Synthesis and Further Studies of Chemical Transformation of the 2-Aryl-3-halogenoquinolin-4(1*H*)-one Derivatives

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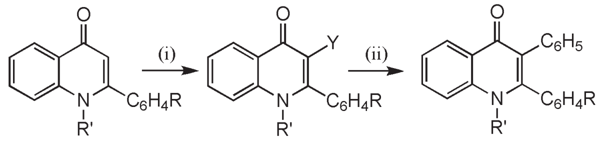

R = H, CH_3 Y = Br, I R' = CH_3

(i) $C_5H_5NHBr_3$, AcOH, r.t. for Y = Br; I_2, Na_2CO_3, THF, r.t. for Y = I.
(ii) $PhB(OH)_2$, $Pd(PPh_3)_4$, 2M Na_2CO_3, DMF, heat

The C-3 brominated and iodinated derivatives were prepared from the corresponding 2-arylquinolin-4(1*H*)-ones and their NMe-4-oxo derivatives using pyridinium tribromide in acetic acid or iodine-Na_2CO_3 mixture in THF. The results of further studies of chemical transformation of the prepared α-haloenones and preliminary antitumour activity of the 3-bromo NH-4-oxo and NMe-4-oxo derivatives are also described.

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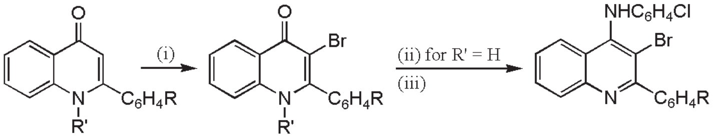
Introduction.

The 2-arylquinolin-4-ones and their quinoline derivatives continue to receive considerable attention in chemistry because of their wide range of pharmacological applications [1-4]. The 2-arylquinolin-4(1*H*)-one derivatives, for example, are known to exhibit antibacterial [1] and antitumour properties [2]. On the other hand, the *N*-substituted 2-arylquinoline derivatives serve as antimalarial agents, immunostimulants and non-nucleoside HIV-1 inhibitors [3,4]. In the course of our ongoing quinolin-4(1*H*)-one studies, we prepared analogues that are modified by changing the position of heteroatoms and the degree of unsaturation in the heterocyclic ring [5-8]. We are currently interested in the synthesis of halogenated quinolone derivatives because of the profound effect a halogen atom can have on the physical, chemical and biological properties of such systems [9]. The 2-arylquinolin-4(1*H*)-ones and their *N*-alkylated derivatives are close analogues of flavones and thioflavones which have been found to undergo C-3 halogenation using various halogenating reagents [10-15]. Whereas there is enormous data on the C-3 halogenation (X = Cl [10], Br [10c-15] or I [10c,15]) of flavones, thiochromones and thioflavones, to our knowledge, corresponding data for C-3 halogenation of the quinolin-4(1*H*)-one derivatives is considerably less documented [16]. Herein we report the results of C-3 halogenation of the 2-arylquinolin-4(1*H*)-ones and their NMe-4-oxo derivatives and further studies of chemical transformation and antitumour activity of these derivatives.

Results and Discussion.

Although the 2-aryl-3-bromoquinolin-4(1*H*)-ones and their NCH_3-4-oxo as well as O-methylquinoline derivatives have been prepared in our laboratory before [5,6], we sought to develop a new, high yield synthetic route that avoids those multiple steps. Pyridinium tribromide-pyridine mixture in dichloromethane has been used before for the C-3 bromination of flavones [11]. However, prolonged

Scheme 1



1 (R' = H); **1NMe** (R' = Me) **2** (R' = H); **2NMe** (R' = Me) **3**

Reagents and conditions: (i) $C_5H_5NHBr_3$, AcOH, r.t., 2h; (ii) $POCl_3$, Δ, 2h;
(iii) 4-Chloroaniline, EtOH, heat, 18h.

reaction times (6 – 48 hours), use of excess reagents and tedious workup presented limitations to these reaction conditions for the current investigation. We therefore explored the use of acetic acid in place of pyridine and subjected substrates **1** (R' = H) and **1NMe** (R' = CH_3) to pyridinium tribromide (2 equiv.) at room temperature. We isolated analytically pure products directly from the reaction mixture after 2 hours and they were found by NMR spectroscopy to correspond to the 3-bromo-4-quinolone **2** (R' = H) and their NCH_3-oxo derivatives **2NMe** (R' = CH_3). Their NMR (^1H and ^{13}C) spectral data are identical to those of the corresponding NH-4-oxo and NCH_3-4-oxo systems prepared by a different route described in our previous communications [5,6]. Due to the operational simplicity as well as easy isolation and purification procedures for the products, the methodology appears to be useful alternative to the pyridinium tribromide-pyridine mixture employed before for the C-3 bromination of flavones [11].

