$^1$H NMR Spectrum: ($DMSOd_6$) 1.55 (s, 9H); 1.95 (m, 2H); 2.15 (m, 2H); 2.50 (m, 4H); 2.60 (t, 2H); 2.85 (t, 2H); 3.75 (m, 6H); 4.05 (s, 3H); 4.30 (t, 2H); 7.00 (m, 2H); 7.35 (s, 1H); 7.55 (s, 1H); 7.80 (d, 1H); 8.65 (s, 1H)

**Example 193**

Using an analogous procedure to that described in Example 192, 4-(1-*tert*butoxycarbonyl-2,3-dihydro-indol-5-yloxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline (169 mg, 0.32 mmol) was reacted with TFA (1 ml) to give, after work-up and purification, **4-(2,3-dihydro-1*H*-indol-5-yl)oxy-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline** (124 mg, 91%).

$^1$H NMR Spectrum: ($CDCl_3$) 1.90 (br, 4H); 2.30 (br, 2H); 2.70 (br d, 6H); 3.10 (t, 2H); 3.65 (t, 2H); 4.05 (s, 3H); 4.30 (t, 2H); 6.70 (d, 1H); 6.80 (dd, 1H); 7.00 (s, 1H); 7.30 (s, 1H); 7.55 (s, 1H); 8.65 (s, 1H)

MS (ESI) : 421 $[MH]^+$

*166166*

The starting material was prepared as follows:

5-Hydroxyindole (2 g, 15 mmol) was dissolved in methanol (60 ml) under argon. Sodium cyanoborohydride (1.89 g, 30 mmol) and trifluoroboron etherate (4.2 ml, 33 mmol) were added and the mixture was heated at reflux for 3 hours then left to cool to ambient temperature. The solvent was evaporated and the residue was partitioned between ethyl acetate and water. Ammonia was added to adjust the pH to 10 and the aqueous phase was extracted with more ethyl acetate. The combined organic phases were washed with water, brine, dried ($MgSO_4$), filtered and the solvent evaporated. The residue was purified by flash chromatography using dichloromethane/methanol (95/5) as solvent. Evaporation of the solvent gave 5-hydroxy-2,3-dihydro-1*H*-indole (1.45 g, 73%) as an off white solid.

$^1$H NMR Spectrum: ($DMSOd_6$+ TFA) 3.15 (t, 2H); 3.70 (t, 2H); 6.75 (dd, 1H); 6.85 (d, 1H); 7.30 (d, 1H)

5-Hydroxy-2,3-dihydro-1*H*-indole (1.5 g, 11.1 mmol) was suspended in a mixture of acetone (7 ml) trichloromethane (7 ml) and THF (6 ml). *tert*-Butoxycarbonylanhydride (2.42 g, 11 mmol) in solution in THF (7 ml) was added dropwise. The reaction mixture was stirred overnight at ambient temperature, the solvent was evaporated, the residue was partitioned between ethyl acetate and water, the organic phase was washed with water, brine, dried

($MgSO_4$), filtered and the solvent evaporated. The solid was purified by flash chromatography using dichloromethane/methanol (95/5) as solvent. Evaporation of the solvent gave 5-hydroxy-(1-*tert*butoxycarbonyl)-2,3-dihydroindole (2.28 g, 87%) as an off white solid.

$^1$H NMR Spectrum: ($CDCl_3$) 3.05 (t, 2H); 3.95 (br s, 2H); 4.70 (br s, 1H); 6.60 (d, 1H); 6.65 (s, 1H); 7.70 (br s, 1H)

Sodium hydride (22 mg, 0.56 mmol) was suspended in anhydrous dimethylformamide under argon. 5-Hydroxy-(1-*tert*butoxycarbonyl)-2,3-dihydroindole (131 mg, 0.56 mmol) was added followed 10 minutes later by 4-chloro-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline (150 mg, 0.47 mmol), (prepared as described for the starting material in Example 9). The reaction mixture was heated at 110 °C for 3 hours, cooled to ambient temperature and partitioned between ethyl acetate and water. The organic phase was washed with water, brine, dried ($MgSO_4$), filtered and the solvent evaporated. The residue was purified by flash chromatography using increasingly polar solvent mixtures starting with dichloromethane/methanol (90/10) and ending with dichloromethane/methanol/methanol saturated with ammonia (80/15/5). Evaporation of the solvent gave 4-(1-*tert*butoxycarbonyl-2,3-dihydro-indol-5-yloxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline (178 mg, 73%) as a white solid.

$^1$H NMR Spectrum: ($DMSOd_6$) 1.60 (s, 9H); 1.80 (m, 4H); 2.20 (m, 2H); 2.55 (m, 4H); 2.70 (t, 2H); 3.15 (t, 2H); 4.05 (br s, 5H); 4.30 (t, 2H); 7.00 (d, 1H); 7.05 (s, 1H); 7.30 (s, 1H); 7.55 (s, 1H); 7.90 (br s, 1H); 8.60 (s, 1H)

**Example 194**

Using an analogous procedure to that described in Example 192, 4-(1-*tert*butoxycarbonyl-2,3-dihydro-indol-5-yloxy)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (191 mg, 0.37 mmol) was reacted with TFA (1 ml) to give, after work-up and purification, **4-(2,3-dihydro-indol-5-yloxy)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline** (103 mg, 67%).

$^1$H NMR Spectrum: ($CDCl_3$) 1.65 (m, 2H); 2.00 (m, 3H); 2.25 (m, 2H); 2.45 (s, 3H); 3.10 (m, 4H); 3.65 (t, 2H); 4.05 (s, 3H); 4.10 (d, 2H); 6.70 (d, 1H); 6.85 (dd, 1H); 7.0 (s, 1H); 7.25 (s, 1H); 7.55 (s, 1H); 8.60 (s, 1H)

MS (ESI) : 421 $[MH]^+$

The starting material was prepared as follows:

Using an analogous procedure to that described in Example 193, 4-chloro-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (150 mg, 0.47 mmol), (prepared as described for the starting material in Example 10), was reacted with 5-hydroxy-(1-*tert*butoxycarbonyl)-2,3-dihydroindole (132 mg, 0.56 mmol), (prepared as described for the starting material in Example 193), to give, after work-up and purification, 4-(1-*tert*butoxycarbonyl-2,3-dihydro-indol-5-yloxy)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (197 mg, 81%) as a white solid.

$^1$H NMR Spectrum: ($CDCl_3$) 1.50 (br s, 11H); 2.00 (m, 5H); 2.30 (s, 3H); 2.90 (d, 2H); 3.15 (t, 2H); 4.05 (br s, 7H); 7.05 (br s, 2H); 7.30 (s, 1H); 7.55 (s, 1H); 7.95 (br s, 1H); 8.60 (s, 1H)

**Example 195**

To a suspension of 4-chloro-6-methoxy-7-(2-piperidinoethoxy)quinazoline (250mg, 0.78mmol), (prepared as described for the starting material in Example 180), in DMF (10ml) was added anhydrous potassium carbonate (320mg, 2.30mmol) and 7-hydroxyquinoline (135mg, 0.94mmol), and the reaction heated under reflux at 90C for 1 hour. The reaction was cooled to ambient temperature and 1N aqueous sodium hydroxide added. The resulting precipitate was filtered, washed with water and acetone, and dried under suction to give **6-methoxy-7-(2-piperidinoethoxy)-4-(quinolin-7-yloxy)quinazoline** (248mg, 0.58mmol, 75%) as a white solid.

$^1$H NMR Spectrum: $d_H$ (300MHz, $CDCl_3$): 1.5 (2H, m; $NCH_2CH_2C\underline{H}_2$), 1.6 (4H, m; 2 x $NCH_2C\underline{H}_2$), 2.6 (4H, t; 2 x $NC\underline{H}_2$); 2.9 (2H, t; $NC\underline{H}_2$), 4.1 (3H, s; $OC\underline{H}_3$), 4.3 (2H, t; $OC\underline{H}_2$), 7.3 (1H, s; Ar$\underline{H}$), 7.4 (1H, dd; Ar$\underline{H}$), 7.5 (1H, dd; Ar$\underline{H}$), 7.6 (1H, s; Ar$\underline{H}$), 7.9 (1H, d; Ar$\underline{H}$), 8.0 (1H, d; Ar$\underline{H}$), 8.2 (1H, d; Ar$\underline{H}$), 8.6 (1H, s; Ar$\underline{H}$) and 8.9 (1H, dd; Ar$\underline{H}$)

*m/z* (ESP+) 431 ($MH^+$, 100%)

**Example 196**

To a suspension of 7-benzyloxy-4-chloro-6-methoxyquinazoline (1.82g, 6.1mmol), (prepared as described for the starting material in Example 1), in DMF (50ml) was added potassium carbonate (2.50g, 18.1mmol) and 7-hydroxyquinoline (1.06g, 7.3mmol), and the reaction heated under reflux at 90C for 4 hours. The reaction was poured into 1N aqueous

sodium hydroxide and the resulting precipitate filtered, washed with water, and dried under suction. Further drying in a vacuum oven gave **7-benzyloxy-6-methoxy-4-(quinolin-7-yloxy)quinazoline** (1.50g, 3.7mmol, 60%) as a cream solid.

$^1$H NMR Spectrum: $d_H$ (300MHz, DMSO-$d_6$): 4.0 (3H, s; OC$\underline{H}_3$), 5.4 (2H, s; OC$\underline{H}_2$), 7.3-7.7 (9H, m; 9 x Ar$\underline{H}$), 7.9 (1H, br s; Ar$\underline{H}$), 8.1 (1H, d; Ar$\underline{H}$), 8.4 (1H, d; Ar$\underline{H}$), 8.5 (1H, s; Ar$\underline{H}$) and 8.9 (1H, d; Ar$\underline{H}$)

**Example 197**

A solution of 7-benzyloxy-6-methoxy-4-(quinolin-7-yloxy)quinazoline (1.50g, 3.70mmol), (prepared as described in Example 196), in trifluoroacetic acid (50ml) was heated at reflux for 150 minutes. The reaction was concentrated *in vacuo* and the reaction neutralised with saturated aqueous ammonium hydroxide. The resulting precipitate was filtered, washed with acetone and dried under suction to give **7-hydroxy-6-methoxy-4-(quinolin-7-yloxy)quinazoline** (0.90g, 2.82mmol, 76%) as a white solid.

$^1$H NMR Spectrum: $d_H$ (300MHz, DMSO-$d_6$): 4.0 (3H, s; OC$\underline{H}_3$), 7.1 (1H, s; Ar$\underline{H}$), 7.3-7.4 (3H, m; 3 x Ar$\underline{H}$), 7.9 (1H, br s; Ar$\underline{H}$), 8.1 (1H, d; Ar$\underline{H}$), 8.4-8.5 (2H, d; 2 x Ar$\underline{H}$) and 8.9 (1H, d; Ar$\underline{H}$)

*m/z* (ESP+) 320 ($MH^+$, 100%)

**Example 198**

To a suspension of 7-hydroxy-6-methoxy-4-(quinolin-7-yloxy)quinazoline (450mg, 1.40mmol), (prepared as described in Example 197), in DMF (50ml) was added anhydrous potassium carbonate (773mg, 5.60mmol) and 4-(2-hydroxyethyl)morpholine (335mg, 1.80mmol), and the reaction heated under reflux for 2 hours. The DMF was evaporated *in vacuo*, and the residue partitioned between dichloromethane and 1N aqueous sodium hydroxide. The mixture was extracted with dichloromethane (3 x 200ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was triturated with hexane/ether to afford a solid which was filtered and dried under suction to give **6-methoxy-7-(2-morpholinoethoxy)-4-(quinolin-7-yloxy)quinazoline** (430mg, 1.00mmol, 71%) as a light brown solid.

$^1$H NMR Spectrum: $d_H$ (300MHz, $CDCl_3$): 2.7 (4H, t; 2 x NC$\underline{H}_2$); 3.0 (2H, t; NC$\underline{H}_2$), 3.7 (4H, t; 2 x OC$\underline{H}_2$), 4.1 (3H, s; OC$\underline{H}_3$), 4.4 (2H, t; OC$\underline{H}_2$), 7.2 (1H, s; Ar$\underline{H}$), 7.4 (1H, dd; Ar$\underline{H}$), 7.5

(1H, dd; ArH), 7.6 (1H, s; ArH), 7.9 (1H, d; ArH), 8.0 (1H, br s; ArH), 8.2 (1H, d; ArH), 8.6 (1H, s; ArH) and 8.9 (1H, dd; ArH)

*m/z* (ESP+) 433 ($MH^+$, 100%)

| | | | | | |
|---|---|---|---|---|---|
| Elemental analysis | Found | C 65.0 | H 5.6 | N 12.6 | |
| $C_{24}H_{24}N_4O_4$ $0.5H_2O$ | Requires | C 65.3 | H 5.7 | N 12.7% | |

**Example 199**

To a solution of 7-hydroxy-6-methoxy-4-(quinolin-7-yloxy)quinazoline (100mg, 0.31mmol), (prepared as described in Example 197), and (*S*)-(+)-5-(hydroxymethyl)-2-pyrrolidinone (101mg, 0.47mmol) in dichloromethane (10ml) was added triphenylphosphine (244mg, 0.93mmol) and DEAD (0.15ml, 162mg, 0.93mmol), and the reaction stirred at ambient temperature overnight. The reaction mixture was placed directly onto a 2g SCX ion-exchange column, and eluted with dichloromethane, then dichloromethane/methanol (4/1), then dichloromethane/methanol/ammonium hydroxide (20/5/1). The appropriate fractions were concentrated *in vacuo*, and the residue triturated with ether to give a solid which was filtered and dried under suction to give **(5*S*)-6-methoxy-7-(5-oxo-pyrrolidin-2-ylmethoxy)-4-(quinolin-7-yloxy)quinazoline** (55mg, 0.13mmol, 43%) as a yellow solid.

$^1$H NMR Spectrum: $d_H$ (300MHz, $CDCl_3$): 2.3-2.5 (4H, m; 2 x pyrrolidinone-C$H_2$), 4.0-4.1 (4H, m; pyrrolidinone-CH; OC$H_3$), 4.2-4.3 (2H, m; OC$H_2$), 6.1 (1H, br s; NH), 7.3 (1H, s; ArH), 7.4 (1H, dd; ArH), 7.5 (1H, dd; ArH), 7.9 (1H, d; ArH), 8.0 (1H, br s; ArH), 8.2 (1H, d; ArH), 8.6 (1H, s; ArH) and 8.9 (1H, dd; ArH)

*m/z* (ESP+) 417 ($MH^+$, 100%)

**Example 200**

To a solution of 4-chloro-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline (100mg, 0.31mmol), (prepared as described for the starting material in Example 9), in DMF (10ml) was added potassium carbonate (124mg, 0.9mmol, 3eq.) followed by 2-hydroxycarbazole (66mg, 0.36mmol, 1.2eq.) and the reaction heated at 100°C for 4 hours. The DMF was removed *in vacuo*, the residue dissolved in dichloromethane and placed onto a 2g SCX ion-exchange column. Elution with dichloromethane, followed by 20% methanol/dichloromethane then 20% methanol/dichloromethane + 3% ammonium hydroxide, gave the crude product as a brown solid. Further purification by silica bond elut

chromatography eluting with dichloromethane to 15% methanol/dichloromethane + 1% ammonium hydroxide, followed by trituration with ether gave **4-(9*H*-carbazol-2-yloxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline** (31mg, 22%) as a white solid.

$^1$H NMR Spectrum: $d_H$ (300MHz, DMSO-$d_6$) 1.7 (4H, m; 2 x pyrrolidine-C$\underline{H}_2$), 2.0 (2H, t; $OCH_2C\underline{H}_2$), 2.5 (4H, m; 2 x pyrrolidine-NC$\underline{H}_2$), 2.6 (2H, t; NC$\underline{H}_2$), 4.0 (3H, s; OC$\underline{H}_3$), 4.2 (2H, t; OC$\underline{H}_2$), 7.1 (1H, br d; Ar$\underline{H}$), 7.2 (1H, t; Ar$\underline{H}$), 7.3-7.4 (3H, m; 3 x Ar$\underline{H}$), 7.5 (1H, br d; Ar$\underline{H}$), 7.6 (1H, s; Ar$\underline{H}$), 8.1-8.2 (2H, m; 2 x Ar$\underline{H}$), 8.5 (1H, s; Ar$\underline{H}$), 11.3 (1H, s; carbazole N$\underline{H}$)

*m/z* (ESP+) 469 ($MH^+$, 100%)

**Example 201**

To a solution of 7-hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline (98 mg, 0.32 mmol), 2-((N-(3,6-dichloropyridazin-4-yl)-N-methyl)amino)ethanol (107 mg, 0.48 mmol), (prepared as described for the starting material in Example 142), triphenylphosphine (168 mg, 0.64 mmol) in methylene chloride (1 ml) and DMF (0.5 ml) cooled at 4°C was added a solution of diethyl azodicarboxylate (101 µl, 0.64 mmol) in methylene chloride (0.4 ml). The mixture was stirred for 12 hours at 4°C and overnight at ambient temperature. The precipitate was filtered, washed with ether and dried under vacuum to give**7-(2-((N-(3,6-dichloropyridazin-4-yl)-N-methyl)amino)ethoxy)-4-(indol-5-ylamino)-6-methoxyquinazoline** (72 mg, 44 %).

MS-ESI : 510-512 $[MH]^+$

$^1$H NMR Spectrum: ($DMSOd_6$) 3.12 (s, 3H) ; 3.85 (s, 3H) ; 4.1 (t, 2H) ; 4.45 (t, 2H) ; 6.45 (s, 1H) ; 7.2 (s, 1H) ; 7.3 (s, 1H) ; 7.35 (m, 2H) ; 7.42 (d, 1H) ; 7.8 (s, 1H) ; 7.85 (s, 1H) ; 8.35 (s, 1H) ; 9.45 (s, 1H)

The starting material was prepared as follows :

A solution of 7-benzyloxy-4-chloro-6-methoxyquinazoline (5g, 16.6 mmol), (prepared as described for the starting material in Example 1), 5-aminoindole (2.4 g, 18.2 mmol) in isopropanol (60 ml) containing 5N hydrogen chloride in isopropanol (260 µl, 1.6 mmol) was refluxed for 90 minutes. After cooling the volatiles were removed under vacuum. The solid was triturated with isopropanol, filtered, washed with isopropanol followed by ether and dried

under vacuum to give 7-benzyloxy-4-(indol-5-ylamino)-6-methoxyquinazoline hydrochloride (6.9g, 96%).

$^1$H NMR Spectrum: ($DMSOd_6$) 4.05 (s, 3H) ; 5.35 (s, 2H) ; 6.5 (s, 1H) ; 7.3 (d, 1H) ; 7.4-7.65 (m, 9H) ; 7.8 (s, 1H) ; 8.3 (s, 1H) ; 8.7 (s, 1H)

A solution of give 7-benzyloxy-4-(indol-5-ylamino)-6-methoxyquinazoline hydrochloride (10g, 23.1 mmol) in methanol (300ml) and DMF (100ml) containing ammonium formate (22gr, 347 mmol) and 10% palladium on charcoal (1g) was stirred overnight at ambient temperature. The solution was filtered over celite and washed with DMF followed by methanol. The filtrate was evaporated. The residue was dissolved in aqueous ammonia 2mM (300ml) and stirred for 15 minutes. The solid was filtered, washed with water followed by ethyl acetate and ether and dried under vacuum at 50°C for 2 days. The solid was purified by column chromatography eluting with methanol/methylene chloride (1/9). The volatiles were removed under vacuum and the solid was left under vacuum at 70°C for 2 days to give 7-hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline (6.8 g, 97%)

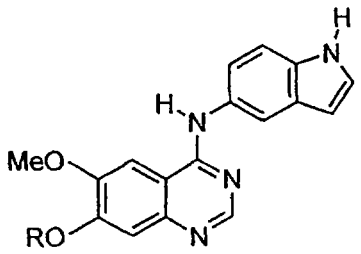
MS-ESI : 307 [MH]+

$^1$H NMR Spectrum: ($DMSOd_6$) 3.98 (s, 3H) ; 6.42 (s, 1H) ; 7.0 (s, 1H) ; 7.3-7.45 (m, 3H) ; 7.85 (s, 2H) ; 8.28 (s, 1H) ; 9.35 (s, 1H) ; 10.25 (br s, 1H) ; 11.05 (s, 1H)

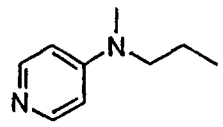
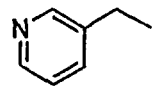
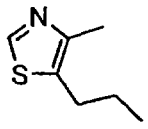
**Examples 202–204**

Using an analogous procedure to that described in Example 201, 7-hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline, (prepared as described for the starting material in Example 201), was used in the synthesis of the compounds described in Table XI.

**Table XI**




| Example number | Weight (mg) | Yield % | MS-ESI $[MH]^+$ | Note | R |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| 202 | 83 | 59 | 441 | a |  |
| 203 | 91 | 72 | 398 | b |  |
| 204 | 76 | 55 | 432 | c |  |

a) 7-Hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline was reacted with 2-(N-methyl-N-(4-pyridyl)amino)ethanol (73mg), (EP 0359389), to give **4-(indol-5-ylamino)-6-methoxy-7-(2-(N-methyl-N-(4-pyridyl)amino)ethoxy)quinazoline**.

$^1$H NMR Spectrum: ($DMSOd_6$) 3.08 (s, 3H) ; 3.9 (t, 2H) ; 3.95 (s, 3H) ; 4.35 (t, 2H) ; 6.45 (s, 1H) ; 6.75 (d, 2H) ; 7.15 (s, 1H) ; 7.35 (m, 2H) ; 7.4 (d, 1H) ; 7.85 (s, 1H) ; 7.9 (s, 1H) ; 8.15 (d, 2H) ; 8.38 (s, 1H) ; 9.45 (s, 1H)

b) 7-Hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline was reacted with 3-hydroxymethyl pyridine (53 mg) to give **4-(indol-5-ylamino)-6-methoxy-7-((3-pyridyl)methoxy)quinazoline**.

$^1$H NMR Spectrum: ($DMSOd_6$) 4.0 (s, 3H) ; 5.35 (s, 2H) ; 6.42 (s, 1H) ; 7.3-7.55 (m, 5H) ; 7.8-8.0 (m, 3H) ; 8.4 (s, 1H) ; 8.6 (d, 1H) ; 8.75 (s, 1H) ; 9.5 (s, 1H)

c) 7-Hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline was reacted with 5-(2-hydroxyethyl)-4-methylthiazole (69 mg) to give **4-(indol-5-ylamino)-6-methoxy-7-(2-(4-methyl-1,3-thiazol-5-yl)ethoxy)quinazoline**.

$^1$H NMR Spectrum: ($DMSOd_6$) 2.45 (s, 3H) ; 3.32 (t, 2H) ; 3.95 (s, 3H) ; 4.32 (t, 2H) ; 6.45 (s, 1H) ; 7.15 (s, 1H) ; 7.3-7.45 (m, 3H) ; 7.85 (s, 1H) ; 7.9 (s, 1H) ; 8.35 (s, 1H) ; 8.85 (s, 1H) ; 9.45 (s, 1H)

**Example 205**

To a solution of 7-hydroxy-6-methoxy-4-(2-methylindol-5-ylamino)quinazoline (102 mg, 0.32 mmol), 4-(3-hydroxypropyl)morpholine (70 mg, 0.48 mmol), (prepared as described for the starting material in Example 60), triphenylphosphine (168 mg, 0.64 mmol) in methylene chloride (1 ml) and DMF (0.5 ml) cooled at 4°C was added a solution of diethyl azodicarboxylate (101 µl; 0.64 mmol) in methylene chloride (0.4 ml). The mixture was stirred for 12 hours at 4°C and overnight at ambient temperature. The mixture was poured onto a column of silica (IST isolute ® 10 g of silica) and was eluted with methylene chloride (15 ml) followed by 5 % methanol in methylene chloride (45 ml) followed by 5 % methanol (saturated with ammonia) in methylene chloride (30 ml) followed by 10 % methanol (saturated with ammonia) in methylene chloride (45 ml) followed by 15 % methanol (saturated with ammonia) in methylene chloride (30 ml). The fractions containing the expected product were evaporated to give **6-methoxy-4-(2-methylindol-5-ylamino)-7-(3-morpholinopropoxy)quinazoline** (63 mg, 44 %).

