Synthesis of Lodopyridone

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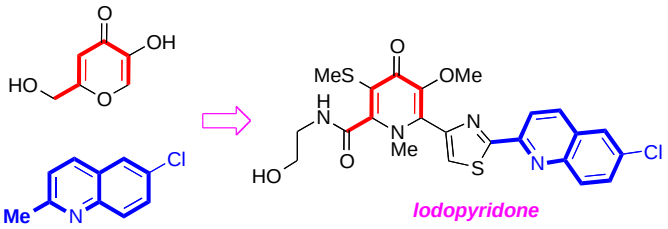

ABSTRACT

The total synthesis of the unusual 4-pyridone marine metabolite lodopyridone has been achieved by late stage manipulation of the related 4-pyrone. Key reactions include a Suzuki-Miyaura coupling to form the tetracyclic core and a modified Corey-Ganem-Gilman reaction to install the ethanolamide side-chain.

Keywords: natural product; synthesis; pyridone; thiazole; quinoline; pyrone

1. INTRODUCTION

Among the wide structural diversity of pyridine-based alkaloids, those containing the 4-pyridone nucleus are relatively rare. Examples include leucenol (mimosine), [1] Δ^5-dehydroalbine,[2] and the recently isolated poronitin B (Figure 1).[3] Isolated from a strain of the *Actinomycete* marine

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bacterium CNQ490 collected near the mouth of the La Jolla submarine canyon in California by Fenical and co-workers,[4] lodopyridone **1** is one of the more unusual 4-pyridone natural products. The structure (Figure 1), which was determined by X-ray crystallography, is based on a fully substituted 4-pyridone nucleus containing unusual substituents such as a thiomethoxy group and a 6-chloroquinolinylthiazole, and the compound is reported to possess moderate biological activity against human colon cancer cells. However, in addition to its unusual structure, it was its reported activity as an inhibitor of human quinone reductase 2 (NQO2, QR2) that attracted our attention,[5] in view of our interest in quinone reductase enzymes.[6,7] We now report a total synthesis of lodopyridone.

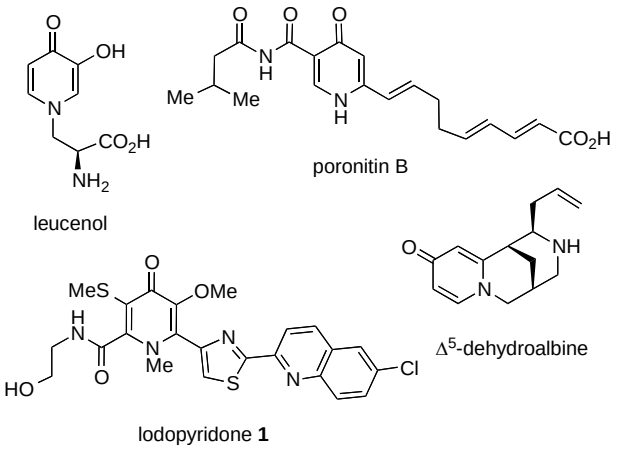
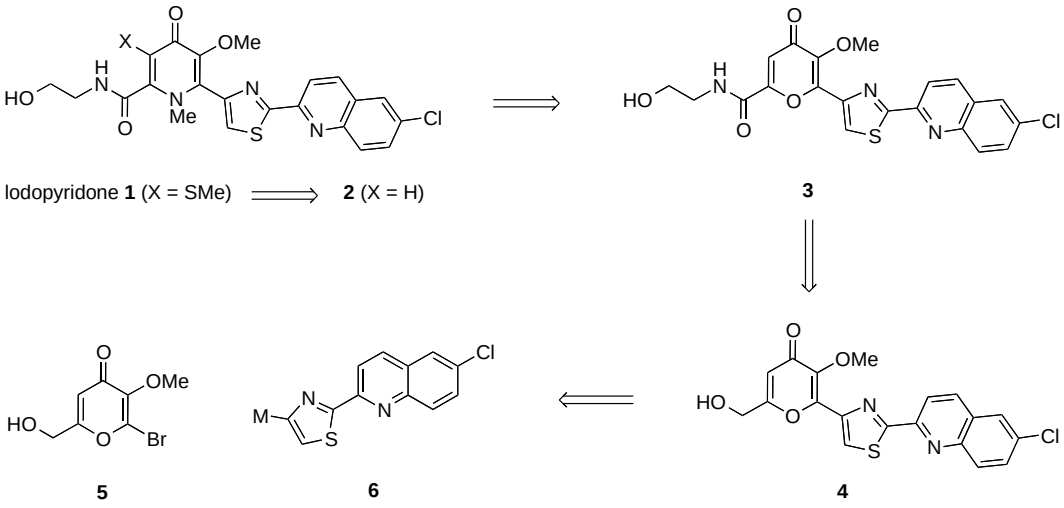


Figure 1. Naturally occurring 4-pyridones.

4-Pyridones are usually readily accessible from 4-pyrones,[8,9] and indeed poronitin B co-occurs with the corresponding 4-pyrone.[3] Therefore we aimed to install the key biaryl carbon-carbon bond on the related 4-pyrone system and convert it into the pyridone at a late stage in the synthesis (Scheme 1). The thiomethoxy group at the pyridone C-3 position could be installed by displacement of the corresponding bromide, which can be obtained by treatment with a suitable

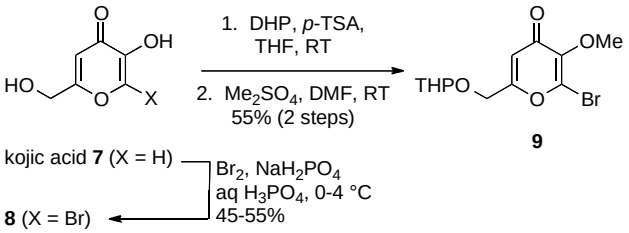
electrophilic brominating agent. The pyridone **2** could be made from the pyrone **3**, with the amide being accessed from the corresponding primary alcohol **4**. Disconnection of the pyrone-thiazole bond gives the bromo-4-pyrone fragment **5** and thiazole-quinoline fragment **6** (M = organometallic coupling partner) that is available by a classical Hantzsch thiazole synthesis. Whilst these studies were in progress, a synthesis of lodopyridone using a related strategy was reported by Koert *et al.*,[10] together with an outline of a biomimetic strategy.[11]



Scheme 1. Proposed retrosynthetic analysis for lodopyridone **1**.

