60 (C9a); 166.12 (C2); 119.27, 123.60, 123.89, 124.76, 130.21, 133.52, 153.34, 158.94, 175.42 (C benzopy). IR: cm^{-1} 1758, 1663, 1618, 1562, 1463, 807.

(3Z)-3-(6-Nitro-4-oxo-1-benzopyran-3-ylmethylene)naphtho[2,1-b]furan-2(3H)-one ***(21)***. Yield: 42% as an orange solid. Mp: 289–290°C (CH_2Cl_2). (Found M^+: 385.0, $C_{22}H_{12}NO_6$ requires 386.34). ^{1}H NMR ($CDCl_3$): δ 7.36 (d, 1H, H_9, $J = 8.9$); 7.54 (ddd, 1H, H_6, $J = 7.0$, 1.2); 7.75 (d, 1H, benzopy-*H*, $J = 9.1$); 7.75 (ddd, 1H, H_5, $J = 7.0$, 1.2); 7.94 (d, 1H, H_7, $J = 8.5$); 7.95 (d, 1H, H_8, $J = 8.9$); 8.45 (d, 1H, H_4, $J = 8.5$); 8.51 (s, 1H, $H_{3'}$); 8.59 (dd, 1H, benzopy-*H*, $J = 9.1$, 2.7); 9.21 (d, 1H, benzopy-*H*, $J = 2.7$); 9.75 (s, 1H, benzopy-*H*). IR: cm^{-1} 1775, 1658, 1625, 1576, 1532, 1462, 1343.

(3E)-3-(4-Oxo-1-benzopyran-3-ylmethylene)benzo[b]furan-2(3H)-one ***(53)***. Yield: 50% as a yellow solid. Mp: 177–178°C (CH_2Cl_2). (Found M^+: 288.8, $C_{18}H_{10}O_4$ requires 290.27). ^{1}H NMR ($CDCl_3$): δ 6.75 (ddd, 1H, H_5, $J = 7.3$, 1.2); 6.83 (dd, 1H, H_7, $J = 7.8$, 1.5); 6.94 (dd, 1H, H_4, $J = 7.8$, 1.5); 7.14 (ddd, 1H, H_6, $J = 7.3$, 1.2); 7.45 (dd, 1H, benzopy-*H*, $J = 7.3$, 1.8); 7.47 (s, 1H, benzopy-*H*); 7.50 (dd, 1H, benzopy-*H*, $J = 8.5$, 1.8); 7.70 (s, 1H, $H_{3'}$); 7.74 (ddd, 1H, benzopy-*H*, $J = 7.3$, 1.8); 8.03 (dd, 1H, benzopy-*H*, $J = 8.5$, 1.8). ^{13}C NMR (DMSO-d_6): 117.40 (C7); 121.00 (C5); 123.77 (C3a); 131.21 (C6); 131.43 (C3'); 131.76 (C4); 132.49 (C3); 156.48 (C7a); 168.49 (C2); 120.04, 120.72, 124.54, 126.90, 127.61, 136.21, 156.73, 157.02, 176.63 (C benzopy). IR: cm^{-1} 1719, 1632, 1614, 1563, 1468.

Method B

A mixture of naphtho[2,1-*b*]furan-3(2*H*)-one **28** (0.30 g, 1.63 mmol) and an aldehyde (1.63 mmol) in anhydrous pyridine (8 mL), under nitrogen, was heated at 90°C until a clear solution was formed. To this solution was added 25 μL of dry piperidine. The resultant solution was heated at 90°C for 2 h. After cooling to room temperature, the reaction mixture was then stirred at 0°C and acidified with 1M HCl until complete precipitation. The resulting precipitate was collected by filtration, washed with water and recrystallized from ethanol.

(2Z)-2-(3,5-Dibromo-4-hydroxybenzylidene)naphtho[2,1-b]furan-3(2H)-one ***(31)***. Yield: 85% as a ochre solid. Mp: 294–295°C (EtOH). (Found M^+: 446.6, $C_{19}H_{10}Br_2O_3$ requires 446.09). ^{1}H NMR (DMSO-d_6): δ 7.00 (s, 1H, $H_{2'}$); 7.63 (dd, 1H, H_6, $J = 7.1$); 7.81 (dd, 1H, H_5, $J = 7.1$); 7.83 (d, 1H, H_9, $J = 9.0$); 8.13 (d, 1H, H_7, $J = 8.1$); 8.27 (s, 2H, Ph-*H*); 8.43 (d, 1H, H_8, $J = 9.0$); 8.50 (br, 1H, O*H*); 8.72 (d, 1H, H_4, $J = 8.1$). ^{13}C NMR (DMSO-d_6): 110.52 (C2'); 113.52 (C3a); 113.90 (C9); 122.84 (C4); 126.28 (C6); 128.69 (C3b); 129.55 (C7); 130.17 (C7a); 130.47 (C5); 139.90 (C8); 146.77 (C2); 167.72 (C9a); 183.44 (C3); 112.47, 126.75, 135.45, 152.70 (C Ph). IR: cm^{-1} 3418, 1633, 1579, 1475, 809.

(2Z)-2-[(3,5-Dimethyl-1H-pyrrol-2-yl)methylene]naphtho[2,1-b]furan-3(2H)-one ***(32)***. Yield: 45% as a bright red solid. Mp: 169–170°C (EI). (Found M^+: 290.1, $C_{19}H_{15}NO_2$ requires 289.33). ^{1}H NMR (DMSO-d_6): δ 2.28 and 2.42 (2s, 6H, 2 × C*H*$_3$); 6.14 (d, 1H, pyr-*H*, $J = 1.9$); 7.63 (d, 1H, H_9, $J = 8.9$); 7.60 (ddd, 1H, H_6, $J = 7.6$, 1.2); 7.78 (ddd, 1H, H_5, $J = 7.6$, 1.2); 8.28 (d, 1H, H_8, $J = 8.9$); 8.09 (d, 1H, H_7, $J = 8.2$); 7.37 (s, 1H, $H_{2'}$); 8.92 (d, 1H, H_4, $J = 8.2$); 13.31 (br, 1H, N*H*). ^{13}C NMR (DMSO-d_6): 11.14, 13.57 (2 × CH_3); 113.19 (C2'); 116.57 (C3a); 113.94 (C9); 122.50 (C4);

125.35 (C6); 129.81 (C3b); 129.03 (C7); 130.02 (C7a); 129.24 (C5); 137.18 (C8); 142.84 (C2); 163.89 (C9a); 179.04 (C3); 113.77, 125.30, 132.11, 136.40 (C pyr). IR: cm^{-1} 3424, 1654, 1584.

