SYNTHESIS OF 5-SUBSTITUTED 3,4-DIHYDRO-3-AMINO-2H-1-BENZOPYRAN DERIVATIVES VIA PALLADIUM-CATALYSED REACTIONS

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Abstract- Syntheses of the previously unknown 5-substituted 3,4-dihydro-3-di-n-propylamino-2H-1-benzopyrans (2-12) from the triflate (1) via palladium-catalysed reactions are described.

In our ongoing research on new classes of compounds possessing a potential effect on the central nervous system,¹⁶ the 3,4-dihydro-3-amino-2H-1-benzopyran moiety has been extensively employed by our group as a precursor to selective 5-HT₁A receptor ligands.⁷⁻¹⁰ Some representatives of this class of compounds such as 5-methoxy- or 5-hydroxy-3,4-dihydro-3-di-n-propylamino-2H-1-benzopyran (5-MeO- or 5-OH-DPAC) have shown high affinity for the 5-HT₁A receptors.⁸,⁹ Structural modification involving the nature of the functionalised groups and the length of the alkyl side chain on the nitrogen atom at the 3-position have been explored previously to assess the affinity and the selectivity for the 5-HT₁A receptors.¹⁰ On the other hand, no studies of the part played by 5-substitution of the 3,4-dihydro-3-amino-2H-1-benzopyran structure on interactions with the serotonergic receptors have been reported in the literature.

Thus, in this paper we report synthetic pathways to introduce various substituents (A) at the 5-position of the benzopyran.
the 3,4-dihydro-3-di-n-propylamino-2H-1-benzopyran. As for the preparation of 5-substituted tetralins, our strategy required the preparation of the triflate (1) which would permit us to introduce a wide range of substituents via well documented palladium-mediated cross-coupling reactions such as the Stille or Suzuki reactions.

Triflate (1) was prepared in 72% yield from 5-hydroxy-3,4-dihydro-2H-1-benzopyran (5-OH-DPAC) by treatment with triflic anhydride in methylene chloride in the presence of pyridine (Scheme 1).

First, Stille coupling reactions were performed on triflate (1). The reaction between vinyltributyltin, compound (1) and lithium chloride was carried out in N,N-dimethylformamide at 90 °C in the presence of a catalytic amount of bis(triphenylphosphine)palladium chloride. The corresponding vinyl compound (2) was isolated in 76% yield. Hydrogenation of 2 over a palladium catalyst in ethanol yielded the ethyl compound (3) in 86% yield (Scheme 1).

In the same way, the keto derivative (4) was prepared in good yield (88%) by reaction of 1 with ethoxyvinyltributyltin followed by a mild acid hydrolysis of the enol ether intermediate.
Aryl derivatives were elaborated through a modified Suzuki coupling reaction\textsuperscript{15} between triflate (1) and selected arylboronic acids in the presence of freshly prepared tetrakis(triphenyl)palladium\textsuperscript{16} (Scheme 2). Thus, the phenyl compound (5) was isolated in 79\% yield. Unfortunately, the 2-nitro and 2-amino derivatives (6) and (7) were obtained in disappointing yields (7-10\%). In both cases, a large amount of the starting material (1) was recovered. Our attempts to optimise the yield by modifying the reaction time and the palladium catalyst were unsuccessful.

The derivative (7) was easily converted in 56\% yield to the corresponding azido compound (8) via the formation of the diazonium salt intermediate followed by addition of sodium azide. The IR spectrum of 8 showed a peak at 2099 cm\(^{-1}\) characteristic of the azido group. The latter compound (8) is a possible photoaffinity labelling marker\textsuperscript{17} for the study of the 5-HT\textsubscript{1A} receptors.\textsuperscript{18}

The cyano group could also be introduced at the 5-position through a palladium-catalysed reaction (Scheme 2).\textsuperscript{19} Compound (9) was synthesised from 1 in 72\% yield using tetrakis(triphenyl)palladium and zinc cyanide in N,N-dimethylformamide. As expected, the IR spectrum of 9 showed a peak at 2228 cm\(^{-1}\) characteristic of a cyano group.