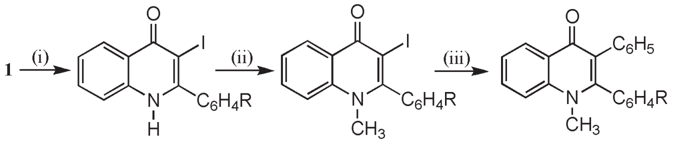
We have previously described the synthesis of the 4-amino-2-arylquinolines which were obtained by NaOEt–promoted Neber rearrangement of O-mesyloximes derived from the 2-aryl-1-methanesulfonyl-2,3-dihydroquinolin-4(1*H*)-ones [8]. However, the known nonbasic nature of amino group of the 4-amino-2-arylquinoline derivatives [17] prevented further derivatization to 4-*N*-substituted derivatives. In this investigation, we resorted to the application of an indirect method for the synthesis of *N*-substituted 2-aryl-3-halogenoquinoline derivatives. This procedure makes use of the known 2-aryl-3-bromo-4-chloroquinoline derivatives [5,6] and takes advantage of the easy displacement of the halogen atom at γ-position by the nucleophile. The previously described 2-aryl-3-bromo-4-chloroquinoline, which are prepared from the NH-4-oxo derivatives **2** and phosphoryl chloride under reflux [5,6] were subjected to 4-chloroaniline in refluxing ethanol to afford the corresponding hitherto unknown 2-aryl-4-(4'-chlorophenyl)aminoquinolines **3** (Scheme 1).

So far very limited methods have been reported for the C-3 iodination of flavone analogues [14,15]. Iodine–cerium(IV) ammonium nitrate [14] and *bis*(pyridine)iodonium(I) tetrafluoroborate (IPy_2BF_4) in dichloromethane [15] were employed previously for the C-3 iodination of thioflavone analogues. We required a simple method that employs readily available and easy-to-handle reagents for the iodination of substrates **1**. Attempted C-3 iodination of **1** using iodine (2 equiv.) in methanol under reflux for 3 days led to the recovery of the starting material. The 3-iodo NH-4-oxo derivatives **4** were obtained in high yields and purity by subjecting substrates **1** to iodine (2 equiv.) and sodium carbonate (1.5 equiv.) mixture in THF at room temperature or under reflux (Scheme 2). The 3-iodo NMe-4-oxo derivatives **4NMe** were, in turn, obtained in high yields (> 60%) and purity without the need for column chromatography by subjecting the corresponding 3-iodo NH-4-oxo derivatives **4** to NaH in THF at room temperature followed by quenching with iodomethane.

The α-haloenones derived from α,β-unsaturated carbonyl compounds provide an important functional group that could facilitate metal-catalyzed carbon-carbon bond formation [18-21]. The 3-haloflavones (X = Br, I), for example, have been found to undergo Suzuki coupling with aromatic boronic acids to yield 2,3-diarylbenzopyran derivatives with a pharmacophore for selective cyclooxygenase-2 inhibition [21]. Consequently, we subjected the 3-iodo derivatives **4NMe** to palladium-mediated coupling reaction with phenylboronic acid in DMF in the presence of 2 *M* sodium carbonate (aq) and isolated the corresponding 2,3-diaryl-4-quinolone derivatives **5** in moderate yields (Scheme 2).

In the last part of this investigation, we assayed varying concentrations (0.2, 0.4, 0.6, 0.8, 1.0, 1.2 µg/ml) of the NH-4-oxo **2** and NMe-4-oxo derivatives **2NMe** prepared in DMSO for potential antitumour activity against human bladder carcinoma cell line, T24. Compound **2c** shows increased activity at concentration of 1.2 µg/ml while **2b** induces proliferation of the tumour cells at doses below 1µg/ml. The NMe-4-oxo derivatives **2NMe**, on the other hand, showed no activity at all concentrations employed in this investigation. This evaluation of antitumour activity provides a preliminary screening for medicinal potential and future development.

Scheme 2



Reagents and conditions: (i) I_2, Na_2CO_3, THF, r.t., 12h; (ii) NaH, THF, MeI, r.t., 12h; (iii) $PhB(OH)_2$, $Pd(PPh_3)_4$, 2M Na_2CO_3 (aq), DMF, Δ, 18h.

EXPERIMENTAL

Melting points were recorded on a Thermocouple digital melting point apparatus and are uncorrected. IR spectra were recorded as powder using FTS 7000 Series Digilab Win-IR Pro spectrometer. NMR spectra were obtained as $CDCl_3$ or DMSO-d_6 solutions using Varian Mercury 300MHz NMR spectrometer and the chemical shifts are quoted relative to the solvent peaks. Low- and high-resolution mass spectra were recorded at an ionization potential of 70eV using Micromass Autospec-TOF (double focusing high resolution) instrument. Elemental (C, H, N) analysis were performed at the ARC Institute for Soil, Climate and Water (Pretoria). The synthesis and characterization of substrates (**1**) [7], (**1NMe**) [7] and the 2-aryl-3-bromo-4-chloroquinolines [5,6] have been described elsewhere.

C-3 Bromination of Compounds (**1**), R' = H.

General Procedure.