(2Z)-2-(1H-Imidazol-4-ylmethylene)naphtho[2,1-b]furan-3(2H)-one ***(33)***. Yield: 68% as a yellow solid. Mp: 259–260°C (EI). (Found M^+: 262.8, $C_{16}H_{10}N_2O_2$ requires 262.27). ^{1}H NMR (DMSO-d_6): δ 7.01 (s, 1H, $H_{2'}$); 7.62 (dd, 1H, H_6, $J = 7.1$); 7.76 (d, 1H, H_9, $J = 9.0$); 7.81 (dd, 1H, H_5, $J = 7.1$); 7.95 and 7.97 (2s, 2H, imid-*H*); 8.13 (d, 1H, H_7, $J = 8.1$); 8.41 (d, 1H, H_8, $J = 9.0$); 8.75 (d, 1H, H_4, $J = 8.1$); 12.79 (s, 1H, N*H*). ^{13}C NMR (DMSO-d_6): 108.60 (C2'); 114.16 (C3a); 113.85 (C9); 122.79 (C4); 126.06 (C6); 128.84 (C3b); 129.48 (C7); 130.01 (C7a); 130.23 (C5); 139.31 (C8); 145.34 (C2); 166.96 (C9a); 182.88 (C3); 123.37, 134.73, 137.97 (C imid). IR: cm^{-1} 3410, 1633, 1573, 1450.

(2Z)-2-[(1-Methyl-1H-imidazol-4-yl) methylene]naphtho[2,1-b]furan-3(2H)-one ***(34)***. Yield: 69% as a yellow solid. Mp: 282–283°C (EtOH). (Found M^+: 276.9, $C_{17}H_{12}N_2O_2$ requires 276.29). ^{1}H NMR (DMSO-d_6): δ 3.86 (s, 3H, CH_3); 6.99 (s, 1H, $H_{2'}$); 7.65 (dd, 1H, H_6, $J = 7.1$); 7.73 (d, 1H, H_9, $J = 9.0$); 7.83 (dd, 1H, H_5, $J = 7.1$); 8.15 (d, 1H, H_7, $J = 8.0$); 8.26 and 8.81 (2s, 2H, imid-*H*); 8.48 (d, 1H, H_8, $J = 9.0$); 8.71 (d, 1H, H_4, $J = 8.0$). ^{13}C NMR (DMSO-d_6): 35.23 (CH_3); 102.49 (C2'); 113.49 (C3a); 113.61 (C9); 122.80 (C4); 126.36 (C6); 128.71 (C3b); 129.60 (C7); 130.18 (C7a); 130.60 (C5); 140.18 (C8); 146.86 (C2); 167.45 (C9a); 182.48 (C3); 126.62, 129.26, 138.94 (C imid). IR: cm^{-1} 1649, 1581, 1452.

(2Z)-2-[(1-Methyl-1H-imidazol-5-yl) methylene]naphtho[2,1-b]furan-3(2H)-one ***(35)***. Yield: 55% as a yellow solid. Mp: 240–241°C (EtOH). (Found M^+: 276.9, $C_{17}H_{12}N_2O_2$ requires 276.29). ^{1}H NMR (DMSO-d_6): δ 3.94 (s, 3H, CH_3); 7.00 (s, 1H, $H_{2'}$); 7.62 (dd, 1H, H_6, $J = 7.3$); 7.78 (d, 1H, H_9, $J = 9.1$); 7.80 (dd, 1H, H_5, $J = 7.3$); 7.95 and 7.97 (2s, 2H, imid-*H*); 8.12 (d, 1H, H_7, $J = 8.2$); 8.41 (d, 1H, H_8, $J = 9.1$); 8.74 (d, 1H, H_4, $J = 8.2$). ^{13}C NMR (DMSO-d_6): 31.62 (CH_3); 100.04 (C2'); 113.93 (C3a); 113.68 (C9); 122.65 (C4); 125.98 (C6); 128.58 (C3b); 129.33 (C7); 129.93 (C7a); 130.13 (C5); 139.29 (C8); 145.67 (C2); 166.72 (C9a); 182.36 (C3); 126.02, 136.60, 141.99 (C imid). IR: cm^{-1} 1636, 1579, 1459.

(2Z)-2-(4-Oxo-1-benzopyran-3-ylmethylene)naphtho[2,1-b]furan-3(2H)-one ***(36)***. Yield: 85% as a yellow solid. Mp: 254–255°C (EtOH). (Found M^+: 339.0, $C_{22}H_{12}O_4$ requires 340.33). ^{1}H NMR ($CDCl_3$): δ 7.43 (d, 1H, H_9, $J = 8.9$); 7.50 (dd, 1H, H_6, $J = 7.0$); 7.46 (dd, 1H, benzopy-*H*, $J = 7.0$); 7.53 (d, 1H, benzopy-*H*, $J = 7.9$); 7.73 (dd, 1H, H_5, $J = 7.0$); 7.70 (dd, 1H, benzopy-*H*, $J = 7.0$); 8.14 (d, 1H, H_8, $J = 8.9$); 7.88 (d, 1H, H_7, $J = 7.9$); 8.30 (d, 1H, benzopy-*H*, $J = 7.9$); 8.86 (d, 1H, H_4, $J = 7.9$); 7.41 (s, 1H, $H_{2'}$); 9.08 (s, 1H, benzopy-*H*). ^{13}C NMR (DMSO-d_6): 102.31 (C2'); 112.66 (C9); 114.36 (C3a); 123.75 (C4); 125.92 (C6); 128.61 (C7); 129.20 (C3b); 130.00 (C5); 130.12 (C7a); 138.94 (C8); 147.67 (C2); 167.34 (C9a); 183.39 (C3); 118.09, 118.28, 123.60, 125.82, 126.48, 134.13, 155.87, 158.77, 175.11 (C benzopy). IR: cm^{-1} 1702, 1658, 1567, 1462.

(2Z)-2-(6-Methyl-4-oxo-1-benzopyran-3-ylmethylene) naphtho[2,1-b]furan-3(2H)-one ***(37)***. Yield: 79% as a yellow solid. Mp: 268–269°C (EtOH). (Found M^+: 377.0, $C_{23}H_{14}O_4$ requires 354.36). ^{1}H NMR ($CDCl_3$): δ 2.48 (s, 3H, CH_3); 7.43 (d, 1H, H_9, $J = 9.0$); 7.42 (d, 1H, benzopy-*H*, $J = 8.5$); 7.52 (ddd, 1H, H_6, $J = 7.0, 1.2$); 7.53 (d, 1H, benzopy-*H*, $J = 8.5$); 7.71 (ddd, 1H, H_5, $J = 7.0, 1.2$); 8.14 (d, 1H, H_8, $J = 9.0$); 7.89 (d, 1H, H_7, $J = 8.0$); 8.09 (br, 1H, benzopy-*H*); 8.88 (d, 1H, H_4, $J = 8.0$); 7.44 (s, 1H, $H_{2'}$); 9.08 (s, 1H, benzopy-*H*). ^{13}C NMR (DMSO-d_6): 20.99 (CH_3); 102.64 (C2'); 112.68 (C9); 114.40 (C3a); 123.79 (C4); 125.92 (C6); 128.62 (C7); 129.23 (C3b); 130.00 (C5); 130.13 (C7a); 138.90 (C8); 147.59 (C2); 167.33 (C9a); 183.44 (C3); 117.88, 118.05, 123.25, 125.81, 135.38, 135.98, 154.18, 158.79, 175.24 (C benzopy). IR: cm^{-1} 1701, 1655, 1562, 1481.