\begin{align*}
5 \quad Z &= H \quad 79\% \\
6 \quad Z &= \text{NO}_2 \quad 7\% \quad (87\% \text{ of starting material}) \\
7 \quad Z &= \text{NH}_2 \quad 10\% \quad (80\% \text{ of starting material}) \\
8 \quad Z &= \text{N}_3 \\
& \quad 56\% \\
& \quad \text{NaNO}_2, \text{H}_2\text{SO}_4, \text{H}_2\text{O} \\
& \quad \text{NaN}_3, \text{H}_2\text{O}
\end{align*}

Scheme 2

In the formation of 9, the amount of palladium in the reaction is stoichiometric. In our hands, reaction attempts with catalytic amounts of palladium reagent gave lower yields. From compound (9), several derivatives were elaborated. Basic hydrolysis of 9 gave the amide (10) in moderate yield (Scheme 2). Similarly, classical reduction of 9 with lithium aluminium hydride led to the aminomethyl compound (11) in 95\% yield (Scheme 3). Finally, alkylation of 11 with chloroacetyl chloride in methylene chloride in the
presence of potassium carbonate gave the chloroacetamide (12) (67% yield), which could serve as a potential precursor for the photochemical synthesis of a more highly annelated benzopyran skeleton.20

Scheme 3

In summary, convenient and effective pathways to the elaboration of new 5-substituted benzopyrans, potent 5-HT1A serotoninergic ligands, via palladium-catalysed coupling reactions have been developed.

EXPERIMENTAL

Melting points were determined using a Büchi SMP-20 melting point apparatus and are uncorrected. The IR spectra of compounds were recorded on a Perkin Elmer FTIR paragon 1000 spectrophotometer. NMR spectra were recorded at 300 °K in CDCl₃ or DMSO-d₆ on a Bruker Avance DPX 250. Chemical shifts are expressed in parts per million and are referenced to TMS. MS spectra were recorded on a Perkin-Elmer SCIEX API 300 using ionspray methodology. Thin layer chromatography was performed on precoated plate of silica gel 60F₂₅₄ (Merck) and the spots visualised using an ultraviolet lamp. Flash chromatography was conducted using Merck silica gel 60 (0.040 mm-0.063 mm) as the stationary phase. Chromatographic eluent mixtures were v/v. Petroleum ether had a bp range of 60-80 °C. All air- and moisture sensitive reactions were conducted under a prepurified argon atmosphere.

5-[Trifluoromethylsulfonyloxy]-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (1). To a stirred solution of 5-hydroxy-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (2.2 g, 8.9 mmol) in CH₂Cl₂ (50 mL) under argon at -30 °C was added pyridine (1.4 mL, 17.0 mmol) followed by trifluoromethanesulfonic anhydride (1.8 mL, 11.2 mmol). The solution was stirred at -20 °C for 2 h and then allowed to reach the ambient temperature. The organic solution was then washed with saturated aqueous NaHCO₃ (30 mL) and H₂O (20 mL), dried (MgSO₄) and evaporated in vacuo. The crude residue was purified by flash chromatography (eluent 94:6 petroleum ether/ethyl acetate) to give 2.45 g (72%) of triflate (1) as a pale yellow oil; ¹H NMR (250 MHz, CDCl₃) δ: 0.88 (t, 6H, J = 7.4 Hz, CH₃); 1.39-1.53 (m, 4H, CH₂); 2.50 (t, 2H, J = 7.0 Hz, CH₂); 2.51 (t, 2H, J = 7.0 Hz, CH₂); 2.70 (dd, 1H, J = 10.6, 16.4 Hz, CH₂Ar); 2.93 (ddd, 1H, J = 1.8, 5.2, 16.4 Hz, CH₂Ar); 3.07-3.19 (m, 1H, CHN); 3.83 (t, 1H, J = 10.2
The stirred solution (0.17 mmol) in DMF (77.93 mmol) was purified by flash chromatography (eluent 9:l petroleum ether/ethyl acetate) to give 1.48 g (76%) of 2 as a pale yellow oil; IR (film): ν 1237 (C-O) cm⁻¹; ¹H NMR (250 MHz, CDCl₃): δ: 0.88 (t, 6H, J = 7.2 Hz, CH₃); 1.38-1.53 (m, 4H, CH₂); 2.43-2.60 (m, 4H, CH₂); 2.70 (dd, 1H, J = 11.0, 16.0 Hz, CH₂Ar); 2.88 (ddd, 1H, J = 2.0, 6.0, 16.0 Hz, CH₂Ar); 3.10-3.23 (m, 1H, CHN); 3.76 (t, 1H, J = 10.4 Hz, CH₂O); 4.25-4.31 (m, 1H, CH₂O); 5.31 (dd, 1H, J = 1.3, 11.0 Hz, =CH₂); 5.64 (dd, 1H, J = 1.3, 17.4 Hz, =CH₂); 6.75 (t, 1H, J = 5.0 Hz, HA); 6.87 (dd, 1H, J = 11.0, 17.4 Hz, CH=); 7.09 (d, 2H, J = 9.1 Hz, HAr); ¹³C NMR (62.90 MHz, CDCl₃): δ: 11.7 (2, CH₃), 21.9 (2, CH₂), 23.1 (CH₂), 52.4 (2, CH₂), 52.7 (CH), 68.1 (CH₂), 112.9, 116.2 (q), 116.6, 118.9 (q, J = 320 Hz, CF₃), 127.6, 148.6 (q), 156.2 (q); MS: m/z 382 (M⁺+1).