MS-ESI : 448 $[MH]^+$

$^1H$ NMR Spectrum: ($DMSOd_6$) 2.0 (m, 2H) ; 2.4 (s, 3H) ; 2.3-2.6 (m, 6H) ; 3.6 (t, 4H) ; 3.95 (s, 3H) ; 4.2 (t, 2H) ; 6.12 (s, 1H) ; 7.12 (s, 1H) ; 7.3 (br s, 2H) ; 7.7 (s, 1H) ; 7.85 (s, 1H) ; 8.35 (s, 1H) ; 9.4 (s, 1H)

The starting material was prepared as follows:

A solution of 2-methyl-5-nitroindole (1 g, 5.7 mmol) in ethanol (25ml) and THF (25 ml) containg 10% palladium on charcoal (128mg) was hydrogenated until uptake of hydrogen ceased. The mixture was filtered and the filtrate was evaporated to give 5-amino-2-methylindole (830 mg, quant.).

$^1H$ NMR Spectrum: ($DMSOd_6$) 2.3 (s, 3H) : 4.3 (br s, 2H) ; 5.8 (s, 1H) ; 6.35 (d, 1H) ; 6.55 (s, 1H) ; 6.95 (d, 1H) ; 10.35 (br s, 1H)

Using an analogous procedure to that described for the synthesis of the starting material in Example 201, 7-benzyloxy-4-chloro-6-methoxyquinazoline (2 g, 6.6 mmol), (prepared as described for the starting material in Example 1), was reacted with 5-amino-2-methylindole (1.07g, 7.3 mmol) to give 7-benzyloxy-6-methoxy-4-(2-methylindol-5-ylamino)quinazoline hydrochloride (2.9 g, quanti.).

MS-ESI : 411 [MH]+

$^1$H NMR Spectrum: ($DMSOd_6$) 2.41 (s, 3H) ; 4.01 (s, 3H) ; 5.33 (s, 2H) ; 6.18 (s, 1H) ; 7.25 (d, 1H) ; 7.3-7.7 (m, 8H) ; 8.3 (s, 1H) ; 8.7 (s, 1H) ; 11.1 (s, 1H) ; 11.4 (s, 1H)

Using an analogous procedure to that described for the synthesis of the starting material in Example 201, 7-benzyloxy-6-methoxy-4-(2-methylindol-5-ylamino)quinazoline hydrochloride (2.87g, 6.4 mmol) was reacted with ammonium formate (6g, 9.6 mmol) to give 7-hydroxy-6-methoxy-4-(2-methylindol-5-ylamino)quinazoline (1.91g, 93%).

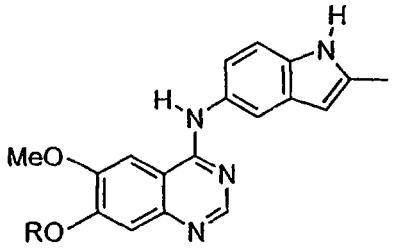
MS-ESI : 321 [MH]+

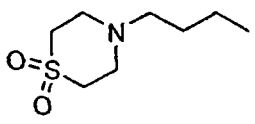
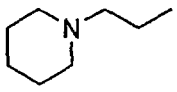
$^1$H NMR Spectrum: ($DMSOd_6$) 2.4 (s, 3H) ; 3.95 (s, 3H) ; 6.12 (s, 1H) ; 7.0 (s, 1H) ; 7.25 (s, 1H) ; 7.7 (s, 1H) ; 7.85 (s, 1H) ; 8.3 (s, 1H) ; 9.35 (s, 1H) ; 10.2 (br s, 1H) ; 10.9 (s, 1H)

**Examples 206–207**

Using an analogous procedure to that described for Example 205, 7-hydroxy-6-methoxy-4-(2-methylindol-5-ylamino)quinazoline, (prepared as described for the starting material in Example 205), was used in the synthesis of the compounds described in Table XII.

**Table XII**




| Example Number | Weight (mg) | Yield % | MS-ESI $[MH]^+$ | Note | R |
|---|---|---|---|---|---|
| 206 | 65 | 41 | 496 | a |  |
| 207 | 62 | 45 | | b |  |

a) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-ylamino)quinazoline (98 mg) was reacted with 3-(1,1-dioxothiomorpholino)-1-propanol (93 mg), (prepared as described for the starting

material in Example 5), to give **7-(3-(1,1-dioxothiomorpholino)propoxy)-6-methoxy-4-(2-methylindol-5-ylamino)quinazoline.**

$^1$H NMR Spectrum: ($DMSOd_6$) 2.0 (m, 2H) ; 2.4 (s, 3H) ; 2.7 (t, 2H) ; 2.95 (m, 4H) ; 3.15 (m, 4H) ; 3.95 (s, 3H) ; 4.2 (t, 2H) ; 6.15 (s, 1H) ; 7.18 (s, 1H) ; 7.28 (m, 2H) ; 7.7 (s, 1H) ; 7.85 (s, 1H) ; 8.35 (s, 1H) ; 9.4 (s, 1H)

b) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-ylamino)quinazoline (98 mg) was reacted with 1-(2-hydroxyethyl)piperidine (62 mg) to give **6-methoxy-4-(2-methylindol-5-ylamino)-7-(2-piperidinoethoxy)quinazoline.**

$^1$H NMR Spectrum: ($DMSOd_6$) 1.4 (m, 2H) ; 1.45-1.6 (m, 4H) ; 2.42 (s, 3H) ; 2.45 (br s, 4H) ; 2.75 (t, 2H) ; 3.95 (s, 3H) ; 4.25 (t, 2H) ; 6.15 (s, 1H) ; 7.15 (s, 1H) ; 7.25 (br s, 2H) ; 7.7 (s, 1H) ; 7.88 (s, 1H) ; 8.35 (s, 1H) ; 9.4 (s, 1H)

**Example 208**

Using an analogous procedure to that described in Example 205, 7-hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline (98 mg, 0.32 mmol), (prepared as described for the starting material in Example 201), was reacted with 3-(1,2,3-triazol-1-yl)propan-1-ol (61 mg, 0.48 mmol) to give **4-(indol-5-ylamino)-6-methoxy-7-(3-(1,2,3-triazol-1-yl)propoxy)quinazoline** (56 mg, 42 %).

MS-ESI : 416 $[MH]^+$

$^1$H NMR Spectrum: ($DMSOd_6$) 2.4 (m, 2H) ; 4.0 (s, 3H) ; 4.2 (t, 2H) ; 4.65 (t, 2H) ; 6.45 (s, 1H) ; 7.15 (s, 1H) ; 7.35 (m, 2H) ; 7.42 (d, 1H) ; 7.75 (s, 1H) ; 7.88 (s, 1H) ; 7.9 (s, 1H) ; 8.2 (s, 1H) ; 8.38 (s, 1H) ; 9.42 (s, 1H)

The starting material was prepared as follows:

A mixture of 1,2,3-triazole (5g, 72.4 mmol) and ethyl acrylate (7.8 ml, 72.4 mmol) containing pyridine (50 drops) was heated at 90$^0$C for 4 hours. After cooling, the volatiles were removed under vacuum and the residue was purified by column chromatography eluting with methylene chloride/ether to give ethyl (1*H*-1,2,3-triazol-1-yl)propanoate (8.96g, 73%).

$^1$H NMR Spectrum: ($CDCl_3$) 1.25 (t, 3H) ; 2.95 (t, 2H) ; 4.15 (q, 2H) ; 4.7 (t, 2H) ; 7.65 (s, 1H) ; 7.7 (s, 1H)

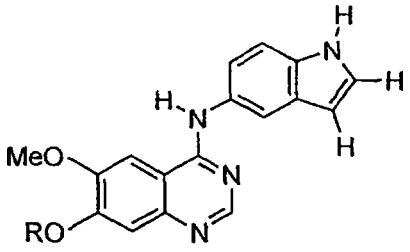
A solution of ethyl (1*H*-1,2,3-triazol-1-yl)propanoate (8.96g, 53 mmol) in THF (50ml) was added dropwise to a suspension of lithium aluminium hydride (3 g, 79 mmol) in THF (250ml) cooled at 0°C. After stirring for 1 hour at 5°C, the mixture was stirred for 1 hour at ambient temperature. The mixture was cooled at 0°C and 4N sodium hydroxide (30ml) was added dropwise. The mixture was filtered and the solid was washed with THF followed by ethyl acetate. The filtrate was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography, eluting with methylene chloride/methanol (94/6) to give 3-(1,2,3-triazol-1-yl)propan-1-ol (6.2 g, 92%).

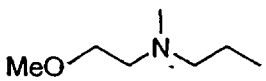
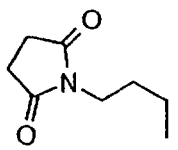
$^1$H NMR Spectrum: ($CDCl_3$) : 2.1-2.2 (m, 3H) ; 3.65 (m, 2H) ; 4.6 (t, 2H) ; 7.6 (s, 1H) ; 7.72 (s, 1H)

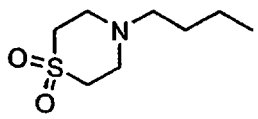
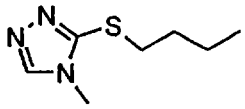
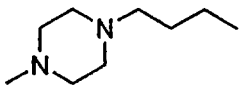
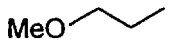
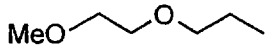
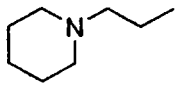
**Examples 209–216**

Using an analogous procedure to that described in Example 208, 7-hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline, (prepared as described for the starting material in Example 201), was used in the synthesis of the compounds described in Table XIII.

**Table XIII**




| Example Number | Weight (mg) | Yield % | MS-ESI $[MH]^+$ | Note | R |
|---|---|---|---|---|---|
| 209 | 77 | 57 | 422 | a |  |
| 210 | 64 | 45 | 446 | b |  |

| | | | | | |
|---|---|---|---|---|---|
| 211 | 76 | 49 | 482 | c |  |
| 212 | 70 | 48 | 462 | d |  |
| 213 | 85 | 59 | 447 | e |  |
| 214 | 62 | 54 | 365 | f |  |
| 215 | 71 | 54 | 409 | g |  |
| 216 | 73 | 55 | 418 | h |  |

a) 7-Hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline (98 mg) was reacted with 2-(N-(2-methoxyethyl)-N-methylamino)ethanol (64 mg), (prepared as described for the starting material in Example 59), to give **4-(indol-5-ylamino)-6-methoxy-7-(2-(N-(2-methoxyethyl)-N-methylamino)ethoxy)quinazoline**.

$^1$H NMR Spectrum: ($DMSOd_6$) 2.35 (s, 3H) ; 2.68 (t, 2H) ; 2.82 (t, 2H) ; 3.25 (s, 3H) ; 3.5 (t, 2H) ; 3.97 (s, 3H) ; 4.22 (t, 2H), 6.45 (s, 1H) ; 7.18 (s, 1H) ; 7.3-7.45 (m, 3H) ; 7.88 (m, 2H) ; 8.35 (s, 1H) ; 9.42 (s, 1H)

b) 7-Hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline (98 mg) was reacted with 1-(3-hydroxypropyl)pyrrolidin-2,5-dione (76 mg) to give **7-(3-(2,5-dioxopyrrolidin-1-yl)propoxy)-4-(indol-5-ylamino)-6-methoxyquinazoline**.

$^1$H NMR Spectrum: ($DMSOd_6$) 2.05 (m, 2H) ; 2.65 (s, 3H) ; 3.6 (t, 2H) ; 3.98 (s, 2H) ; 4.15 (t, 2H) ; 6.45 (s, 1H) ; 7.1 (s, 1H) ; 7.3-7.45 (m, 3H) ; 8.7 (s, 1H) ; 8.8 (s, 1H) ; 8.35 (s, 1H) ; 9.45 (s, 1H)

The starting material was prepared as follows:

A solution of pyrrolidine-2,5-dione (5g, 50.5 mmol) and 3-bromopropan-1-ol (6.85 ml, 76 mmol) in acetonitrile (80ml) contaning potassium carbonate (14g, 100 mmol) was refluxed overnight. After cooling, the mixture was filtered and the filtrate was evaporated. The residue was dissolved in methylene chloride and purified by column chromatography, eluting with ethylacetate/petroleum ether (4/1). After evaporation of the volatiles, the residue was distilled at 100-125°C under about 0.1 mm Hg to give 1-(3-hydroxypropyl)pyrrolidin-2,5-dione (2.6 g, 34%).

$^1$H NMR Spectrum: ($CDCl_3$) 1.8 (m, 2H) ; 2.52 (t, 1H) ; 2.78 (s, 4H) ; 3.58 (q, 2H) ; 3.7 (t, 2H)

c) 7-Hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline (98 mg) was reacted with 3-(1,1-dioxothiomorpholino)-1-propanol (93mg), (prepared as described for the starting material in Example 5), to give **7-(3-(1,1-dioxothiomorpholino)propoxy)-4-(indol-5-ylamino)-6-methoxyquinazoline**.

$^1$H NMR Spectrum: ($DMSOd_6$) 2.0 (m, 2H) ; 2.7 (t, 2H) ; 2.95 (br s, 4H) ; 3.15 (br s, 4H) ; 3.97 (s, 3H) ; 4.2 (t, 2H) ; 6.45 (s, 1H) ; 7.2 (s, 1H) ; 7.3-7.5 (m, 3H) ; 7.9 (2s, 2H) ; 8.35 (s, 1H) ; 9.42 (s, 1H)

d) 7-Hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline (98 mg) was reacted with 3-((4-methyl-4*H*-1,2,4-triazol-3-yl)sulphanyl)propan-1-ol (83 mg) to give **4-(indol-5-ylamino)-6-methoxy-7-(3-((4-methyl-4*H*-1,2,4-triazol-3-yl)sulphanyl)propoxy)quinazoline**.

$^1$H NMR Spectrum: ($DMSOd_6$) 2.22 (m, 2H) ; 3.3 (m, 2H) ; 3.65 (s, 3H) ; 3.95 (s, 3H) ; 4.25 (t, 2H) ; 6.45 (s, 1H) ; 7.15 (s, 1H) ; 7.3-7.45 (m, 3H) ; 7.88 (s, 1H) ; 8.0 (s, 1H) ; 8.35 (s, 1H) ; 8.58 (s, 1H) ; 9.45 (s, 1H)

The starting material was prepared as follows:

A solution of 4-methyl-4-*H*-1,2,4-triazole-3-thiol (1.72g, 15 mmol) and 3-bromopropan-1-ol (1.39g, 10 mmol) in DMF (10ml) containing potassium carbonate (1.57g, 14 mmol) was heated at 40°C for 30 minutes. The mixture was then partitioned between saturated ammonium chloride and ethyl acetate. The aqueous layer was evaporated to dryness and the residue was triturated with ethyl acetate and methylene chloride. The suspension was

filtered and the filtrate was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography eluting with methylene chloride/methanol (9/1) to give 3-((4-methyl-4*H*-1,2,4-triazol-3-yl)sulphanyl)propan-1-ol (510mg , 30%).

$^1$H NMR Spectrum: ($CDCl_3$) 2.02 (m, 2H) ; 3.45 (t, 2H) ; 3.55 (s, 3H) ; 3.75 (t, 2H) ; 8.15 (s, 1H)

e) 7-Hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline (98 mg) was reacted with 1-(3-hydroxypropyl)-4-methylpiperazine (76 mg), (prepared as described for the starting material in Example 133), to give **4-(indol-5-ylamino)-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline**.

$^1$H NMR Spectrum: ($DMSOd_6$) 2.0 (m, 2H) ; 2.2 (s, 3H) ; 2.25-2.55 (m, 10H) ; 4.0 (s, 3H) ; 4.2 (t, 2H) ; 6.45 (s, 1H) ; 7.15 (s, 1H) ; 7.35 (m, 2H) ; 7.42 (d, 1H) ; 7.88 (br s, 2H) ; 8.38 (s, 1H) ; 9.42 (s, 1H)

f ) 7-Hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline (98 mg) was reacted with 2-methoxyethanol (37 mg) to give **4-(indol-5-ylamino)-6-methoxy-7-(2-methoxyethoxy)quinazoline**.

$^1$H NMR Spectrum: ($DMSOd_6$) 3.4 (s, 3H) ; 3.75 (t, 2H) ; 3.98 (s, 3H) ; 4.38 (t, 2H) ; 6.45 (s, 1H) ; 7.18 (s, 1H) ; 7.35 (m, 2H) ; 7.42 (d, 1H) ; 7.85 (s, 1H) ; 7.9 (s, 1H) ; 8.38 (s, 1H) ; 9.5 (s, 1H)

g) 7-Hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline (98 mg) was reacted with 2-(2-methoxyethoxy)ethanol (58 mg) to give **4-(indol-5-ylamino)-6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)quinazoline**.

$^1$H NMR Spectrum: ($DMSOd_6$) 3.3 (s, 3H) ; 3.5 (t, 2H) ; 3.65 (t, 2H) ; 3.85 (t, 2H) ; 4.0 (s, 3H) ; 4.28 (t, 2H) ; 6.45 (s, 1H) ; 7.18 (s, 1H) ; 7.35 (m, 2H) ; 7.45 (d, 1H) ; 7.88 (s, 1H) ; 7.9 (s, 1H) ; 8.35 (s, 1H) ; 9.45 (s, 1H)

h) 7-Hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline (98 mg) was reacted with 1-(2-hydroxyethyl)piperidine (62 mg) to give **4-(indol-5-ylamino)-6-methoxy-7-(2-piperidinoethoxy)quinazoline**.

$^1$H NMR Spectrum: ($DMSOd_6$) 1.3-1.6 (m, 6H) ; 2.5 (br s, 4H) ; 2.7 (t, 2H) ; 3.98 (s, 3H) ; 4.25 (t, 2H) ; 6.45 (s, 1H) ; 7.18 (s, 1H) ; 7.35 (m, 2H) ; 7.42 (d, 1H) ; 7.9 (br s, 2H) ; 8.38 (s, 1H) ; 9.42 (s, 1H)

**Example 217-223**

Using an analogous procedure to that described in Example 205, 7-hydroxy-4-(indol-6-ylamino)-6-methoxyquinazoline was used in the synthesis of the compounds described in Table XIV.

The starting material was prepared as follows:

Using an analogous procedure to that described for the preparation of the starting material in Example 201, 6-nitroindole (500mg, 3 mmol) was hydrogenated to give 6-aminoindole (395mg, quant.).

$^1$H NMR Spectrum: ($DMSOd_6$) 6.41 (s, 1H) ; 6.6 (dd, 1H) ; 6.63 (s, 1H) ; 7.0 (t, 1H) ; 7.4 (d, 1H) ; 7.87 (br s, 1H)

Using an analogous procedure to that described for the preparation of the starting material in Example 201, 7-benzyloxy-4-chloro-6-methoxyquinazoline (2.5 g, 8.3 mmol), (prepared as described for the starting material in Example 1), was reacted with 6-aminoindole (1.5g, 11.4 mmol) to give 7-benzyloxy-4-(indol-6-ylamino)-6-methoxyquinazoline hydrochloride (3.18g, 89%).

MS-ESI : 397 [MH]+

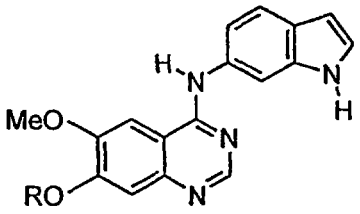
$^1$H NMR Spectrum: ($DMSOd_6$) 4.02 (s, 3H) ; 5.35 (s, 2H) ; 6.5 (s, 1H) ; 7.25 (dd, 1H) ; 7.35-7.6 (m, 5H) ; 7.63 (d, 1H) ; 7.72 (s, 1H) ; 8.3 (s, 1H) ; 8.75 (s, 1H) ; 11.3 (br s, 1H)

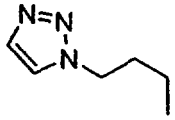
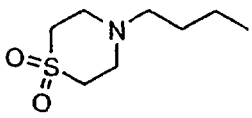
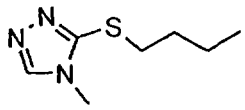
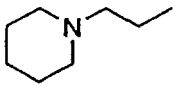
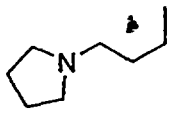
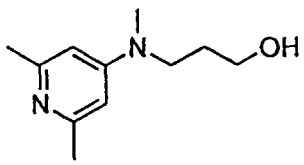
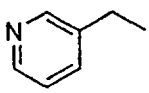
Using an analogous procedure to that described for the preparation of the starting material in Example 201, 7-benzyloxy-4-(indol-6-ylamino)-6-methoxyquinazoline hydrochloride was treated with ammonium formate (655mg, 10.4 mmol) to give 7-hydroxy-4-(indol-6-ylamino)-6-methoxyquinazoline (162 mg, 76%).

MS-ESI : 307 [MH]+

$^1$H NMR Spectrum: ($DMSOd_6$) 4.0 (s, 3H) ; 6.4 (s, 1H) ; 7.0 (s, 1H) ; 7.3 (m, 2H) ; 7.5 (d, 1H) ; 7.85 (s, 1H) ; 8.0 (s, 1H) ; 8.35 (s, 1H) ; 9.35 (s, 1H) ; 11.05 (s, 1H)

**Table XIV**



| Example number | Weight (mg) | Yield % | MS-ESI $[MH]^+$ | Note | R |
|---|---|---|---|---|---|
| 217 | 46 | 35 | 416 | a |  |
| 218 | 57 | 37 | 482 | b |  |
| 219 | 37 | 25 | 462 | c |  |
| 220 | 38 | 29 | 418 | d |  |
| 221 | 10 | 7 | 418 | e |  |
| 222 | 94 | 61 | 483 | f |  |
| 223 | 56 | 44 | 398 | g |  |

a) 7-Hydroxy-4-(indol-6-ylamino)-6-methoxyquinazoline (98 mg) was reacted with 3-(1,2,3-triazol-1-yl)propan-1-ol (61 mg), (prepared as described for the starting material in Example 208), to give **4-(indol-6-ylamino)-6-methoxy-7-(3-(1,2,3-triazol-1-yl)propoxy)quinazoline.**

$^1$H NMR Spectrum: ($DMSOd_6$) 2.42 (t, 2H) ; 4.02 (s, 3H) ; 4.2 (t, 2H) ; 4.62 (t, 2H) ; 6.42 (s, 1H) ; 7.15 (s, 1H) ; 7.3 (m, 2H) ; 7.55 (d, 1H) ; 7.75 (s, 1H) ; 7.92 (s, 1H) ; 8.02 (s, 1H) ; 8.2 (s, 1H) ; 8.42 (s, 1H) ; 9.45 (s, 1H)

b) 7-Hydroxy-4-(indol-6-ylamino)-6-methoxyquinazoline (98 mg) was reacted with 3-(1,1-dioxothiomorpholino)-1-propanol (93mg), (prepared as described for the starting material in Example 5), to give **7-(3-(1,1-dioxothiomorpholino)propoxy)-4-(indol-6-ylamino)-6-methoxyquinazoline.**

$^1$H NMR Spectrum: ($DMSOd_6$) 2.0 (m, 2H) ; 2.7 (t, 2H) ; 2.95 (br s, 4H) ; 3.12 (br s, 4H) ; 4.0 (s, 3H) ; 4.2 (t, 2H) ; 6.42 (s, 1H) ; 7.2 (s, 1H) ; 7.3 (m, 2H) ; 7.55 (d, 1H) ; 7.9 (s, 1H) ; 8.02 (s, 1H) ; 8.42 (s, 1H) ; 9.48 (s, 1H)

c) 7-Hydroxy-4-(indol-6-ylamino)-6-methoxyquinazoline (98 mg) was reacted with 3-((4-methyl-4*H*-1,2,4-triazol-3-yl)sulphanyl)propan-1-ol (83 mg), (prepared as described for the starting material in Example 212), to give **4-(indol-6-ylamino)-6-methoxy-7-(3-((4-methyl-4*H*-1,2,4-triazol-3-yl)sulphanyl)propoxy)quinazoline.**

$^1$H NMR Spectrum: ($DMSOd_6$) 2.22 (t, 2H) ; 3.3 (t, 2H) ; 3.6 (s, 3H) ; 4.0 (s, 3H) ; 4.28 (t, 2H) ; 6.4 (s, 1H) ; 7.18 (s, 1H) ; 7.3 (m, 2H) ; 7.53 (d, 1H) ; 7.9 (s, 1H) ; 8.02 (s, 1H) ; 8.42 (s, 1H) ; 8.58 (s, 1H) ; 9.45 (s, 1H)

d) 7-Hydroxy-4-(indol-6-ylamino)-6-methoxyquinazoline (98 mg) was reacted with 1-(2-hydroxyethyl)piperidine (62 mg) to give **4-(indol-6-ylamino)-6-methoxy-7-(2-piperidinoethoxy)quinazoline.**

$^1$H NMR Spectrum: ($DMSOd_6$) 1.3-1.6 (m, 6H) ; 2.5 (br s, 4H) ; 2.75 (t, 2H) ; 4.0 (s, 3H) ; 4.25 (t, 2H) ; 6.42 (s, 1H) ; 7.2 (s, 1H) ; 7.3 (m, 2H) ; 7.55 (d, 1H) ; 7.9 (s, 1H) ; 8.02 (s, 1H) ; 8.42 (s, 1H) ; 9.45 (s, 1H)

e) 7-Hydroxy-4-(indol-6-ylamino)-6-methoxyquinazoline (98 mg) was reacted with 1-(3-hydroxypropyl)pyrrolidine (62 mg) to give **4-(indol-6-ylamino)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline.**

The starting material was prepared as follows:

A solution of pyrrolidine (50 g, 0.7 mol) and 3-chloropropan-1-ol (66.15 g, 0.7 mol) in acetonitrile (1 l) containing potassium carbonate (145 g, 1.05 mol) was refluxed for 20 hours. After cooling, the mixture was filtered, the solid was washed with acetonitrile and the filtrate was evaporated. The residue was distilled at about 130°C under about 70 mmHg to give 1-(3-hydroxypropyl)pyrrolidine (62.1 g, 69%).