(2Z)-2-(6-Chloro-4-oxo-1-benzopyran-3-ylmethylene) naphtho[2,1-b]furan-3(2H)-one ***(38)***. Yield: 76% as a yellow solid. Mp: > 300°C (EtOH). ^{1}H NMR ($CDCl_3$): δ 7.52 (d, 1H, H_9, $J = 9.2$); 7.46 (d, 1H, benzopy-*H*, $J = 8.8$); 7.57 (dd, 1H, H_6, $J = 7.2$); 7.69 (dd, 1H, benzopy-*H*, $J = 8.8, 2.4$); 7.75 (dd, 1H, H_5, $J = 7.2$); 8.18 (d, 1H, H_8, $J = 9.2$); 7.92 (d, 1H, H_7, $J = 8.0$); 8.30 (d, 1H, benzopy-*H*, $J = 2.4$); 8.89 (d, 1H, H_4, $J = 8.0$); 7.41 (s, 1H, $H_{2'}$); 9.12 (s, 1H, benzopy-*H*). ^{13}C NMR (DMSO-d_6): 102.88 (C2'); 112.60 (C9); 114.37 (C3a); 123.84 (C4); 126.06 (C6); 128.66 (C7); 129.41 (C3b); 130.15 (C5); 130.17 (C7a); 139.08 (C8); 147.61 (C2); 166.89 (C9a); 184.05 (C3); 116.78, 120.03, 123.60, 125.95, 134.40, 140.62, 152.98, 158.68, 175.23 (C benzopy). IR: cm^{-1} 1695, 1656, 1579, 1457, 816.

Method C

A mixture of 4-aminonaphtho[2,1-*b*]furan-3(2*H*)-one **29** (0.30 g, 1.51 mmol) or 5-methoxynaphtho

[2,1-*b*]furan-3(2*H*)-one **30** (0.30 g, 1.40 mmol) and an aldehyde (1.40 mmol) in anhydrous ethanol (8 mL), under nitrogen, was heated at 90°C until a clear solution was formed. To this solution was added dry piperidine (0.15 eq). The resultant solution was heated at 90°C for 3 h. After cooling, the resulting precipitate was collected by filtration and recrystallized from ethanol or another appropriate solvent.

(2Z)-4-Amino-2-(3,5-dibromo-4-hydroxybenzylidene) naphtho[2,1-b]furan-3(2H)-one ***(39)***. Yield: 48% as a brown solid. Mp: 246–248°C (CH_2Cl_2). (Found M^+: 461.0, $C_{19}H_{11}Br_2NO_3$ requires 461.10). ^{1}H NMR (DMSO-d_6): δ 6.85 (d, 1H, H_5, $J = 7.6$); 7.02 (s, 1H, $H_{2'}$); 7.17 (d, 1H, H_7, $J = 7.6$); 7.28 (dd, 1H, H_6, $J = 7.6$); 7.65 (d, 1H, H_9, $J = 9.1$); 8.24 (d, 1H, H_8, $J = 9.1$); 8.25 (s, 2H, Ph-*H*). ^{13}C NMR (DMSO-d_6): 112.10 (C2'); 112.55 (C5); 113.22 (C9); 114.71 (C3a); 116.52 (C7); 117.28 (C3b); 127.21 (C6); 132.62 (C7a); 141.99 (C8); 146.24 (C2); 146.48 (C4); 167.82 (C9a); 183.51 (C3); 112.52, 125.95, 135.41, 153.31 (C Ph). IR: cm^{-1} 3308, 1619, 1582, 1474, 823.

(2Z)-4-Amino-2-[(3,5-dimethyl-1H-pyrrol-2-yl) methylene]naphtho[2,1-b]furan-3(2H)-one ***(40)***. Yield: 20% as a red solid. Mp: 198–200°C (EtOH). (Found M^+: 304.1, $C_{19}H_{17}N_2O_2$ requires 304.34). ^{1}H NMR (DMSO-d_6): δ 2.29 and 2.43 (2s, 6H, 2 × C*H*$_3$); 6.18 (s, 1H, pyr-*H*); 6.84 (d, 1H, H_5, $J = 7.2$); 7.15 (d, 1H, H_7, $J = 7.2$); 7.28 (dd, 1H, H_6, $J = 7.2$); 7.40 (s, 2H, N*H*$_2$); 7.43 (s, 1H, $H_{2'}$); 7.47 (d, 1H, H_9, $J = 9.0$); 8.10 (d, 1H, H_8, $J = 9.0$); 12.97 (br, 1H, N*H*). ^{13}C NMR (DMSO-d_6): 11.40, 13.90 (2 × CH_3); 112.30 (C2'); 116.54 (C3a); 114.45 (C9); 146.56 (C4); 126.69 (C6); 117.39 (C3b); 116.52 (C7); 132.11 (C7a); 112.90 (C5); 139.39 (C8); 142.01 (C2); 164.16 (C9a); 177.66 (C3); 115.05, 124.64, 133.85, 137.71 (C pyr). IR: cm^{-1} 3380, 1633, 1543, 1446.

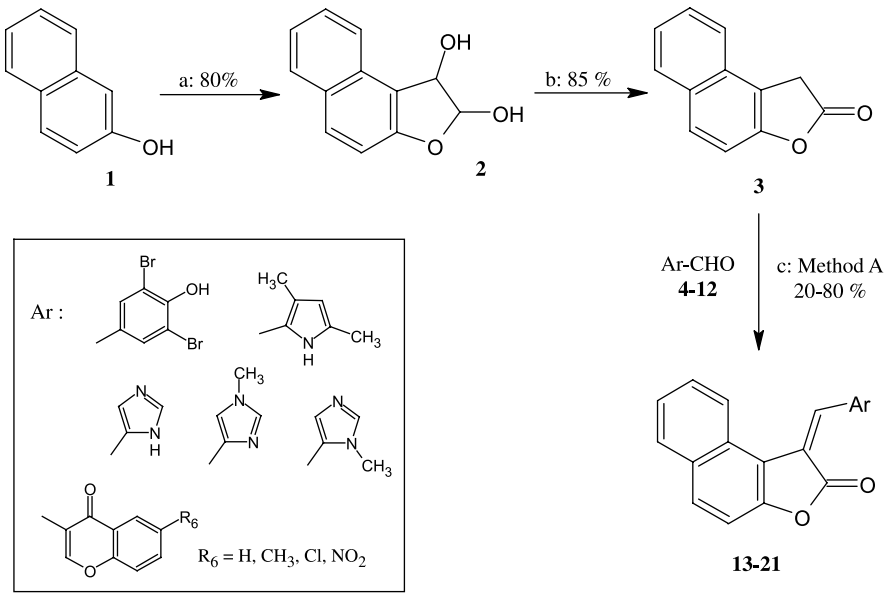
(2Z)-4-Amino-2-(1H-imidazol-4-ylmethylene) naphtho[2,1-b]furan-3(2H)-one ***(41)***. Yield: 80% as a purple solid. Mp: 190–192°C (acetone). (Found M^+: 277.0, $C_{16}H_{11}N_3O_2$ requires 277.28). ^{1}H NMR (DMSO-d_6): δ 6.83 (d, 1H, H_5, $J = 7.0$); 7.05 and 7.14 (2s, 2H, imid-*H*); 7.15 (s, 1H, $H_{2'}$); 7.15 (d, 1H, H_7, $J = 7.0$); 7.28 (dd, 1H, H_6, $J = 7.0$); 7.60 (d, 1H, H_9, $J = 9.0$); 7.97 (s, 2H, N*H*$_2$); 8.24 (d, 1H, H_8, $J = 9.0$); 12.82 (s, 1H, N*H*). ^{13}C NMR (DMSO-d_6): 109.98 (C2'); 115.27 (C3a); 113.19 (C9); 146.52 (C4); 127.04 (C6); 117.43 (C3b); 116.38 (C7); 132.47 (C7a); 112.29 (C5); 141.43 (C8); 144.94 (C2); 167.14 (C9a); 182.96 (C3); 123.73, 134.01, 137.62 (C imid). IR: cm^{-1} 3328, 1616, 1532, 1449.