5-Vinyl-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (2). To a mixture of 1 (2.50 g, 6.56 mmol), LiCl (836 mg, 16.67 mmol) and bis(triphenylphosphine)palladium chloride (15% Pd, 230 mg, 0.33 mmol) in DMF (30 mL) under argon was added vinyltributyltin (2.30 mL, 7.87 mmol). The stirred solution was heated at 90 °C for 5 h. The solvent was then removed in vacuo and the remaining residue was purified by flash chromatography (elucent 9:1 petroleum ether/ethyl acetate) to give 1.48 g (76%) of 2 as a pale yellow oil; IR (film): ν 1235 (C-O) cm⁻¹; ¹H NMR (250 MHz, CDCl₃): δ: 0.88 (t, 6H, J = 7.2 Hz, CH₃); 1.38-1.53 (m, 4H, CH₂); 2.43-2.60 (m, 4H, CH₂); 2.70 (dd, 1H, J = 11.0, 16.0 Hz, CH₂Ar); 2.88 (ddd, 1H, J = 2.0, 6.0, 16.0 Hz, CH₂Ar); 3.10-3.23 (m, 1H, CHN); 3.76 (t, 1H, J = 10.4 Hz, CH₂O); 4.25-4.31 (m, 1H, CH₂O); 5.31 (dd, 1H, J = 1.3, 11.0 Hz, =CH₂); 5.64 (dd, 1H, J = 1.3, 17.4 Hz, =CH₂); 6.75 (t, 1H, J = 5.0 Hz, HA); 6.87 (dd, 1H, J = 11.0, 17.4 Hz, CH=); 7.09 (d, 2H, J = 9.1 Hz, HAr); ¹³C NMR (62.90 MHz, CDCl₃): δ: 11.7 (2, CH₃), 22.0 (2, CH₂), 26.0 (CH₂), 52.7 (2, CH₂), 53.4 (CH), 67.3 (CH₂), 116.0, 116.1, 117.9, 119.7 (q), 126.9, 134.0, 138.3 (q), 154.6 (q); MS: m/z 260 (M⁺+1); Anal. Calcd for C₁₇H₂₅NO: C, 78.72; H, 9.71; N, 5.40. Found: C, 78.95; H, 9.90; N, 5.35.