A stirred solution of **1** (1 equiv.) in acetic acid (5 ml per mmol of **1**) was treated with pyridinium tribromide (2 equiv.) at room temperature. The mixture was stirred at room temperature for 3 hours and then quenched with aqueous sodium thiosulphate. The precipitate was washed with ice-cold ethanol and dried *in vacuo* to afford pure (**2**) [5]. The following 2-aryl-3-bromoquinolin-4(1*H*)-one derivatives (**2**) were prepared: 3-bromo-2-phenylquinolin-4(1*H*)-one (**2a**) (80%); 3-bromo-2-(4'-fluorophenyl)quinolin-4(1*H*)-one (**2b**) (95%); 3-bromo-2-(4'-chlorophenyl)quinolin-4(1*H*)-one (**2c**) (87%) and 3-bromo-2-(4'-methoxyphenyl)quinolin-4(1*H*)-one (**2d**) (95%).

C-3 Bromination of the 2-Aryl-1-methylquinolin-4(1*H*)-ones (**1NMe**), R' = Me.

General Procedure.

A similar procedure applied to (**1**) was employed for the C-3 bromination of (**1NMe**), however, the mixture was quenched with ice-cold water and the precipitate was collected by filtration and taken-up into chloroform. The organic solution was washed sequentially with saturated sodium bicarbonate, aqueous sodium thiosulphate and brine. The organic solution was dried (Na_2SO_4), filtered and the solvent was evaporated under reduced pressure to afford analytically (^{1}H NMR and ^{13}C NMR data) pure products (**2NMe**) [5,6]. The following 2-aryl-3-bromo-1-methylquinolin-4(1*H*)-one derivatives were prepared: 3-bromo-1-methyl-2-phenylquinolin-4(1*H*)-one (**2aNMe**) (85%); 3-bromo-2-(4'-fluorophenyl)-1-methylquinolin-4(1*H*)-one (**2bNMe**) (90%); 3-bromo-2-(4'-chlorophenyl)-1-methylquinolin-4(1*H*)-one (**2cNMe**) (93%) and 3-bromo-2-(4'-methoxyphenyl)-1-methylquinolin-4(1*H*)-one (**2dNMe**) (70%).

Preparation of 2-Aryl-3-bromo-4-(4"-chlorophenyl)aminoquinolines (**3**).

General Procedure.

A stirred mixture of 2-aryl-3-bromo-4-chloroquinoline (1 equiv.) and 4-chloroaniline (5 equiv.) in ethanol (5 ml per mmol of quinoline) was boiled under reflux for 18 h. The mixture was allowed to cool to room temperature and then quenched with ice-cold water. The mixture was extracted with chloroform and the combined organic phases were washed with brine and then dried ($MgSO_4$). The salt was filtered off and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography to afford (**3**).

3-Bromo-4-(4"-chlorophenyl)amino-2-phenylquinoline (**3a**).

The reaction of 3-bromo-4-chloro-2-phenylquinoline with 4-chloroaniline in refluxing ethanol followed by column chromatography (4:1 Pet. ether-EtOAc, v/v) afforded (**3a**) as white solid (62%) m.p. 190 – 192 °C. ^{1}H NMR (300MHz, $CDCl_3$) δ 6.65 (1H, s), 6.83 (2H, d, J = 9.0 Hz), 7.21 (2H, d, J = 9.0 Hz), 7.33 (1H, dt, J = 0.9 and 7.8 Hz), 7.44 - 7.53 (3H, m), 7.62 - 7.71 (4H, m), 8.10 (1H, d, J = 8.1 Hz); ^{13}C NMR (75MHz, $CDCl_3$) δ 110.5, 120.3, 121.4, 124.5, 126.0, 127.8, 128.0, 128.7, 129.1, 129.3, 129.9, 130.1, 140.8, 142.0, 144.8, 147.6, 159.1; FT-IR (neat) ν_{max} 760.3, 809.6, 1394.5, 1487.9, 1573.4, 2924.2, 3379.3 cm^{-1}. HRMS (EI) calculated for $C_{21}H_{14}N_2{}^{35}Cl^{79}Br$: 408.0029. Found: 408.0029.

Anal. Calcd. for $C_{21}H_{14}N_2{}^{35}Cl^{79}Br$: C, 61.60; H, 3.44; N, 6.84. Found: C, 61.99; H, 3.46; N, 6.82.

3-Bromo-4-(4"-chlorophenyl)amino-2-(4'-fluorophenyl)quinoline (**3b**).

The reaction of 3-bromo-4-chloro-2-phenylquinoline with 4-chloroaniline in refluxing ethanol followed by column chromatography (4:1 Pet. ether-EtOAc, v/v) afforded (**3b**) as white solid (68%) m.p. 181 – 183 °C. ^{1}H NMR (300MHz, $CDCl_3$) δ 6.65 (1H, br s), 6.83 (2H, d, J = 9.0 Hz), 7.14 - 7.25 (4H, m), 7.33 (1H, dt, J = 1.2 and 8.4 Hz), 7.62 - 7.72 (4H, m), 8.08 (1H, d, J = 8.1 Hz); ^{13}C NMR (75MHz, $CDCl_3$) δ 110.2, 115.1 (d, $^2J_{CF}$ = 21.6 Hz), 120.3, 121.4, 124.5, 126.1, 127.9, 129.3, 130.0, 130.1, 131.2 (d, $^3J_{CF}$ = 8.3 Hz), 136.8 (d, $^4J_{CF}$ = 3.5 Hz), 142.0, 144.9, 147.5, 158.0, 163.0 (d, $^1J_{CF}$ = 246.5 Hz); FT-IR (neat) ν_{max} 767.7, 815.9, 1157.3, 1394.5, 1482.0, 1508.3, 1568.5, 3256.2 cm^{-1}. HRMS (EI) calculated for $C_{21}H_{13}N_2F^{35}Cl^{79}Br$: 425.9935 Found: 425.9935.