(2Z)-4-Amino-2-[(1-methyl-1H-imidazol-4-yl) methylene]naphtho[2,1-b]furan-3(2H)-one ***(42)***. Yield: 60% as a purple solid. Mp: 228–229°C (acetone). (Found M^+: 291.3, $C_{17}H_{13}N_3O_2$ requires 291.304). ^{1}H NMR (DMSO-d_6): δ 3.82 (s, 3H, C*H*$_3$); 6.83 (d, 1H, H_5, $J = 8.0$); 6.96 (s, 1H, $H_{2'}$); 7.15 (d, 1H, H_7, $J = 8.0$); 7.16 (s, 2H, N*H*$_2$); 7.28 (dd, 1H, H_6, $J = 8.0$); 7.60 (d, 1H, H_9, $J = 9.0$); 7.87 and 8.04 (2s, 2H, imid-*H*); 8.24 (d, 1H, H_8, $J = 9.0$). ^{13}C NMR (DMSO-d_6): 33.41 (CH_3); 109.51 (C2'); 114.92 (C3a); 112.90 (C9); 146.61 (C4); 127.19 (C6); 117.06 (C3b); 116.35 (C7); 132.19 (C7a); 112.16 (C5); 141.35 (C8); 144.84 (C2); 167.35 (C9a); 182.79 (C3); 126.86, 133.43, 140.14 (C imid). IR: cm^{-1} 3318, 1614, 1531, 1458.

(2Z)-4-Amino-2-[(1-methyl-1H-imidazol-5-yl) methylene]naphtho[2,1-b]furan-3(2H)-one ***(43)***. Yield: 30% as a brown solid. Mp: 137–139°C (EtOH). (Found M^+: 291.4, $C_{17}H_{13}N_3O_2$ requires 291.304). ^{1}H NMR (DMSO-d_6): δ 3.86 (s, 3H, C*H*$_3$); 6.83 (d, 1H, H_5, $J = 7.6$); 7.05 (s, 1H, $H_{2'}$); 7.15 (d, 1H, H_7, $J = 7.6$); 7.15 (s, 2H, N*H*$_2$); 7.28 (dd, 1H, H_6, $J = 7.6$); 7.64 (d, 1H, H_9, $J = 8.9$); 7.96 and 7.99 (2s, 2H, imid-*H*); 8.25 (d, 1H, H_8, $J = 8.9$). ^{13}C NMR (DMSO-d_6): 31.65 (CH_3); 101.60 (C2'); 115.22 (C3a); 113.23 (C9); 146.49 (C4); 127.15 (C6); 117.36 (C3b); 116.48 (C7); 132.59 (C7a); 112.40 (C5); 141.66 (C8); 145.45 (C2); 167.11 (C9a); 182.65 (C3); 127.15, 136.92, 141.66 (C imid). IR: cm^{-1} 3360, 1619, 1577, 1459.

(2Z)-4-Amino-2-(4-Oxo-1-benzopyran-3-ylmethylene) naphtho[2,1-b]furan-3(2H)-one ***(44)***. Yield: 55% as a brown solid. Mp: 265–266°C (acetone). (Found M^+: 354.9, $C_{22}H_{13}NO_4$ requires 355.35). ^{1}H NMR (DMSO-d_6): δ 6.79 (d, 1H, H_5, $J = 7.6$); 6.99 (br, 2H, N*H*$_2$); 7.13 (d, 1H, H_7, $J = 7.6$); 7.27 (dd, 1H, H_6, $J = 7.6$); 7.31 (d, 1H, H_9, $J = 9.0$); 7.44 (s, 1H, $H_{2'}$); 7.47 (ddd, 1H, benzopy-*H*, $J = 7.8, 1.5$); 7.54 (dd, 1H, benzopy-*H*, $J = 7.8, 1.5$); 7.74 (ddd, 1H, benzopy-*H*, $J = 7.8, 1.5$); 8.06 (d, 1H, H_8, $J = 9.0$); 8.31 (dd, 1H, benzopy-*H*, $J = 7.8, 1.5$); 9.07 (s, 1H, benzopy-*H*). ^{13}C NMR (DMSO-d_6): 103.20 (C2'); 113.19 (C9); 114.63 (C3a); 147.00 (C4); 127.33 (C6); 116.59 (C7); 116.99 (C3b); 112.68 (C5); 135.20 (C7a); 142.48 (C8); 146.48 (C2); 168.04 (C9a); 183.41 (C3); 117.21, 118.97, 122.98, 125.81, 126.56, 132.69, 155.68, 160.17, 174.59 (C benzopy). IR: cm^{-1} 3415, 1644, 1611, 1561, 1462.