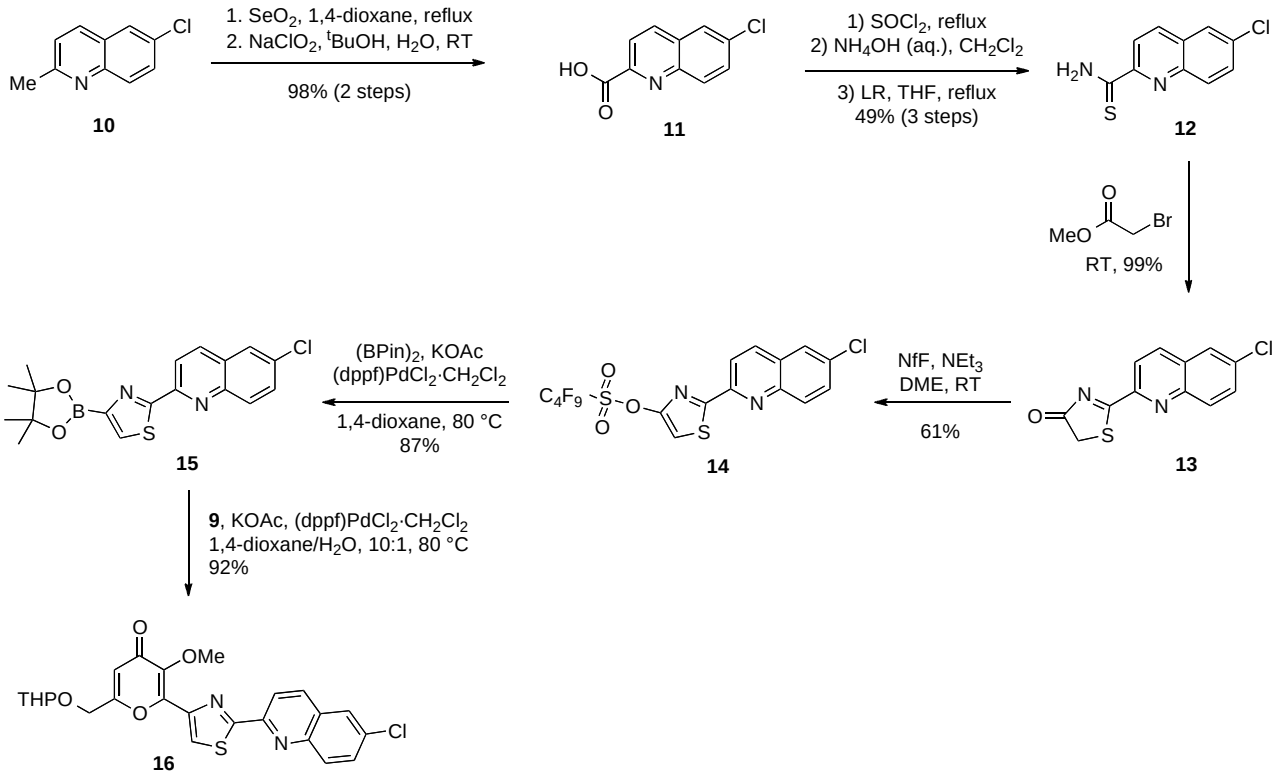
2. RESULTS AND DISCUSSION

The synthesis of the halo-pyrone fragment begins with the previously reported bromination of commercially available kojic acid **7** (Scheme 2).[12] Regioselective bromination of the pyrone at C-6, was followed by selective protection of the primary alcohol under acidic conditions, and methylation of the more acidic C-5 alcohol provided the bromopyrone **9** on multi-gram scale.



Scheme 2. Synthesis of bromopyrone fragment.

The thiazole-quinoline fragment was readily built up from 6-chloro-2-methylquinoline **10**. Oxidation of the methyl group with selenium(IV) oxide to the aldehyde, followed by Pinnick oxidation to the carboxylic acid **11** was achieved in excellent overall yield, and conversion into the amide *via* the acid chloride, followed by treatment with Lawesson's reagent (LR) gave the thioamide **12**. Stirring thioamide **12** in neat methyl bromoacetate gave the thiazolone **13** in quantitative yield. Attempts to convert thiazolone **13** into the corresponding triflate proceeded in a disappointing 31% yield, a result subsequently noted by Koert *et al.* during their synthesis.[10] Fortunately the corresponding nonaflate **14**, could be synthesized in a greatly improved 61% yield. Model studies on the bromopyrone **9** showed Stille coupling to be highly effective, but when it came to test the transmetallation of the nonoflate **14**, coupling with bis(pinacolato)diboron proved to be more effective. A number of palladium based catalyst systems were investigated and it was found that the (diphenylphosphino)ferrocene ligand was highly effective for the metallation of nonaflate. Provided the potassium acetate base is thoroughly dried, the nonaflate **14** undergoes smooth conversion into the pinacolboronic ester **15** which was coupled following partial purification. Gratifyingly the Suzuki-Miyaura coupling of the bromopyrone **9** and the boronato **15** proceeded in excellent yield, and the structure of the tetracycle **16** was confirmed unambiguously by X-ray crystallography (Figure 2).



Scheme 3. Synthesis of quinoline-thiazole-pyrone.