Anal. Calcd. for $C_{21}H_{13}N_2F^{35}Cl^{79}Br$: C, 58.97; H, 3.06; N, 6.55. Found: C, 59.15; H, 3.13; N, 6.50.

3-Bromo-2-(4'-chlorophenyl)-4-(4"-chlorophenyl)aminoquinoline (**3c**).

The reaction of 3-bromo-4-chloro-2-phenylquinoline with 4-chloroaniline in refluxing ethanol followed by column chromatography (4:1 Pet. ether-EtOAc, v/v) afforded (**3c**) as white solid (53%) m.p. 188 – 190 °C. ^{1}H NMR (300MHz, $CDCl_3$) δ 6.65 (1H, br s), 6.82 (2H, d, J = 9.0 Hz), 7.21 (2H, d, J = 9.0 Hz), 7.34 (1H, t, J = 7.5 Hz), 7.47 (2H, J = 8.4 Hz), 7.61 - 7.69 (4H, m), 8.07 (1H, d, J = 8.1 Hz); ^{13}C NMR (75MHz, $CDCl_3$) δ 109.9, 120.4, 121.4, 124.5, 126.1, 128.0, 128.3, 129.3, 130.0, 130.1, 130.7, 134.9, 139.1, 141.9, 145.0, 147.6, 157.8; FT-IR (neat) ν_{max} 762.6, 825.5, 1084.7, 1394.5, 1486.6, 1574.1, 3369.6 cm^{-1}. HRMS (EI) calculated for $C_{21}H_{13}N_2{}^{35}Cl_2{}^{79}Br$: 441.9935 Found: 441.9935.

Anal. Calcd. for $C_{21}H_{13}N_2{}^{35}Cl_2{}^{79}Br$: C, 56.79; H, 2.95; N, 6.31. Found: C, 56.97; H, 3.28; N, 5.94.

3-Bromo-4-(4"-chlorophenyl)amino-2-(4'-methoxyphenyl)quinoline (**3d**).

The reaction of 3-bromo-4-chloro-2-phenylquinoline with 4-chloroaniline in refluxing ethanol followed by column chromatography (4:1 Pet. ether-EtOAc, v/v) afforded (**3d**) as white solid (52%) m.p. 192 – 194 °C. ^{1}H NMR (300MHz, $CDCl_3$) δ 3.87 (3H, s), 6.62 (1H, br s), 6.81 (2H, d, J = 8.4 Hz), 7.01 (2H, d, J = 8.4 Hz), 7.20 (2H, d, J = 9.0 Hz), 7.31 (1H, dt, J = 0.9 and 8.9 Hz), 7.61 - 7.69 (4H, m), 8.08 (1H, d, J = 8.7 Hz*)*; ^{13}C NMR (75MHz, CDCl$_3$) δ 55.3, 110.8, 113.4, 120.1, 121.4, 124.5, 125.8, 127.7, 129.3, 129.8, 130.1, 130.8, 133.2, 142.1, 144.7, 147.6, 158.7, 160.0; FT-IR (neat) ν_{max} 767.7, 824.2, 1178.5, 1240.2, 1394.2, 1486.5, 1573.0, 1600.1, 2928.8, 3378.0 cm^{-1}. HRMS (EI) calculated for $C_{22}H_{16}N_2O^{35}Cl^{79}Br$: 438.0135. Found: 438.0135.

Anal. Calcd. for $C_{22}H_{16}N_2O^{35}Cl^{79}Br$: C, 60.09; H, 3.67; N, 6.37. Found: C, 59.83; H, 6.10; N, 3.30.

C-3 Iodination of the 2-Arylquinolin-4(1*H*)-ones (**1**).

General Procedure.

A stirred mixture of (**1**) (1 equiv.), iodine (2 equiv.) and sodium carbonate (1.5 equiv.) in THF (5 ml per mmol of **1**) was stirred at room temperature for 18 hours. The mixture was quenched with sodium thiosulphate and the precipitate was collected by filtration and washed with ice-cold water. The following products **4** were prepared:

3-Iodo-2-phenylquinolin-4(1*H*)-one (**4a**).