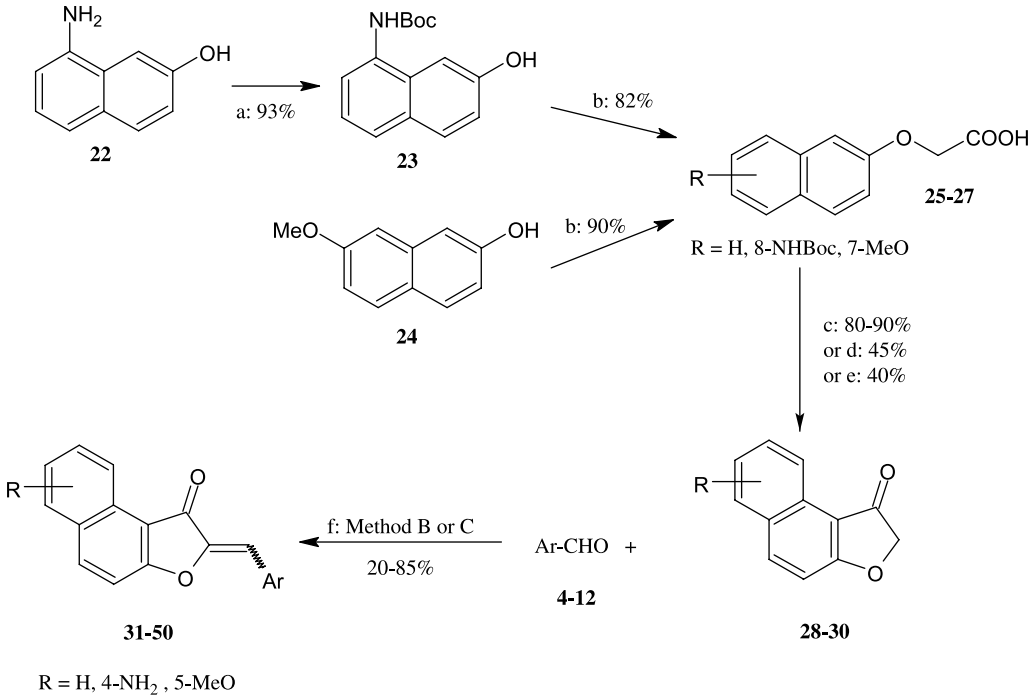
(2Z)-2-(3,5-Dibromo-4-hydroxybenzylidene)-5-methoxynaphtho[2,1-b]furan-3(2H)-one ***(45)***. Yield: 50% as a yellow solid. Mp: 278–280°C (acetone). (Found M^+: 474.2, $C_{20}H_{12}Br_2O_4$ requires 476.11).



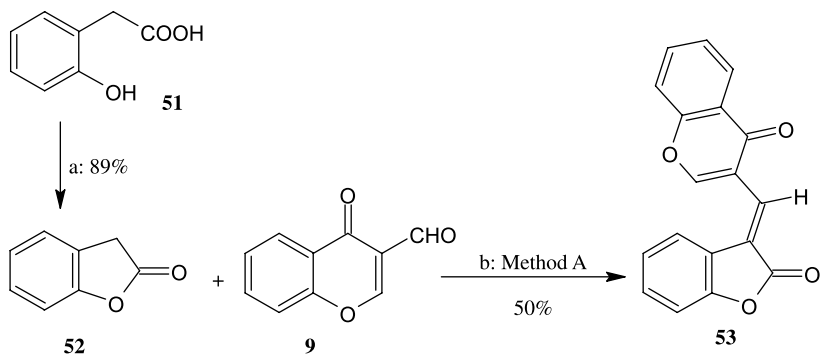
Scheme 1. Preparation of 3-(arylmethylene)naphtho[2,1-*b*]furan-2(3*H*)-ones **13-21**. (a) Glyoxal, 30°C, 80%. (b) 3M HCl/$CHCl_3$, 50°C, 85%. (c) Method A: PTSA, toluene, 90°C, 20–80%.

^{1}H NMR (DMSO-d_6): δ 3.97 (s, 3H, CH_3O); 6.80 (s, 1H, $H_{2'}$); 7.21 (dd, 1H, H_6, J = 8.8, 2.7); 7.56 (d, 1H, H_9, J = 9.1); 8.00 (d, 1H, H_7, J = 8.8); 8.04 (s, 2H, Ph-*H*); 8.20 (d, 1H, H_8, J = 9.1); 8.25 (d, 1H, H_4, J = 2.7). ^{13}C NMR (DMSO-d_6): 55.52 (CH_3O); 102.35 (C4); 110.65 (C9); 115.22 (C2'); 116.07 (C3a); 116.95 (C6); 124.83 (C7a); 130.74 (C3b); 130.74 (C7); 136.82 (C8); 142.74 (C2); 160.38 (C5); 165.08 (C9a); 181.01 (C3); 112.97, 126.98, 135.87, 153.10 (C Ph). IR: cm^{-1} 1626, 1562, 1469, 831.

(2Z)-2-[(3,5-Dimethyl-1H-pyrrol-2-yl)methylene]-5-methoxynaphtho[2,1-b]furan-3(2H)-one ***(46)***. Yield: 40% as a red solid. Mp: 185–187°C (EtOH). (Found M^+: 319.0, $C_{19}H_{17}N_2O_2$ requires 319.35).



Scheme 2. Preparation of 2-(arylmethylene)naphtho[2,1-*b*]furan-3(2*H*)-ones **31-50**. (a) Boc_2O, THF/CH_2Cl_2 (1:1.4), reflux, 93%. (b) (1) 5,7M NaOH, (2) $BrCH_2COOH$/THF, reflux, 82-90%. (c) (1) $SOCl_2$, DMF cat., (2) $AlCl_3$, CH_2Cl_2, 0°C then reflux, 80–90%. (d) PPA, 90°C, 45%. (e) P_2O_5, $MeSO_3H$, 40°C, 40%. (f) Method B: piperidine, pyridine, 90°C; Method C: piperidine, ethanol, 90°C, 20–85%.



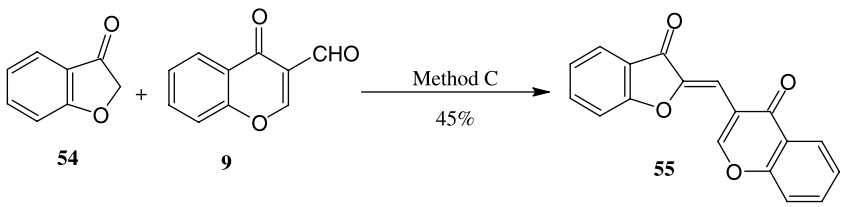
Scheme 3. Synthesis of 3-(4-oxo-1-benzopyran-3-ylmethylene)benzofuran-2(3*H*)-one **53**. (a) PTSA, xylene, reflux. (b) Method A: PTSA, toluene, 90°C.

^{1}H NMR (DMSO-d_6): δ 2.29 and 2.44 (2s, 6H, 2 × CH_3); 4.00 (s, 3H, CH_3O); 6.14 (s, 1H, pyr-*H*); 7.23 (dd, 1H, H_6, J = 9.0, 2.0); 7.37 (s, 1H, $H_{2'}$); 7.45 (d, 1H, H_9, J = 9.0); 8.04 (d, 1H, H_7, J = 9.0); 8.28 (d, 1H, H_8, J = 9.0); 8.34 (d, 1H, H_4, J = 2.0); 13.19 (br, 1H, N*H*). ^{13}C NMR (DMSO-d_6): 11.66, 14.14 (2 × CH_3); 55.93 (CH_3O); 102.79 (C4); 110.61 (C9); 113.90 (C2'); 115.10 (C3a); 117.24 (C6); 124.73 (C7a); 130.71 (C3b); 131.24 (C7); 137.58 (C8); 143.11 (C2); 160.85 (C5); 164.72 (C9a); 179.59 (C3); 114.10, 124.79, 132.38, 136.43 (C pyr). IR: cm^{-1} 3449, 1626, 1590, 1470.