5-Ethyl-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (3). A mixture of 2 (532 mg, 2.05 mmol) and 10% Pd/C (53 mg) in ethanol (10 mL) was shaken in a Parr apparatus under 50 psi of hydrogen at rt for 6 h. The catalyst was filtered through celite and the solvent was removed in vacuo. The crude residue was purified by flash chromatography (elucent 9:1 petroleum ether/ethyl acetate) to give 461 mg (86%) of 3 as a colourless oil; IR (film): ν 1235 (C-O) cm⁻¹; ¹H NMR (250 MHz, CDCl₃): δ: 0.89 (t, 6H, J = 7.4 Hz, CH₃); 1.23 (t, 3H, J = 7.5 Hz, 3H, CH₃); 1.41-1.55 (m, 4H, CH₂); 2.45-2.61 (m, 6H, CH₂); 2.65 (dd, 1H, J = 11.0, 16.0 Hz, CH₂Ar); 2.83 (ddd, 1H, J = 1.8, 5.2, 16.0 Hz, CH₂Ar); 3.12-3.24 (m, 1H, CHN); 3.77 (t, 1H, J = 10.3 Hz, CH₂O); 4.26-4.33 (m, 1H, CH₂O); 6.69 (d, 1H, J = 8.1 Hz, HA); 6.77 (d, 1H, J = 8.1 Hz, HA); 7.06 (t, 1H, J = 8.1 Hz, HA); ¹³C NMR (62.90 MHz, CDCl₃): δ: 11.8 (2, CH₃), 14.1 (CH₃), 22.0 (2, CH₂), 25.4 (CH₂), 25.6 (CH₂), 52.7 (2, CH₂), 53.5 (CH), 67.2 (CH₂), 114.2, 119.9, 120.0 (q), 126.8, 143.7 (q), 154.5 (q); MS: m/z 262 (M⁺+1); Anal. Calcd for C₁₇H₂₇NO: C, 78.11; H, 10.41; N, 5.36. Found: C, 77.93; H, 10.25; N, 5.15.

5-Acetyl-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (4). To a mixture of 1 (1.30 g, 3.41 mmol), LiCl (435 mg, 10.24 mmol) and bis(triphenylphosphine)palladium chloride (15% Pd, 120 mg, 0.17 mmol) in DMF (20 mL) under argon was added (1-ethoxyvinyl)tributyltin (1.38 mL, 4.09 mmol). The stirred solution was heated at 90 °C for 3.5 h. The solvent was then removed in vacuo and the crude
residue was purified by flash chromatography (eluent 9:1 petroleum ether/ethyl acetate) to give a pale yellow oil. The oil was then treated with 10% HCl at rt for 1 h. Solid K$_2$CO$_3$ was added to adjust the pH to 9. The basic solution was extracted with ethyl acetate (2 x 15 mL). The organic phase was dried (MgSO$_4$) and evaporated in vacuo to give 829 mg (88%) of 4 as a colourless oil; IR (film): ν 1685 (C=O), 1256, 1237 (C-O) cm$^{-1}$; $^1$H NMR (250 MHz, CDC$_3$) δ: 0.87 (t, 6H, J = 7.3 Hz, CH$_3$); 1.37-1.51 (m, 4H, CH$_2$); 2.45-2.60 (m, 4H, CH$_2$N); 2.57 (s, 3H, COCH$_3$); 3.06-3.12 (m, 3H, CH$_2$Ar + CHN); 3.78-3.86 (m, 1H, CH$_2$O); 4.31-4.25 (m, 1H, CH$_2$O); 6.96 (dd, 1H, J = 1.1, 8.0 Hz, H$_A$); 7.15 (t, 1H, J = 8.0 Hz, H$_A$); 7.30 (dd, 1H, J = 1.1, 8.0 Hz, H$_A$). $^{13}$C NMR (62.90 MHz, CDC$_3$) δ: 11.7 (2, CH$_3$), 21.9 (2, CH$_2$), 27.0 (CH$_2$), 29.7 (CH$_3$), 52.7 (2, CH$_2$), 53.2 (CH), 67.8 (CH$_2$), 120.4, 122.0, 122.1 (q), 126.5, 138.6 (q), 155.2 (q), 201.4 (CO); MS: $m/z$ 276 (M$^+$+1); Anal. Calcd for C$_{17}$H$_{17}$NO$_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.40; H, 9.29, N, 5.13.