The crude product was recrystallised to afford (**4a**) as white solid (85%) m.p. 284 – 286 °C (EtOH). ^{1}H NMR (300MHz, DMSO-d_6) δ 7.40 (1H, t, J = 8.1 Hz), 7.57 (5H, s), 7.84 - 7.73 (2H, m), 8.14 (1H, d, J = 8.1 Hz) and 12.30 (1H, s); ^{13}C NMR (75MHz, DMSO-d_6) δ 85.9, 118.3, 122.9, 124.2, 125.5, 128.4, 129.0, 129.8, 132.2, 137.9, 139.3, 153.1, 173.6; FT-IR (neat) ν_{max} 755.6, 869.7, 1468.3, 1539.5, 1566.2, 1624.8, 1673.9, 3361.9 cm^{-1}; MS (EI) m/z (%) = 347 [M$^+$] (86), 220 (62), 165 (36), 131 (62), 69 (100), 28 (96). HRMS (EI) calculated for $C_{15}H_{10}NOI$: 346.9807. Found: 346.9807.

Anal. Calcd. for $C_{15}H_{10}NOI$: C, 51.89; H, 2.90; N, 4.03. Found: C, 51.28; H, 3.20; N, 3.85.

2-(4'-Fluorophenyl)-3-iodoquinolin-4(1*H*)-one (**4b**).

The crude product was recrystallised to afford (**4b**) as white solid (83%) m.p. 196 – 198 °C (EtOH). ^{1}H NMR (300MHz, DMSO-d_6) δ 7.40 - 7.50 (3H, m), 7.65 - 7.72 (4H, m), 8.14 (1H, d, J = 7.8 Hz), 12.33 (1H, s); ^{13}C NMR (75MHz, DMSO-d_6) δ 86.2, 115.3 (d, $^{2}J_{CF}$ = 21.9 Hz), 118.6, 121.0, 124.2, 125.5, 131.6 (d, $^{3}J_{CF}$ = 8.6 Hz), 132.1, 134.6 (d, $^{4}J_{CF}$ = 3.2 Hz), 139.6, 152.4, 162.7 (d, $^{1}J_{CF}$ = 245.3 Hz), 173.5; FT-IR (neat) ν_{max} 754.7, 818.0, 1157.8, 1224.8, 1466.3, 1535.3, 1601.8, 1622.1, 3414.4 cm^{-1}; MS (EI) m/z (%) = 365 [M$^+$] (89), 238 (42), 69 (88), 28 (100). HRMS (EI) calculated for $C_{15}H_9NOFI$: 364.9713. Found: 364.9713.

Anal. Calcd. for $C_{15}H_9NOFI$: C, 49.34; H, 2.48; N, 3.84. Found: C, 49.30; H, 3.00; N, 3.71.

2-(4'-Chlorophenyl)-3-iodoquinolin-4(1*H*)-one (**4c**).

The crude product was recrystallised to afford (**4c**) as white solid (92%) m.p. 254 – 256 °C (EtOH). ^{1}H NMR (300MHz, DMSO-d_6) δ 7.40 (1H, t, J = 7.2 Hz), 7.58 - 7.73 (6H, m), 8.13 (1H, d, J = 7.8 Hz), 12.4 (1H, s); ^{13}C NMR (75MHz, DMSO-d_6) δ 86.0, 118.4, 120.9, 124.4, 125.6, 128.5, 131.1, 132.3, 134.7, 136.7, 139.3, 152.1, 173.6; FT-IR (neat) ν_{max} 758.6, 995.7, 1090.0, 1539.5, 1626.2, 3401.0 cm^{-1}; MS (EI) m/z (%) = 381 [M$^+$] (70), 254 (32), 69 (31) and 28 (100). HRMS (EI) calculated for $C_{15}H_9NO^{35}ClI$: 380.9417. Found: 380.9417.

Anal. Calcd. for $C_{15}H_9NO^{35}ClI$: C, 47.21; H, 2.38; N, 3.67. Found: C, 47.37; H, 2.31; N, 3.62.

3-Iodo-2-(4'-methoxyphenyl)quinolin-4(1*H*)-one (**4d**).

The crude product was recrystallised to afford (**4d**) as white solid (80%) m.p. 262 – 264 °C (EtOH). ^{1}H NMR (300MHz, DMSO-d_6) δ 3.84 (3H, s), 7.10 (2H, d, J = 8.7 Hz), 7.37 (1H, t, J = 7.2 Hz), 7.51 (2H, d, J = 8.4 Hz), 7.63 - 7.68 (2H, m), 8.12 (1H, d, J = 8.4 Hz), 12.30 (1H, s); ^{13}C NMR (75MHz, DMSO-d_6) δ 55.4, 86.2, 113.6, 118.3, 120.8, 124.1, 125.5, 130.2, 130.6, 132.1, 139.3, 152.9, 160.3, 173.6; FT-IR (neat) ν_{max} 759.8, 1024.2, 1253.6, 1544.3, 1608.6, 1624.1, 3390.7 cm^{-1}; MS (EI) m/z (%) = 377 [M$^+$] (100), 250 (37), 69 (28), 28 (72). HRMS (EI) calculated for $C_{16}H_{12}NO_2I$: 376.993. Found: 376.9913.