MS-ESI : 130 [MH]+

$^1$H NMR Spectrum: ($CDCl_3$) 1.6-1.8 (m, 6H) ; 2.55 (br s, 4H) ; 2.75 (t, 2H) ; 3.85 (t, 2H) ; 5.2-5.8 (br s, 1H)

f) 7-Hydroxy-4-(indol-6-ylamino)-6-methoxyquinazoline (98 mg) was reacted with 3-((N-(2,6-dimethyl-4-pyridyl)-N-methyl)amino)propan-1-ol (93mg) to give **7-(3-((N-(2,6dimethyl-4-pyridyl)-N-methyl)amino)propoxy)-4-(indol-6-ylamino)-6-methoxyquinazoline.**

$^1$H NMR Spectrum: ($DMSOd_6$) 2.08 (m, 2H) ; 2.22 (s, 6H) ; 2.95 (s, 3H) ; 3.6 (t, 2H) ; 4.05 (s, 3H) ; 4.15 (t, 2H) ; 6.35 (s, 2H) ; 6.42 (s, 1H) ; 7.15 (s, 1H) ; 7.3 (m, 2H) ; 7.55 (d, 1H) ; 7.92 (s, 1H) ; 8.02 (s, 1H) ; 8.4 (s, 1H) ; 9.45 (s, 1H)

The starting material was prepared as follows:

A solution of 4-chloro-2,6-dimethylpyridine (2.12 g, 15 mmol) and 3-(N-methylamino)-propan-1-ol (4g, 45 mmol) containing 2N hydrogen chloride in ether (10 drops) was heated at 140°C for 1 hour. The mixture was diluted with water (10ml) and poured onto a suspension of $MgSO_4$ (125g) in ethyl acetate (200ml). The mixture ws filtered. The filtrate was evaporated and the residue was triturated with ether. The solid was filtered and dried under vacuum to give 3-((N-(2,6-dimethyl-4-pyridyl)-N-methyl)amino)propan-1-ol (1.76 g, 61%).

MS-EI : 194 [M.]+

$^1$H NMR Spectrum: ($CDCl_3$) 1.75-1.95 (m, 2H) ; 2.4 (s, 6H) ; 3.0 (s, 3H) ; 3.48 (t, 2H) ; 3.7 (t, 2H) ; 6.25 (s, 2H)

g) 7-Hydroxy-4-(indol-6-ylamino)-6-methoxyquinazoline (98 mg) was reacted with 3-hydroxymethyl pyridine (53 mg) to give **4-(indol-6-ylamino)-6-methoxy-7-((3-pyridyl)methoxy)quinazoline.**

$^1$H NMR Spectrum: ($DMSOd_6$) 4.02 (s, 3H) ; 5.35 (s, 2H) ; 6.42 (s, 1H) ; 7.22-7.4 (m, 3H) ; 7.5 (m, 1H) ; 7.55 (d, 1H) ; 7.95 (s, 1H) ; 7.97 (d, 1H) ; 8.0 (s, 1H) ; 8.42 (s, 1H) ; 8.6 (d, 1H) ; 8.78 (s, 1H) ; 9.5 (s, 1H)

**Example 224**

Using an analogous procedure to that described in Example 208, 7-hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline (98 mg, 0.32 mmol), (prepared as described for the starting material in Example 201), was reacted with (E)-4-(pyrrolidin-1-yl)but-2-en-1-ol (68 mg, 0.48 mmol), (prepared as described for the starting material in Example 129). After evaporation of the fractions containing the expected product, the residue was triturated with isopropanol (1 ml) containing 6.2 N hydrogen chloride in isopropanol (100 µl). After stirring at ambient temperature for 10 minutes, ether (500 µl) was added. The precipitate was filtered and washed several times with ether to give **4-(indol-5-ylamino)-6-methoxy-7-((*E*)4-(pyrrolidin-1-yl)but-2-en-1-yloxy)quinazoline** hydrochloride (14 mg, 10 %).

MS-ESI : 430 $[MH]^+$

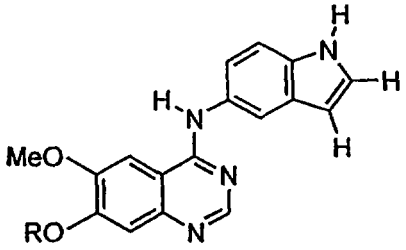
$^1$H NMR Spectrum: ($DMSOd_6$) 1.85-2.7 (br s, 4H) ; 2.95-3.1 (br s, 2H) ; 3.0 (m, 2H) ; 3.4-3.5 (m, 2H) ; 3.8 (d, 2H) ; 4.0 (s, 3H) ; 4.8 (d, 2H) ; 6.0-6.3 (m, 2H) ; 6.5 (s, 1H) ; 7.2-7.53 (m, 4H) ; 7.75 (s, 1H) ; 8.25 (s, 1H) ; 8.8 (br s, 1H)

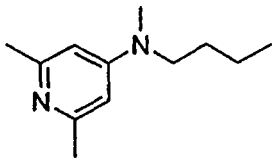
**Example 225**

7-Hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline, (prepared as described for the starting material in Example 201), was treated as follows. After purification by chromatography and evaporation of the solvent, the residue was triturated in a solution of isopropanol (1 ml) containing 6.2 N hydrogen chloride in isopropanol (100 µl). After stirring for 10 minutes at ambient temperature, ether (500 µl) was added. The solid was filtered and dried under vacuum to give 7-hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline hydrochloride.

Using an analogous procedure to that described in Example 224, 7-hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline hydrochloride was used in the synthesis of the compounds described in Table XV.

**Table XV**



| Example Number | Weight (mg) | Yield % | MS-ESI $[MH]^+$ | Note | R |
|---|---|---|---|---|---|
| 225 | 77 | 50 | 483 | a |  |

a) 7-Hydroxy-4-(indol-5-ylamino)-6-methoxyquinazoline hydrochloride (98 mg) was reacted with 3-((N-(2,6-dimethyl-4-pyridyl)-N-methyl)amino)propan-1-ol (93mg), (prepared as described for the starting material in Example 222), to give **7-(3-((N-(2,6-dimethyl-4-pyridyl)-N-methyl)amino)propoxy)-4-(indol-5-ylamino)-6-methoxyquinazoline**.
$^1$H NMR Spectrum: ($DMSOd_6$) 2.2 (m, 2H) ; 2.5 (2br s, 6H) ; 3.2 (s, 3H) ; 3.8 (t, 2H) ; 4.1 (s, 3H) ; 4.25 (t, 2H) ; 6.52 (s, 1H) ; 6.75 (br s, 1H) ; 6.9 (br s, 1H) ; 7.35 (dd, 1H) ; 7.45 (br s, 2H) ; 7.5 (d, 1H) ; 7.8 (s, 1H) ; 8.4 (s, 1H) ; 8.75 (s, 1H)

**Example 226**

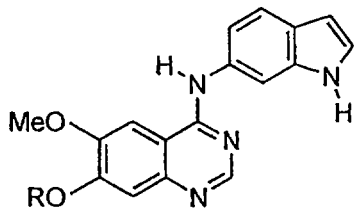
Using an analogous procedure to that described in Example 224, 7-hydroxy-4-(indol-6-ylamino)-6-methoxyquinazoline, (prepared as described for the starting material in Example 217), (98 mg, 0.32 mmol) was reacted with 4-(3-hydroxypropyl)morpholine (70 mg, 0.48 mmol), (prepared as described for the starting material in Example 60), to give **4-(indol-6-ylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline** hydrochloride (26 mg, 19 %).
MS-ESI : 434 $[MH]^+$

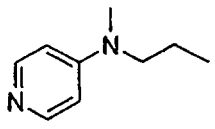
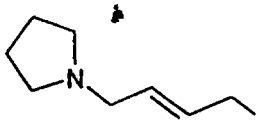
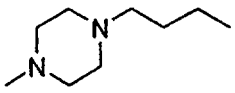
$^1$H NMR Spectrum: ($DMSOd_6$, $CF_3COOD$) 2.35 (m, 2H) ; 3.15 (m, 2H) ; 3.3 (t, 2H) ; 3.52 (d, 2H) ; 3.8 (t, 2H) ; 4.0 (d, 2H) ; 4.1 (s, 3H) ; 4.3 (t, 2H) ; 6.5 (s, 0.5 H, partly exchanged) ; 7.3 (d, 1H) ; 7.4 (s, 1H) ; 7.45 (s, 1H) ; 7.65 (d, 1H) ; 7.75 (s, 1H) ; 8.3 (s, 1H) ; 8.75 (s, 1H)

**Examples 227–229**

Using an analogous procedure to that described in Example 226, 7-hydroxy-4-(indol-6-ylamino)-6-methoxyquinazoline, (prepared as described for the starting material in Example 217), was used in the synthesis of the compounds described in Table XVI.

**Table XVI**




| Example number | Weight (mg) | Yield % | MS-ESI $[MH]^+$ | Note | R |
|---|---|---|---|---|---|
| 227 | 24 | 17 | 441 | a |  |
| 228 | 14 | 10 | 430 | b |  |
| 229 | 15 | 10 | 447 | c |  |

a) 7-Hydroxy-4-(indol-6-ylamino)-6-methoxyquinazoline (98 mg) was reacted with 2-((N-methyl-N-(4-pyridyl))amino)ethanol (73 mg), (EP 0359389A1), to give **4-(indol-6-ylamino)-6-methoxy-7-(2-((N-methyl-N-(4-pyridyl))amino)ethoxy)quinazoline** hydrochloride.

$^1$H NMR Spectrum: ($DMSOd_6$) 3.3 (s, 3H) ; 4.0 (s, 3H) ; 4.18 (t, 2H) ; 4.45 (t, 2H) ; 6.5 (s, 1H) ; 7.35 (d, 1H) ; 7.35-7.5 (m, 4H) ; 7.62 (d, 1H) ; 7.75 (s, 1H) ; 8.3 (d, 2H) ; 8.4 (s, 1H) ; 8.75 (s, 1H)

b) 7-Hydroxy-4-(indol-6-ylamino)-6-methoxyquinazoline (98 mg) was reacted with (E)-4-(pyrrolidin-1-yl)but-2-en-1-ol (68 mg, 0.48 mmol), (prepared as described for the starting material in Example 129) to give **4-(indol-6-ylamino)-6-methoxy-7-((*E*)-4-(pyrrolidin-1-yl)but-2-en-1-yloxy)quinazoline** hydrochloride.

$^1$H NMR Spectrum: ($DMSOd_6$) 1.8-2.1 (m, 4H) ; 2.9-3.1 (m, 2H) ; 3.4-3.5 (br s, 2H) ; 3.87 (d, 2H) ; 4.05 (s, 3H) ; 4.9 (d, 2H) ; 6.1 (m, 1H) ; 6.3 (m, 1H) ; 6.5 (s, 1H) ; 7.25 (d, 1H) ; 7.45 (m, 2H) ; 7.65 (d, 1H) ; 7.75 (s, 1H) ; 8.3 (s, 1H) ; 8.8 (s, 1H)

c) 7-Hydroxy-4-(indol-6-ylamino)-6-methoxyquinazoline (98 mg) was reacted with 1-(3-hydroxypropyl)-4-methylpiperazine (76 mg), (prepared as described for the starting material in Example 133), to give **4-(indol-6-ylamino)-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline** hydrochloride.

**Example 230**

Using an analogous procedure to that described in Example 224, 7-hydroxy-6-methoxy-4-(2-methylindol-5-ylamino)quinazoline (102 mg, 0.32 mmol), (prepared as described for the starting material in Example 205), was reacted with 1-(3-hydroxypropyl)-2-methylimidazole (67 mg, 0.48 mmol), (EP 0060696 A1), to give **6-methoxy-7-(3-(2-methylimidazol-1-yl)propoxy)-4-(2-methylindol-5-ylamino)quinazoline** (53 mg, 37 %).

MS-ESI : 443 $[MH]^+$

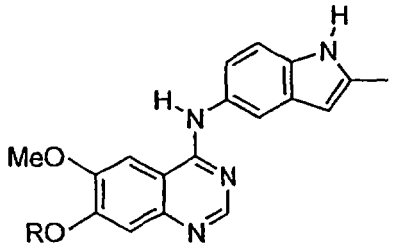
$^1$H NMR Spectrum: ($DMSOd_6$) 2.42 (s, 3H) ; 2.62 (s, 3H) ; 4.03 (s, 3H) ; 4.3 (t, 2H) ; 4.35 (t, 2H) ; 6.2 (s, 1H) ; 7.22 (d, 1H) ; 7.35 (d, 1H) ; 7.45 (s, 1H) ; 7.6 (dd, 1H) ; 7.65 (dd, 1H) ; 7.7 (s, 1H) ; 8.35 (s, 1H) ; 8.75 (s, 1H)

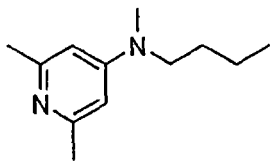
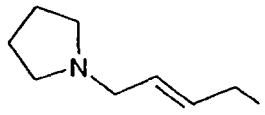
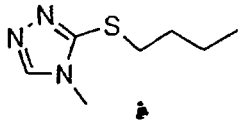
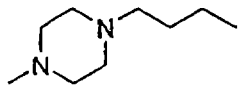
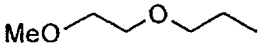
**Examples 231–235**

Using an analogous procedure to that described in Example 224, 7-hydroxy-6-methoxy-4-(2-methylindol-5-ylamino)quinazoline (102 mg, 0.32 mmol), (prepared as

described for the starting material in Example 205), was used in the synthesis of the compounds described in Table XVII.

**Table XVII**



| Example number | Weight (mg) | Yield % | MS-ESI $[MH]^+$ | Note | R |
|---|---|---|---|---|---|
| 231 | 49 | 31 | 497 | a |  |
| 232 | 25 | 18 | 444 | b |  |
| 233 | 23 | 15 | 476 | c |  |
| 234 | 33 | 22 | 461 | d |  |
| 235 | 26 | 19 | 423 | e |  |

a) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-ylamino)quinazoline (102 mg) was reacted with 3-((N-(2,6-dimethyl-4-pyridyl)-N-methyl)amino)propan-1-ol (93mg), (prepared as described for the starting material in Example 222), to give **7-(3-((N-(2,6-dimethyl-4-pyridyl)-N-methyl)amino)propoxy)-6-methoxy-4-(2-methylindol-5-ylamino)quinazoline.**

$^1$H NMR Spectrum: (DMSO$d_6$) 2.2 (m, 2H) ; 2.4 (s, 6H) ; 2.45 (s, 3H) ; 3.15 (s, 3H) ; 3.75 (t, 2H) ; 4.02 (s, 3H) ; 4.25 (t, 2H) ; 6.2 (s, 1H) ; 6.72 (br s, 1H) ; 6.85 (br s, 1H) ; 7.2 (dd, 1H) ; 7.3-7.4 (m, 2H) ; 7.62 (s, 1H) ; 8.3 (s, 1H) ; 8.7 (s, 1H)

b) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-ylamino)quinazoline (102 mg) was reacted with (E)-4-(pyrrolidin-1-yl)but-2-en-1-ol (68 mg, 0.48 mmol), (prepared as described for the starting material in Example 129) to give **6-methoxy-4-(2-methylindol-5-ylamino)-7-((*E*)-4-(pyrrolidin-1-yl)but-2-en-1-yloxy)quinazoline**.

$^1$H NMR Spectrum: (DMSO$d_6$) 1.8-2.1 (m, 4H) ; 2.4 (s, 3H) ; 2.9-3.1 (m, 2H) ; 3.4-3.6 (m, 2H) ; 3.9 (d, 2H) ; 4.05 (s, 3H) ; 4.9 (d, 2H) ; 6.1 (m, 1H) ; 6.2 (s, 1H) ; 6.3 (d,t, 1H) ; 7.2 (m, 1H) ; 7.37 (d, 1H) ; 7.4 (s, 1H) ; 7.32 (s, 1H) ; 8.3 (s, 1H) ; 8.75 (s, 1H)

c) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-ylamino)quinazoline (102 mg) was reacted with 3-((4-methyl-4*H*-1,2,4-triazol-3-yl)sulphanyl)propan-1-ol (83 mg), (prepared as described for the starting material in Example 212), to give **6-methoxy-4-(2-methylindol-5-ylamino)-7-(3-((4-methyl-4*H*-1,2,4-triazol-3-yl)sulphanyl)propoxy)quinazoline**.

$^1$H NMR Spectrum: (DMSO$d_6$) 2.25 (m, 2H) ; 2.45 (s, 3H) ; 3.35 (t, 2H) ; 3.65 (s, 3H) ; 4.05 (s, 3H) ; 4.35 (t, 2H) ; 6.2 (s, 1H) ; 7.2 (d, 1H) ; 7.35 (s, 1H) ; 7.37 (d, 1H) ; 7.62 (s, 1H) ; 8.25 (s, 1H) ; 8.75 (s, 1H) ; 8.9 (s, 1H)

d) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-ylamino)quinazoline (102 mg) was reacted with 1-(3-hydroxypropyl)-4-methylpiperazine (76 mg), (prepared as described for the starting material in Example 133), to give **6-methoxy-4-(2-methylindol-5-ylamino)-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline**.

e) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-ylamino)quinazoline (102 mg) was reacted with 2-(2-methoxyethoxy)ethanol to give **6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)-4-(2-methylindol-5-ylamino)quinazoline**.

$^1$H NMR Spectrum: (DMSO$d_6$) 2.45 (s, 3H) ; 3.28 (s, 3H) ; 3.5 (t, 2H) , 3.65 (t, 2H) ; 3.9 (t, 2H) ; 4.02 (s, 3H) ; 4.33 (t, 2H) ; 6.2 (s, 1H) ; 7.2 (d, 1H) ; 7.4 (m, 2H) ; 7.63 (s, 1H) ; 8.28 (s, 1H) ; 8.73 (s, 1H)

**Example 236**

A solution of 4-chloro-6-methoxy-7-((1-cyanomethylpiperidin-4-yl)methoxy)quinazoline (200 mg, 0.58 mmol) and 5-hydroxyindole (85 mg, 0.63 mmol) in DMF (3 ml) containing cesium carbonate (282 mg, 0.86 mmol) was stirred at 90°C for 90 minutes. After cooling, the mixture was poured onto water (25 ml). The precipitate was filtered, dried under vacuum and purified by reverse phase column chromatography on silica (kromasil ® C18) eluting with methanol/water (1 % acetic acid) (1/1). The fractions containing the expected product were combined and evaporated to give **7-((1-cyanomethyl)piperidin-4-ylmethoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline** (44 mg, 17 %).

MS-ESI : 444 $[MH]^+$

$^1H$ NMR Spectrum: ($DMSOd_6$, $CF_3COOD$) 1.7 (m, 2H) ; 2.15 (d, 2H) ; 2.2-2.35 (m, 1H) ; 3.20 (t, 2H) ; 3.65 (d, 2H) ; 4.1 (s, 3H) ; 4.25 (d, 2H) ; 4.62 (s, 2H) ; 6.5 (s, 0.5 H, partly exchanged) ; 7.1 (dd, 1H) ; 7.5 (s, 1H) ; 7.5-7.6 (m, 3H) ; 7.85 (s, 1H) ; 9.1 (s, 1H)

The starting material was prepared as follows:

To a suspension of 6-methoxy-7-(piperidin-4-ylmethoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one hydrochloride (34 g, 84 mmol), (prepared as described for the starting material in Example 12), in water cooled at $0^0C$ was added 1N sodium hydroxide until the mixture was at pH8. The solution was extracted with trichloromethane and the organic layer was dried ($MgSO_4$), filtered and evaporated to give 6-methoxy-7-(piperidin-4-ylmethoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (29g).

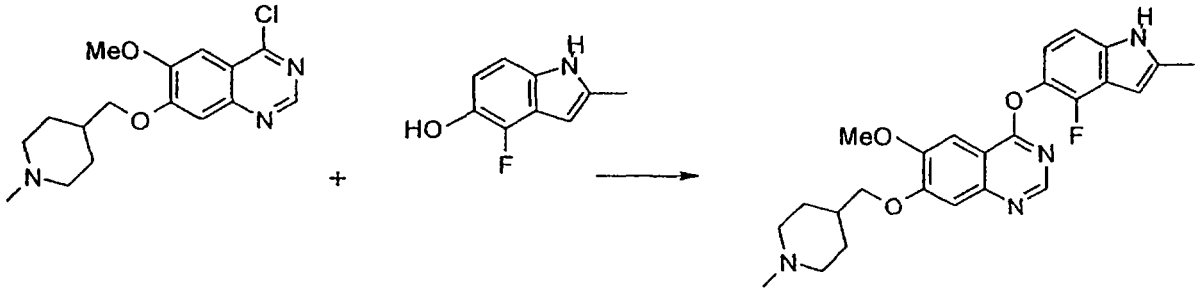
To a solution of 6-methoxy-7-(piperidin-4-ylmethoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (28.9 g, 72 mmol) and aqueous formaldehyde 12 M (11.95 ml, 141 mmol) in methanol/THF (1/1) (580 ml) was added sodium cyanoborohydride (5.7 g, 86 mmol) in portions. After stirring for 90 minutes at ambient temperature, the volatiles were removed under vacuum and the residue was partitioned between methylene chloride and water. The organic layer was separated, dried ($MgSO_4$) and evaporated. The residue was dissolved in methanol saturated with ammonia (500 ml). The mixture was stirred for 36 hours at ambient temperature. The volatiles were removed under vacuum. The residue was triturated with a mixture ether/methylene chloride, filtered, washed with ether and dried under vacuum. The solid was dissolved in thionyl chloride (180 ml) and DMF (1.8 ml) was added.