5-Phenyl-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (5). To a stirred solution of 1 (800 mg, 2.10 mmol) in toluene (30 mL) under argon was added freshly prepared tetrakis(triphenylphosphine)palladium (122 mg, 0.10 mmol). The mixture was allowed to stir for 30 min at rt. Phenylboronic acid (384 mg, 3.1 mmol) in ethanol (15 mL) was then added, followed immediately by saturated aqueous NaHCO$_3$ (15 mL). The heterogeneous solution was thereafter refluxed for 5 h. Brine solution was then added, the two layers were separated and the aqueous phase was extracted with methylene chloride (3 x 30 mL). The combined organic extracts were dried (MgSO$_4$) and evaporated in vacuo. The crude residue was purified by flash chromatography (eluent 95:5 petroleum ether/ethyl acetate) to afford 580 mg (89%) of 5 as a crystalline compound: mp 69-71 °C (ethyl acetate-petroleum ether); IR (KBr): ν 1235 (C-O) cm$^{-1}$; $^1$H NMR (250 MHz, CDC$_3$) δ: 0.81 (t, 6H, J = 7.4 Hz, CH$_3$); 1.30-1.45 (m, 4H, CH$_2$); 2.42 (t, 4H, J = 7.5 Hz, CH$_2$N); 2.46-2.57 (m, 1H, CH$_2$Ar); 2.72 (dd, 1H, J = 10.7, 16.1 Hz, CH$_2$); 3.86 (t, 1H, J = 10.1 Hz, CH$_2$); 4.26-4.32 (m, 1H, CH$_2$O); 6.81-6.85 (m, 2H, H$_A$); 7.14 (t, 1H, J = 7.8 Hz, H$_A$); 7.30-7.44 (m, 5H, H$_A$); $^{13}$C NMR (62.90 MHz, CDC$_3$) δ: 11.7 (2, CH$_3$), 21.8 (2, CH$_2$), 27.4 (CH$_2$), 52.7 (2, CH$_2$), 53.6 (CH), 67.7 (CH$_2$), 115.5, 119.6 (q), 122.0, 126.9, 127.0, 128.1 (2), 129.0 (2), 141.0 (q), 143.4 (q), 154.5 (q); MS: $m/z$ 310 (M$^+$+1); Anal. Calcd for C$_{17}$H$_{17}$NO$_2$: C, 81.51; H, 8.79; N, 4.53. Found: C, 81.70; H, 8.86; N, 4.42.

5-(3-Nitrophenyl)-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (6). Following the same procedure used for 5 but substituting phenylboronic acid by 3-nitrophenylboronic acid, purification of the residue by flash chromatography (eluent 95:5 petroleum ether/ethyl acetate) yielded 1 (87%) then 6 (7%) as a crystalline compound: mp 83-85 °C (ethyl acetate-petroleum ether); IR (KBr): ν 1527, 1345 (NO$_2$), 1237 (C-O) cm$^{-1}$; $^1$H NMR (250 MHz, CDC$_3$) δ: 0.80 (t, 6H, J = 7.4 Hz, CH$_3$); 1.30-1.42 (m, 4H, CH$_2$); 2.43 (t, 4H, J = 7.5 Hz, CH$_2$N); 2.46-2.57 (m, 1H, CH$_2$Ar); 2.72 (dd, 1H, J = 10.7, 16.1 Hz, CH$_2$Ar);
3.02-3.13 (m, 1H, CHAr); 3.89 (t, 1H, J = 10.2 Hz, CH₂O); 4.29-4.34 (m, 1H, CH₂O); 6.80 (br d, 1H, J = 7.4 Hz, H₈); 6.89 (br d, 1H, J = 7.4 Hz, H₆); 7.18 (t, 1H, J = 7.4 Hz, H₇); 7.56-7.69 (m, 2H, H₄); 8.21-8.23 (m, 2H, H₅); ¹³C NMR (62.90 MHz, CDCl₃) δ 11.7 (2, CH₃), 21.8 (2, CH₂), 27.5 (CH₂), 52.7 (2, CH₂), 53.5 (CH), 67.6 (CH₂), 116.7, 119.5 (q), 119.5, 121.9, 122.1, 124.0, 127.3, 129.2, 135.2, 140.7 (q), 142.7 (q), 148.1 (q), 154.8 (q); MS: m/z 355 (M⁺+1); Anal. Calcd for C₂₁H₂₆N₂O₃: C, 71.16; H, 7.39; N, 7.90. Found: C, 70.98; H, 7.17; N, 7.93.