Anal. Calcd. for $C_{16}H_{12}NO_2I$: C, 50.95; H, 3.21; N, 3.71. Found: C, 50.51; H, 3.60; N, 3.39.

N-Methylation of the 2-Aryl-3-iodoquinolin-4(1*H*)-ones (**4**).

General Procedure.

A stirred suspension of 3-iodo derivative (**4**) (1 equiv.) in dry THF (5 mL per mmol of **4**) was treated with NaH (1.5 equiv.) at room temperature under nitrogen atmosphere. After 30 minutes, the mixture was treated with iodomethane (1.5 equiv.) and stirring was continued for 2 hours at room temperature and the mixture was quenched with cold water. The product was extracted with chloroform, washed with brine and dried (MgSO$_4$). The solvent was evaporated to afford analytically pure (**4NMe**).

3-Iodo-1-methyl-2-phenylquinolin-4(1*H*)-one (**4aNMe**).

The crude product was recrystallised to afford (**4aNMe**) as white solid (65%) m.p. 227 – 229 °C (EtOH). ^{1}H NMR (300MHz, CDCl$_3$) δ 3.57 (3H, s), 7.26 (2H, dd, J = 2.0 and 7.7 Hz), 7.43 (1H, dt, J = 0.9 and 7.6 Hz), 7.50 -7.56 (4H, m), 7.71 (1H, dt, J = 1.5 and 7.9 Hz), 8.53 (1H, dd, J = 1.5 and 8.1 Hz); δ_C (75MHz, CDCl$_3$) 39.2, 89.2, 115.6, 122.9, 124.4, 127.9, 128.2, 129.2, 129.7, 132.6, 139.4, 140.7, 155.2, 174.1; FT-IR (neat) ν_{max} 750.3, 1074.3, 1394.5, 15245.4, 1593.0, 1616.3 cm^{-1}; MS (EI) m/z (%) = 361 [M$^+$] (100), 234 (49). HRMS (EI) calculated for $C_{16}H_{12}NOI$: 360.9964. Found: 360.9964.

Anal. Calcd. for $C_{16}H_{12}NOI$: C, 53.21; H, 3.35; N, 3.89. Found: C, 53.28; H, 3.59; N, 3.93.

2-(4'-Fluorophenyl)-3-iodo-1-methylquinolin-4(1*H*)-one (**4bNMe**).

The crude product was recrystallised to afford (**4bNMe**) as white solid (88%) m.p. 211 - 213°C (EtOH). ^{1}H NMR (300MHz, CDCl$_3$) δ 3.56 (3H, s), 7.21 - 7.26 (4H, m), 7.42 (1H, t, J = 7.5 Hz), 7.50 (1H, d, J = 8.2 Hz), 7.69 (1H, dt, J = 1.8 and 7.9 Hz) and 8.67 (1H, dd, J = 1.5 and 8.1 Hz); δ_C (75MHz, CDCl$_3$) 39.2, 89.7, 115.7, 116.5 (d, $^{2}J_{CF}$ = 21.9 Hz), 122.9, 124.6, 127.8, 130.4 (d, $^{3}J_{CF}$ = 8.3 Hz), 132.7, 135.4 (d, $^{4}J_{CF}$ = 3.7 Hz), 140.7, 154.2, 163.1 (d, $^{1}J_{CF}$ = 249.3 Hz), 174.0; FT-IR (neat) ν_{max} 765.7, 859.6, 1217.9, 1488.7, 1589.0, 1612.6 cm^{-1}; MS (EI) m/z (%) = 379 [M$^+$] (100), 252 (51). HRMS (EI) calculated for $C_{16}H_{11}NOFI$: 378.9870. Found: 378.9869.

Anal. Calcd. for $C_{16}H_{11}NOFI$: C, 50.68; H, 2.92; N, 3.69. Found: C, 50.68; H, 3.06; N, 3.68.

2-(4'-Chlorophenyl)-3-iodo-1-methylquinolin-4(1*H*)-one (**4cNMe**).

The crude product was recrystallised to afford (**4cNMe**) as white solid (75%) m.p. 246 – 248 °C (EtOH). ^{1}H NMR (300MHz, CDCl$_3$) δ 3.56 (3H, s), 7.24 (2H, dd, J = 1.8 and 7.6

Hz), 7.42 (1H, dt, J = 0.9 and 7.5 Hz), 7.52 (1H, d, J = 8.1 Hz), 7.55 (2H, dd, J = 1.2 and 7.8 Hz), 7.72 (1H, dt, J = 1.8 and 7.8 Hz), 8.53 (1H, dd, J = 1.5 and 8.1 Hz); δ_C (75MHz, $CDCl_3$) 39.2, 89.3, 115.6, 122.9, 124.7, 127.9, 129.6, 129.8, 132.8, 135.9, 137.6, 140.7, 154.0, 174.0; FT-IR (neat) ν_{max} 767.7, 860.2, 1153.6, 1396.5, 1482.4, 1590.1, 1613.6 cm^{-1}; MS (EI) m/z (%) = 397 (25), 395 [M$^+$] (91), 268 (43), 28 (100). HRMS (EI) calculated for $C_{16}H_{11}NO^{35}ClI$: 394.9574. Found: 394.9574.