After stirring at 80°C for 75 minutes the volatiles were removed under vacuum. The residue was azeotroped with toluene twice and the solid was partitioned between methylene chloride and water and the pH of the aqueous layer was adjusted to 9 with 2N sodium hydroxide. The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on aluminium oxide eluting with methylene chloride, followed by methylene chloride/ethyl acetate (70/30 followed by 50/50) followed by ethyl acetate and ethyl acetate/methanol (80/20) to give 4-chloro-6-methoxy-7((1-methylpiperidin-4-yl)methoxy)quinazoline (11.2 g) (identical to the starting material prepared in Example 10) and 4-chloro-6-methoxy-7-((1-(cyanomethyl)piperidin-4-yl)methoxy)quinazoline (2.55 g).

MS-ESI : 347 $[MH]^+$

$^1H$ NMR Spectrum: ($DMSOd_6$) 1.42 (m, 2H) ; 1.85 (d, 2H) ; 1.8-1.9 (m, 1H) ; 2.2 (t, 2H) ; 2.85 (d, 2H) ; 3.75 (s, 2H) ; 4.05 (s, 3H) ; 4.15 (d, 2H) ; 7.42 (s, 1H) ; 7.5 (s, 1H) ; 8.9 (s, 1H)

**Example 237**




A solution of 4-chloro-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline (2 gr, 6.22 mmol), (prepared as described for the starting material in Example 10), and 4-fluoro-5-hydroxy-2-methylindole (1.23 g, 7.46 mmol) in DMF (30 ml) containing potassium carbonate ( 1.28 g, 9.33 mmol) was stirred at 95°C for 2 hours. After cooling, the volatiles were removed under vacuum and the residue was triturated with ether, filtered and dried under vacuum. The residue was purified by column chromatography eluting with methanol/methylene chloride (1/9) followed by methanol/methanol saturated with ammonia/methylene chloride (20/1/79 followed by 20/5/75). The fractions containing the expected product were combined and evaporated. The solid was triturated with methanol, filtered and dried under vacuum to give **4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline** (1.95 g, 69 %).

MS-ESI : 451 $[MH]^+$

$^1$H NMR Spectrum ($DMSOd_6$) 1.4 (m, 2H) ; 1.8 (d, 2H) ; 1.7-1.9 (m, 1H) ; 1.9 (t, 2H) ; 2.2 (s, 3H) ; 2.45 (s, 3H) ; 2.8 (d, 2H) ; 4.02 (s, 3H) ; 4.1 (d, 2H) ; 6.25 (s, 1H) ; 7.0 (dd, 1H) ; 7.2 (d, 1H) ; 7.4 (s, 1H) ; 7.62 (s, 1H) ; 8.5 (s, 1H)

Elemental analysis: Found C 64.2 H 6.5 N 11.7

$C_{25}H_{27}FN_4O_3$ 0.91methanol 0.08$CH_2Cl_2$ 0.1$H_2O$ Requires C 63.9 H 6.4 N 11.5%

The starting material was prepared as follows:

To a solution of 2-fluoro-4-nitroanisole (9.9 g, 58 mmol) and 4-chlorophenoxyacetonitrile (10.7 g, 64 mmol) in DMF (50 ml) cooled at -15°C was added potassium *tert*-butoxide (14.3 g, 127 mmol) in DMF (124 ml). After stirring for 30 minutes at -15°C, the mixture was poured onto cooled 1N hydrochloric acid. The mixture was extracted with ethyl acetate. The organic layer was washed with 1N sodium hydroxide, brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography eluting with methylene chloride. The fractions containing the expected product were combined and evaporated. The residue was dissolved in ethanol (180 ml) and acetic acid (24 ml) containing 10 % palladium on charcoal (600 mg) and the mixture was hydrogenated under 3 atmospheres pressure for 2 hours. The mixture was filtered, and the volatiles were removed under vacuum. The residue was partitioned between ethyl acetate and water. The organic layer was separated, and washed with saturated sodium hydrogen carbonate followed by brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography eluting with methylene chloride to give a mixture of 4-fluoro-5-methoxyindole and 6-fluoro-5-methoxyindole (5.64 g, 59 %) in a ratio 1/2.

$^1$H NMR Spectrum: ($DMSOd_6$) 3.85 (s, 3H) ; 6.38 (s, 1H, 6-Fluoro) ; 6.45 (s, 1H ; 4-Fluoro) ; 6.9-7.4 (m, 3H)

A solution of 4-fluoro-5-methoxyindole and 6-fluoro-5-methoxyindole in a ratio 1/2 (496 mg, 3 mmol), di-*tert*butyl dicarbonate (720 mg, 3.3 mmol) in acetonitrile (12 ml) containing DMAP (18 mg, 0.15 mmol) was stirred at ambient temperature for 24 hours. The volatiles were removed under vacuum. The residue was dissolved in ethyl acetate, washed with 1N hydrochloric acid, followed by water, brine, dried ($MgSO_4$) and evaporated to give a mixture of 4-fluoro-5-methoxy-1-*tert*-butoxycarbonylindole and 6-fluoro-5-methoxy-1-*tert*-butoxycarbonylindole in a ratio 1/2 (702 mg, 88 %).

$^1$H NMR Spectrum: (DMSO$d_6$) 1.65 (s, 9H) ; 3.9 (s, 3H) ; 6.6 (d, 1H, 6-fluoro) ; 6.72 (d, 1H, 4-fluoro) ; 7.2 (t, 1H, 6-fluoro) ; 7.4 (d, 1H, 4-fluoro) ; 7.62 (d, 1H, 6-fluoro) ; 7.68 (d, 1H, 4-fluoro) ; 7.78 (s, 1H, 4-fluoro) ; 7.85 (s, 1H, 6-fluoro)

To a solution of 4-fluoro-5-methoxy-1-*tert*-butoxycarbonylindole and 6-fluoro-5-methoxy-1-*tert*-butoxycarbonylindole in a ratio 1/2 (8.1 g, 30.5 mmol) in THF (100 ml) cooled at -65°C was added *tert*-butyllithium (1.7 M) (23 ml, 35.7 mmol). After stirring for 4 hours at -70°C, methyl iodide (8.66 g, 61 mmol) was added and the mixture was left to warm-up to ambient temperature. Water was added and the mixture was extracted with ether. The organic layer was washed with water, brine, dried ($MgSO_4$) and evaporated and was used directly in the next step.

The crude product was dissolved in methylene chloride (100 ml) and TFA (25 ml) was added. After stirring for 1 hour at ambient temperature, the volatiles were removed under vacuum. The residue was dissolved in ethyl acetate and the organic layer was washed with 1N sodium hydroxide, followed by water, brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography, eluting with ethyl acetate/petroleum ether (3/7) to give 6-fluoro-5-methoxy-2-methylindole (1.6 g) and 4-fluoro-5-methoxy-2-methylindole (0.8 g, 48 %).

6-fluoro-5-methoxy-2-methylindole:

MS-ESI : 180 $[MH]^+$

$^1$H NMR Spectrum: (DMSO$d_6$) 2.35 (s, 3H) ; 3.8 (s, 3H) ; 6.05 (s, 1H) ; 7.1 (s, 1H) ; 7.12 (s, 1H) ; 10.8 (s, 1H)

4-fluoro-5-methoxy-2-methylindole:

MS-ESI : 180 $[MH]^+$

$^1$H NMR Spectrum: (DMSO$d_6$) 2.35 (s, 3H) ; 3.8 (s, 3H) ; 6.15 (s, 1H) ; 6.9 (t, 1H) ; 7.05 (d, 1H) ; 11.0 (s, 1H)

To a solution of 4-fluoro-5-methoxy-2-methylindole (709 mg, 3.95 mmol) in methylene chloride (9 ml) cooled at -30°C was added a solution of boron tribromide (2.18 g, 8.7 mmol) in methylene chloride (1 ml). After stirring for 1 hour at ambient temperature, the mixture was poured onto water and was diluted with methylene chloride. The pH of the aqueous layer was adjusted to 6. The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography, eluting

with ethyl acetate/petroleum ether (3/7) to give 4-fluoro-5-hydroxy-2-methylindole (461 mg, 70 %).

MS-ESI : 166 $[MH]^+$

$^1H$ NMR Spectrum: ($DMSOd_6$) 2.35 (s, 3H) ; 6.05 (s, 1H) ; 6.65 (dd, 1H) ; 6.9 (d, 1H) ; 8.75 (s, 1H) ; 10.9 (s, 1H)

$^{13}C$ NMR Spectrum: ($DMSOd_6$) 13.5 ; 94,0 ; 106,0 ; 112 ; 118.5 (d) ; 132 (d) ; 136 (d) ; 136.5 ; 142.5 (d)

Alternatively the 4-fluoro-5-hydroxy-2-methylindole may be prepared as follows:

To a suspension of sodium hydride (5.42 g, 226 mmol) (prewashed with pentane) in THF (100 ml) cooled at 10°C was added ethyl acetoacetate (29.4 g, 226 mmol) while keeping the temperature below 15°C. After completion of addition, the mixture was further stirred for 15 minutes and cooled to 5°C. A solution of 1,2,3-trifluoro-4-nitrobenzene (20 g, 113 mmol) in THF (150 ml) was added while keeping the temperature below 5°C. The mixture was then left to warm up to ambient temperature and stirred for 24 hours. The volatiles were removed under vacuum and the residue was partitioned between ethyl acetate and 2N aqueous hydrochloric acid. The organic layer was washed with water, brine, dried ($MgSO_4$) and evaporated. The residue was dissolved in concentrated hydrochloric acid (650 ml) and acetic acid (600 ml) and the mixture was refluxed for 15 hours. After cooling, the volatiles were removed under vacuum and the residue was partitioned between aqueous sodium hydrogen carbonate (5 %) and ethyl acetate. The organic layer was washed with sodium hydrogen carbonate, water, brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography eluting with ethylacetate/petroleum ether (75/25) to give 3-acetylmethyl-1,2-difluoro-4-nitrobenzene (17.5 g, 72 %).

$^1H$ NMR Spectrum: ($CDCl_3$) 2.4 (s, 3H) ; 4.25 (s, 2H) ; 7.25 (dd, 1H) ; 8.0 (dd, 1H)

A solution of 3-acetylmethyl-1,2-difluoro-4-nitrobenzene (500 mg, 2.3 mmol) in methylene chloride (5 ml) containing montmorillonite K10 (1 g) and trimethyl orthoformate (5 ml) was stirred for 24 hours at ambient temperature. The solid was filtered, washed with methylene chloride and the filtrate was evaporated to give 1,2-difluoro-3-(2,2-dimethoxypropyl)-4-nitrobenzene (534 mg, 88 %).

$^1H$ NMR Spectrum: ($CDCl_3$) 1.2 (s, 3H) ; 3.2 (s, 6H) ; 3.52 (s, 2H) ; 7.18 (dd, 1H) ; 7.6 (m, 1H)

To a solution of benzyl alcohol (221 mg, 2.05 mmol) in DMA (1.5 ml) was added 60% sodium hydride (82 mg, 2.05 mmol). The mixture was stirred for 1 hour at ambient temperature. A solution of 1,2-difluoro-3-(2,2-dimethoxypropyl)-4-nitrobenzene (534 mg, 2.05 mmol) in DMA (1.5 ml) was added and the mixture was stirred for 3 hours at ambient temperature. The mixture was diluted with 1N hydrochloric acid (10 ml) and extracted with ethyl acetate. The organic layer was evaporated and the residue was dissolved in THF (2 ml) and 6N hydrochloric acid (0.3 ml) was added. The mixture was stirred for 1 hour at ambient temperature and the solvents were removed under vacuum. The residue was partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried ($MgSO_4$) and evaporated. The solid was triturated with ether, filtered, washed with ether and dried under vacuum to give 3-acetylmethyl-1-benzyloxy-2-fluoro-4-nitrobenzene (350 mg, 56 %).

$^1$H NMR Spectrum: ($CDCl_3$) 2.35 (s, 3H) ; 4.25 (s, 2H) ; 5.25 (s, 2H) ; 7.0 (dd, 1H) ; 7.32-7.5 (m, 5H) ; 8.0 (dd, 1H)

A solution of 3-acetylmethyl-1-benzyloxy-2-fluoro-4-nitrobenzene (300 mg, 0.99 mmol) in ethanol (10 ml) and acetic acid (1 ml) containing 10 % palladium on charcoal (30 mg) was hydrogenated at 2 atmospheres pressure for 2 hours. The mixture was filtered and the filtrate was evaporated. The residue was dissolved in ethyl acetate and the organic layer was washed with aqueous sodium hydrogen carbonate, brine and evaporated to give 4-fluoro-5-hydroxy-2-methylindole. The residue was purified by column chromatography eluting with ethyl acetate/petroleum ether (3/7) to give 4-fluoro-5-hydroxy-2-methylindole (63 mg, 30%). Analytical data as above.

Alternatively the 4-fluoro-5-methoxy-2-methylindole can be prepared as follows:

A solution of sodium methoxide (freshly prepared from sodium (1.71g) and methanol (35ml)) was added to a solution of 1,2-difluoro-3-(2,2-dimethoxypropyl)-4-nitrobenzene (16.2 g, 62 mmol), (prepared as described above), in methanol (200ml) cooled at 5$^0$C. The mixture was left to warm to ambient temperature and was stirred for 3 days. The volatiles were removed under vacuum and the residue was partitioned between ethyl acetate and 2N hydrochloric acid (1ml). The organic layer was concentrated to a total volume of 100ml and THF (100ml) and 6N hydrochloric acid (25ml) were added. The mixture was stirred for 1 hour at ambient temperature. The volatiles were removed under vacuum and the residue was

partitioned between ethyl acetate and water. The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography eluting with ethyl acetate/petroleum ether (3/7) to give 3-acetylmethyl-2-fluoro-1-methoxy-4-nitrobenzene (12.7 g, 90%).

MS-ESI : 250 [MNa]+

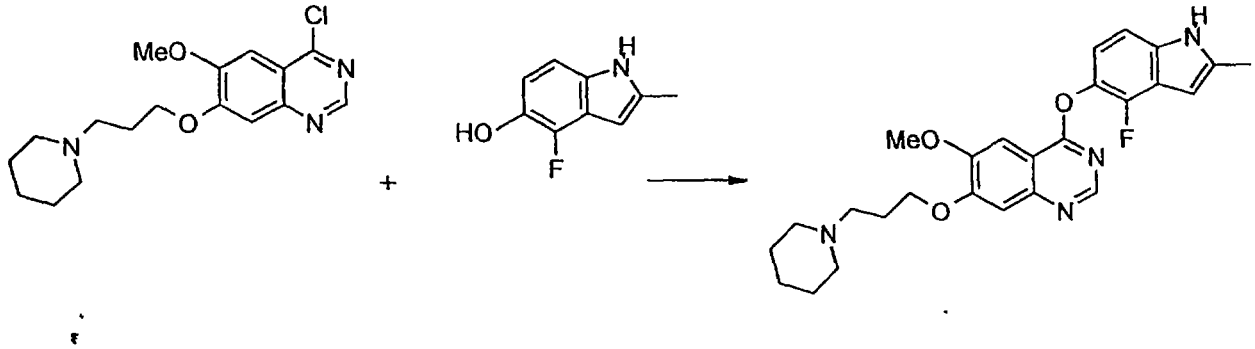
$^1$H NMR Spectrum: ($CDCl_3$) 2.38 (s, 3H) ; 4.0 (s, 3H) ; 4.25 (s, 2H) ; 7.0 (dd, 1H) ; 8.05 (d, 1H)

To a solution of 3-acetylmethyl-2-fluoro-1-methoxy-4-nitrobenzene (11.36g, 50 mmol) in acetone (200ml) was added 4M aqueous ammonium acetate (700ml) followed by a solution of titanium trichloride (15% in water, 340ml) dropwise. The mixture was stirred for 10 minutes at ambient temperature and the mixture was extracted with ether. The organic layer was washed with 0.5N aqueous sodium hydroxide followed by water, brine, dried ($MgSO_4$) and the volatiles were removed under vacuum. The residue was purified by column chromatography eluting with methylene chloride to give 4-fluoro-5-methoxy-2-methylindole (8.15g, 90%).

$^1$H NMR Spectrum: (DMSO) 2.35 (s, 3H) ; 3.8 (s, 3H) ; 6.1 (s, 1H) ; 6.85 (dd, 1H) ; 7.02 (d, 1H)

Cleavage of 4-fluoro-5-methoxy-2-methylindole with boron tribromide to give 4-fluoro-5-hydroxy-2-methylindole is described above.

**Example 238**



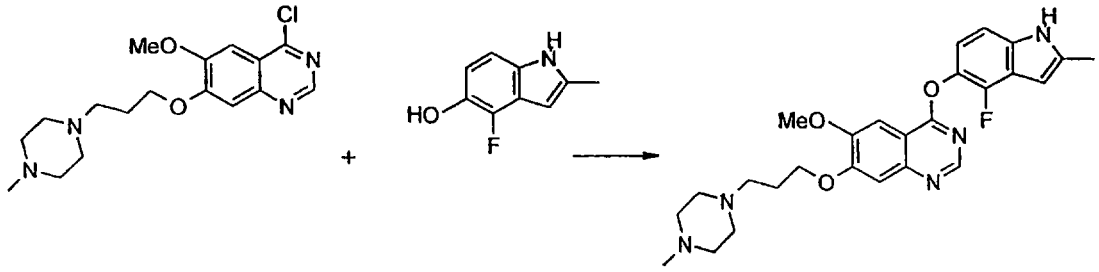

Using an analogous procedure to that described in Example 237, 4-chloro-6-methoxy-7-(3-piperidinopropoxy)quinazoline (1.65 g, 4.89 mmol), (prepared as described for the starting material in Example 67), was reacted with 4-fluoro-5-hydroxy-2-methylindole (970 mg, 5.88 mmol), (prepared as described for the starting material in Example 237), to give 4-

**(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline** ( 1.9 g, 83 %).

MS-ESI : 465 $[MH]^+$

$^1H$ NMR Spectrum: ($DMSOd_6$) 1.4 (br s, 2H) ; 1.5 (m, 4H) ; 1.95 (m, 2H) ; 2.25-2.5 (m, 6H) ; 2.45 (s, 3H) ; 4.0 (s, 3H) ; 4.25 (t, 2H) ; 6.25 (s, 1H) ; 7.0 (dd, 1H) ; 7.15 (d, 1H) ; 7.4 (s, 1H) ; 7.6 (s, 1H) ; 8.5 (s, 1H)

**Example 239**

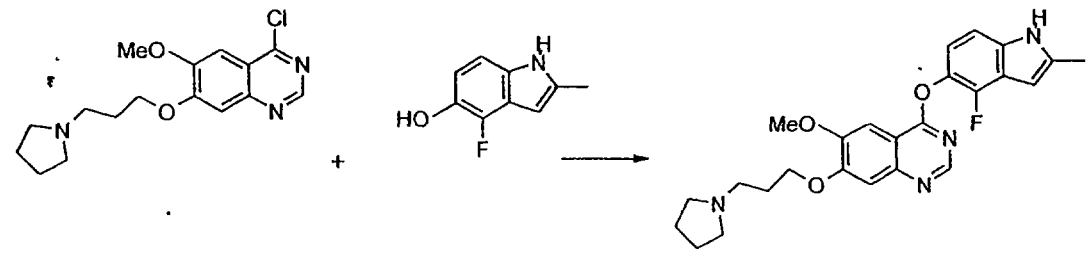


Using an analogous procedure to that described in Example 237, 4-chloro-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline (106 mg, 0.30 mmol), (prepared as described for the starting material in Example 176), was reacted with 4-fluoro-5-hydroxy-2-methylindole (60 mg, 0.36 mmol), (prepared as described for the starting material in Example 237), to give **4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline** ( 100 mg, 70 %).

MS-ESI : 480 $[MH]^+$

$^1H$ NMR Spectrum: ($DMSOd_6$) 2.0 (t, 2H) ; 2.15 (s, 3H) ; 2.45 (s, 3H) ; 2.2-2.6 (m, 10H) ; 4.02 (s, 3H) ; 4.25 (t, 2H) ; 6.25 (s, 1H) ; 7.0 (dd, 1H) ; 7.18 (d, 1H) ; 7.4 (s, 1H) ; 7.62 (s, 1H) ; 8.5 (s, 1H)

**Example 240**



Using a procedure identical to that described in Example 237, 4-chloro-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline ( 2 g, 6.22 mmol), (prepared as described for the

starting material in Example 9), was reacted with 4-fluoro-5-hydroxy-2-methylindole (1.23 g, 7.46 mmol), (prepared as described for the starting material in Example 237), to give **4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline** ( 1.41 g, 50 %).

MS-ESI : 451 [MH]+

$^1$H NMR Spectrum: ($DMSOd_6$) 1.7 (br s, 4H) ; 2.0 (m, 2H) ; 2.41 (s, 3H) ; 2.5 (br s, 4H) ; 2.6 (t, 2H) ; 4.0 (s, 3H) ; 4.25 (t, 2H) ; 6.25 (s, 1H) ; 7.0 (dd, 1H) ; 7.2 (d, 1H) ; 7.4 (s, 1H) ; 7.6 (s, 1H) ; 8.5 (s, 1H)

| | | | | | |
|---|---|---|---|---|---|
| Elemental analysis : | Found | C 63.3 | H 6.4 | N 11.9 | |
| $C_{25}H_{27}FN_4O_3$ 1.08 $H_2O$ ; 0.16 methanol | Requires | C 63.6 | H 6.3 | N 11.8% | |

**Example 241**

A solution of 4-chloro-6-methoxy-7-(2-(1-methylpiperidin-4-yl)ethoxy)quinazoline (300 mg, 0.9 mmol) and 4-fluoro-5-hydroxyindole (162 mg, 1 mmol), (prepared as described for the starting material in Example 242), in DMF (4.5 ml) containing potassium carbonate (185 mg, 1.3 mmol) was stirred at 90°C for 1 hour. After cooling, the mixture was filtered and the solid was washed with DMF. The filtrate was evaporated and the residue was purified by column chromatography, eluting with methylene chloride followed by methanol/methylene chloride (1/99) followed by methanol saturated with ammonia/methylene chloride (2/98). The fractions containing the expected product were combined and evaporated. The solid was triturated with ether, filtered, washed with ether and dried under vacuum to give **4-(4-fluoroindol-5-yloxy)-6-methoxy-7-(2-(1-methylpiperidin-4-yl)ethoxy)quinazoline** (282 mg, 69%).

MS-ESI : 451 [MH]+

$^1$H NMR Spectrum: ($DMSOd_6$) 1.2-1.3 (m, 2H) ; 1.4-1.55 (m, 1H) ; 1.7-1.9 (m, 6H) ; 2.15 (s, 3H) ; 2.75 (d, 2H) ; 4.0 (s, 3H) ; 4.3 (t, 2H) ; 6.55 (s, 1H) ; 7.1 (dd, 1H) ; 7.3 (d, 1H) ; 7.4 (s, 1H) ; 7.5 (s, 1H) ; 7.6 (s, 1H) ; 8.5 (s, 1H) ; 11.5 (s, 1H)

The starting material was prepared as follows:

To a solution of 4-(2-hydroxyethyl)-(1-*tert*-butoxycarbonyl)piperidine (12.9 g, 56 mmol), (prepared as described for the starting material in Example 126), in *tert*-butyl methyl ether (120 ml) containing 1,4-diazabicyclo[2.2.2]octane (9.8 g, 87 mmol) cooled at -5°C was

added a solution of tosyl chloride (14.5 gr, 76 mmol) in *tert*-butyl methyl ether (120ml) dropwise whilst keeping the temperature below 0°C. After completion of addition, the mixture was left to warm up to ambient temperature and stirred for 1 hour. The mixture was poured onto petroleum ether (240 ml). The precipitae was filtered and washed with petroleum ether. The filtrate was evaporated and the residue was dissolved in ether. The ether layer was washed with 0.5 N hydrochloric acid, followed by saturated sodium hydrogen carbonate, dried ($MgSO_4$) and evaporated to give 4-(2-(4-methylphenylsulphonyloxy)ethyl)-1-*tert*-butoxycarbonylpiperidine (20.9 g, 97%).