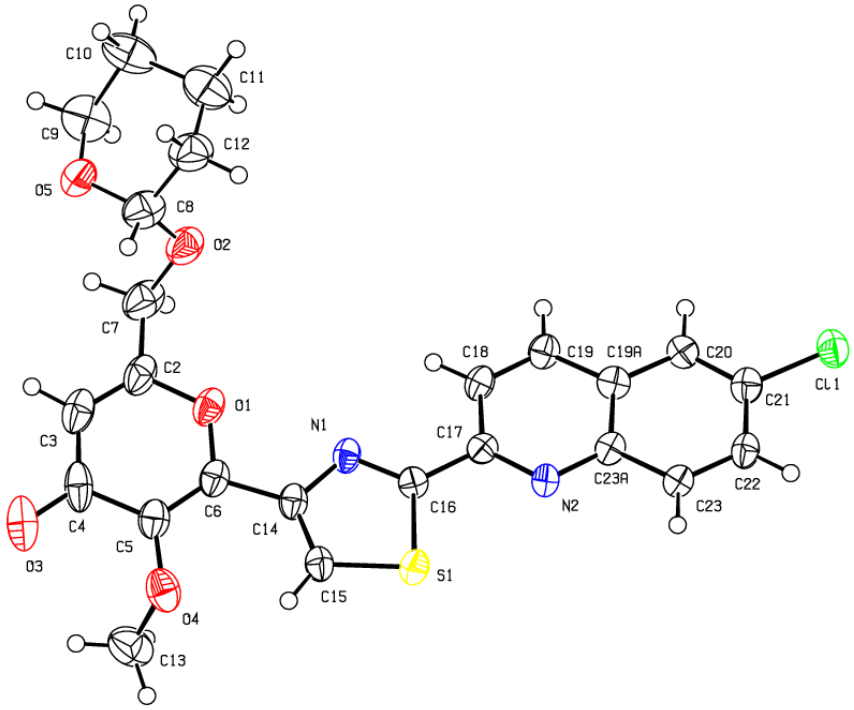
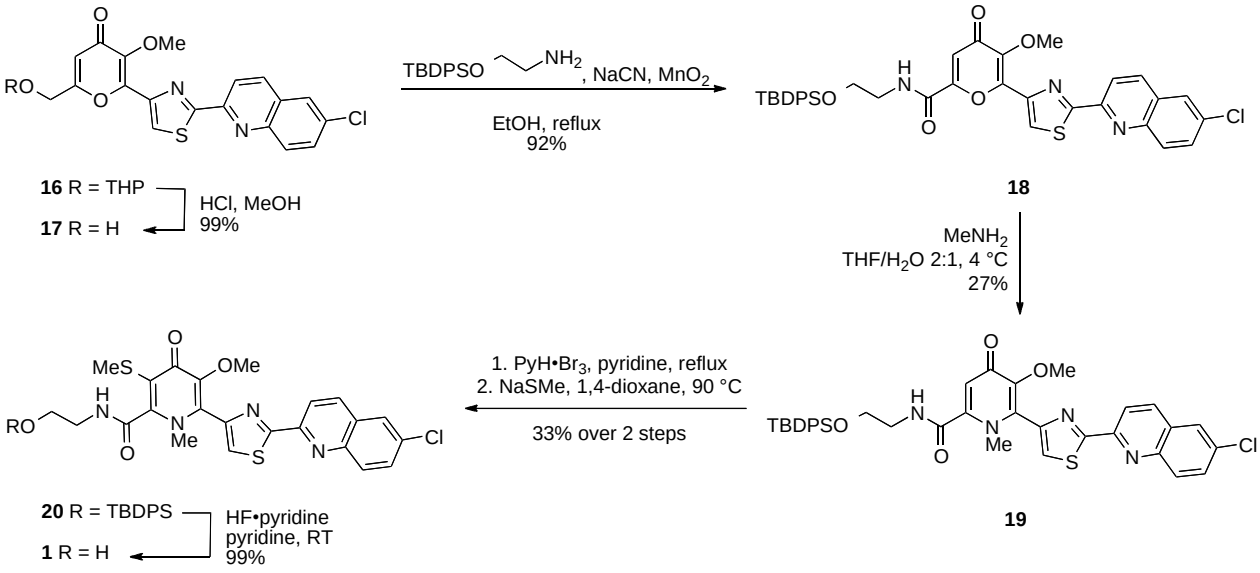


Figure 2. X-ray crystal structure of quinoline-thiazole-pyrone **16**.

With the key C-6 biaryl bond in place, the insertion of the amide side chain was the next task (Scheme 4). Although the deprotection of the THP ether was trivial, the oxidation of the primary alcohol to the carboxylic acid proved problematic, Jones oxidation, for example, being unsuccessful. We suspect that poor solubility of the pyrone **17** and the presence of the basic quinoline may have contributed to this failure. Fortunately the modified Corey-Ganem-Gilman conditions developed by Taylor *et al.* allowed the amide side chain to be installed in a single reaction,[13] achieving both oxidation and amide coupling. It was necessary to use ethanol as a solvent due to the inherent insolubility of the pyrone **17** but despite, this none of the corresponding ethyl ester was observed. Furthermore, upon formation of the silyl protected ethanolamide the solubility of the compound in organic solvents was greatly enhanced.

Conversion of pyrone **18** into pyridone **19** also proved problematic; anhydrous ethanolic or THF solutions of methylamine returned only the starting pyrone, whilst in the presence of water competing transamination of the amide was observed, and the pyridone **19** was only isolated in a dissapointing 27% yield. With the pyridone **19** in hand the next step was to introduce the methanethiolate group at the pyridone C-3 position which we planned to achieve *via* the displacement of the corresponding bromide. Bromination of the pyridone **19** required relatively forcing conditions, necessitating more than 6 hours with pyridinium tribromide in pyridine at reflux. This is in contrast to the related work that showed when the C-6 position is unsubstituted, the pyridone underwent selective C-3 bromination at room temperature in the presence of *N*-bromosuccinimide.[10] Nevertheless displacement of the bromide occurred easily by heating with sodium methanethiolate to give **20** as the sole product. No side reactions were observed and copper(I) catalysts were necessary in contrast to the conditions described in the literature for a related transformation.[10] Finally, deprotection of the silyl protecting group by treatment with hydrogen fluoride/pyridine complex in pyridine gave lodopyridone **1**. Comparison of the NMR data with those reported for the natural product by Fenical *et al.*[4] confirmed the successful completion of the synthesis.



Scheme 4. Completion of the synthesis of lodopyridone.

We have successfully completed the second total synthesis of lodopyridone. We have developed a Suzuki coupling strategy for the synthesis of the key pyrone-thiazole bond and demonstrated that the corresponding pyrone can be converted into lodopyridone after the biaryl bond is formed. Finally we have shown that the amide side chain can be installed in one step from the primary alcohol, overcoming the inherent solubility problems associated with this compound.

3. EXPERIMENTAL SECTION

3.1 General information

Commercially available reagents were used throughout without purification unless otherwise stated. All anhydrous solvents were used as supplied, except tetrahydrofuran and dichloromethane that were freshly distilled according to standard procedures. Reactions were routinely carried out under an argon atmosphere unless otherwise stated, and all glassware was

flame-dried before use. Light petroleum refers to the fraction with bp 40-60 ºC. Ether refers to diethyl ether.

Analytical thin layer chromatography was carried out on aluminum backed plates coated with silica gel, and visualized under UV light at 254 and/or 360 nm and/or by chemical staining. Flash chromatography was carried out using silica gel, with the eluent specified.

Infrared spectra were recorded using an FT-IR spectrometer over the range 4000-600 cm^{-1}. NMR spectra were recorded at 400 or 500 MHz (^{1}H frequency, 100 or 125 MHz ^{13}C frequency). Chemical shifts are quoted in parts per million (ppm), and are referenced to residual H in the deuterated solvent as the internal standard. Coupling constants, *J*, are quoted in Hz. In the ^{13}C NMR spectra, signals corresponding to CH, CH_2, or CH_3 groups are assigned from DEPT. Mass spectra were recorded on a time-of-flight mass spectrometer using electrospray ionization (ESI), or an EI magnetic sector instrument.