5-(3-Aminophenyl)-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (7). Following the same procedure used for 5 but substituting phenylboronic acid by 3-aminophenylboronic acid, purification of the residue by flash chromatography (eluents 9:5 petroleum ether/ethyl acetate) yielded 1 (80%) then 6 (10%) as a pale yellow oil; IR (film): v 3461, 3375 (N-H), 1239 (C-O) cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ: 0.83 (t, 6H, J = 7.4 Hz, CH₃); 1.33-1.45 (m, 4H, CH₂); 2.44 (t, 4H, J = 7.6 Hz, CH₂N); 2.67-2.71 (m, 2H, CH₂Ar); 3.00-3.14 (m, 1H, CHN); 3.70 (br s, 2H, NH₂); 3.86 (t, 1H, J = 10.1 Hz, CH₂O); 4.26-4.31 (m, 1H, CH₂O); 6.63-6.83 (m, 5H, H₄); 7.12 (t, 1H, J = 8.1 Hz, H₈); 7.19 (t, 1H, J = 7.7 Hz, H₅); ¹³C NMR (62.90 MHz, CDCl₃) δ: 11.7 (2, CH₃), 21.8 (2, CH₂), 27.3 (CH₂), 52.7 (2, CH₂), 53.7 (CH), 67.8 (CH₂), 113.8, 115.4, 115.8, 119.6, 119.6 (q), 121.9, 126.8, 129.0, 142.2 (q), 143.6 (q), 146.2 (q), 154.5 (q); MS: m/z 325 (M⁺+1); Anal. Calcd for C₂₁H₂₆N₂O: C, 77.74; H, 8.70; N, 8.63. Found: C, 77.53; H, 8.55; N, 8.42.

5-(3-Azidophenyl)-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (8). 7 (126 mg, 0.38 mmol) was dissolved in water (4 mL) and 14 drops of sulphuric acid and then placed in an ice bath. To this stirred solution was added a solution of NaN₃ (30 mg, 0.42 mmol) in water (4 mL). It was then allowed to continue stirring for 30 min. A solution of NaN₃ (46 mg, 0.70 mmol) in water (4 mL) was added thereafter. The solution was then stirred for a further 40 min. The pH was adjusted to 10 by the addition of 10% NaOH solution and the resulting solution was extracted with methylene chloride (2 x 10 mL). The combined organic extracts were dried (MgSO₄) and evaporated. The residue was purified by flash chromatography (eluents 9:1 petroleum ether/ethyl acetate) to give 76 mg (56 %) of 8 as a pale yellow solid: mp 60-61 °C (ethyl acetate-petroleum ether); IR (KBr): v 2099 (N₃), 1235 (C-O) cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ: 0.83 (t, 6H, J = 7.4 Hz, CH₃); 1.30-1.50 (m, 4H, CH₂); 2.43 (t, 4H, J = 7.5 Hz, CH₂N); 2.57 (ddd, 1H, J = 16.2, 5.6, 2.0 Hz, CH₂Ar); 2.69 (dd, 1H, J = 16.2, 10.4 Hz, CH₂Ar); 3.01-3.13 (m, 1H, CHN); 3.87 (t, 1H, J = 10.2 Hz, CH₂O); 4.27-4.33 (m, 1H, CH₂O); 6.77-6.87 (m, 2H, H₄); 6.98-7.26 (m, 4H, H₈); 7.39 (t, 1H, J = 7.8 Hz, H₆); ¹³C NMR (62.90 MHz, CDCl₃) δ: 11.7 (2, CH₃), 21.9 (2, CH₂), 27.5 (CH₂), 52.7 (2, CH₂), 53.6 (CH), 67.7 (CH₂), 116.0, 117.7, 119.5 (q), 119.6, 121.8, 125.7, 127.0, 129.52, 139.9 (q), 142.3 (q), 142.8 (q), 154.6 (q); MS: m/z 351 (M⁺+1); Anal. Calcd for C₂₁H₂₆N₄O: C, 71.97; H, 7.48; N, 15.99. Found: C, 72.29; H, 7.60; N, 16.10.
5-Cyano-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (9). A stirred mixture of 1 (845 mg, 2.22 mmol), freshly prepared tetrakis(triphenylphosphine)palladium (2.56 g, 2.22 mmol) and zinc cyanide (156 mg, 1.33 mmol) in DMF (20 mL) under argon was heated at 90 °C overnight. The solvent was removed in vacuo and the residue was extracted with methylene chloride (40 mL). The organic phase was then washed with saturated aqueous NaHCO₃ (2 x 10 mL). The organic phase was dried (MgSO₄) and evaporated in vacuo. The crude residue was purified by flash chromatography (95:5, then 9:1 petroleum ether/ethyl acetate) to give 406 mg (71 %) of 9 as a colourless oil; IR (film): v 2227 (CN), 1248 (C-O) cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ: 0.89 (t, 6H, J = 7.4 Hz, CH₃); 1.39-1.53 (m, 4H, CH₂); 2.42-2.61 (m, 4H, CH₂N); 2.90 (dd, 1H, J = 10.7, 16.6 Hz, CH₂Ar); 3.08 (ddd, 1H, J = 1.9, 5.1, 16.6 Hz, CH₂Ar); 3.12-3.24 (m, 1H, CHN); 3.85 (t, 1H, J = 10.3 Hz, 1H, CH₂O); 4.27-3.34 (m, 1H, CH₂O); 7.01 (dd, 1H, J = 1.6, 7.9 Hz, HAr); 7.18 (t, 1H, J = 7.9 Hz, HAr); 7.24 (dd, 1H, J = 1.6, 7.9 Hz, HAr); ¹³C NMR (62.90 MHz, CDCl₃) δ: 11.7 (2, CH₃), 21.9 (2, CH₂), 26.8 (CH₂), 52.5 (CH₂), 52.7 (CH), 68.3 (CH₂), 113.5, 117.5, 121.3, 125.0, 125.5, 127.7, 155.0 (q); MS: m/z 259 (M⁺+1); Anal. Calcd for C₁₆H₂₂N₂O: C, 74.38; H, 8.58; N, 10.84. Found: C, 74.11; H, 8.70; N, 11.00.