(2Z)-2-(1H-Imidazol-4-ylmethylene)-5-methoxynaphtho[2,1-b]furan-3(2H)-one ***(47)***. Yield: 85% as a yellow solid. Mp: 251–252°C (EtOH). (Found M$^+$: 292.3, $C_{17}H_{12}N_2O_3$ requires 292.29). ^{1}H NMR (DMSO-d_6): δ 4.01 (s, 3H, CH_3O); 7.03 (s, 1H, $H_{2'}$); 7.18 (dd, 1H, H_6, J = 8.8, 2.4); 7.41 (d, 1H, H_9, J = 8.8); 7.89 (d, 1H, H_7, J = 8.8); 7.90 (2s, 2H, imid-*H*); 8.19 (d, 1H, H_8, J = 8.8); 8.20 (d, 1H, H_4, J = 2.4). ^{13}C NMR (DMSO-d_6): 55.54 (CH_3O); 102.16 (C4); 107.83 (C2'); 110.45 (C9); 113.35 (C3a); 117.40 (C6); 124.98 (C7a); 130.62 (C3b); 130.97 (C7); 138.81 (C8); 145.29 (C2); 160.88 (C5); 167.11 (C9a); 182.68 (C3); 122.79, 133.50, 137.79 (C imid). IR: cm^{-1} 3449, 1629, 1579, 1473.

(2Z)-2-[(1-Methyl-1H-imidazol-4-yl)methylene]-5-methoxynaphtho[2,1-b]furan-3(2H)-one ***(48)***. Yield: 80% as a yellow solid. Mp: 212–213°C (EtOH). (Found M$^+$: 306.6, $C_{18}H_{14}N_2O_2$ requires 306.32). ^{1}H NMR (DMSO-d_6): δ 3.81 (s, 3H, CH_3); 3.93 (s, 3H, CH_3O); 6.86 (s, 1H, $H_{2'}$); 7.27 (dd, 1H, H_6, J = 9.0, 2.4); 7.52 (d, 1H, H_9, J = 8.9); 8.03 (d, 1H, H_7, J = 9.0); 8.15 (d, 1H, H_4, J = 2.4); 7.85 and 8.06 (2s, 2H, imid-*H*); 8.32 (d, 1H, H_8, J = 8.9). ^{13}C NMR (DMSO-d_6): 33.61 (CH_3); 55.60 (CH_3O); 102.20 (C4); 107.73 (C2'); 110.41 (C9); 113.36 (C3a); 117.49 (C6); 125.03 (C7a); 130.66 (C3b); 131.06 (C7); 138.96 (C8); 145.37 (C2); 160.97 (C5); 167.15 (C9a); 182.75 (C3); 126.75, 133.79, 140.16 (C imid). IR: cm^{-1} 1630, 1582, 1472.

(2Z)-2-[(1-Methyl-1H-imidazol-5-yl)methylene]-5-methoxynaphtho[2,1-b]furan-3(2H)-one ***(49)***. Yield: 80% as a yellow solid. Mp: 247–249°C (EtOH). (Found M$^+$: 306.6, $C_{18}H_{14}N_2O_2$ requires 306.32). ^{1}H NMR (DMSO-d_6): δ 3.98 (s, 3H, CH_3O); 3.86 (s, 3H, CH_3); 6.96 (s, 1H, $H_{2'}$); 7.27 (dd, 1H, H_6, J = 9.0, 2.4); 7.60 (d, 1H, H_9, J = 8.9); 7.90 and 7.92 (2s, 2H, imid-*H*); 8.05 (d, 1H, H_7, J = 9.0); 8.34 (d, 1H, H_8, J = 8.9); 8.15 (d, 1H, H_4, J = 2.4). ^{13}C NMR (DMSO-d_6): 31.62 (CH_3); 55.63 (CH_3O); 99.50 (C2'); 102.36 (C4); 110.57 (C9); 113.28 (C3a); 117.45 (C6); 125.17 (C7a); 130.57 (C3b); 131.15 (C7); 139.10 (C8); 145.79 (C2); 161.02 (C5); 167.10 (C9a); 182.12 (C3); 125.85, 136.35, 141.81 (C imid). IR: cm^{-1} 1628, 1582, 1473.



Scheme 4. Synthesis of 2-(4-oxo-1-benzopyran-3-ylmethylene)benzofuran-3(2*H*)-one **55**. Method C: piperidine, ethanol, 90°C.

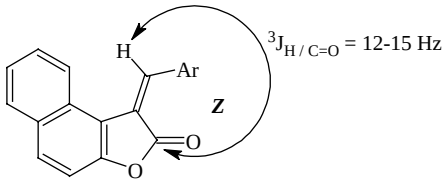


Figure 3. Determination of the *Z* configuration by $^3\mathcal{J}$(C, H) vicinal couplings.

(2Z)-2-(4-Oxo-1-benzopyran-3-ylmethylene)-5-methoxynaphtho[2,1-b]furan-3(2H)-one ***(50)***. Yield: 80% as a yellow solid. Mp: 282–284°C (acetone). (Found M^+: 369.7, $C_{23}H_{14}O_5$ requires 370.35). ^{1}H NMR ($CDCl_3$): δ 3.99 (s, 3H, C*H*$_3$O); 7.11 (s, 1H, $H_{2'}$); 7.27 (dd, 1H, H_6, $\mathcal{J}$ = 9.1, 2.4); 7.59 (d, 1H, H_9, $\mathcal{J}$ = 8.9); 7.63 (dd, 1H, benzopy-*H*, $\mathcal{J}$ = 7.6); 7.81 (d, 1H, benzopy-*H*, $\mathcal{J}$ = 7.6); 7.95 (dd, 1H, benzopy-*H*, $\mathcal{J}$ = 7.6); 8.06 (d, 1H, H_7, $\mathcal{J}$ = 9.1); 8.13 (d, 1H, H_4, $\mathcal{J}$ = 2.4); 8.22 (d, 1H, benzopy-*H*, $\mathcal{J}$ = 7.6); 8.39 (d, 1H, H_8, $\mathcal{J}$ = 8.9); 9.35 (s, 1H, benzopy-*H*). IR: cm^{-1} 1651, 1624, 1581, 1466.