3.2 6-Bromo-5-hydroxy-2-hydroxymethyl-*4H*-pyran-4-one 8

A solution of bromine (2.25 mL, 43.91 mmol) and monobasic sodium phosphate (26.78 g, 0.22 mol) in water (74 mL) was added slowly to a stirred suspension of kojic acid **7** (5.25 g, 37.21 mmol) in orthophosphoric acid (27 mL) at 0 °C, the suspension was warmed to 4 ˚C and stirred for 72 h. The suspension was filtered and the solid obtained was dried azeotropically with toluene to give the title compound **8** as a colorless solid (4.36 g, 53%); mp 168-170 °C (lit.,[12] mp 169-170 °C); (Found: $[M+Na]^+$, 242.9269. $C_6H_5{}^{79}BrNaO_4{}^+$ requires 242.9269); ν_{max} ($CHCl_3$) 3043, 2927, 1602, 1240 cm^{-1}; δ_H (400 MHz; DMSO-d_6) 9.88 (1H, s), 6.37 (1H, br t, *J* 0.6), 5.74 (1H, t, *J* 6.2), 4.31 (2H, dd, *J* 6.2, 0.6); δ_c (100 MHz; DMSO-d_6) 172.2 (C), 168.9 (C), 144.1 (C), 129.2 (C), 109.5 (CH), 59.2 (CH_2).

3.3 6-Bromo-5-hydroxy-2-[(tetrahydro-*2H*-pyran-2-yloxy)methyl]-*4H*-pyran-4-one

para-Toluenesulfonic acid (9 mg, 0.46 mmol) was added to a suspension of alcohol **8** (512 mg, 2.33 mmol) and 2,3-dihydropyran (0.41 mL, 4.49 mmol) in dichloromethane (22 mL) and the mixture was stirred at room temperature for 2 h then concentrated *in vacuo*. The residue was purified by chromatography on silica eluted with 75 - 100% ethyl acetate in light petroleum to give the title compound as a pale yellow oil (703 mg, 99%); (Found: $[M+Na]^+$, 326.9822. $C_{11}H_{13}{}^{79}BrNaO_5{}^+$ requires 326.9844); ν_{max} ($CHCl_3$) 3632, 3410, 3009, 2946, 1640, 1017 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.01 (1H, br s), 6.54 (1H, s), 4.73 (1H, t, *J* 3.1), 4.55 (1H, d, *J* 14.8), 4.38 (1H, d, *J* 14.8), 3.83 (1H, td, *J* 9.1, 3.1), 3.28 - 3.63 (1H, m), 1.05 - 1.99 (6H, m); δ_C (100 MHz; $CDCl_3$) 172.3 (C), 166.7 (C), 144.3 (C), 128.0 (C), 110.0 (CH), 98.3 (CH), 64.1 (CH_2), 62.0 (CH_2), 30.0 (CH_2), 25.1 (CH_2), 18.7 (CH_2).

3.4 6-Bromo-5-methoxy-2-[(tetrahydro-*2H*-pyran-2-yloxy)methyl]-*4H*-pyran-4-one 9

Potassium hydroxide (2.23 g, 39.74 mmol) was added in one portion to a stirred solution of the above THP protected pyrone (6.03 g, 19.82 mmol) and iodomethane (2.47 mL, 39.68 mmol) in dimethyl sulfoxide (20 mL), and the solution was stirred at room temperature for 10 h. The mixture was diluted with water (100 mL) and dichloromethane (50 mL), the aqueous phase was extracted with dichloromethane (5 × 20 mL) and the combined organic extracts washed with water (15 mL), brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluted with 50 - 100% ethyl acetate in light petroleum to give the title compound **9** as a red oil (3.45 g, 55%); (Found: $[M+Na]^+$, 340.9991. $C_{12}H_{15}{}^{79}BrNaO_5{}^+$ requires 341.0001; ν_{max} ($CHCl_3$) 3004, 2946, 1653, 1441, 1036 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 6.48 (1H, t, *J*

0.7), 4.73 (1H, t, *J* 3.1), 4.52 (1H, dd, *J* 14.7, 0.7), 4.34 (1H, dd, *J* 14.7 0.7), 3.91 (3H, s), 3.73 - 4.05 (1H, m), 3.27 - 3.62 (1H, m), 1.42 - 1.89 (6H, m); δ_C (100 MHz; $CDCl_3$) 173.9 (C), 165.0 (C), 146.2 (C), 139.3 (C), 113.7 (CH), 98.0 (CH), 63.5 (CH_2), 61.7 (CH_2), 59.8 (CH_3), 29.7 (CH_2), 24.8 (CH_2), 18.4 (CH_2).

3.5 6-Chloroquinoline-2-carbaldehyde

6-Chloro-2-methylquinoline (2.00 g, 11.26 mmol) was added to a suspension of selenium(IV) oxide (7.50 g, 67.56 mmol) in 1,4-dioxane (113 mL) in one portion at 50 °C, and the stirred suspension was heated to reflux for 1.5 h. The mixture was filtered hot through Celite and concentrated *in vacuo*. The residue was suspended in ethyl acetate (40 mL) with sonication, and the selenium impurities precipitated by addition of light petroleum (30 mL). The suspension was filtered through a short pad of silica, washed with 30% ethyl acetate in light petroleum and concentrated *in vacuo* to give the title compound as a yellow solid (2.11 g, 98 %); mp 135-136 °C (lit.,[14] mp 140 °C); (Found: $[M+Na^+]$, 214.0034. $C_{10}H_6{}^{35}ClNNaO^+$ requires 214.0036); ν_{max} ($CHCl_3$) 2989, 1713, 1458, 1185 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 10.24 (1H, d, *J* 0.7), 8.26 (1H, d, *J* 8.5), 8.22 (1H, dt, *J* 9.0, 0.7,), 8.08 (1H, d, *J* 8.5), 7.93 (1H, d, *J* 2.3), 7.79 (1H, dd, *J* 9.0, 2.3); δ_C (100 MHz; $CDCl_3$) 193.3 (CH), 152.7 (C), 146.3 (C), 136.5 (CH), 135.3 (C), 132.0 (CH), 131.6 (CH), 130.6 (C), 126.6 (CH), 118.3 (CH).