5-Carbamoyl-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (10). A stirred solution of 9 (100 mg, 0.39 mmol) and NaOH (1.10 g, 0.27 mol) in ethanol/water (1:1) (8 mL) was refluxed overnight. The pH was adjusted to 6 by addition of 10% HCl and the solution was then extracted with methylene chloride (3 x 10 mL). The combined organic extracts were dried (MgSO₄) and evaporated to give 10 (80 mg, 75 %) as a pale yellow oil; IR (film): v 3392, 3202 (NH₂), 1646 (CO), 1250 (C-O) cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ: 0.91 (t, 6H, J = 7.4 Hz, CH₃); 1.44-1.59 (m, 4H, CH₂); 2.56-2.67 (m, 4H, CH₂N); 3.07-3.11 (m, 2H, CH₂Ar); 3.18-3.28 (m, 1H, CHN); 3.94 (t, 1H, J = 10.1 Hz, CH₂O); 4.31-4.37 (m, 1H, CH₂O); 6.93 (dd, 1H, J = 8.0, 1.4 Hz, HAr); 7.06 (dd, 1H, J = 8.0, 1.4 Hz, HAr); 7.15 (t, 1H, J = 8.0 Hz, HAr); 7.22 (br s, 2H, NH₂); ¹³C NMR (62.90 MHz, CDCl₃) δ: 11.7 (2, CH₃), 21.3 (2, CH₂), 52.5 (2, CH₂), 53.2 (CH), 67.6 (CH₂), 119.1, 119.2, 120.3, 127.1, 136.1 (q), 155.0 (q), 171.9 (q); MS: m/z 277 (M⁺+1); Anal. Calcd for C₁₆H₂₄N₂O₂: C, 69.53; H, 8.75; N, 10.14. Found: C, 69.63; H, 8.59; N, 10.33.