(2Z)-2-(4-Oxo-1-benzopyran-3-ylmethylene) benzofuran-3(2H)-one ***(55)***. Yield: 45% as a yellow solid. Mp: 234–235°C (CH_2Cl_2). (Found M^+: 290.1, $C_{18}H_{10}O_4$ requires 290.27). ^{1}H NMR ($CDCl_3$): δ 7.25 (ddd, 1H, H_5, $\mathcal{J}$ = 7.6, 1.2); 7.31 (dd, 1H, H_7, $\mathcal{J}$ = 8.0, 1.2); 7.36 (s, 1H, $H_{2'}$); 7.46 (ddd, 1H, benzopy-*H*, $\mathcal{J}$ = 7.6, 1.6); 7.52 (dd, 1H, benzopy-*H*, $\mathcal{J}$ = 8.0, 1.6); 7.68 (ddd, 1H, H_6, $\mathcal{J}$ = 7.6, 1.2); 7.72 (ddd, 1H, benzopy-*H*, $\mathcal{J}$ = 7.6, 1.6); 7.81 (dd, 1H, H_4, $\mathcal{J}$ = 8.0, 1.2); 8.30 (dd, 1H, benzopy-*H*, $\mathcal{J}$ = 8.0, 1.6); 9.08 (s, 1H, benzopy-*H*). ^{13}C NMR (DMSO-d_6): 102.23 (C2'); 112.76 (C7); 121.73 (C3a); 123.83 (C5); 124.85 (C4); 136.94 (C6); 147.14 (C2); 165.57 (C7a); 183.58 (C3); 118.10, 118.29, 123.59, 125.85, 126.50, 134.16, 155.89, 158.78, 175.14 (C benzopy). IR: cm^{-1} 1703, 1653, 1557, 1462.

Pharmacology

MTT cytotoxicity assay. The murine L1210 leukemia cell line was maintained in RPMI 1640 medium (Gibco) supplemented with 10% foetal calf serum, 2 mM L-glutamine, 100 U/mL penicillin, 100 μg/mL streptomycin and 10 mM Hepes buffer (pH 7.4). Cytotoxicity was measured by the microculture tetrazolium assay [6]. Briefly, L1210 cells were exposed to graded concentrations of drugs for 48 h (4 doubling times). Results are expressed as IC_{50}, the concentration which reduced by 50% the optical density of treated cells with respect to the density of untreated cells.

SRC kinase inhibition. Inhibitors were diluted on a robotic Tecan Evo150 platform.The kinase assay was performed with 4 μL of diluted inhibitor (10% DMSO), 10 μL of kinase assay buffer 4 × concentrated (80 mM $MgCl_2$ – 200 mM Hepes – 0.4 mM EDTA – 2 mM dTT), 10 μL substrate peptide (KVEKIGEGYYGVVYK – 370 nM) and 6 μL Src kinase (stock GTP purified diluted with 1 × kinase assay buffer to 200 nM). 10 μL co-substrate (40 μM ATP with 0.2 μCi P^{33}-γ-ATP) was added with a robotic Precision 2000 (Biotek) platform. The assay was incubated for 20 min at 30°C then stopped by adding 200 μL 0.85% *ortho*-phosphoric acid, then transferred to a phosphocellulose filter microplate (Whatman – P81). Three washes were performed with 200 μL 0.85% *ortho*-phosphoric acid and the filter plate was dried with 200 μL acetone. The remaining activity was measured on a topcount with 25 μL Scintillation solution (Packard Ultima Gold).

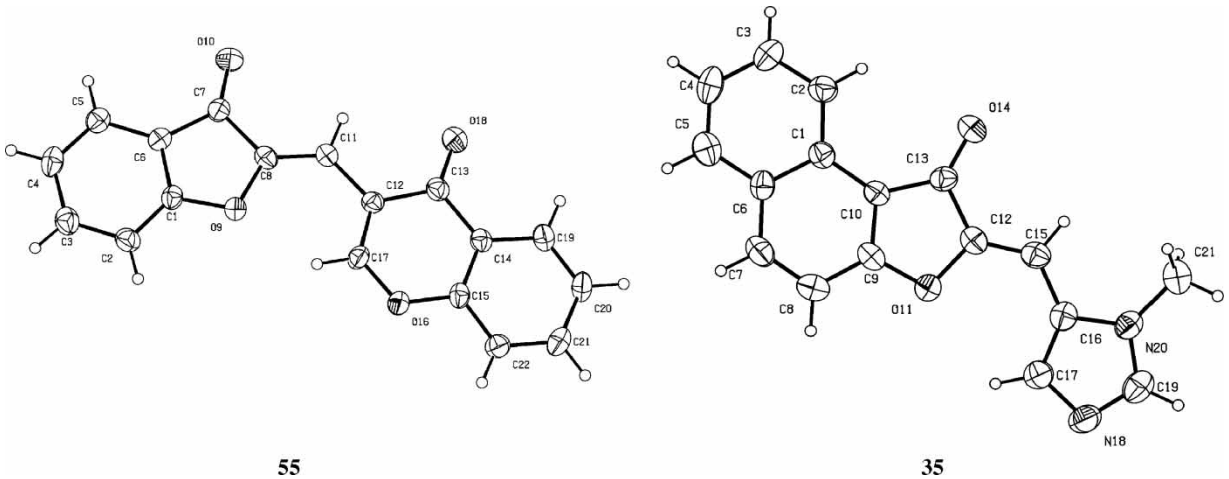


Figure 4. Views of **55** and **35** with our numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.

Results and discussion

Chemistry

The methylenenaphthofuranones **13–21** and **31–50** were prepared by a Knoevenagel reaction, condensing the formyl derivatives **4-12** with the naphthofuranones **3** or **28–30**. In the case of naphthofuran-2-(3*H*)-ones, this aldolization-crotonization was realized under acidic conditions (method A) [7]. The methylenenaphthofuran-3-(2*H*)-ones **31–50** were obtained in more satisfactory yields under basic catalysis (method B or C) [8,9]. Naphthofuran-2-(3*H*)-one **3** was synthesized by condensation of glyoxal with 2-naphthol, in basic medium, according to the method described by Kito (Scheme 1) [10].

The regioselective cyclization of the naphthoxyacetic acids **25–27** obtained by alkylation [11] of the corresponding 2-naphthols, afforded the naphthofuran-3(2*H*)-ones **28–30** (Scheme 2) [12]. Three methods of cyclization were tested: (i) Friedel-Crafts reaction in presence of $AlCl_3$ [12], (ii) heating at 90°C in polyphosphoric acid and (iii) under Eaton conditions, in presence of phosphorus pentoxide and methanesulfonic acid [13].

To obtain the 4-aminonaphthofuran-3(2*H*)-one **26** in a satisfactory yield, Boc- protection of the amino group was necessary [14].

The methylenebenzofuranones **53** and **55** were also prepared by a Knoevenagel condensation, starting from the benzofuranones **52** [15] and **54**, respectively (Schemes 3 and 4).

In all cases this Knoevenagel reaction led to a unique stereoisomer. In the naphthofuran-2(3*H*)-ones series, the stereochemistry of these α,β-unsaturated lactones was determined by vicinal C,H spin coupling constants. The use of ^{13}C NMR ^{13}C-^{1}H coupling constants of the ketonic carbon of the target compounds **13–21** and the β-ethylenic proton afforded the results shown in Figure 3: the coupling constant was located between 12 and 15 Hz, a value that corresponds to the *Z* isomers, as previously evidenced by Kingsbury and Letcher's works [16,17]. According to the precedent work [18], the coupling constant of the *E* isomers was about 6-8 Hz.