3.6 6-Chloroquinoline-2-carboxylic acid 11

A solution of monobasic sodium phosphate (3.87 g, 32.22 mmol) and sodium chlorite (3.87 g, 42.76 mmol) in water (39 mL) was added slowly to a solution of 6-chloroquinoline-2-carbaldehyde (852 mg, 4.45 mmol) in *tert*-butanol (89 mL). The solution was stirred at room

temperature for 2 h, concentrated *in vacuo*, diluted with water (68 mL) and ethyl acetate (50 mL), then acidified to pH 4. The precipitate was collected by filtration to give a colorless solid (870 mg, 95 %). The aqueous layer was extracted with ethyl acetate (5 × 15 mL) and the combined organic extracts washed with brine (2 × 15 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give more colourless solid (80 mg, 7%) giving the title compound (>99% combined yield); mp 234-236 °C (lit.,[15] mp 227-228 °C); (Found: $[M+Na^+]$, 229.9996. $C_{10}H_6{}^{35}ClNNaO_2{}^+$ requires 229.9985); ν_{max} ($CHCl_3$) 3691, 3002, 1769, 1602, 1334 cm^{-1}; δ_H (300 MHz; DMSO-d_6) 8.53 (1H, d, *J* 8.5, CH), 8.25 (1H, d, *J* 2.4, CH), 8.18 (1H, d, *J* 9.0, CH), 8.15 (1H, d, *J* 8.5, CH) 7.87 (1H, dd, *J* 9.0, 2.4, CH); δ_C (75 MHz; DMSO-d_6) 166.1 (C), 149.3 (C), 145.2 (C), 137.0 (CH), 132.9 (C), 131.8 (CH), 130.1 (CH), 129.5 (C), 126.7 (CH), 121.7 (CH).

3.7 6-Chloroquinoline-2-carboxamide

A suspension of 6-chloroquinoline-2-carboxylic acid **11** (1.00 g, 4.82 mmol) in thionyl chloride (10 mL) was heated to reflux for 40 min. The reaction mixture was concentrated *in vacuo*, and the residue dissolved in dichloromethane (48 mL) and cooled to 0 °C. Ammonium chloride (1.29 g, 24.08 mmol) was added, followed by dropwise addition of triethylamine (6.70 mL, 48.15 mmol) and the reaction mixture stirred for 15 min at 0 °C. Aqueous sodium hydroxide solution (2 M; 30 mL) was added and the suspension filtered to give an orange solid. The organic phase was washed with sodium hydroxide (2 M; 2 × 30 mL), brine (14 mL), dried (Na_2SO_4) and concentrated *in vacuo* before purification by chromatography on silica, eluting with 50 - 100 % ethyl acetate in light petrol to give the title compound as a colorless solid (730 mg, 73 %); mp 228-230 °C; (Found: $[M+Na^+]$, 229.0142. $C_{10}H_7{}^{35}ClN_2NaO$ requires 229.0145); ν_{max} ($CHCl_3$) 3517, 3394, 3011, 1692, 1562 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.36 (1H, d, *J* 8.5), 8.27 (1H, d, *J* 8.5),

8.09 (1H, d, *J* 9.0), 8.05 (1H, br s), 7.91 (1H, d, *J* 2.3), 7.74 (1H, dd, *J* 9.0, 2.3), 5.63 (1H, br s); δ_C (100 MHz; $CDCl_3$) 166.4 (C), 149.6 (C), 145.0 (C), 136.7 (CH), 134.1 (C), 131.4 (CH), 131.3 (CH), 130.0 (C), 126.5 (CH), 119.8 (CH); *m/z* (ESI) 231/229 ($M+Na^+$, 29/90%)

3.8 6-Chloroquinoline-2-thiocarboxamide 12

Lawesson's reagent (2.43 g, 5.98 mmol) was added to a stirred solution of 6-chloroquinoline-2-carboxamide (336 mg, 1.77 mmol) in tetrahydrofuran (35 mL) and the mixture was then heated to reflux for 2.5 h. After concentration *in vacuo*, the residue was purified by chromatography on silica, eluting with 30 - 100 % dichloromethane in light petroleum to give the title compound as a yellow solid (258 mg, 67 %); mp 170-172 °C; (Found: C, 53.93; H, 3.17; N, 12.32. $C_{10}H_7ClN_2S$ requires C, 53.93; H, 3.17; N, 12.58); (Found: $[M+H^+]$, 223.0102. $C_{10}H_8{}^{35}ClN_2S$ requires 223.0097); ν_{max} ($CHCl_3$) 3482, 3335, 2993, 1576, 1492, 1305, 836 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 9.71 (1H, br s), 8.89 (1H, d, *J* 8.7), 8.24 (1H, d, *J* 8.7, CH), 8.10 (1H, d, *J* 9.0, CH), 7.90 (1H, d, *J* 2.1), 7.74 (1H, dd, *J* 9.0, 2.3), 7.72 (1H, br s); δ_C (100 MHz; $CDCl_3$) 195.6 (C), 149.7 (C), 143.9 (C), 135.9 (CH), 134.2 (C), 131.5 (CH), 131.4 (CH), 129.6 (C), 126.4 (CH), 122.2 (CH).

3.9 2-(6-Chloroquinolin-2-yl)thiazol-4-ol 13

A suspension of 6-chloroquinoline-2-thiocarboxamide **12** (1.16 g, 5.22 mmol) in methyl bromoacetate (60 mL) was stirred at room temperature for 1 h. The mixture was diluted with dichloromethane (150 mL), the suspension filtered and the solid washed with dichloromethane (3 × 50 mL) to give the title compound **13** as a yellow solid (1.35 g, 99%); mp 137-129 °C; (Found $[M+H^+]$, 263.0039. $C_{12}H_7{}^{35}ClN_2OS^+$ requires 263.0041); ν_{max} (ATR) 2870, 1717, 1602, 1310 cm^{-1}; δ_H (300 MHz; DMSO-d_6) 8.48 (1H, d, *J* 8.5), 8.20 (1H, d, *J* 8.5), 8.19 (1H, d, *J* 2.5), 8.04 (1H,

d, *J* 9.0), 7.81 (1H, dd, *J* 9.0, 2.5), 6.49 (1H, s); δ_C (75 MHz; DMSO-d_6) 163.3 (C), 163.1 (C), 150.9 (C), 145.5 (C), 137.1 (CH), 131.4 (C), 131.0 (CH), 130.7 (CH), 128.9 (C), 126.9 (CH), 118.0 (CH), 94.3 (CH).

3.10 Nonofluorobutanesulfonyl 2-(6-chloroquinolin-2-yl)thiazol-4-ol 14

Triethylamine (0.86 mL, 6.26 mmol) and nonofluorobutanesulfonyl fluoride (1.3 mL, 7.24 mmol) was added to a suspension of 2-(6-chloroquinolin-2-yl)thiazol-4-ol **13** (1.26 g, 4.81 mmol) in 1,2-dimethoxyethane (48 mL) and the mixture stirred for 2 h at room temperature under an argon atmosphere. Additional triethylamine (0.86 mL, 6.26) and nonofluorobutanesulfonyl fluoride (1.3 mL, 7.24 mmol) were added and the mixture stirred for a further 10 h. The mixture was concentrated *in vacuo* and the residue purified by chromatography on silica, eluting with 5 - 10% ethyl acetate in light petroleum to give **14** as a pale yellow solid (1.59 g, 61%); mp 132-134 °C; ν_{max} ($CHCl_3$) 3130, 3001, 1491, 1242, 1146, 982 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 8.27 (1H, d, *J* 8.6), 8.19 (1H, d, *J* 8.6), 8.07 (1H, d, *J* 9.0), 7.85 (1H, d, *J* 2.3), 7.70 (1H, dd, *J* 9.0, 2.3), 7.26 (1H, s); δ_C (75 MHz; $CDCl_3$) 167.0 (C), 151.0 (C), 149.7 (C), 145.9 (C), 136.5 (CH), 133.6 (C), 131.4 (CH), 131.0 (CH), 129.5 (C), 126.5 (CH), 118.2 (CH), 109.7 (CH); nonaflate carbons not observed; δ_F (282 MHz; $CDCl_3$) –80.6 (3F, tt, *J* 9.9, 2.2, CF_3), –108.3 (2F, ttq, *J* 13.6, 4.5, 2.4, CF_2), –120.8 (2F, m, CF_2), –125.7 (2F, m, CF_2); *m/z* (MALDI) 545 ($M+H^+$, 100%)