$^1$H NMR Spectrum: ($CDCl_3$) 0.95-1.05 (m, 4H) ; 1.45 (s, 9H) ; 1.4-1.6 (m, 3H)2.45 (s, 3H) ; 2.62 (t, 2H) ; 3.9-4.1 (m, 2H) ; 4.1 (t, 2H) ; 7.35 (d, 2H) ; 7.8 (d, 2H)

A suspension of 7-hydroxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (7 g, 23 mmol), (prepared as described for the starting material in Example 12), 4-(2-(4-methylphenylsulphonyloxy)ethyl)-1-*tert*-butoxycarbonylpiperidine (11.4 g, 30 mmol) in DMF (70 ml) containing potassium carbonate (6.32 g, 46 mmol) was stirred at 100°C for 3 hours. After cooling, the volatiles were removed under vacuum and the residue was partitioned between ether and water. The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and evaporated. The solid was triturated with pentane, filtered and dried under vacuum to give 7-(2-(1-*tert*butoxycarbonylpiperidin-4-yl)ethoxy)-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (10.5 g, 88 %).

MS-ESI : 540 $[MNa]^+$

$^1$H NMR Spectrum: ($CDCl_3$) 1.2 (s, 9H) ; 1.15-1.25 (m, 2H) ; 1.48 (s, 9H) ; 1.65-1.75 (m, 1H) ; 1.7 (d, 2H) ; 1.9 (dd, 2H) ; 2.72 (t, 2H) ; 4.0 (s, 3H) ; 4.0-4.2 (m, 2H) ; 4.2 (t, 2H) ; 5.95 (s, 2H) ; 7.1 (s, 1H) ; 7.65 (s, 1H) ; 8.2 (s, 1H)

A solution of 7-(2-(1-*tert*butoxycarbonylpiperidin-4-yl)ethoxy)-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (10.5 g, 20 mmol) in methylene chloride (100 ml) containing TFA (25 ml) was stirred for 1 hour at ambient temperature. Water (50 ml) and methylene chloride (100 ml) were added and the pH of the aqueous layer was adjusted to 8 with solid sodium hydrogen carbonate. The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and evaporated. The residue was triturated with ether and the solid was filtered and dried under vacuum to give 7-(2-(piperidin-4-yl)ethoxy)-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (8.3 g, 100 %).

$^1$H NMR Spectrum: ($CDCl_3$) 1.2 (s, 9H) ; 1.65 (m, 2H) ; 1.9 (br s, 2H) ; 1.8-1.9 (m, 1H) ; 2.0 (d, 2H) ; 2.9 (t, 2H) ; 3.45 (d, 2H) ; 4.0 (s, 3H) ; 4.2 (t, 2H) ; 5.95 (s, 2H) ; 7.1 (s, 1H) ; 7.65 (s, 1H) ; 8.2 (s, 1H)

To a solution of 7-(2-(piperidin-4-yl)ethoxy)-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (6 g, 14.4 mmol) in methanol (30 ml) and methylene chloride (60 ml) was added 37% aqueous formaldehyde (2.2 ml ; 28.9 mmol) followed by acetic acid (990 µl ; 17.3 mmol). Sodium borohydride triacetate (4.6 g, 21.6 mmol) was added in portions. After stirring for 1 hour at ambient temperature, the volatiles were removed under vacuum and the residue was partitioned between water (50 ml) and methylene chloride (50 ml). The pH of the aqueous layer was adjusted to 7, washed with water, brine, dried ($MgSO_4$) and evaporated. The solid was triturated with ether, filtered, washed with ether and dried under vacuum to give 7-(2-(1-methylpiperidin-4-yl)ethoxy)-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (4.2 g, 68 %).

MS-ESI : 432 $[MH]^+$

$^1$H NMR Spectrum: ($CDCl_3$) 1.22 (s, 9H) ; 1.68 (br s, 3H) ; 1.9 (m, 4H) ; 2.32 (br s, 2H) ; 2.52 (s, 3H) ; 3.18 (d, 2H) ; 4.0 (s, 3H) ; 4.2 (t, 2H) ; 5.95 (s, 2H) ; 7.1 (s, 1H) ; 7.65 (s, 1H) ; 8.2 (s, 2H)

A solution of 7-(2-(1-methylpiperidin-4-yl)ethoxy)-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (4.2 g, 9.7 mmol) in methanol saturated with ammonia (150 ml) was stirred overnight at ambient temperature. The volatiles were removed under vacuum and the residue was triturated with ether. The solid was filtered, washed with ether and dried under vacuum to give 7-(2-(1-methylpiperidin-4-yl)ethoxy)-6-methoxy-3,4-dihydroquinazolin-4-one (3.12 g, 100 %).

MS-ESI : 318 $[MH]^+$

$^1$H NMR Spectrum: ($DMSOd_6$) 1.3 (m, 2H) ; 1.58 (br s, 1H) ; 1.72 (dd, 2H) ; 1.8 (d, 2H) ; 2.4 (s, 3H) ; 2.2-2.45 (m, 2H) ; 3.0 (br s, 2H) ; 3.85 (s, 3H) ; 4.15 (t, 2H) ; 7.15 (s, 1H) ; 7.45 (s, 1H) ; 8.0 (s, 1H)

A solution of 7-(2-(1-methylpiperidin-4-yl)ethoxy)-6-methoxy-3,4-dihydroquinazolin-4-one (3.1 g , 9.8 mmol) in thionyl chloride (40 ml) containing DMF (400 µl) was refluxed for 4 hours. After cooling, the volatiles were removed under vacuum. The residue was partitioned between methylene chloride and water and the pH of the aqueous layer was adjusted to 11 with solid sodium hydrogen carbonate and aqueous ammonia. The organic

layer was separated, dried ($MgSO_4$) and evaporated. The residue was triturated with ether, filtered, washed with ether and dried under vacuum to give 4-chloro-6-methoxy-7-(2-(1-methylpiperidin-4-yl)ethoxy)quinazoline (1.83 g, 54 %).

MS-ESI : 336 $[MH]^+$

$^1H$ NMR Spectrum: ($CDCl_3$) 1.4-1.7 (m, 3H) ; 1.8 (d, 2H) ; 1.9 (dd, 2H) ; 2.05 (t, 2H) ; 2.35 (s, 3H) ; 2.95 (d, 2H) ; 4.05 (s, 3H) ; 4.25 (t, 2H) ; 7.3 (s, 1H) ; 7.4 (s, 1H) ; 8.88 (s, 1H)

**Example 242**

A solution of 4-chloro-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline (213 mg, 0.662 mmol), (prepared as described for the starting material in Example 10), and 6-fluoro-5-hydroxyindole (120 mg, 0.794 mmol) in DMF (3 ml) containing potassium carbonate (137 mg, 0.994 mmol) was stirred at 95°C for 3.5 hours. After cooling, the mixture was poured onto water. The mixture was filtered and the solid was washed with water. The solid was dissolved in methylene chloride. The organic layer was dried ($MgSO_4$), and evaporated. The residue was triturated with ether/ethyl acetate and the solid was filtered and dried under vacuum to give **4-(6-fluoroindol-5-yloxy)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline** (135 mg, 46 %).

MS-ESI : 437 $[MH]^+$

$^1H$ NMR Spectrum: ($DMSOd_6$) 1.3-1.45 (m, 2H) ; 1.8 (d, 2H) ; 1.9 (t, 2H) ; 1.7-1.9 (m, 1H) ; 2.17 (s, 3H) ; 2.8 (d, 2H) ; 4.0 (s, 3H) ; 4.1 (d, 2H) ; 6.48 (br s, 1H) ; 7.38 (d, 1H) ; 7.4 (s, 1H) ; 7.42 (t, 1H) ; 7.58 (d, 1H) ; 7.6 (s, 1H) ; 8.5 (s, 1H)

| | | | | |
|---|---|---|---|---|
| Elemental analysis | Found | C 65.0 | H 5.8 | N 12.7 |
| $C_{24}H_{25}FN_4O_3$ 0.4 $H_2O$ | Requires | C 65.0 | H 5.9 | N 12.6% |

The starting material was prepared as follows:

A mixture of 2-fluoro-4-nitrophenol (15gr, 95.5 mmol) and benzyl bromide (18g, 105 mmol) in acetone (125 ml) containing potassium carbonate (26.5 gr, 190 mmol) was refluxed for 2 hours. The volatiles were removed and the residue was partitioned between 2N hydrochloric acid and ethyl acetate. The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and the volatiles were removed under vacuum. The solid was triturated with petroleum ether to give 2-fluoro-4-nitro-benzyloxybenzene (23g, 97%).

$^1H$ NMR Spectrum: ($CDCl_3$) 5.3 (s, 2H) ; 7.1 (t, 1H) ; 7.35-7.55 (m, 5H) ; 8.0( m, 2H)

To a solution of potassium *tert*-butoxide (1.72g, 15.4 mmol) in DMF (15 ml) cooled at -30°C, was added dropwise a solution of 2-fluoro-4-nitro-benzyloxybenzene (1.73g, 7 mmol) and 4-chlorophenoxyacetonitrile (1.29 g, 7.7 mmol) while maintaining the temperature below -25°C. After completion of addition, the mixture was stirred for 30 minutes at -20°C and then poured onto a mixture of cold 1N hydrochloric acid and ether. The organic layer was separated, washed with 1N sodium hydroxide, followed by water, brine, dried ($MgSO_4$). The volatiles were removed under vacuum and the residue was purified by column chromatography eluting with methylene chloride/petroleum ether (3/1) to give a mixture of 3-cyanomethyl-2-fluoro-4-nitrobenzyloxybenzene and 5-cyanomethyl-2-fluoro-4-nitrobenzyloxybenzene ( 1.2 g, 60%).

$^1$H NMR Spectrum: ($DMSOd_6$) 4.22 (s, 2H, 3-cyanomethyl isomer) ; 4.3 (s, 2H, 5-cyanomethyl isomer); 5.32 (s, 2H, 5-cyanomethyl isomer) ; 5.36 (s, 2H, 3-cyanomethyl isomer); 7.3-7.7 (m, 6H); 8.1 (d, 1H, 3-cyanomethyl isomer); 8.2 (d, 1H, 5-cyanomethyl isomer)

A solution of a mixture of 3-cyanomethyl-2-fluoro-4-nitrobenzyloxybenzene and 5-cyanomethyl-2-fluoro-4-nitrobenzyloxybenzene (23g, 80.4 mmol) in ethanol (220ml) and acetic acid (30ml) containing 10% palladium on charcoal (600mg) was hydrogenated under 3 atmospheres pressure until hydrogen uptake ceased. The mixture was filtered and the filtrate was evaporated under vacuum. The residue was purified on column chromatography using a Prochrom® equipment eluting with methylene chloride/petroleum ether (20/80) to give 4-fluoro-5-hydroxyindole (2.48g) and 6-fluoro-5-hydroxyindole (3.5 g).

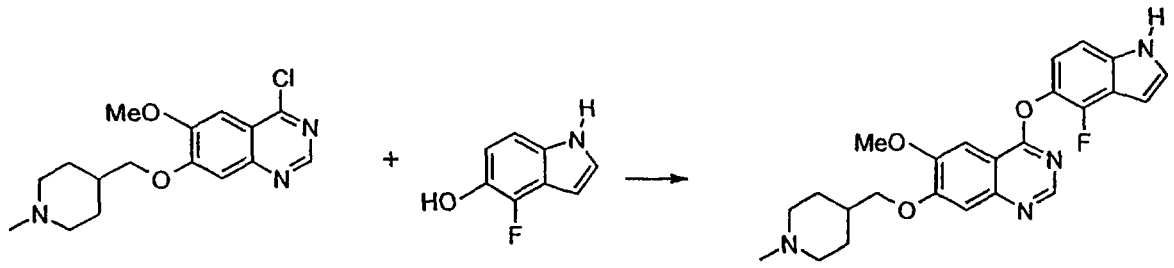
4-fluoro-5-hydroxyindole:

$^1$H NMR Spectrum: ($DMSOd_6$) 6.32 (s, 1H) ; 6.75 (dd, 1H) ; 7.0 (d, 1H) ; 7.28 (dd, 1H) ; 8.8 (br s, 1H) ; 11.05 (br s, 1H)

6-fluoro-5-hydroxyindole:

$^1$H NMR Spectrum: ($DMSOd_6$) 6.25 (s, 1H) ; 7.0 (d, 1H) ; 7.12 (d, 1H) ; 7.2 (dd, 1H) ; 9.0 (br s, 1H)

**Example 243**



A solution of 4-chloro-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline (213 mg, 0.662 mmol), (prepared as described for the starting material in Example 10), and 4-fluoro-5-hydroxyindole (120 mg, 0.794 mmol), (prepared as described for the starting material in Example 242), in DMF (3 ml) containing potassium carbonate (137 mg, 0.994 mmol) was stirred at 95°C for 3 hours. After cooling, the mixture was partitioned between ethyl acetate and water. The organic layer was washed with water, brine, dried ($MgSO_4$) and evaporated. The residue was triturated in cold ether. The solid was filtered and dried under vacuum to give **4-(4-fluoroindol-5-yloxy)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline** (77 mg, 26 %).

MS - ESI : 437 $[MH]^+$

$^1H$ NMR Spectrum: ($DMSOd_6$) 1.3-1.5 (m, 2H) ; 1.8 (d, 2H) ; 1.9 (t, 2H) ; 1.7-1.95 (m, 1H) ; 2.2 (s, 3H) ; 2.8 (d, 2H) ; 4.02 (s, 3H) ; 4.1 (d, 2H) ; 6.55 (s, 1H) ; 7.1 (t, 1H) ; 7.3 (d, 1H) ; 7.4 (s, 1H) ; 7.48 (t, 1H) ; 7.62 (s, 1H) ; 8.5 (s, 1H)

| | | | |
|---|---|---|---|
| Elemental analysis | Found | C 64.8 | H 5.8 N 12.6 |
| $C_{24}H_{25}FN_4O_3$ 0.4 $H_2O$ | Requires | C 65.0 | H 5.9 N 12.6% |

**Example 244**

A mixture of 4-chloro-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline (282 mg, 0.662 mmol), 6-fluoro-5-hydroxyindole (120 mg, 0.794 mmol), (prepared as described for the starting material in Example 242), in DMF (3 ml) containing potassium carbonate (137 mg, 0.994 mmol) was heated at 95°C for 3 hours. After cooling, the residue was poured in water (12 ml) and the pH was adjusted to 8. The mixture was extracted with ethyl acetate. The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and evaporated. The residue was purified by preparative column chromatography on $C^{18}$ silica eluting with 60 % methanol in aqueous ammonium carbonate (2g ammonium carbonate/litre saturated with $CO_2$). The fractions containing the expected product were combined and evaporated. The residue was triturated with ether and the solid was filtered, dried under

vacuum to give **4-(6-fluoroindol-5-yloxy)-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline** (147 mg, 48 %).

MS-ESI : 466 $[MH]^+$

$^1H$ NMR Spectrum: ($DMSOd_6$, $CF_3COOD$) 2.3-2.4 (m, 2H) ; 3.0 (s, 3H) ; 3.2-3.9 (m, 8H) ; 3.5 (t, 2H) ; 4.1 (s, 3H) ; 4.4 (t, 2H) ; 6.52 (d, 1H) ; 7.45 (d, 1H) ; 7.48 (s, 1H) ; 7.6 (s, 1H) ; 7.65 (d, 1H) ; 7.82 (s, 1H) ; 9.0 (s, 1H)

| | | | | | |
|---|---|---|---|---|---|
| Elemental analysis | Found | C 62.1 | H 6.4 | N 14.2 | |
| $C_{25}H_{28}FN_5O_3$ 0.9 $H_2O$ | Requires | C 62.3 | H 6.2 | N 14.5% | |

The starting material was prepared as follows:

To a suspension of 7-hydroxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (29g, 94.7 mmol), (prepared as described for the starting material in Example 12), in methylene chloride (280ml) colled at $5^0C$ was added triphenylphosphine (37.1g, 141.6 mmol) followed by 3-bromo-1-propanol (12.8 ml, 141.6 mmol) and diethyl azodicarboxylate (2.4 ml, 141.6 mmol) dropwise. After stirring for 2 hours at ambient temperature, the volatiles were removed under vacuum and the residue was purified by column chromatography eluting with methylene chloride/methanol (98/2). The fractions containing the expected product were combined and evaporated and the solid was triturated with ether, filtered, washed with ether and dried under vacuum to give 7-(3-bromopropoxy)-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (37.22 g, 92%).

MS-ESI : 427-429 [MH]+

$^1H$ NMR Spectrum: ($DMSOd_6$) 1.18 (s, 9H) ; 2.32 (m, 2H) ; 3.7 (t, 2H) ; 3.92 (s, 3H) ; 4.28 (t, 2H) ; 5.95 (s, 2H) ; 7.2 (s, 1H) ; 7.5 (s, 1H) ; 8.4 (s, 1H)

A suspension of 7-(3-bromopropoxy)-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (36.7 g, 86 mmol) in 1-methylpiperazine (370ml) was stirred at 100°C for 90 minutes. After removal of the volatiles under vacuum, the residue was partitioned between methylene chloride and aqueous ammonium chloride. The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and evaporated. The solid was triturated with ether, filtered, washed with ether and dried under vacuum to give 7-(3-(4-methylpiperazin-1-yl)propoxy)-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (31.9 gr, 83%).

MS-ESI : 447 [MH]+

$^1$H NMR Spectrum: (DMSO$d_6$, $CF_3COOD$) 1.15 (s, 9H) ; 2.25 (t, 2H) ; 2.5 (s, 3H) ; 3.45 (t, 2H) ; 3.2-4.0 (m, 8H); 3.9 (s, 3H) ; 4.25 (t, 2H) ; 5.95 (s, 2H) ; 7.22 (s, 1H) ; 7.55 (s, 1H) ; 8.6 (s, 1H)

A suspension of 7-(3-(4-methylpiperazin-1-yl)propoxy)-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (31.8 g, 71.3 mmol) in methanol saturated with ammonia was stirred at ambient temperature overnight. The volatiles were removed under vacuum. The solid was triturated with ether containing about 10% of methylene chloride, filtered, washed with ether containing about 10% methylene chloride and dried under vacuum to give 7-(3-(4-methylpiperazin-1-yl)propoxy)-6-methoxy-3,4-dihydroquinazolin-4-one (22.63g, 95%).

MS-ESI : 333 [MH]+

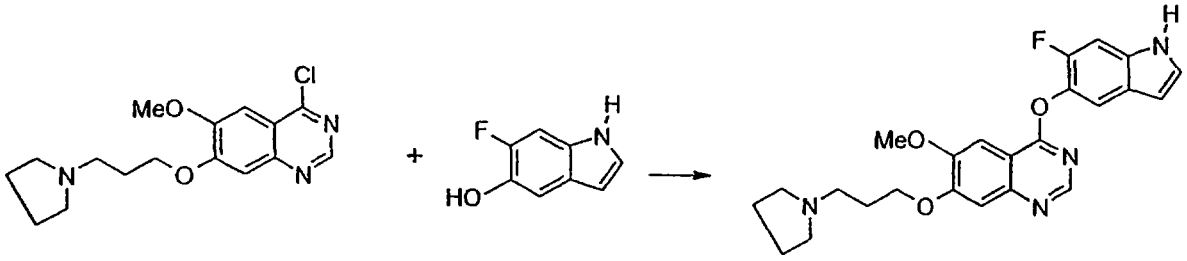
$^1$H NMR Spectrum: (DMSO$d_6$) 1.92 (m, 2H) ; 2.15 (s, 3H) ; 2.2-2.5 (m, 10H) ; 3.88 (s, 3H) ; 4.15 (t, 2H) ; 7.1 (s, 1H) ; 7.45 (s, 1H) ; 7.98 (s, 1H)

A solution of 7-(3-(4-methylpiperazin-1-yl)propoxy)-6-methoxy-3,4-dihydroquinazolin-4-one (22.6 g, 68 mmol) in thionyl chloride (300ml) cotaining DMF (5 ml) was refluxed for 2 hours. After cooling, the volatiles were removed under vacuum and the residue was azeotroped with toluene twice. The solid was dissolved in methulene chloride and water was added. The mixture was cooled to $0^0$C and the pH of the aqueous layer was adjusted to 7 with solid hydrogen carbonate and then raised to 10 with 6N Sodium hydroxide. The organic layer was separated and the aqueous layer was extracted with methylene chloride. The organic layer was washed with brine, dried ($MgSO_4$), filtered and the volatiles were removed under vacuum. The residue was triturated with ether, filtered, washed with ether and dried under vacuum to give 4-chloro-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline (16.3 gr, 68%).

MS-ESI : 351-353 [MH]+

$^1$H NMR Spectrum: (DMSO$d_6$) 1.98 (t, 2H) ; 2.18 (s, 3H) ; 2.45 (t, 2H) ; 2.22-2.5 (m, 8H) ; 4.05 (s, 3H) ; 4.28 (t, 2H) ; 7.4 (s, 3H) ; 7.45 (s, 1H) ; 8.9 (s, 1H)

**Example 245**



Using an analogous procedure to that described in Example 243, 4-chloro-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline (213 mg, 0.662 mmol), (prepared as described for the starting material in Example 9), was reacted with 6-fluoro-5-hydroxyindole (120 mg, 0.794 mmol), (prepared as described for the starting material in Example 242), in DMF (3 ml) containing potassium carbonate (137 mg, 0.993 mmol) to give **4-(6-fluoroindol-5-yloxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline** (154 mg, 53 %).

MS-ESI : 437 $[MH]^+$

$^1$H NMR Spectrum: ($DMSOd_6$) 1.7-1.8 (m, 4H) ; 2.0-2.1 (m, 2H) ; 2.48 (br s, 4H) ; 2.6 (t, 2H) ; 4.02 (s, 3H) ; 4.3 (t, 2H) ; 6.5 (s, 1H) ; 7.4 (d, 1H) ; 7.4 (s, 1H) ; 7.45 (t, 1H) ; 7.6 (d, 1H) ; 7.62 (s, 1H) ; 8.52 (s, 1H)

Elemental analysis Found C 65.4 H 6.0 N 12.9

$C_{24}H_{25}HN_4O_3$ 0.2 $H_2O$ Requires C 65.5 H 5.8 N 12.7%

**Example 246**

To a solution of 6-methoxy-4-(2-methylindol-5-yloxy)-7-(piperidin-4-ylmethoxy)quinazoline (500 mg, 1.2 mmol), (prepared as described in Example 70), in methanol (11.5 ml) containing potassium iodide (99 mg, 0.6 mmol) was added 4-(2-chloroethyl)morpholine hydrochloride (134 mg, 0.72 mmol) followed by sodium hydrogen carbonate (151 mg, 1.8 mmol). After stirring for 1 hour at reflux, 4-(2-chloroethyl)morpholine hydrochloride (134 mg, 0.72 mmol) and sodium hydrogen carbonate (151 mg, 1.8 mmol) were added. After stirring 1 hour at reflux, the mixture was cooled and the precipitate was filtered, washed with methanol followed by water and dried over phosphorus pentoxide to give **6-methoxy-4-(2-methylindol-5-yloxy)-7-(1-(2-morpholinoethyl)piperidin-4-ylmethoxy)quinazoline** (470 mg, 73 %).