5-Aminomethyl-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (11). To a stirred solution of 9 (355 mg, 1.38 mmol) in dry THF (10 mL) was added lithium aluminium hydride (209 mg, 5.50 mmol). The solution was stirred for 5 h at rt. Water (15 mL) was then added to the solution, and the mixture was extracted with ethyl acetate (4 x 20 mL). The combined organic extracts were dried (MgSO₄) and evaporated in vacuo to give 342 mg (95%) of 11 as a pale yellow oil; IR (film): v 3373 (NH₂), 1240 (C-O) cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ: 0.92 (t, J = 7.4 Hz, 6H, CH₃); 1.43-1.57 (m, 4H, CH₂); 2.41 (br s, 2H, NH₂); 2.57 (t, 2H, J = 7.8 Hz, CH₂N); 2.58 (t, 2H, J = 7.8 Hz, CH₂N); 2.67-2.89 (m, 2H, CH₂Ar); 3.18-3.24 (m, 1H, CHN); 3.79 (t, 1H, J = 10.2 Hz, CH₂O); 3.86 (s, 2H, CH₂NH₂); 4.29-4.36 (m, 1H, CH₂O).
CH₂O); 6.76 (d, 1H, J = 8.6 Hz, HA); 6.94 (d, 1H, J = 8.6 Hz, HA); 7.13 (t, 1H, J = 8.6 Hz, HA); \(^{13}\)C NMR (62.90 MHz, CDCl₃) δ: 11.8 (2, CH₃), 21.0 (2, CH₂), 25.2 (CH₂), 43.2 (CH₂), 52.7 (2, CH₂), 53.4 (CH), 67.3 (CH₂), 115.4, 119.1, 119.7 (q), 127.1, 142.2 (q), 154.7 (q). MS: m/z 263 (M⁺+1); Anal. Calcd for C₁₆H₁₆N₂O₂: C, 74.24; H, 9.99; N, 10.68. Found: C, 73.13; H, 9.78; N, 10.65.

5-Chloroacetamidothieno-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (12). To a solution of 11 (336 mg, 1.28 mmol) in methylene chloride (8 mL) at 0 °C under argon were added anhydrous K₂CO₃ (195 mg, 1.41 mmol) and then chloroacetyl chloride (0.1 mL, 1.41 mmol). The suspension was then stirred overnight. Water (20 mL) was added and the two phases were separated. The aqueous phase was extracted with further methylene chloride (2 x 20 mL) and the combined extracts were dried (MgSO₄) and evaporated in vacuo. The crude residue was purified by flash chromatography (eluent: 4:6 petroleum ether/ethyl acetate) to give 290 mg (67%) of 12 as colourless crystals: mp 78-80 °C (ethyl acetate-petroleum ether); IR (KBr): ν 1646 (CO), 1238 (C=O) cm⁻¹; \(^{1}\)H NMR (250 MHz, CDCl₃) δ: 0.88 (t, 6H, J = 7.4 Hz, CH₃); 1.38-1.53 (m, 4H, CH₂); 2.51 (t, 2H, J = 6.9 Hz, CH₂N); 2.52 (t, 2H, J = 6.9 Hz, CH₂N); 2.66 (dd, 1H, J = 10.8, 16.2 Hz, CH₂Ar); 2.82 (ddd, 1H, J = 1.8, 5.8, 16.2 Hz, CH₂Ar); 3.15-3.27 (m, 1H, CHN); 3.79 (t, 1H, J = 10.3 Hz, CH₂O); 4.11 (s, 2H, CH₂Cl); 4.26-4.33 (m, 1H, CH₂O); 4.40-4.58 (m, 2H, CH₂); 6.71 (br s, 1H, NH); 6.79 (d, 1H, J = 8.0 Hz, Hₐ); 6.82 (d, 1H, J = 8.0 Hz, Hₐ); 7.10 (t, 1H, J = 8.0 Hz, Hₐ); \(^{13}\)C NMR (62.90 MHz, CDCl₃) δ: 11.7 (2, CH₃), 21.9 (2, CH₂), 25.4 (CH₂), 41.4 (CH₂), 42.6 (CH₂), 52.7 (2, CH₂), 53.2 (CH), 67.5 (CH₂), 116.6, 120.3, 120.5, 127.3, 136.2 (q), 155.0 (q), 165.6 (CO); MS: m/z 339 (M⁺+1, CI), 341 (M⁺+1, Cl); Anal. Calcd for C₁₈H₂₇N₂O₂Cl: C, 63.80; H, 8.03; N, 8.27. Found: C, 64.06; H, 8.27; N, 8.34.

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REFERENCES


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