3.11 6-[2-(6-Chloroquinolin-2-yl)thiazol-4-yl]-5-methoxy-2-[(tetrahydro-2*H*-pyran-2-yloxy)methyl]-4*H*-pyran-4-one 16

(a) Potassium acetate (361 mg, 3.68 mmol) and bis(diphenylphosphino)ferrocenepalladium dichloride dichloromethane adduct (75 mg, 92 µmol) were added to a degassed solution of

Nonofluorobutanesulfonyl 2-(6-chloroquinolin-2-yl)thiazol-4-ol **14** (1.00 g, 1.84 mmol) and bis(pinacolato)diboron (514 mg, 2.02 mmol) in 1,4-dioxane (18 mL) and the mixture degassed with argon and sonication for a second time before heating to 80 °C for 4 h. The mixture was concentrated *in vacuo* before purification by chromatography on silica, eluting with 50% ethyl acetate in light petroleum to give a *ca.* 1:1 mixture of the 2-(6-chloroquinolin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiazole **15** and pinacol (770 mg total) as a yellow residue (600 mg, 87%) that was used without further purification; δ_H (300 MHz; $CDCl_3$) 8.53 (1H, d, *J* 8.6), 8.14 (1H, s), 8.14 (1H, d, *J* 8.6), 8.06 (1H, d, *J* 8.9), 7.81 (1H, d, *J* 2.4), 7.66 (1H, dd, *J* 8.9, 2.2), 1.41 (12H, s); δ_C (75 MHz; $CDCl_3$) 170.2 (C), 151.6 (C), 146.1 (C), 135.7 (CH), 134.6 (CH), 132.7 (C), 131.0 (CH), 130.8 (CH), 129.2 (C), 126.4 (CH), 119.6 (CH), 84.5 (CH), 24.9 (CH_3); one carbon unobserved;

(b) Potassium acetate (376 mg, 3.83 mmol) and bis(diphenylphosphino)ferrocenepalladium dichloride dichloromethane adduct (52 mg, 64 μmol) was added to a degassed solution of 2-(6-chloroquinolin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiazole **15** (475 mg, 1.28 mmol) and bromopyrone **9** (1.97 mg, 6.20 mmol) in 1,4-dioxane (13 mL) and the mixture degassed with argon and sonication for a second time before heating to 80 °C for 3 h. The mixture was concentrated *in vacuo* and purified by chromatography on silica, eluting with 50% ethyl acetate in light petroleum to give the title compound **17** as a pale yellow solid (571 mg, 92%); mp 159-161 °C; (Found: $[M+H^+]$, 485.0941. $C_{24}H_{22}{}^{35}ClN_2O_5S^+$ requires 485.0933); ν_{max} ($CHCl_3$) 3007, 2947, 1652, 1620, 1413, 1389 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 8.40 (1H, d, *J* 8.7), 8.32 (1H, s), 8.20 (1H, d, *J* 8.6), 8.08 (1H, d, *J* 9.0), 7.84 (1H, d, *J* 2.3), 7.69 (1H, dd, *J* 9.0, 2.3), 6.60 (1H, t, *J* 0.8), 4.85 (1H, t, *J* 3.4), 4.71 (1H, dd, *J* 14.8, 0.8), 4.54 (1H, dd, *J* 14.8, 0.8), 4.05 (3H, s), 3.82-3.96 (1H, m), 3.56-3.67 (1H, m), 1.48-1.94 (6H, m); δ_C (75 MHz; $CDCl_3$) 176.2

(C), 168.9 (C), 164.0 (C), 150.8 (C), 150.4 (C), 146.2 (C), 146.1 (C), 144.9 (C), 136.2 (CH), 133.2 (C), 131.1 (CH), 131.1 (CH), 129.3 (C), 126.4 (CH), 126.1 (CH), 118.6 (CH), 113.5 (CH), 98.2 (CH), 64.1 (CH_2), 61.9 (CH_2), 59.8 (CH_3), 30.1 (CH_2), 25.2 (CH_2), 18.7 (CH_2); *m/z* (ESI) 487/485 ($M+H^+$, 37/100%), 509/507 ($M+Na^+$, 12/33%).

3.12 2-(2-(6-Chloroquinolin-2-yl)thiazol-4-yl)-6-(hydroxymethyl)-3-methoxy-4*H*-pyran-4-one 17

Methanolic hydrogen chloride (2 M; 20 mL, 40 mmol) was added to a suspension of 6-[2-(6-chloroquinolin-2-yl)thiazol-4-yl]-5-methoxy-2-[(tetrahydro-2*H*-pyran-2-yloxy)methyl]-4*H*-pyran-4-one **16** (296 mg, 611 µmol) and the mixture stirred at room temperature for 40 min under an argon atmosphere. The mixture was concentrated *in vacuo*, and the residue triturated with methanol and the suspension filtered to give the title compound **17** as a pale yellow solid (245 mg, 99%) which was used without further purification; mp 137-139 °C; δ_H (300 MHz; $CDCl_3$) 8.58 (1H, s), 8.58 (1H, d, *J* 8.6), 8.37 (1H, d, *J* 8.6), 8.24 (1H, d, *J* 2.4), 8.12 (1H, d, *J* 9.2), 7.86 (1H, dd, *J* 9.1, 2.4), 6.44 (1H, s), 4.45 (2H, s), 3.94 (3H, s); δ_C (75 MHz; $CDCl_3$) 175.2 (C), 168.1 (C), 167.8 (C), 150.5 (C), 149.7 (C), 145.7 (C), 145.6 (C), 144.2 (C), 137.5 (CH), 132.1 (C), 131.3 (CH), 130.9 (CH), 129.3 (C), 127.3 (CH), 127.0 (CH), 118.4 (CH), 111.9 (CH), 59.6 (CH_2), 59.5 (CH_3).