Anal. Calcd. for $C_{16}H_{11}NO^{35}ClI$: C, 48.58; H, 2.88; N, 3.54. Found: C, 49.05; H, 2.98; N, 3.53.

3-Iodo-2-(4'-methoxyphenyl)-1-methylquinolin-4(1*H*)-one (**4dNMe**).

The crude product was recrystallised to afford (**4dNMe**) as white solid (73%) m.p. 192 – 194 °C (EtOH). ^{1}H NMR (300MHz, $CDCl_3$) δ 3.66 (3H, s), 3.96 (3H, s), 7.13 (2H, d, J = 8.7 Hz), 7.26 (2H, d, J = 8.7 Hz), 7.50 (1H, dt, J = 0.9 and 7.4 Hz), 7.60 (1H, d, J = 8.7 Hz), 7.78 (1H, dt, J = 1.8 and 7.8 Hz), 8.60 (1H, dd, J = 0.9 and 7.9 Hz); δ_C (75.0MHz, $CDCl_3$) 39.2, 55.4, 90.0, 114.5, 115.7, 122.9, 124.4, 127.9, 129.7, 131.8, 132.6, 140.8, 155.3, 160.4, 174.2; FT-IR (neat) ν_{max} 762.3, 1248.2, 1502.4, 1590.3, 1614.4 cm^{-1}; MS (EI) m/z (%) = 265 [M$^+$] (100), 237 (34), 222 (26), 51 (53), 28 (58). HRMS (EI) calculated for $C_{17}H_{14}NO_2I$: 391.038. Found: 391.029.

Anal. Calcd. for $C_{17}H_{14}NO_2I$: C, 52.19; H, 3.61; N, 3.58. Found: C, 52.31; H, 4.00; N, 3.57.

Palladium Catalyzed Cross-coupling Reactions of (**4NMe**).

General Procedure.

A stirred mixture of β-haloenone (**4NMe**) (1 equiv.), phenylboronic acid (2 equiv.) and $Pd(PPh_3)_4$ (5% of β-haloenone) in a two-necked flask equipped with a stirrer bar, rubber septum and a condenser was flushed with nitrogen gas. The flask was filled through a syringe with DMF (5 ml per mmol of β-haloenone) and aqueous 2 *M* Na_2CO_3 (2 ml per mmol of β-haloenone). The mixture was boiled under reflux for 18 hours and then cooled to room temperature. The mixture was poured into ice-cold water and the precipitate was taken-up into chloroform, washed with brine, dried and evaporated to afford **5**.

1-Methyl-2,3-diphenylquinolin-4(1*H*)-one (**5a**).

The residue was recrystallised from ethanol to afford (**5a**) as white solid (58%) m.p. 241 – 243 °C (EtOH). ^{1}H NMR (300MHz, $CDCl_3$) δ 3.53 (3H, s), 7.00 - 7.26 (10H, m), 7.42 (1H, t, J = 7.8 Hz), 7.56 (1H, d, J = 8.4 Hz), 7.71 (1H, dt, J = 1.5 and 7.8 Hz), 8.57 (1, dd, J = 1.2 and 8.0 Hz); ^{13}C NMR (75MHz, $CDCl_3$) δ 37.6, 115.7, 123.5, 124.2, 126.0, 126.6, 127.3, 127.4, 128.3, 128.7, 129.5, 131.3, 132.2, 135.0, 135.7, 141.3, 152.0, 176.2; FT-IR (neat) ν_{max} 700.5, 752.9, 1317.4, 1477.5, 1496.8, 1569.5, 1585.5, 1614.4 cm^{-1}. MS (EI) m/z (%) = 311 [M$^+$] (92), 310 (100), 294 (53), 262 (43). HRMS (EI) calculated for $C_{22}H_{17}NO$: 311.1310. Found: 311.1310.

Anal. Calcd. for $C_{22}H_{17}NO$: C, 84.86; H, 5.50; N, 4.49. Found: C, 85.00; H, 5.40; N, 4.44.

2-(4'-Fluorophenyl)-1-methyl-3-phenylquinolin-4(1*H*)-one (**5b**).

The residue was recrystallised to afford (**5b**) as white solid (52%) m.p. 284 – 286 °C (EtOH). ^{1}H NMR (300MHz, $CDCl_3$) δ 3.53 (3H, s), 7.00 - 7.15 (6H, m), 7.26 (3H, m), 7.42 (1H, t, J = 7.8 Hz), 7.55 (1H, d, J = 8.4 Hz), 7.72 (1H, dt, J = 1.3 and 8.6 Hz), 8.55 (1H, dd, J = 1.2 and 8.1 Hz); ^{13}C NMR (75MHz, $CDCl_3$) δ 37.6, 115.4 (d, $^2J_{CF}$ = 21.7 Hz), 115.8, 123.6, 124.5, 126.2, 126.6, 127.3, 127.5, 131.0 (d, $^4J_{CF}$ = 3.4 Hz), 131.2, 131.5 (d, $^3J_{CF}$ = 8.3 Hz), 132.3, 135.6, 141.3, 150.9, 162.4 (d, $^1J_{CF}$ = 248.4 Hz), 176.2; FT-IR (neat) ν_{max} 760.0, 1216.6, 1317.4, 1489.4, 1587.4, 1659.7 cm^{-1}; MS (EI) m/z (%) = 345 [M$^+$] (100), 328 (43.0), 77 (25). HRMS (EI) calculated for $C_{22}H_{16}NOF$: 329.1216. Found: 329.1216.