For the naphthofuran-3(2*H*)-ones the same consideration was not possible; nevertheless an X-ray analysis allowed the stereochemistry assigment of these compounds.

The 3D spatial structures of compounds **55** and **35** were established by X-ray crystallography [19] indicating the (*Z*)-isomerism of the methylene double bond in the solid state (Figure 4). In **35** the system was found to be quite planar, e.g. C(8) deviates by 0.0037(1)Å from the least-square plane defined by all the atoms, whereas in compound **55** the angle between the least-squares planes of the benzofuranone and benzopyranone moieties was approximately 4.93(2)°. The lengths of C(8)-C(11) and C(12)-C(15) bonds in **55** and **35**, 1.317(5) and 1.345(5)Å respectively, corresponded to those typically observed for the C = C double bonds [20], while those of C(11)–C(12) (compound **55**) and C(15)-C(16) (compound **35**) single bonds were observed at 1.452(5) and 1.434(5)Å, as logically expected.

Pharmacology

The cytotoxic activities of most of the studied compounds were evaluated *in vitro* on murine L1210 cells. IC_{50} values are reported in Tables I and II.

Comparison between the cytotoxic activities observed in compounds **18** and **53** on the one hand and **36** and **55** on the other hand brings to the fore the favourable effect induced by replacement of the benzofuranone core by a naphthofuranone one; moreover a 5-fold increase of activity was observed when the ketonic group was in position-3 in the latter series, with IC_{50} values of 8.6 and 1.6 μM, respectively for **18** and **36**. As far as the pharmacomodulation of the 3-naphthofuranone core (by introduction of an amino or a methoxy group at C^4 or C^5) is concerned, although only one congener was tested in each sub-series, it seems to lead to more active

Table I. Pharmacological evaluation of 2-(arylmethylene)naphtho[2,1-*b*]furan-2(3*H*)-ones **13–21** and benzofuran-2(3*H*)-one **53**.

					SRC % inhibition	
N°	Ar	Method A Reaction time	Yield (%)	IC_{50} (μM) L1210	10μM	1μM
13	3,5-dibromo-4-hydroxyphenyl	20 h	76	> 10	19.8	0
14	3,5-dimethylpyrrol-2-yl	36 h	20	nd[a]	8.6	nd[a]
15	imidazol-4-yl	17 h	40	> 10	20	3.2
16	1-methylimidazol-4-yl	20 h	80	44.7	2.6	3.7
17	1-methylimidazol-5-yl	18 h	40	45	−42.9	−9.4
18	4-oxo-1-benzopyran-3-yl	1 h	72	8.6	−2.7	1
19	6-methyl-4-oxo-1-benzopyran-3-yl	3 h	67	ins[b]	6.3	nd[a]
20	6-chloro-4-oxo-1-benzopyran-3-yl	3 h	71	ins[b]	2.1	nd[a]
21	6-nitro-4-oxo-1-benzopyran-3-yl	3 h	42	ins[b]	7.35	nd[a]
53	3-(4-oxo-1-benzopyran-3-ylmethylene) benzo[*b*]furan-2(3*H*)-one			45.3	3.43	nd[a]

[a]nd: not determined.[b]ins: insoluble

Table II. Pharmacological evaluation of 2-(arylmethylene)naphtho[2,1-*b*]furan-3(2*H*)-ones and benzofuran-3(2*H*)-one **55**.

N°	Ar	R	Method	Reaction time	Yield (%)	IC_{50} (μM) L1210	SRC % inhibition	
							10μM	1μM
31	3,5-dibromo-4-hydroxyphenyl	H	B	1 h	85	> 10	26.1	1.8
32	3,5-dimethylpyrrol-2-yl	H	B	2.5 h	45	> 10	2.5	− 1.8
33	imidazol-4-yl	H	B	1.5 h	68	> 10	16.8	− 2.9
34	1-methylimidazol-4-yl	H	B	1.5 h	69	39.2	8.7	− 4.3
35	1-methylimidazol-5-yl	H	B	2 h	55	15.3	23	nd[a]
36	4-oxo-1-benzopyran-3-yl	H	B	1 h	85	1.6	− 37.7	11.3
37	6-methyl-4-oxo-1-benzopyran-3-yl	H	B	5 h	79	> 100	− 39.3	1.4
38	6-chloro-4-oxo-1-benzopyran-3-yl	H	B	4 h	76	ins[b]	1	nd[a]
39	3,5-dibromo-4-hydroxyphenyl	4-NH_2	C	3 h	48	9.5	38.2	nd[a]
41	imidazol-4-yl	4-NH_2	C	4 h	80	nd[a]	12.5	nd[a]
42	1-methylimidazol-4-yl	4-NH_2	C	4 h	60	nd[a]	3.5	nd[a]
45	3,5-dibromo-4-hydroxyphenyl	5-CH_3O	C	3 h	50	nd[a]	6.75	nd[a]
46	3,5-dimethylpyrrol-2-yl	5-CH_3O	C	4 h	40	nd[a]	7.1	nd[a]
47	imidazol-4-yl	5-CH_3O	C	6 h	85	7.8	10.8	nd[a]
48	1-methylimidazol-4-yl	5-CH_3O	C	3 h	80	nd[a]	9.9	nd[a]
49	1-methylimidazol-5-yl	5-CH_3O	C	3 h	80	nd[a]	2.6	nd[a]
50	4-oxo-1-benzopyran-3-yl	5-CH_3O	C	2 h	80	nd[a]	nd[a]	
55	2-(4-oxo-1-benzopyran-3-ylmethylene) benzo[*b*]furan-3(2*H*)-one					16.4	3.7	nd[a]

[a]nd: not determined. [b]ins: insoluble

compounds: $IC_{50} = 9.5$ and 7.8 μM for **39** and **47** instead of $IC_{50} > 10$ μM for **31** and **33**.

The 4-benzopyranone moiety present in those compounds seemed to be an interesting pharmacophore whilst the introduction of other appendages, such as hydroxyphenyl, pyrrolyl or imidazolyl, decreased the level of activity. Attempted evaluation of the incidence of homocycle substitution of 4-benzopyranone (by methyl, chloro or nitro groups) failed due to their insolubility in the assay medium; the only tested compound, **37**, was inactive. Study of the effect of **36** on cell cycle phases showed that, at a concentration of 5 μM, it induced an increase of cells in S and G2 phases; at this concentration, 40% of cells were apoptotic cells (data not shown).

Most of these compounds were also investigated for their ability to inhibit human recombinant SRC kinase. None of them was found to potently inhibit this kinase at a 10 μM concentration.

In conclusion, we have synthesized 3-arylmethylenenaphthofuranone analogues of 3-arylmethyleneindolin-2-ones, known as anti-proliferative compounds. The promising result for a member of this new family (compound **36**) prompts us to envision the exploration of new naphtho[1,2-*b*]furan-3-ones, naphtho[2,3-*b*]furan-3-ones and, by analogy with SU5416, benzo[*e*]indolinones.

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