3.13 *N*-[2-(*tert*-Butyldiphenylsiloxy)ethyl]-6-[2-(6-chloroquinolin-2-yl)thiazol-4-yl]-5-methoxy-4-oxo-4*H*-pyran-2-carboxamide 18

Sodium cyanide (25 mg, 500 µmol) and manganese(IV) oxide (326 mg, 3.75 mmol) were added to a stirred suspension of 2-(2-(6-chloroquinolin-2-yl)thiazol-4-yl)-6-(hydroxymethyl)-3-

methoxy-4*H*-pyran-4-one **17** (100 mg, 250 µmol) and *tert*-butyldiphenylsiloxyethanamine (374 mg, 1.25 mmol) in ethanol (8 mL) and the mixture stirred and heated to reflux for 1 h under an argon atmosphere. The mixture was concentrated *in vacuo*, triturated with 30% ethyl acetate in light petroleum and the solid filtered to give **18** an orange solid (109 mg, 64%). The filtrate was concentrated *in vacuo* and purified by chromatography on silica, eluting with 2% methanol in dichloromethane to give the title compound as an orange oil (48 mg, 28%, total yield 92%). On a 120 mg scale (300 µmol) the yield reduced to 50%; (Found: $[M+H^+]$, 696.1754. $C_{36}H_{32}ClN_3O_5SSi^+$ requires 696.1750); ν_{max} ($CHCl_3$) 3014, 2934, 2860, 1689, 1650, 1472, 1320 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 8.39 (1H, s), 8.20 (1H, d, *J* 8.4), 8.07 (1H, d, *J* 9.0), 7.85 (1H, d, *J* 8.4), 7.78 (1H, d, *J* 2.3), 7.71 (1H, dd, *J* 9.0, 2.3), 7.57-7.63 (4H, m), 7.39-7.48 (1H, m), 7.24-7.39 (6H, m), 4.13 (3H, s), 3.96 (2H, t, *J* 5.4), 3.72 (2H, q, *J* 5.4), 0.97 (9H, s); δ_C (75 MHz; $CDCl_3$) 175.9 (C), 172.2 (C), 169.3 (C), 158.7 (C), 153.4 (C), 150.4 (C), 146.1 (C), 136.2 (CH), 135.5 (C), 135.3 (CH), 133.3 (C), 133.2 (C), 131.2 (CH), 131.0 (CH), 129.8 (CH), 129.2 (C), 127.8 (C), 127.8 (CH), 126.9 (CH), 126.4 (CH), 118.4 (CH), 116.4 (CH), 62.6 (CH_2), 59.8 (CH_3), 42.2 (CH_2), 26.8 (CH_3), 19.2 (C).

3.14 *N*-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-[2-(6-chloroquinolin-2-yl)thiazol-4-yl]-5-methoxy-1-methyl-4-oxo-1,4-dihydropyridine-2-carboxamide 19

Aqueous methylamine (25-30%, 1 mL, 5.63-6.76 mmol) was added to a stirred solution of *N*-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-6-[2-(6-chloroquinolin-2-yl)thiazol-4-yl]-5-methoxy-4-oxo-4*H*-pyran-2-carboxamide **18** (32 mg, 47 µmol) in THF (2 mL) at 0 °C and the mixture warmed slowly to 4 °C and stirred for 8 h under an argon atmosphere. The mixture was concentrated *in vacuo* and purified by chromatography on silica, eluting with 3-5% methanol in dichloromethane

to give the title compound **19** as a yellow oil (9 mg, 27%); (Found: [M+H$^+$], 709.2067. $C_{38}H_{39}{}^{35}ClN_4O_4SSi^+$ requires 709.2080); ν_{max} ($CHCl_3$) 3011, 2932, 2859, 1678, 1610, 1472 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 8.28 (1H, d, *J* 8.7), 8.18 (1H, d, *J* 8.7), 8.08 (1H, d, *J* 9.1), 7.83 (1H, d, *J* 2.3), 7.75 (1H, s), 7.69 (1H, dd, *J* 9.1, 2.3), 7.65-7.69 (4H, m), 7.34-7.48 (6H, m,), 6.61 (1H, s), 3.89 (2H, t, *J* 5.2), 3.74 (3H, s), 3.60 (2H, q, *J* 5.2), 3.48 (3H, s), 1.08 (9H, s); δ_C (75 MHz; $CDCl_3$) 173.6 (C), 169.3 (C), 163.5 (C), 150.7 (C), 149.0 (C), 146.0 (C), 145.9 (C), 145.3 (C), 138.9 (C), 136.2 (CH), 135.5 (CH), 133.2 (C), 131.2 (CH), 130.9 (CH), 129.8 (CH), 129.2 (C), 127.8 (CH), 127.5 (CH), 126.4 (CH), 125.5 (CH), 118.5 (CH), 117.3 (CH), 62.3 (CH_2), 59.9 (CH_3), 42.3 (CH_2), 39.6 (CH_3), 26.8 (CH_3), 19.2 (C); *m/z* (ESI) 711/709 (M+H$^+$, 52/100%).

3.15 3-Bromo-*N*-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-6-(2-(6-chloroquinolin-2-yl)thiazol-4-yl)-5-methoxy-1-methyl-4-oxo-1,4-dihydropyridine-2-carboxamide

A stirred solution of *N*-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-6-[2-(6-chloroquinolin-2-yl)thiazol-4-yl]-5-methoxy-1-methyl-4-oxo-1,4-dihydropyridine-2-carboxamide **19** (3 mg, 4 µmol) and pyridinium tribromide (26 mg, 146 µmol) in pyridine (3 mL) was heated to reflux for 3 h. The mixture was concentrated *in vacuo* and purified by chromatography on silica eluting with 4% methanol in dichloromethane to give the title compound as an orange residue (3 mg, 99%); (Found: [M+H$^+$], 787.1179. $C_{38}H_{37}{}^{79}Br^{35}ClN_4O_4SSi^+$ requires 787.1172); ν_{max} ($CHCl_3$) 3008, 2960, 1673, 1592, 1489, 1144 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.62 (1H, br s), 8.28 (1H, d, *J* 8.6), 8.18 (1H, d, *J* 8.6), 8.10 (1H, d, *J* 9.1), 7.85 (1H, d, *J* 2.1), 7.73 (2H, dd, *J* 9.1), 7.67-7.70 (4H, m), 7.34-7.44 (6H, m), 3.96 (2H, t, *J* 4.9), 3.70 (3H, s), 3.65-3.69 (2H, m), 3.96 (3H, br s); 1.07 (1H, s); δ_C (75 MHz; $CDCl_3$) 169.3 (C), 161.9 (C), 150.7 (C), 149.1 (C), 147.0, (C), 146.1 (C), 145.2 (C), 144.7 (C), 141.0 (C), 136.4 (CH), 135.5 (CH), 134.8 (CH), 133.4 (C), 133.2 (C), 131.3

(CH), 131.0 (CH), 129.9 (CH), 129.6 (C), 129.3 (C), 127.9 (CH), 126.5 (CH), 118.5 (CH), 62.0 (CH_2), 60.0 (CH_3), 42.3 (CH_2), 40.4 (CH_3), 26.9 (CH_3), 19.2 (C); *m/z* (ESI) 787/788/789/790/791/792 ($M+H^+$, 29/13/39/20/16/7%).