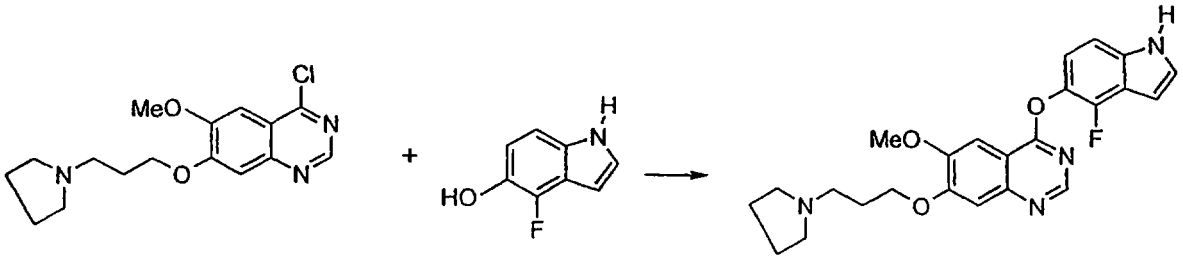
MS-ESI : 532 $[MH]^+$

$^1$H NMR Spectrum: ($DMSOd_6$) 1.3-1.45 (m, 2H) ; 1.8 (d, 2H) ; 1.7-1.9 (m, 1H) ; 2.0 (t, 2H) ; 2.3-2.45 (m, 8H) ; 2.4 (s, 3H) ; 2.95 (d, 2H) ; 3.6 (t, 4H) ; 4.0 (s, 3H) ; 4.08 (d, 2H) : 6.18 (s,

1H) ; 6.9 (dd, 1H) ; 7.3 (s, 1H) ; 7.35 (d, 1H) ; 7.4 (s, 1H) ; 7.6 (s, 1H) ; 8.5 (s, 1H) ; 11.05 (s, 1H)

| | | | | |
|---|---|---|---|---|
| Elemental analysis | Found | C 65.3 | H 7.1 | N 12.6 |
| $C_{30}H_{37}N_5O_4$ 0.6 $H_2O$ 0.6 Methanol | Requires | C 65.4 | H 7.3 | N 12.5% |

**Example 247**



A solution of 4-chloro-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline (1.76 g, 5.47 mmol), (prepared as described for the starting material in Example 9), 4-fluoro-5-hydroxyindole (0.992 g, 6.57 mmol), (prepared as described for the starting material in Example 242), in DMF (25 ml) containing potassium carbonate (1.14 g ; 8.21 mmol) was heated at 95°C for 1 hour. After cooling, the mixture was filtered and washed with DMF. The filtrate was evaporated and the residue was purified by column chromatography eluting with methanol/methylene chloride (1/9) followed by methanol/methanol chloride/methanol (containing ammonia) (16/80/4). The fractions containing the expected product were combined and evaporated. The residue was repurified by column chromatography eluting with a gradient of methylene chloride/methanol (80/20 to 40/60). The fractions containing the expected product were combined and evaporated. The residue was triturated in cold methanol and the solid was filtered, washed with ether and dried under vacuum to give **4-(4-fluoroindol-5-yloxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline** (1.24 g, 52 %).

MS-ESI : 437 $[MH]^+$

$^1H$ NMR Spectrum: ($DMSOd_6$) 1.7 (br s, 4H) ; 2.0 (m, 2H) ; 2.45 (br s, 4H) ; 2.6 (t, 2H) ; 4.05 (s, 3H) ; 4.28 (t, 2H) ; 6.58 (s, 1H) ; 7.1 (t, 2H) ; 7.35 (d, 1H) ; 7.4 (s, 1H) ; 7.5 (t, 1H) ; 7.65 (s, 1H) ; 8.52 (s, 1H)

| | | | | |
|---|---|---|---|---|
| Elemental analysis | Found | C 65.3 | H 5.9 | N 12.6 |
| $C_{24}H_{25}FN_4O_3$ 0.19 Methanol, 0.17 $H_2O$ | Requires | C 65.2 | H 5.9 | N 12.6% |

**Example 248**

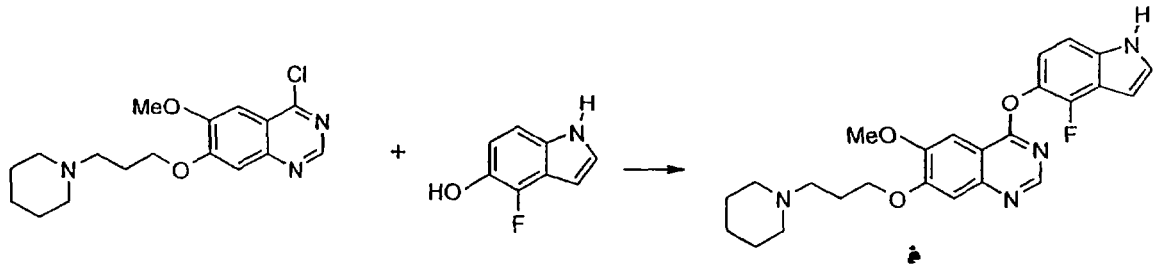
A mixture of 4-chloro-6-methoxy-7-(3-piperidinopropoxy)quinazoline (222 mg, 0.662 mmol), (prepared as described for the starting material in Example 67), and 6-fluoro-5-hydroxyindole (120 mg, 0.794 mmol), (prepared as described for the starting material in Example 242), in DMF (3 ml) containing potassium carbonate (137 mg, 0.993 mmol) was heated at 95°C for 3.5 hours. After cooling the mixture was poured onto water and extracted with ethyl acetate. The organic layers were washed with water, brine, dried ($MgSO_4$) and evaporated. The residue was triturated with ether, filtered and dried under vacuum to give **4-(6-fluoroindol-5-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline** (139 mg, 46 %).

MS-ESI : 451 $[MH]^+$

$^1H$ NMR Spectrum: ($DMSOd_6$) 1.35-1.45 (m, 2H) ; 1.45-1.6 (m, 4H) ; 2.0 (m, 2H) ; 2.35 (br s, 4H) ; 2.42 (t, 2H) ; 4.05 (s, 3H) ; 4.25 (t, 2H) ; 6.5 (s, 1H) ; 7.4 (d, 1H) ; 7.42 (s, 1H) ; 7.44 (t, 1H) ; 7.6 (d, 1H) ; 7.65 (s, 1H) ; 8.5 (s, 1H)

| | | | | |
|---|---|---|---|---|
| Elemental analysis | Found | C 65.9 | H 6.2 | N 12.3 |
| $C_{25}H_{27}FN_4O_3$ 0.3 $H_2O$ | Requires | C 65.9 | H 6.1 | N 12.3% |

**Example 249**




Using an analogous procedure to that described in Example 244, 4-chloro-6-methoxy-7-(3-piperidinopropoxy)quinazoline (407 mg, 1.21 mmol), (prepared as described for the starting material in Example 67), 4-fluoro-5-hydroxyindole (220 mg, 1.45 mmol) (prepared as described for the starting material in Example 242), and potassium carbonate (251 mg, 1.82 mmol) in DMF (6 ml) were heated at 95°C for 90 minutes and purified to give **4-(4-fluoroindol-5-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline** (367 mg, 67 %).

MS-ESI : 451 $[MH]^+$

$^1H$ NMR Spectrum: ($DMSOd_6$) 1.35-1.45 (m, 2H) ; 1.55 (m, 4H) ; 2.0 (m, 2H) ; 2.38 (br s, 4H) ; 2.45 (t, 2H) ; 4.02 (s, 3H) ; 4.25 (t, 2H) ; 6.55 (s, 1H) ; 7.12 (dd, 1H) ; 7.32 (d, 1H) ; 7.4 (s, 1H) ; 7.5 (s, 1H) ; 7.65 (s, 1H) ; 8.52 (s, 1H)

| | | | | |
|---|---|---|---|---|
| Elemental analysis | Found | C 66.0 | H 6.2 | N 12.4 |

| | | | | | |
|---|---|---|---|---|---|
| $C_{25}H_{27}FN_4O_3$ 0.2 $H_2O$ | Requires | C | 66.1 | H 6.1 | N 12.3% |

**Example 250**

Using an analogous procedure to that described in Example 248, 4-chloro-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline (268 mg, 0.833 mmol), (prepared as described for the starting material in Example 9), was reacted with 6-fluoro-5-hydroxy-2-methylindole (165 mg, 1 mmol) in DMF (3.5 ml) containing potassium carbonate (173 mg, 1.25 mmol) to give **4-(6-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline** (215 mg, 57 %).

MS-ESI : 451 $[MH]^+$

$^1$H NMR Spectrum: ($DMSOd_6$) 1.65-1.8 (br s, 4H) ; 2.02 (m, 2H) ; 2.4 (s, 3H) ; 2.48 (br s, 4H) ; 2.6 (t, 2H) ; 4.02 (s, 3H) ; 4.3 (t, 2H) ; 6.18 (s, 1H) ; 7.25 (d, 1H) ; 7.4 (s, 1H) ; 7.45 (d, 1H) ; 7.6 (s, 1H) ; 8.5 (s, 1H)

| | | | | | |
|---|---|---|---|---|---|
| Elemental analysis | Found | C | 65.6 | H 6.1 | N 12.2 |
| $C_{25}H_{27}FN_4O_3$ 0.4 $H_2O$ | Requires | C | 65.6 | H 6.1 | N 12.2% |

The starting material was prepared as follows:

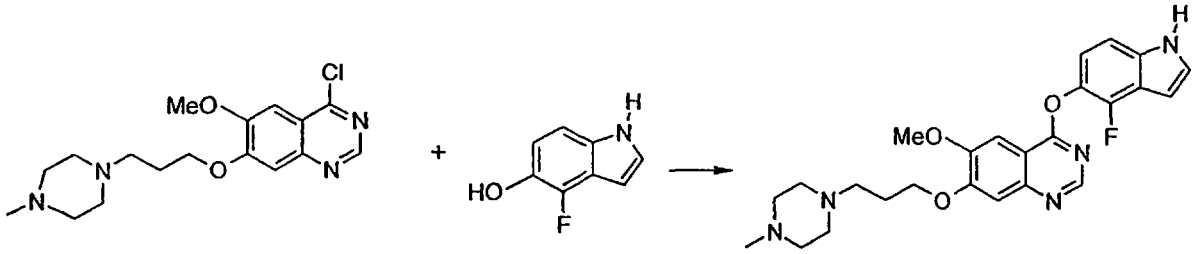
To a solution of 6-fluoro-5-methoxy-2-methylindole (1.23 g, 6.86 mmol), (prepared as described for the starting material in Example 237), in methylene chloride (15 ml) cooled at -30°C was added a solution of boron tribromide (3.78 g, 15.1 mmol) in methylene chloride (2 ml). After stirring for 90 minutes at ambient temperature, the mixture was poured onto ice and diluted with methylene chloride. The pH of the aqueous layer was adjusted to 6. The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography eluting with ethylacetate/petroleum ether (8/2) to give 6-fluoro-5-hydroxy-2-methylindole (905 mg, 80 %).

MS-ESI : 166 $[MH]^+$

$^1$H NMR Spectrum: ($DMSOd_6$) 2.3 (s, 3H) ; 5.95 (s, 1H) ; 6.9 (d, 1H) ; 7.0 (d, 1H) ; 8.85 (s, 1H) ; 10.6 (s, 1H)

$^{13}$C NMR Spectrum: ($DMSOd_6$) 13.3 ; 97.4 (d) ; 98.3 ; 105.5 ; 124.5 ; 128.8 (d) ; 135.6 ; 138.5 (d) ; 148.3 (d).

**Example 251**



A mixture of 4-chloro-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline (232 mg, 0.662 mmol), (prepared as described for the starting material in Examples 176 or 244), and 4-fluoro-5-hydroxyindole (120 mg, 0.794 mmol), (prepared as described for the starting material in Example 242), in DMF (3 ml) containing potassium carbonate (137 mg, 1 mmol) was stirred at 95°C for 3 hours. After cooling, the residue was poured onto water (12 ml) and extracted with ethyl acetate. The organic layer was washed with water, brine, dried ($MgSO_4$) and evaporated. The residue was purified by reversed phase $C_{18}$ column chromatography eluting with methanol/ammonium carbonate (2g of ammonium carbonate/litre saturated with $CO_2$) (60/40 followed by 70/30). The fractions containing the expected product were combined and evaporated. The residue was dissolved in ethyl acetate, dried ($MgSO_4$) and the volatiles were removed under vacuum. The residue was triturated with ether, filtered and dried under vacuum to give **4-(4-fluoroindol-5-yloxy)-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline** (130 mg, 42 %).

MS-ESI : 466 $[MH]^+$

$^1H$ NMR Spectrum: ($DMSOd_6$, $CF_3COOD$) 2.3-2.4 (m, 2H) ; 2.97 (s, 3H) ; 3.2-4.1 (m, 8H) ; 3.5 (t, 2H) ; 4.07 (s, 3H) ; 4.4 (t, 2H) ; 6.6 (d, 1H) ; 7.15 (t, 1H) ; 7.38 (d, 1H) ; 7.5 (d, 1H) ; 7.6 (s, 1H) ; 7.82 (s, 1H) ; 8.95 (s, 1H)

| | | | | |
|---|---|---|---|---|
| Elemental analysis | Found | C 64.4 | H 6.1 | N 15.0 |
| $C_{25}H_{28}FN_5O_3$ | Requires | C 64.5 | H 6.1 | N 15.0% |

**Example 252**

A mixture of 6-methoxy-4-(2-methylindol-5-yloxy)-7-(piperidin-4-ylmethoxy)quinazoline (600 mg, 1.43 mmol), (prepared as described in Example 70), 1-(2-chloroethyl)-pyrrolidine (292 mg, 1.72 mmol) in methanol (14 ml) containing sodium carbonate (262 mg, 4.3 mmol) and potassium iodide (48 mg, 0.29 mmol) was heated at 50°C for 20 hours. After cooling, the volatiles were removed under vacuum. The residue was purified by preparation HPLC on reverse $C_{18}$ silica eluting with methanol/aqueous ammonium

carbonate (2g ammonium carbonate per litre saturated with $CO_2$) (60/40 followed by 70/30). The fractions containing the expected product were combined and the volatiles were removed under vacuum. The residue was triturated with ether and the solid was filtered, washed with ether and dried under vacuum to give **6-methoxy-4-(2-methylindol-5-yloxy)-7-(1-(2-(pyrrolidin-1-yl)ethyl)-piperidin-4-ylmethoxy)quinazoline** (102 mg, 20 %).

MS-ESI : 516 $[MH]^+$

$^1H$ NMR Spectrum: ($DMSOd_6$) 1.3-1.5 (m, 2H) ; 1.6-1.75 (m, 4H) ; 1.8 (d, 2H) ; 1.7-1.9 (m, 1H) ; 1.95 (t, 2H) ; 2.45 (s, 3H) ; 2.4-2.5 (m, 5H) ; 2.95 (d, 2H) ; 3.35 (d, 2H) ; 4.0 (s, 3H) ; 4.1 (d, 2H) ; 6.18 (s, 1H) ; 6.9 (d, 1H) ; 7.25 (s, 1H) ; 7.35 (d, 1H) ; 7.38 (s, 1H) ; 7.6 (s, 1H) ; 8.5 (s, 1H) ; 11.05 (s, 1H)

| | | |
|---|---|---|
| Elemental analysis | Found | C 68.6 H 7.2 N 13.3 |
| $C_{30}H_{37}N_5O_3$ 0.5 $H_2O$ | Requires | C 68.7 H 7.3 N 13.4% |

**Example 253**

A mixture of 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (110 mg, 0.325 mmol), (prepared as described for the starting material in Example 1), and 6-fluoro-5-hydroxyindole (59 mg, 0.39 mmol), (prepared as described for the starting material in Example 242), in DMF (1.8 ml) containing potassium carbonate (67 mg, 0.487 mmol) was heated at 90°C for 2 hours. After cooling, water was added. The solid was separated and triturated with methanol. Water was added and the solid was filtered, washed with water and dried under vacuum to give **4-(6-fluoroindol-5-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline** (55 mg, 41 %).

MS-ESI : 453 $[MH]^+$

$^1H$ NMR Spectrum: ($DMSOd_6$) 1.95-2.05 (m, 2H) ; 2.45 (br s, 4H) ; 2.5 (t, 2H) ; 3.62 (t, 4H) ; 4.02 (s, 3H) ; 4.3 (t, 2H) ; 6.5 (s, 1H) ; 7.4 (d, 1H) ; 7.45 (s, 1H) ; 7.47 (t, 1H) ; 7.58 (d, 1H) ; 7.62 (s, 1H) ; 8.5 (s, 1H)

| | | |
|---|---|---|
| Elemental analysis | Found | C 61.6 H 5.5 N 11.9 |
| $C_{24}H_{25}FN_4O_4$ 0.8 $H_2O$ | Requires | C 61.7 H 5.7 N 12.0% |

**Example 254**

To a solution of 7-hydroxy-4-(indol-5-yloxy)-6-methoxyquinazoline (183 mg, 0.6 mmol), (prepared as described for the starting material in Example 107), triphenylphosphine

(235 mg, 0.89 mmol) and 4-(2-hydroxyethyl)morpholine (93 mg, 0.72 mmol) in methylene chloride (4 ml) cooled at 10°C was added diethyl azodicarboxylate (140 µl, 0.89 mmol). After stirring at ambient temperature for 3 hours, the mixture was left overnight at 5°C. The mixture was poured onto a column of silica and eluted with methylene chloride followed by methanol/methylene chloride (2/98) followed by 3N ammonia methanol/methylene chloride (2/98). The fractions containing the expected products were combined and evaporated to give **4-(indol-5-yloxy)-6-methoxy-7-(2-morpholinoethoxy)quinazoline** (137 mg, 55 %).

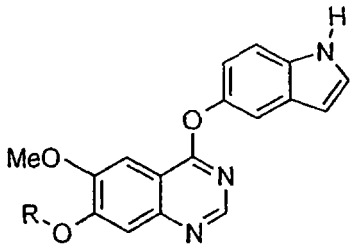
MS-ESI : 421 $[MH]^+$

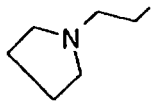
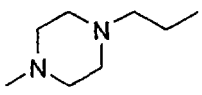
$^1H$ NMR Spectrum: ($DMSOd_6$, $CF_3COOD$) 3.30 (t, 2H) ; 3.65 (d, 2H) ; 3.7-3.8 (m, 4H) ; 4.05 (d, 2H) ; 4.1 (s, 3H) ; 4.7 (t, 2H) ; 6.5 (s, 1H) ; 7.05 (dd, 1H) ; 7.4-7.6 (m, 3H) ; 7.65 (s, 1H) ; 7.82 (s, 1H) ; 9.0 (s, 1H)

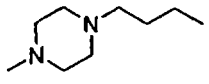
**Examples 255–257**

Using an analogous procedure to that described in Example 254, 7-hydroxy-4-(indol-5-yloxy)-6-methoxyquinazoline (183 mg, 0.6 mmol), (prepared as described for the starting material in Example 107), was used to prepare the compounds in Table XVIII.

**Table XVIII**




| Example number | Weight (mg) | Yield % | MS-ESI $[MH]^+$ | R | Note |
|---|---|---|---|---|---|
| 255 | 123 | 51 | 405 |  | a |
| 256 | 124 | 48 | 434 |  | b |

| | | | | | |
|---|---|---|---|---|---|
| 257 | 165 | 62 | 448 |  | c |

a) 7-Hydroxy-4-(indol-5-yloxy)-6-methoxyquinazoline (183 mg, 0.6 mmol) was reacted with 1-(2-hydroxyethyl)pyrrolidine (82 mg) to give **4-(indol-5-yloxy)-6-methoxy-7-(2-(pyrrolidin-1-yl)ethoxy)quinazoline**.

$^1$H NMR Spectrum: ($DMSOd_6$) 1.72 (br s, 4H) ; 2.6 (br s, 4H) ; 2.9 (t, 2H) ; 4.0 (s, 3H) ; 4.3 (t, 2H) ; 6.48 (s, 1H) ; 7.0 (dd, 1H) ; 7.4-7.5 (m, 3H) ; 7.6 (s, 1H) ; 8.5 (s, 1H) ; 11.3 (br s, 1H)

b) 7-Hydroxy-4-(indol-5-yloxy)-6-methoxyquinazoline (183 mg, 0.6 mmol) was reacted with 4-(2-hydroxyethyl)-1-methylpiperazine (103 mg) to give **4-(indol-5-yloxy)-6-methoxy-7-(2-(4-methylpiperazin-1-yl)ethoxy)quinazoline**.

$^1$H NMR Spectrum: ($DMSOd_6$, $CF_3COOD$) 2.5 (s, 3H) ; 3.35 (t, 2H) ; 3.65 (d, 2H) ; 3.7-3.8 (m, 4H) ; 4.05 (d, 2H) ; 4.1 (s, 3H) ; 4.7 (t, 2H) ; 7.05 (dd, 1H) ; 7.45 (s, 1H) ; 7.5-7.6 (m, 2H) ; 7.65 (s, 1H) ; 7.82 (s, 1H) ; 9.0 (s, 1H)

The starting material was prepared as follows:-

2-Bromoethanol (2.36g, 19mmol) was added dropwise to a mixture of 1-methylpiperazine (1.26g, 13mmol) and potassium carbonate (5.0g, 36mmol) in absolute ethanol (150ml) and the mixture heated at reflux for 18 hours. The mixture was allowed to cool and the precipitates were removed by filtration and the solvent volatiles were removed by evaporation. The residue was treated with acetone/methylene chloride, the insolubles were removed by filtration and the solvent was removed from the filtrate by evaporation to give 4-(2-hydroxyethyl)-1-methylpiperazine (870mg, 48%) as a light brown oil.

$^1$H NMR Spectrum: ($CDCl_3$) 2.18(s, 3H); 2.3-2.7(br m, 8H); 2.56(t, 2H); 3.61(t, 2H)

MS - ESI: 145 $[MH]^+$

c) 7-Hydroxy-4-(indol-5-yloxy)-6-methoxyquinazoline (183 mg, 0.6 mmol) was reacted with 1-(3-hydroxypropyl)-4-methylpiperazine (113 mg), (prepared as described for the starting material in Example 133), to give **4-(indol-5-yloxy)-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline**.

$^1$H NMR Spectrum: ($DMSOd_6$) 2.15 (s, 3H) ; 2.3-2.4 (br s, 4H) ; 2.5-2.6 (m, 4H) ; 2.8 (t, 2H) ; 4.0 (s, 3H) ; 4.35 (t, 2H) ; 6.45 (s, 1H) ; 7.0 (dd, 1H) ; 7.4-7.5 (m, 4H) ; 7.62 (s, 1H) ; 8.5 (s, 1H)

**Example 258**

A solution of (2*R*)-7-(2-acetoxy-3-(pyrrolidin-1-yl)propoxy)-4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxyquinazoline (570 mg, 1.12 mmol) in methanol saturated with ammonia (7 ml) was stirred overnight at ambient temperature. The volatiles were removed under vacuum and the residue was purified by column chromatography eluting with methylene chloride/methanol containing ammonia (approximately 3N) to give **(2*R*)-7-(2-hydroxy-3-(pyrrolidin-1-yl)propoxy)-4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxyquinazoline** (390mg ; 75% ).

MS-ESI : 467 [MH]+

$^1$H NMR Spectrum: ($DMSOd_6$, $CF_3COOD$) 1.85-2.0 (m, 2H) ; 2.0-2.15 (m, 2H) ; 2.42 (s, 3H) ; 3.15 (m, 2H) ; 3.4 (d, 2H) ; 3.65 (m, 2H) ; 4.1(s, 3H) ; 4.32 (d, 2H) ; 4.4 (m, 1H) ; 7.05 (dd, 1H) ; 7.22 (d, 1H) ; 7.6 (s, 1H) ; 7.85 (s, 1H) ; 9.02 (s, 1H)

The starting material was prepared as follows:

A suspension of 7-hydroxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (1.2 g, 3.91 mmol), (prepared as described for the starting material in Example 12), and 2-(*R*)-(-)-Glycidyl tosylate (1.25 g, 5.47 mmol) in DMF (10 ml) containing potassium carbonate (1.61 g, 11.7 mmol) was stirred at 60°C for 4 hours. After cooling, the mixture was filtered and the solid was washed with DMA. The filtrate was evaporated and the residue was partitioned between ethyl acetate and aqueous ammonia. The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography eluting with ethyl acetate. The fractions containing the expected product were combined and evaporated to give (2*R*)-7-(oxiran-2-ylmethoxy)-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (1.21 g, 85 %).