Anal. Calcd. for $C_{22}H_{16}NOF$: C, 80.22; H, 4.89; N, 4.25. Found: C, 80.30; H, 4.91; N, 4.08.

2-(4'-Chlorophenyl)-1-methyl-3-phenylquinolin-4(1*H*)-one (**5c**).

The residue was recrystallised from ethanol to afford (**5c**) as white solid (74%) m.p. 267 – 269 °C (EtOH). ^{1}H NMR (300MHz, $CDCl_3$) δ 3.53 (3H, s), 7.01 (2H, d, J = 7.2 Hz), 7.05 - 7.16 (5H, m), 7.26 (2H, d, J = 8.4 Hz), 7.44 (1H, t, J = 7.5 Hz), 7.56 (1H, d, J = 8.7 Hz), 7.73 (1H, dt, J = 1.5 and 7.8 Hz), 8.56 (1H, dd, J = 1.5 and 8.0 Hz); ^{13}C NMR (75MHz, $CDCl_3$) δ 37.6, 115.7, 123.7, 124.4, 126.3, 126.5, 127.3, 127.6, 128.7, 130.9, 131.2, 132.4, 133.4, 134.8, 135.4, 141.4, 150.7, 176.2; FT-IR (neat) ν_{max} 758.4, 1070.4, 1308.9, 1476.0, 1572.0, 1590.5, 1615.1 cm^{-1}; MS (EI) m/z (%) = 345 [M$^+$] (60.5), 344 (95.5), 28 (100). HRMS (EI) calculated for $C_{22}H_{16}NO^{35}Cl$: 345.0920. Found: 345.0921.

Anal. Calcd. for $C_{22}H_{16}NO^{35}Cl$: C, 76.41; H, 4.66; N, 4.05. Found: C, 76.58; H, 4.86; N, 4.08.

2-(4'-Methoxyphenyl)-2-phenyl-1-methylquinolin-4(1*H*)-one (**5d**).

The residue was recrystallised to afford (**5d**) as white solid (63%) m.p. 266 – 268 °C (EtOH). ^{1}H NMR (300MHz, DMSO-d_6) δ 3.49 (3H, s), 3.69 (3H, s), 6.74 (2H, d, J = 9.0 Hz), 6.91 - 7.06 (7H, m), 7.35 (1H, dt, J = 1.2 and 7.5 Hz), 7.62 (1H, d, J = 7.8 Hz), 7.69 (1H, dt, J = 1.2 and 8.4 Hz), 8.32 (1H, dd, J = 1.2 and 8.0 Hz); ^{13}C NMR (75MHz, DMSO-d_6) δ 37.2, 54.6, 113.2, 116.1, 122.9, 123.3, 125.3, 125.8, 125.9, 126.6, 126.8, 130.5, 130.9, 131.7, 136.0, 140.9, 151.7, 158.9, 175.0; FT-IR (neat) ν_{max} 768.1, 1244.1, 1320.1, 1489.9, 1566.2, 1587.7, 1603.1 cm^{-1}; MS (EI) m/z (%) = 341 [M$^+$] (49.0), 340 (72.5), 28 (100). HRMS (EI) calculated for $C_{23}H_{19}NO_2$: 341.1416. Found: 341.1415.

Anal. Calcd. for $C_{23}H_{19}NO_2$: C, 80.92; H, 5.61; N, 6.84. Found: C, 81.19; H, 5.79; N, 4.33.

Cell Culture.

Human bladder carcinoma cell line, T24 was incubated at a 37 °C in a humidified atmosphere containing 5% CO_2 in air. Cells were maintained in Dubelco's minimum essential medium (Lab Specialist Services, SA), supplemented with 10% Fetal Bovine Serum (Highveld Biologicals, SA). No antibiotics were used and cells from stock flasks were stained with 0.2 % Trypan blue to determine viable cells.

Cell Viability.

Cells were seeded in 24-well culture plates at a density of 20 000 cells per well. After 24 hours cells were exposed to varying concentrations of test compounds (0.2, 0.4, 0.6, 0.8, 1.0, 1.2 μg/ml) prepared in DMSO so that the final concentration of DMSO in the medium did not exceed 0.67% and the control cells were exposed to 0.67% DMSO. Growth was terminated after 48 hours by fixation with 1% glutaraldehyde. Crystal violet was used to stain the nucleus. The chromophore was extracted and results were analyzed following literature procedure [22]. Absorbances of the samples were read at 570nm on an ELx 800 Universal Microplate Reader. Three wells were analyzed for each concentration and the growth studies were repeated for each test agent.

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