3.16 *N*-(2-((*tert*-Butyldiphenylsiloxy)ethyl)-6-(2-(6-chloroquinolin-2-yl)thiazol-4-yl)-5-methoxy-1-methyl-3-(methylthio)-4-oxo-1,4-dihydropyridine-2-carboxamide 20

Sodium thiomethoxide (3 mg, 43 μmol) was added to a stirred suspension of 3-bromo-*N*-(2-((*tert*-butyldiphenylsiloxy)ethyl)-6-(2-(6-chloroquinolin-2-yl)thiazol-4-yl)-5-methoxy-1-methyl-4-oxo-1,4-dihydropyridine-2-carboxamide (3 mg, 4 μmol) in 1,4-dioxane (3 mL) and the mixture heated to 90 °C for 3 h. The mixture was concentrated *in vacuo* and partitioned between dichloromethane (5 mL) and water (3 mL), the aqueous phase was extracted with dichloromethane (3 × 5 mL) and the combined organic extracts washed with brine (3 mL), dried (Na_2SO_4), concentrated *in vacuo* and purified by chromatography on silica, eluting with dichloromethane-10% methanol in dichloromethane to give the title compound **20** as a yellow residue (1 mg, 33%); (Found: [$M+H^+$], 755.1922. $C_{39}H_{40}{}^{35}ClN_4O_4S_2Si^+$ requires 755.1944); ν_{max} ($CHCl_3$) 3002, 2956, 1661, 1592, 1262 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 8.30 (1H, d, *J* 8.6), 8.19 (1H, d, *J* 8.6), 8.11 (1H, d, *J* 9.1), 7.85 (1H, d, *J* 2.3), 7.81 (1H, s), 7.72 (1H, dd, *J* 9.1, 2.3), 7.65-7.70 (4H, m), 7.35-7.46 (6H, m), 3.96 (2H, t, *J*, 5.2), 3.75 (3H, s), 3.65 (2H, t, *J* 5.2), 3.46 (3H, s), 2.35 (3H, s), 1.08 (9H, s); δ_C (126 MHz; $CDCl_3$) 171.2 (C), 169.4 (C), 162.5 (C), 150.8 (C), 148.3 (C), 147.7 (C), 146.2 (C), 145.3 (C), 137.4 (C), 136.3 (CH), 135.5 (CH), 133.4 (CH), 133.1 (C), 131.3 (CH), 131.1 (CH), 130.0 (C), 129.3 (C), 127.9 (CH), 126.5 (CH), 125.8 (CH), 121.8 (C), 118.5 (CH), 62.1 (CH_2), 60.0 (CH_3), 42.3 (CH_2), 39.6 (CH_3), 26.9 (CH_3), 19.2 (C), 17.3 (CH_3); *m/z* (ESI) 755/757 ($M+H^+$, 42/25%). Data consistent with the literature.[10]

3.17 Lodopyridone 1

A solution of hydrogen fluoride pyridine complex in pyridine (30%, 0.1 mL, 1.50 mmol) was added to a stirred solution of *N*-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-6-(2-(6-chloroquinolin-2-yl)thiazol-4-yl)-5-methoxy-1-methyl-3-(methylthio)-4-oxo-1,4-dihydropyridine-2-carboxamide **20** (2 mg, 3 μmol) in pyridine (2 mL) and the mixture stirred for 2 h at room temperature. The mixture was quenched with saturated aqueous potassium carbonate solution (3 mL), concentrated *in vacuo* partitioned between dichloromethane (5 mL) and water (3 mL). The aqueous phase was extracted with dichloromethane (3 × 3 mL) and the combined organic extracts washed with brine, dried (Na_2SO_4), concentrated *in vacuo* and purified by chromatography on silica, eluting with 3-5% methanol in dichloromethane to give lodopyridone (**1**) as a colorless gum (1 mg, 99%); ν_{max} ($CHCl_3$) 3073, 2958, 2929, 2857, 1661, 1592, 1488, 1280, cm^{-1}; δ_H (500 MHz; $CDCl_3$) 8.63 (1H, br s) 8.24 (1H, d, *J* 8.6, CH) 8.11 (1H, d, *J* 8.6) 8.03 (1H, d, *J* 9.1) 7.79 (1H, s) 7.78 (1H, d, *J* 2.2) 7.69 (1H, dd, *J* 9.0, 2.4) 3.99 (2H, br s) 3.77 (3H, s) 3.72 (2H, br s) 3.57 (3H, s) 2.36 (3H, s); δ_C (126 MHz; $CDCl_3$) 172.3 (C), 169.5 (C), 162.5 (C), 150.7 (C), 149.8 (C), 147.6 (C), 146.1 (C), 144.9 (C), 138.6 (C), 136.3 (CH), 133.4 (C), 131.3 (CH), 131.0 (CH), 129.2 (C), 126.4 (CH), 125.8 (CH), 122.0 (C), 118.5 (CH), 61.4 (CH_2), 60.4 (CH_3), 43.2 (CH_2), 40.0 (CH_3), 18.0 (CH_3); δ_H (500 MHz; DMSO-d_6) 8.95 (1H, t, *J* 5.7) 8.55 (1H, d, *J* 8.5) 8.33 (1H, d, *J* 8.5) 8.27 (1H, s) 8.25 (1H, d, *J* 2.4) 8.13 (1H, d, *J* 9.0) 7.87 (1H, dd, *J* 9.0, 2.4) 4.73 (1H, t, *J* 5.0), 3.67 (3H, s) 3.54 (2H, br s) 3.36 (3H, s) 2.29 (3H, s); δ_C (126 MHz; DMSO-d_6) 170.9 (C), 168.5 (C), 161.9 (C), 150.6 (C), 149.1 (C), 147.0 (C), 145.6 (C), 145.2 (C), 137.5 (CH), 136.9 (CH), 132.0 (C), 131.3 (CH), 130.9 (CH), 129.2 (C), 127.0 (CH), 126.4 (CH), 119.9 (C), 118.4 (C), 59.3 (CH_3), 59.2 (CH_2), 41.7 (CH_2), 38.9 (CH_3), 16.2 (CH_3). Data consistent with the literature.[4]

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