MS-ESI : 363 $[MH]^+$

$^1$H NMR Spectrum: ($DMSOd_6$) 1.12 (s, 9H) ; 2.75 (m, 1H) ; 2.9 (t, 1H) ; 3.4 (m, 1H) ; 3.93 (s, 3H) ; 4.0 (dd, 1H) ; 4.52 (dd, 1H) ; 5.9 (s, 2H) ; 7.2 (s, 1H) ; 7.52 (s, 1H) ; 8.35 (s, 1H)

A solution of (2*R*)-7-(oxiran-2-ylmethoxy)-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (1.1 g, 3 mmol) and pyrrolidine (216 mg, 3 mmol) in trichloromethane (15 ml) was refluxed for 11 hours. The volatiles were removed under vacuum and the residue was purified by column chromatography eluting with methylene chloride/methanol (85/15 followed by 70/30) to give (2*R*)-7-(2-hydroxy-3-(pyrrolidin-1-yl)propoxy)-6-methoxy-3-((pivaloyloxymethyl)-3,4-dihydroquinazolin-4-one (1.18 g, 90 %).
$^1$H NMR Spectrum: ($DMSOd_6$) 1.15 (s, 9H) ; 1.7 (br s, 4H) ; 2.48 (m, 1H) ; 2.5 (br s, 4H) ; 2.65 (dd, 1H) ; 3.9 (s, 3H) ; 4.0 (br s, 1H) ; 4.05 (dd, 1H) ; 4.18 (dd, 1H) ; 4.95 (br s, 1H) ; 5.9 (s, 2H) ; 7.2 (s, 1H) ; 7.5 (s, 1H) ; 8.35 (s, 1H)

A solution of (2*R*)-7-(2-hydroxy-3-(pyrrolidin-1-yl)propoxy)-6-methoxy-3-((pivaloyloxymethyl)-3,4-dihydroquinazolin-4-one (778 mg, 1.8 mmol) in methanol saturated with ammonia (20 ml) was stirred for 24 hours at ambient temperature. The volatiles were removed under vacuum. The residue was triturated with ether and the residue was filtered, washed with ether and dried under vacuum to give (2*R*)-7-(2-hydroxy-3-(pyrrolidin-1-yl)propoxy)-6-methoxy-3,4-dihydroquinazolin-4-one (800 mg, quant.).
$^1$H NMR Spectrum: ($DMSOd_6$, $CF_3COOD$) 1.92 (m, 2H) ; 2.05 (m, 2H) ; 3.15 (m, 2H) ; 3.35 (d, 2H) ; 3.62 (m, 2H) ; 3.98 (s, 3H) ; 4.18 (d, 2H) ; 4.32 (m, 1H) ; 7.35 (s, 1H) ; 7.6 (s, 1H) ; 9.2 (s, 1H)

A mixture of (2*R*)-7-(2-hydroxy-3-(pyrrolidin-1-yl)propoxy)-6-methoxy-3,4-dihydroquinazolin-4-one (803 mg, 2.51 mmol) in acetic anhydride (1.2 ml, 12.5 mmol) was stirred at ambient temperature for 1 hour. Water (360 µl, 20 mmol) was added and stirring was continued for 90 minutes. The mixture was partitioned between aqueous sodium hydrogen carbonate and methylene chloride. The organic layer was separated, washed with brine, dried ($MgSO_4$) and evaporated. The residue was triturated with ether, filtered and dried under vacuum to give (2*R*)-7-(2-acetoxy-3-(pyrrolidin-1-yl)propoxy)-6-methoxy-3,4-dihydroquinazolin-4-one (595 mg, 65%).
MS-ESI : 362 [MH]+
$^1$H NMR Spectrum: ($DMSOd_6$) 1.7 (br s, 4H) ; 2.05 (s, 3H) ; 2.5 (br s, 4H) ; 2.72 (m, 2H) ; 3.9 (s, 3H) ; 4.3 (m, 2H) ; 5.25 (m, 1H) ; 7.2 (s, 1H) ; 7.45 (s, 1H) ; 8.0 (s, 1H)

A solution of (2*R*)-7-(2-acetoxy-3-(pyrrolidin-1-yl)propoxy)-6-methoxy-3,4-dihydroquinazolin-4-one (556mg, 1.54 mmol) in thionyl chloride (6 ml) containing DMF (3 drops) was heated at 80°C for 4 hours. The volatiles were removed under vacuum. The

residue was dissolved in methylene chloride and the organic layer was washed with aqueous sodium hydrogen carbonate, brine, dried ($MgSO_4$) and evaporated to give (2*R*)-7-(2-acetoxy-3-(pyrrolidin-1-yl)propoxy)-4-chloro-6-methoxyquinazoline (530mg, 90%).

$^1$H NMR Spectrum: ($DMSOd_6$) 1.7 (br s, 4H) ; 2.05 (s, 3H) ; 2.55 (br s, 4H) ; 2.75 (br s, 2H) ; 4.02 (s, 3H) ; 4.35-4.5 (m, 2H) ; 5.3 (m, 1H) ; 7.4 (s, 1H) ; 7.5 (s, 1H) ; 7.9 (s, 1H)

A suspension of (2*R*)-7-(2-acetoxy-3-(pyrrolidin-1-yl)propoxy)-4-chloro-6-methoxyquinazoline (530 mg, 1.4 mmol) and 4-fluoro-5-hydroxy-2-methylindole (277 mg, 1.68 mmol), (prepared as described for the starting material in Example 237), in DMF (8 ml) containing potassium carbonate (290 mg, 2.1 mmol) was stirred at 90°C for 2 hours. After cooling, the volatiles were removed under vacuum and the residue was purified by column chromatography eluting with methylene chloride/methanol (95/5) to give (2*R*)-7-(2-acetoxy-3-(pyrrolidin-1-yl)propoxy)-4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxyquinazoline (580 mg, 81 %).

$^1$H NMR Spectrum: ($DMSOd_6$) 1.7 (br s, 4H) ; 2.05 (s, 3H) ; 2.4 (s, 3H) ; 2.52 (br s, 4H) ; 2.65-2.82 (m, 2H) ; 4.0 (s, 3H) ; 4.4 (m, 2H) ; 5.3 (m, 1H) ; 6.25 (s, 1H) ; 7.0 (dd, 1H) ; 7.18 (d, 1H) ; 7.48 (s, 1H) ; 7.62 (s, 1H) ; 8.5 (s, 1H)

**Example 259**

A solution of 4-chloro-6-methoxy-7(3-(pyrrolidin-1-yl)propoxy)quinazoline (61 mg, 0.19 mmol), (prepared as described for the starting material in Example 9), and 5-aminoindole (30 mg, 0.23 mmol) in isopropanol (2 ml) containing 6.2 N hydrogen chloride in isopropanol (33 µl) was heated at 80°C for 6 hours. After cooling, the precipitate was filtered, washed with ether and dried under vacuum to give **4-(indol-5-ylamino)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline** hydrochloride (80 mg, 72 %).

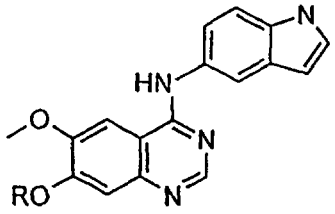
MS - ESI : 418 $[MH]^+$

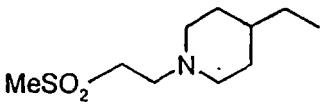
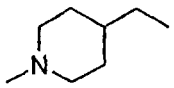
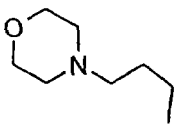
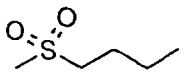
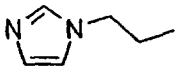
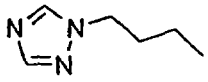
$^1$H NMR Spectrum: ($DMSOd_6$, $CF_3COOD$) 1.9 (m, 2H) ; 2.05 (m, 2H) ; 2.3 (m, 2H) ; 3.1 (m, 2H) ; 3.4 (t, 2H) ; 3.65 (m, 2H) ; 4.05 (s, 3H) ; 4.35 (t, 2H) ; 6.5 (s, 0.5H, partly exchanged) ; 7.3 (d, 1H) ; 7.4 (s, 1H) ; 7.45 (s, 1H) ; 7.55 (d, 1H) ; 7.8 (s, 1H) ; 8.25 (s, 1H) ; 8.8 (s, 1H)

**Example 260–265**

Using an analogous procedure to that described in Example 259, 5-aminoindole (30 mg, 0.23 mmol) was used in the synthesis of the compounds described in Table XIX.

**Table XIX**



| Example number | Weight (mg) | Yield (%) | MS-ESI $[MH]^+$ | Note | R |
|---|---|---|---|---|---|
| 260 | 101 | 76 | 510 | a |  |
| 261 | 92 | 83 | 418 | b |  |
| 262 | 92 | 80 | 434 | c |  |
| 263 | 84 | 80 | 427 | d |  |
| 264 | 78 | 79 | 401 | e |  |
| 265 | 72 | 70 | 416 | f |  |

a) 4-Chloro-6-methoxy-7-((1-(2-methylsulphonylethyl)piperidin-4-yl)methoxy)quinazoline (78 mg), (prepared as described for the starting material in Example 12), was reacted with 5-aminoindole to give **4-(indol-5-ylamino)-6-methoxy-7-((1-(2-methylsulphonylethyl)piperidin-4-yl)methoxy)quinazoline** hydrochloride.

$^1$H NMR Spectrum: (DMSOd6) 1.65-1.8 (m, 2H) ; 2.05 (d, 2H) ; 2.2 (br s, 1H) ; 3.1 (br s, 2H) ; 3.2 (s, 3H) ; 3.5 (br s, 2H) ; 3.6 (d, 2H) ; 3.8 (m, 2H) ; 4.05 (s, 3H) ; 4.1 (d, 2H) ; 6.5 (s, 1H)

; 7.3 (d, 1H) ; 7.42 (m, 2H) ; 7.5 (d, 1H) ; 7.8 (s, 1H) ; 8.4 (s, 1H) ; 8.7 (s, 1H) ; 11.15 (br s, 1H) ; 11.32 (s, 1H) . 11.5 (s, 1H).

b) 4-Chloro-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline (61 mg), (prepared as described for the starting material in Example 10), was reacted with 5-aminoindole to give **4-(indol-5-ylamino)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline** hydrochloride.

$^1$H NMR Spectrum: ($DMSOd_6$) 1.6-1.8 (m, 2H) ; 2.02 (d, 2H) ; 2.15 (br s, 1H) ; 2.75 (s, 3H) ; 3.0 (br s, 2H) ; 3.45 (d, 2H) ; 4.02 (s, 3H) ; 4.1 (d, 2H) ; 6.5 (s, 1H) ; 7.3 (d, 1H) ; 7.4 (m, 2H) ; 7.5 (d, 1H) ; 7.8 (s, 1H) ; 8.3 (s, 1H) ; 8.7 (s, 1H) ; 10.4 (br s, 1H) ; 11.3 (s, 1H)

The presence of a second form of the piperidine ring (due to protonation effects) is detectable in the NMR Spectrum as a doublet at 4.3 ppm (approximately 20 % of parent compound).

c) 4-Chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (64 mg), (prepared as described for the starting material in Example 1), was reacted with 5-aminoindole to give **4-(indol-5-ylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline** hydrochloride.

$^1$HNMR Spectrum ($DMSOd_6$ ; $CF_3COOD$) : 2.35 (m, 2H) ; 3.15 (t, 2H) ; 3.3 (t, 2H) ; 3.57 (d, 2H) ; 3.8 (m, 2H) ; 4.02 (d, 2H) ; 4.03 (s, 3H) ; 4.3 (t, 2H) ; 6.5 (d, 1H) ; 7.3 (dd, 1H) ; 7.4 (s, 1H) ; 7.45 (s, 1H) ; 7.52 (d, 1H) ; 7.8 (s, 1H) ; 8.25 (s, 1H) ; 8.78 (s, 1H)

d) 4-Chloro-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline (62 mg), (prepared as described for the starting material in Example 50), was reacted with 5-aminoindole in the presence of 6.2N hydrogen chloride in isopropanol (4 µl) to give **4-(indol-5-ylamino)-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline** hydrochloride.

$^1$H NMR Spectrum: ($DMSOd_6$, $CF_3COOD$) 2.2-2.4 (m, 2H) ; 3.07 (s, 3H) ; 3.35 (t, 2H) ; 4.05 (s, 3H) ; 4.35 (t, 2H) ; 6.5 (d, 0.5 H, partly exchanged) ; 7.2-7.35 (m, 2H) ; 7.45 (s, 1H) ; 7.5 (d, 1H) ; 7.8 (s, 1H) ; 8.2 (s, 1H) ; 8.75 (s, 1H)

e) 4-Chloro-7-(2-(imidazol-1-yl)ethoxy)-6-methoxyquinazoline (58 mg) was reacted with 5-aminoindole in the presence of 6.2N hydrogen chloride in isopropanol (4 µl) to give **4-(indol-5-ylamino)-7-(2-(imidazol-1-yl)ethoxy)-6-methoxyquinazoline** hydrochloride.

$^1$H NMR Spectrum: ($DMSOd_6$, $CF_3COOD$) 4.03 (s, 3H) ; 4.65 (t, 2H) ; 4.8 (t, 2H) ; 6.5 (d, 1H, partly exchanged) ; 7.30 (d, 1H) ; 7.4 (s, 1H) ; 7.45 (s, 1H) ; 7.52 (d, 1H) ; 7.75 (s, 1H) ; 7.8 (s, 1H) ; 7.9 (s, 1H) ; 8.25 (s, 1H) ; 8.75 (s, 1H) ; 9.25 (s, 1H)

The starting material was prepared as follows:

Diethyl azodicarboxylate (435mg, 2.5mmol) was added dropwise to a suspension of 7-hydroxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (612mg, 2mmol), (prepared as described for the starting material in Example 12), 2-(imidazol-1-yl)ethanol (280mg, 2.5mmol), (J. Med. Chem. 1993, **25** 4052-4060), and triphenylphosphine (655mg, 2.5mmol) in methylene chloride (10ml) at 5°C. The mixture was stirred for 10 minutes at 5°C and then 1 hour at ambient temperature. The mixture was poured directly on to a silica column and eluted with methylene chloride/methanol (95/5) to give 7-(2-(imidazol-1-yl)ethoxy)-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (640mg, 80%).

$^1$H NMR Spectrum: ($CDCl_3$) 1.19(s, 9H); 3.98(s, 3H); 4.34(m, 2H); 4.45(m, 2H); 5.94(s, 2H); 7.02(s, 1H); 7.07(s, 1H); 7.11(s, 1H); 7.64(s, 1H); 7.67(s, 1H); 8.17(s, 1H)

MS - ESI: 423 $[MNa]^+$

| | | | | |
|---|---|---|---|---|
| Elemental Analysis: | Found | C 58.3 | H 6.4 | N 13.9 |
| $C_{20}H_{24}N_4O_5$ 0.7$H_2O$ | Requires | C 58.2 | H 6.2 | N 13.6% |

A solution of 7-(2-(imidazol-1-yl)ethoxy)-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (640mg, 1.6mmol) in saturated methanolic ammonia (10ml) was stirred for 15 hours at ambient temperature. The volatiles were removed by evaporation, the solid was triturated with ether, collected by filtration and dried under vacuum to give 7-(2-(imidazol-1-yl)ethoxy)-6-methoxy-3,4-dihydroquinazolin-4-one (412mg, 90%).

$^1$H NMR Spectrum: ($DMSOd_6$) 3.89(s, 3H); 4.4-4.5(m, 4H); 6.9(s, 1H); 7.16(s, 1H); 7.28(s, 1H); 7.47(s, 1H); 7.7(s, 1H); 7.99(s, 1H)

MS - ESI: 287 $[MH]^+$

| | | | | |
|---|---|---|---|---|
| Elemental Analysis: | Found | C 57.8 | H 5.2 | N 19.3 |
| $C_{14}H_{14}N_4O_3$ 0.3$H_2O$ | Requires | C 57.7 | H 5.1 | N 19.2% |

A mixture of 7-(2-(imidazol-1-yl)ethoxy)-6-methoxy-3,4-dihydroquinazolin-4-one (412mg, 1.44mmol), thionyl chloride (5 ml) and DMF (0.2ml) was heated at reflux for 1 hour. The mixture was diluted with toluene and the volatiles were removed by evaporation. The

residue was suspended in methylene chloride, cooled to 0°C and aqueous sodium hydrogen carbonate solution was added. The resulting precipitate was collected by filtration and dried under vacuum to give 4-chloro-7-(2-(imidazol-1-yl)ethoxy)-6-methoxyquinazoline (258mg, 59%).

$^1$H NMR Spectrum: ($DMSOd_6$) 4.01(s, 3H); 4.47(m, 2H); 4.53(m, 2H); 6.89(s, 1H); 7.27(s, 1H); 7.41(s, 1H); 7.49(s, 1H); 7.70(s, 1H); 8.88(s, 1H)

MS - ESI: 327 $[MNa]^+$

f) 4-Chloro-6-methoxy-7-(3-(1*H*-1,2,4-triazol-1-yl)propoxy)quinazoline (61 mg) was reacted with 5-aminoindole in the presence of 6.2N hydrogen chloride in isopropanol (4 µl) to give **4-(indol-5-ylamino)-6-methoxy-7-(3-(1*H*-1,2,4-triazol-1-yl)propoxy)quinazoline** hydrochloride.

$^1$H NMR Spectrum: ($DMSOd_6$, $CF_3COOD$) 2.5 (m, 2H) ; 4.0 (s, 3H) ; 4.3 (t, 2H) ; 4.6 (t, 2H) ; 6.52 (d, 0.5H partly exchanged) ; 7.3 (s, 1H) ; 7.35 (d, 1H) ; 7.45 (s, 1H) ; 7.55 (d, 1H) ; 7.8 (s, 1H) ; 8.16 (s, 1H) ; 8.66 (s, 1H) ; 8.77 (s, 1H) ; 9.43 (s, 1H)

**Example 266**

A mixture of 4-chloro-6-methoxy-7-(3-piperidinopropoxy)quinazoline (144mg, 0.43mmol), (prepared as described for the starting material in Example 67), potassium carbonate (91mg, 0.66mmol) and 3-fluoro-7-hydroxyquinoline (77mg, 0.47mmol), (prepared as described for the starting material in Example 157), in DMF (3ml) was stirred at 100°C for 2 hours and then allowed to cool to ambient temperature. The reaction mixture was evaporated to dryness and the residue chromatographed on silica eluting with methanol/dichloromethane/aqueous ammonia (0.880) (5/100/1). The relevant fractions were combined and evaporated to dryness to give **4-(3-fluoro-quinolin-7-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline** (87mg, 44%).

$^1$H NMR Spectrum: ($DMSOd_6$) 1.37(m, 2H); 1.49(m, 4H); 1.96(m, 2H); 2.34(m, 4H); 2.43(t, 2H); 4.00(s, 3H); 4.23(t, 2H); 7.38(s, 1H); 7.62(s, 1H); 7.69(dd, 1H); 8.00(d, 1H); 8.12(d, 1H); 8.34(dd, 1H); 8.54(s, 1H); 8.98(d, 1H)

MS (ESI): 463 $(MH)^+$

**Example 267**

A mixture of 4-chloro-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline (218mg, 0.68mmol),(prepared as described for the starting material in Example 9), potassium carbonate (138mg, 1.13mmol) and 3-fluoro-7-hydroxyquinoline (117mg, 0.72mmol), (prepared as described for the starting material in Example 157), in DMF (4.5ml) was stirred at 100°C for 4 hours and then allowed to cool to ambient temperature. The reaction mixture was evaporated to dryness and the residue taken up in dichloromethane, washed with water, brine and dried ($MgSO_4$). The organic fractions were evaporated to dryness and the residue recrystallised from acetonitrile to give **4-(3-fluoro-quinolin-7-yloxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline** (86mg, 28%).

$^1$H NMR Spectrum: ($DMSOd_6$) 1.90(m, 2H); 2.00(m, 2H); 2.27(m, 2H); 3.02(m, 2H); 3.32(m, 2H); 3.59(m, 2H); 4.00(s, 3H); 4.33(t, 2H); 7.43(s, 1H); 7.62(s, 1H); 7.70(dd, 1H); 7.99(d, 1H); 8.11(d, 1H); 8.35(dd, 1H); 8.54(s, 1H); 8.97(d, 1H)

MS (ESI): 449 $(MH)^+$

**Example 268**

A mixture of 7-hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (280 mg, 0.87 mmol), (prepared as described in Example 49), potassium carbonate (370 mg, 2.68 mmol) and 4-(1-methyl-2-oxopiperidin-4-yl)methyl-4-toluene sulphonate (260 mg, 0.87 mmol) in DMF (8 ml) was stirred at 95°C for 4 hours and allowed to cool to ambient temperature. The reaction mixture was diluted with acetone, filtered and the filtrate evaporated *'in vacuo'* to give a residue which was purified by column chromatography, eluting with dichloromethane/methanol/0.88 ammonia (100/8/1). The relevant fractions were combined and evaporated *'in vacuo'* to give an oil which crystallised on trituration with diethyl ether to give **6-methoxy-4-(2-methylindol-5-yloxy)-7-(1-methyl-2-oxopiperidin-4-ylmethoxy)quinazoline** (66 mg, 17%).

m. p. 250 – 251°C

$^1$H NMR Spectrum: ($DMSO-d_6$) 1.66 (m, 1H), 2.10 (m, 2H), 2.40 (s, 3H), 2.50 (m, 2H), 2.84 (s, 3H), 3.34 (m, 2H), 3.99 (s, 3H), 4.12 (d, 2H), 6.12 (s, 1H), 6.86 (m, 1H), 7.25 (d, 1H), 7.30 (d, 1H), 7.38 (s, 1H), 7.59 (s, 1H), 8.48 (s, 1H) and 10.98 (br s, 1H).

MS (ESI) : 447 $(MH)^+$

Elemental analysis Found C 66.8 H 5.9 N 12.4

$C_{25}H_{26}N_4O_4$ 0.2 $H_2O$ Requires C 66.7 H 5.9 N 12.5%

The starting material was prepared as follows:-

A solution of 4-hydroxymethyl-1-methyl-2-piperidone (120 mg, 0.84 mmol), (Yakugaku Zasshi 88, (5), 573 - 582, (1968)), in dichloromethane was treated with triethylamine (187 mg, 1.85 mmol) followed by p-toluenesulphonyl chloride (176 mg, 0.92 mmol) and the mixture stirred at ambient temperature overnight. The reaction mixture was diluted with dichloromethane and washed successively with aqueous sodium hydrogen carbonate, water and brine. The dichloromethane solution was dried over magnesium sulphate, filtered and the filtrate evaporated '*in vacuo*' to give a dark oily residue. This was washed several times with diethyl ether to remove the product from insoluble impurities, the washings combined and evaporated '*in vacuo*' to give 4-(1-methyl-2-oxopiperidin-4-yl)methyl-4-toluene sulphonate as a light brown oil (130 mg, 52%). This was used without further purification.

MS (ESI) : 298 $(MH)^+$ and impurities

**Example 269**

A mixture of (2*R*)-6-methoxy-4-(2-methylindol-5-yloxy)-7-(oxiran-2-ylmethoxy)quinazoline (300 mg, 0.79 mmol), and 1-methylpiperazine (0.26 ml, 2.38 mmol) in DMF (10 ml) was stirred at 70° C for 24 hours and allowed to cool to ambient temperature. The solvents were removed *in vacuo* and the residue purified by silica column chromatography, gradient elution (dichloromethane, 5% methanol/95% dichloromethane, dichloromethane/methanol/0.88 ammonia (100/8/1) and evaporated *in vacuo* to give **(2*R*)-7-(2-hydroxy-3-(4-methylpiperazin-1-yl)propoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline** (344 mg, 91 %).

$^1H$ NMR Spectrum: (DMSO-$d_6$) 2.10 (s, 3H), 2.4 (m, 13H), 3.98 (s, 3H), 4.06 (m, 3H), 4.90 (br s, 1H), 6.12 (s, 1H), 6.85 (dd, 1H), 7.3 (m, 2H), 7.58 (s, 1H), 8.42 (s, 1H) and 10.98 (br s, 1H)

MS (ESI) : 478 $(MH)^+$

Elemental analysis: Found C 61.3 H 6.3 N 13.8

$C_{26}H_{30}N_4O_4$ 0.2$H_2O$.0.5dichloromethane Requires C 61.9 H 6.2 N 13.4%

The starting material was prepared as follows:

A mixture of 7-hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (300 mg, 0.93 mmol), (prepared as described in Example 49), potassium carbonate (385 mg, 2.79 mmol) and (2R)-(-)- glycidyl tosylate (426 mg, 2.79 mmol) in DMF (15 ml) was stirred at 60°C for 2 hours and allowed to cool to ambient temperature. The reaction mixture was filtered and the filtrate exaporated *in vacuo*. The residue was dissolved in dichloromethane and washed with saturated sodium hydrogen carbonate solution. The organic layer was then dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a yellow solid. This was triturated with ether, filtered off and dried to give (2*R*)-6-methoxy-4-(2-methylindol-5-yloxy)-7-(oxiran-2-ylmethoxy)quinazoline as a yellow solid (185 mg, 53 %).

$^1$H NMR Spectrum: ($DMSOd_6$) 2.40 (s, 3H), 2.75 (m, 1H), 2.90 (m, 1H), 3.40 (m, 1H), 3.98 (s, 3H), 4.05 (m, 1H), 4.60 (m, 1H), 6.15 (s, 1H), 6.85 (dd, 1H), 7.30 (m, 2H) 7.40 (s, 1H), 7.60 (s, 1H), 8.45 (s, 1H) and 10.98 (s, 1H)

MS (ESI) : 378 $(MH)^+$

**Example 270**

A mixture of (2*R*)-6-methoxy-4-(2-methylindol-5-yloxy)-7-(oxiran-2-ylmethoxy)quinazoline (300 mg, 0.79 mmol), (prepared as described for the starting material in Example 269), and diethylamine (0.25 ml, 2.38 mmol) in DMF (10 ml) was stirred at 70 °C for 24 hours and allowed to cool to ambient temperature. The solvents were removed *in vacuo* and the residue purified by silica column chromatography, gradient elution (dichloromethane,

5% methanol/95% dichloromethane, dichloromethane/methanol/0.88 ammonia (100/8/1)) to give (2*R*)-**7-(3-(N,N-diethylamino)-2-hydroxypropoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline** (288 mg, 81 %).

$^1$H NMR Spectrum: (DMSO-$d_6$) 0.95 (t, 6H), 2.10 (s, 3H), 2.4 (m, 6H), 3.98 (s, 3H), 4.14 (m, 3H), 4.84 (br s, 1H), 6.12 (s, 1H), 6.85 (dd, 1H), 7.3 (m, 3H), 7.58 (s, 1H), 8.42 (s, 1H) and 10.98 (br s, 1H)

MS (ESI) : 448 $(MH)^+$

| | | | | |
|---|---|---|---|---|
| Elemental analysis: | Found | C 64.3 | H 6.6 | N 12.0 |
| $C_{25}H_{30}N_4O_4$ 0.4dichloromethane | Requires | C 64.0 | H 6.4 | N 11.6% |

**Example 271**

A mixture of 7-benzyloxy-6-methoxy-4-(3-methylindol-5-yloxy)quinazoline (7.76 g, 18.9 mmol), ammonium formate (17.82 g, 282 mmol) and 10% palladium on charcoal (800 mg) in DMF (350 ml) was stirred at ambient temperature for 1 hour. The catalyst was filtered off through celite and the cake washed with DMF. The solvent was removed *in vacuo* and the residue stirred with a saturated solution of sodium hydrogen carbonate for 2 hours. The suspension was then filtered, washed with water and dried to give **7-hydroxy-6-methoxy-4-(3-methylindol-5-yloxy)quinazoline** (5.49 g, 91%).

$^1$H NMR Spectrum: (DMSO-$d_6$) 2.20 (s, 3H), 3.98 (s, 3H), 6.98 (dd, 1H), 7.18 (s, 1H), 7.20 (s, 1H), 7.35 (m, 3H), 7.58 (s, 1H), 8.40 (s, 1H) and 10.82 (br s, 1H)

MS (ESI) : 322 $(MH)^+$

The starting material was prepared as follows:

A mixture of 7-benzyloxy-4-chloro-6-methoxyquinazoline (7.859 g, 26.1 mmol), (prepared as described for the starting material in Example 1), potassium carbonate (18.03 g, 130 mmol) and 5-hydroxy-3-methylindole (5.00 g, 34.0 mmol), (Journal of Organic Chemistry 1993, 58, 3757 ), in DMA (600 ml) was stirred at 75 °C for 2 hours and allowed to cool to ambient temperature. The reaction mixture was filtered and the filtrate evaporated *in vacuo*. The crude solid was purified by silica column chromatography, eluting with 2.5% methanol/97.5% dichloromethane to give 7-benzyloxy-6-methoxy-4-(3-methylindol-5-yloxy)quinazoline (7.791 g, 73 %).

$^1$H NMR Spectrum: ($CDCl_3$) 2.30 (s, 3H), 4.10 (s, 3H), 5.36 (s, 2H), 7.04 (m, 2H), 7.43 (m, 8H), 7.62 (s, 1H), 8.02 (s, 1H), and 8.60 (s, 1H)

MS (ESI) : 412 $(MH)^+$

**Example 272**

A mixture of 7-hydroxy-6-methoxy-4-(3-methylindol-5-yloxy)quinazoline (800 mg, 2.49 mmol), (prepared as described in Example 271), potassium carbonate (687 mg, 4.98 mmol) and 1-chloro-3-morpholinopropane (448 mg, 2.74 mmol), (prepared as described for the starting material in Example 1), in DMF (20 ml) was stirred at 80 °C for 2 hours and allowed to cool to ambient temperature. The reaction mixture was filtered and the filtrate evaporated *in vacuo*. The residue was purified by silica column chromatography, gradient

elution (dichloromethane, 5% methanol/95% dichloromethane, methanol/dichloromethane/0.880 saturated aqueous ammonia (100/8/1)) and the product was recrystallised from ethanol to give **6-methoxy-4-(3-methylindol-5-yloxy)-7-(3-morpholinopropoxy)quinazoline** (570 mg, 51 %).

$^1$H NMR Spectrum: (DMSO-$d_6$) 1.98 (m, 2H), 2.20 (s, 3H), 2.40 (t, 4H), 2.50 (m, 2H), 3.60 (t, 4H), 3.98 (s, 3H), 4.20 (t, 2H), 6.98 (dd, 1H), 7.18 (s, 1H), 7.35 (m, 3H), 7.60 (s, 1H), 8.45 (s, 1H), and 10.82 (br s, 1H)

MS (ESI) : 449 $(MH)^+$

| | | | | |
|---|---|---|---|---|
| Elemental analysis: | Found | C 64.2 | H 6.0 | N 11.8 |
| $C_{25}H_{28}N_4O_4$ 0.7$H_2O$ 0.7ethanol | Requires | C 64.2 | H 6.9 | N 11.4% |

**Example 273**

A mixture of 7-hydroxy-6-methoxy-4-(3-methylindol-5-yloxy)quinazoline (800 mg, 2.49 mmol), (prepared as described for the starting material in Example 271), potassium carbonate (1.031 g, 7.47 mmol) and 4-(2-chloroethyl)morpholine hydrochloride (510 mg, 2.74 mmol) in DMF (25 ml) was stirred at 80 °C for 2 hours and allowed to cool to ambient temperature. The reaction mixture was filtered and the filtrate removed *in vacuo*. The residue was purified by silica column chromatography, gradient elution (dichloromethane, 5% methanol/95% dichloromethane, methanol/dichloromethane/0.880 saturated aqueous ammonia (100/8/1)) and the product recrystallised from ethanol to give **6-methoxy-4-(3-methylindol-5-yloxy)-7-(2-morpholinoethoxy)quinazoline** (510 mg, 47 %).

$^1$H NMR Spectrum: (DMSO-$d_6$) 2.20 (s, 3H), 2.55 (t, 4H), 2.80 (t, 2H), 3.60 (t, 4H), 3.98 (s, 3H), 4.30 (t, 2H), 6.98 (dd, 1H), 7.18 (s, 1H), 7.35 (m, 2H), 7.40 (s, 1H), 7.60 (s, 1H), 8.45 (s, 1H), and 10.82 (br s, 1H)

MS (ESI) : 449 $(MH)^+$

| | | | | |
|---|---|---|---|---|
| Elemental analysis: | Found | C 64.1 | H 6.3 | N 12.2 |
| $C_{24}H_{26}N_4O_4$ 0.4$H_2O$ 0.8ethanol | Requires | C 64.3 | H 6.1 | N 11.7% |

**Example 274**

A mixture of 7-hydroxy-6-methoxy-4-(3-methylindol-5-yloxy)quinazoline (1.00 g, 3.11 mmol), (prepared as described for the starting material in Example 271), potassium carbonate (1.288 g, 9.33 mmol) and 4-(4-methylphenylsulphonyloxymethyl)-1-*tert*-

butoxycarbonylpiperidine (1.264 g, 3.42 mmol), (prepared as described for the starting material in Example 10), in DMF (35 ml) was stirred at 80 °C for 2 hours and allowed to cool to ambient temperature. The reaction mixture was filtered and the solvent removed *in vacuo*. The residue was purified by silica column chromatography, 5% methanol/95% dichloromethane and the product was recrystallised from ethanol to give **6-methoxy-4-(3-methylindol-5-yloxy)-7-(1-*tert*-butoxycarbonylpiperidin-4-ylmethoxy)quinazoline** (1.011 g, 63 %).

$^1$H NMR Spectrum: (DMSO-$d_6$) 1.3 (m, 4H), 1.42 (s, 9H), 1.90 (d, 2H), 2.10 (m, 1H), 2.28 (s, 3H), 2.80 (m, 2H), 3.98 (s, 3H), 4.08 (d, 2H), 6.98 (dd, 1H), 7.18 (s, 1H), 7.35 (m, 3H), 7.60 (s, 1H), 8.45 (s, 1H), and 10.82 (br s, 1H)

MS (ESI) : 519 $(MH)^+$

**Example 275**

A mixture of 7-hydroxy-6-methoxy-4-(3-methylindol-5-yloxy)quinazoline (600 mg, 1.87 mmol), (prepared as described for the starting material in Example 271), potassium carbonate (773 mg, 5.60 mmol) and 3-(1,1-dioxothiomorphlino)propoxy tosylate (1.296 g, 3.74 mmol) in DMF (30 ml) was stirred at 75 °C overnight and allowed to cool to ambient temperature. The reaction mixture was filtered and the solvent removed *in vacuo*. The residue was purified by silica column chromatography, gradient elution (dichloromethane, 5% methanol/95% dichloromethane, methanol/dichloromethane/0.880 saturated aqueous ammonia (100/8/1)) and the product recrystallised from ethanol to give **7-(3-(1,1-dioxothiomorpholino)propoxy)-6-methoxy-4-(3-methylindol-5-yloxy)quinazoline** (525 mg, 56%).

$^1$H NMR Spectrum: (DMSO-$d_6$) 1.98 (m, 2H), 2.17 (s, 3H), 2.65 (t, 2H), 2.90 (t, 4H), 3.10 (t, 4H), 3.98 (s, 3H), 4.25 (t, 2H), 6.95 (dd, 1H), 7.15 (s, 1H), 7.30 (d, 1H), 7.35 (m, 2H), 7.60 (s, 1H), 8.45 (s, 1H), and 10.82 (br s, 1H)

MS (ESI) : 497 $(MH)^+$

| | | | | |
|---|---|---|---|---|
| Elemental analysis: | Found | C 58.4 | H 5.5 | N 11.1 |
| $C_{25}H_{28}N_4O_5S$ $0.8H_2O$ | Requires | C 58.8 | H 5.8 | N 11 0% |

**Example 276**

A mixture of 6-methoxy-4-(3-methylindol-5-yloxy)-7-(1-*tert*-butoxycarbonylpiperidin-4-ylmethoxy)quinazoline (1.290 g, 2.49 mmol), (prepared as described in Example 274), in 25% trifluoroacetic acid/75% dichloromethane solution (75 ml) was stirred at ambient temperature for 2 hours. The solvents were then removed *in vacuo* and the dark yellow gum triturated with concentrated ammonia. The resulting solid was filtered off and dried to give **6-methoxy-4-(3-methylindol-5-yloxy)-7-(piperidin-4-ylmethoxy)quinazoline** (648 mg, 62%).

$^1$H NMR Spectrum: (DMSO-$d_6$) 1.35 (m, 2H), 1.80 (m, 2H), 2.05 (m, 1H), 2.10 (s, 3H), 2.70 (m, 2H), 3.10 (m, 2H), 3.98 (s, 3H), 4.05 (d, 2H), 6.98 (dd, 1H), 7.18 (s, 1H), 7.34 (m, 3H), 7.60 (s, 1H), 8.45 (s, 1H), and 10.82 (br s, 1H)

MS (ESI) : 419 $(MH)^+$

**Example 277**

A mixture of 6-methoxy-4-(3-methylindol-5-yloxy)-7-(piperidin-4-ylmethoxy)quinazoline (460 mg, 1.10 mmol), (prepared as described in Example 276), triethylamine (5 ml) and chloroacetonitrile (0.38 ml, 6.05 mmol) in methanol (5 ml) was stirred at ambient temperature for 24 hours. The solvents were removed *in vacuo* and the residue purified by silica column chromatography using gradient elution (dichloromethane, 5% methanol/95% dichloromethane, methanol/dichloromethane/0.880 saturated aqueous ammonia (100/8/1)) and the product recrystallised from acetonitrile to give **7-(1-cyanomethylpiperidin-4-ylmethoxy)-6-methoxy-4-(3-methylindol-5-yloxy)quinazoline** (178 mg, 35 %).

$^1$H NMR Spectrum: (DMSO-$d_6$) 1.40 (m, 2H), 1.80 (m, 4H), 2.20 (m, 4H), 2.81 (m, 2H), 3.65 (s, 2H), 3.98 (s, 3H), 4.05 (d, 2H), 6.98 (dd, 1H), 7.15 (s, 1H), 7.35 (m, 3H), 7.60 (s, 1H), 8.45 (s, 1H), and 10.83 (br s, 1H)

MS (ESI) : 458 $(MH)^+$

| | | | | | |
|---|---|---|---|---|---|
| Elemental analysis: | Found | C 66.3 | H 6.1 | N 14.8 | |
| $C_{26}H_{27}N_5O_3$ 0.7$H_2O$ | Requires | C 66.4 | H 6.1 | N 14.9% | |

**Example 278**

A mixture of 7-hydroxy-6-methoxy-4-(3-methylindol-5-yloxy)quinazoline (1.35 g, 4.2 mmol), (prepared as described for the starting material in Example 271), potassium carbonate

(1.74 g, 12.6 mmol) and (2*R*)-(-)- glycidyl tosylate (1.92 g, 8.4 mmol) in DMF (25 ml) was stirred at 60 °C for 2 hours and allowed to cool to ambient temperature. The reaction mixture was filtered and the solvent removed *in vacuo*. The residue was dissolved in dichloromethane and washed with saturated sodium hydrogen carbonate solution. The organic layer was then dried ($MgSO_4$), filtered and solvent removed *in vacuo* to give a solid. This was triturated with ether and the solid filtered off and dried to give **(2*R*)-6-methoxy-4-(3-methylindol-5-yloxy)-7-(oxiran-2-ylmethoxy)quinazoline** (842 mg, 53 %).

$^1$H NMR Spectrum: (DMSO-$d_6$) 2.20 (s, 3H), 2.80 (m, 1H), 2.90 (m, 1H), 3.42 (m, 1H), 3.98 (s, 3H), 4.02 (m, 1H), 4.60 (m, 1H), 6.98 (dd, 1H), 7.18 (s, 1H) 7.35 (m, 3H), 7.60 (s, 1H), 8.45 (s, 1H) and 10.82 (s, 1H)

MS (ESI) : 378 $(MH)^+$

**Example 279**

A mixture of (2*R*)-6-methoxy-4-(3-methylindol-5-yloxy)-7-(oxiran-2-ylmethoxy)quinazoline (300 mg, 0.65 mmol), (prepared as described in Example 278), and piperidine (0.2 ml, 2.04 mmol) in DMF (5 ml) was stirred at 60 °C for 24 hours and allowed to cool to ambient temperature. The solvents were removed *in vacuo* and the residue purified by silica column chromatography, gradient elution (dichloromethane, 5% methanol/95% dichloromethane, 1% 0.880 saturated aqueous ammonia/10% methanol/89% dichloromethane) **(2*R*)-7-(2-hydroxy-3-piperidinopropoxy)-6-methoxy-4-(3-methylindol-5-yloxy)quinazoline** (237 mg, 78 %).

$^1$H NMR Spectrum: (DMSO-$d_6$) 1.38 (m, 2H), 1.50 (m, 4H), 2.34 (m, 9H), 3.98 (s, 3H), 4.16 (m, 3H), 4.85 (br s, 1H), 6.98 (dd, 1H), 7.18 (s, 1H), 7.35 (m, 3H), 7.60 (s, 1H), 8.42 (s, 1H) and 10.82 (br s, 1H)

MS (ESI) : 464 $(MH)^+$

| | | | | |
|---|---|---|---|---|
| Elemental analysis: | Found | C 66.3 | H 6.6 | N 12.1 |
| $C_{26}H_{30}N_4O_4$ 0.5methanol | Requires | C 66.5 | H 6.7 | N 11.7% |

**Example 280**

A mixture of (2*R*)-6-methoxy-4-(3-methylindol-5-yloxy)-7-(oxiran-2-ylmethoxy)quinazoline (300 mg, 0.65 mmol), (prepared as described in Example 278), and pyrrolidine (0.17 ml, 2.04 mmol) in DMF (5 ml) was stirred at 60 °C for 24 hours and allowed

to cool to ambient temperature. The solvents were removed *in vacuo* and the residue purified by silica column chromatography using gradient elution (dichloromethane, 5% methanol/95% dichloromethane, methanol/dichloromethane/0.880 saturated aqueous ammonia (100/8/1)) to give **(2*R*)-7-(2-hydroxy-3-(pyrrolidin-1-yl)propoxy)-6-methoxy-4-(3-methylindol-5-yloxy)quinazoline** (257 mg, 88 %).

$^1$H NMR Spectrum: (DMSO-$d_6$) 1.65 (m, 4H), 1.98 (m, 2H), 2.20 (s, 3H), 2.50 (m, 2H), 2.62 (m, 2H), 3.98 (s, 3H), 4.17 (m, 3H), 6.98 (dd, 1H), 7.18 (s, 1H), 7.35 (m, 3H), 7.60 (s, 1H), 8.42 (s, 1H) and 10.82 (br s, 1H)

MS (ESI) : 449 $(MH)^+$

| | | | | | |
|---|---|---|---|---|---|
| Elemental analysis: | Found | C 64.1 | H 6.4 | N 12.6 | |
| $C_{25}H_{28}N_4O_4$ 1.0$H_2O$ | Requires | C 64.4 | H 6.5 | N 12.0% | |

**Example 281**

A mixture of (2*R*)-6-methoxy-4-(3-methylindol-5-yloxy)-7-(oxiran-2-ylmethoxy)quinazoline (350 mg, 0.93 mmol), (prepared as described in Example 278), and 1-methylpiperazine (0.31 ml, 2.78 mmol) in DMF (5 ml) was stirred at 60 °C for 24 hours and allowed to cool to ambient temperature. The solvents were removed *in vacuo* and the residue purified by silica column chromatography using gradient elution (dichloromethane, 5% methanol/95% dichloromethane, methanol/dichloromethane/0.880 saturated aqueous ammonia (100/8/1)) to give **(2*R*)-7-(2-hydroxy-3-(4-methylpiperazin-1-yl)propoxy)-6-methoxy-4-(3-methylindol-5-yloxy)quinazoline** (352 mg, 80 %).

$^1$H NMR Spectrum: (DMSO-$d_6$) 2.10 (s, 3H), 2.20 (s, 3H), 2.40 (m, 10H), 3.98 (s, 3H), 4.13 (m, 3H), 6.98 (dd, 1H), 7.18 (s, 1H), 7.35 (m, 3H), 7.60 (s, 1H), 8.42 (s, 1H) and 10.82 (br s, 1H)

MS (ESI) : 478 $(MH)^+$

| | | | | | |
|---|---|---|---|---|---|
| Elemental analysis: | Found | C 61.6 | H 6.4 | N 14.4 | |
| $C_{26}H_{31}N_5O_4$ 1.0$H_2O$.0.25Methanol | Requires | C 61.6 | H 6.8 | N 13.9% | |

**Example 282**

A mixture of (2*R*)-6-methoxy-4-(3-methylindol-5-yloxy)-7-(oxiran-2-ylmethoxy)quinazoline (350 mg, 0.93 mmol), (prepared as described in Example 278), and morpholine (0.24 ml, 2.78 mmol) in DMF (5 ml) was stirred at 60 °C for 24 hours and

allowed to cool to ambient temperature. The solvents were removed *in vacuo* and the residue purified by silica column chromatography using gradient elution (dichloromethane, 5% methanol/95% dichloromethane, methanol/dichloromethane/0.880 saturated aqueous ammonia (100/8/1)) to give **(2*R*)-7-(2-hydroxy-3-morpholinopropoxy)-6-methoxy-4-(3-methylindol-5-yloxy)quinazoline** (398 mg, 93 %).

$^1$H NMR Spectrum: (DMSO-$d_6$) 2.20 (s, 3H), 2.44 (m, 6H), 3.48 (t, 4H), 3.98 (s, 3H), 4.13 (m, 3H), 4.98 (br s, 1H), 6.98 (dd, 1H), 7.18 (s, 1H), 7.35 (m, 3H), 7.60 (s, 1H), 8.42 (s, 1H) and 10.82 (br s, 1H)

MS (ESI) : 465 $(MH)^+$

| | | | | | |
|---|---|---|---|---|---|
| Elemental analysis: | Found | C 58.5 | H 6.0 | N 11.2 | |
| $C_{25}H_{28}N_4O_5$ 2.5$H_2O$. | Requires | C 58.9 | H 6.5 | N 11.0% | |

**Example 283**

A mixture of (2*R*)-6-methoxy-4-(3-methylindol-5-yloxy)-7-(oxiran-2-ylmethoxy)quinazoline (350 mg, 0.93 mmol), (prepared as described in Example 278), and 2.0 M dimethylamine in ethanol (4.60 ml, 9.30 mmol) in DMF (5 ml) was stirred at 60 °C for 24 hours and allowed to cool to ambient temperature. The solvents were removed *in vacuo* and the residue purified by silica column chromatography, gradient elution (dichloromethane, 5% methanol/95% dichloromethane, methanol/dichloromethane/0.880 saturated aqueous ammonia (100/8/1)) to give **(2*R*)-7-(2-hydroxy-3-dimethylaminopropoxy)-6-methoxy-4-(3-methylindol-5-yloxy)quinazoline** (308 mg, 78 %).

$^1$H NMR Spectrum: (DMSO-$d_6$) 2.10 (m, 9H), 2.20 (m, 2H), 3.98 (s, 3H), 4.13 (m, 3H), 4.98 (br s, 1H), 6.98 (dd, 1H), 7.18 (s, 1H), 7.35 (m, 3H), 7.60 (s, 1H), 8.42 (s, 1H) and 10.82 (br s, 1H)

MS (ESI) : 423 $(MH)^+$

| | | | | | |
|---|---|---|---|---|---|
| Elemental analysis: | Found | C 65.5 | H 6.2 | N 13.2 | |
| $C_{23}H_{20}N_4O_4$ | Requires | C 65.4 | H 6.2 | N 13.3% | |

**Example 284**

A mixture of (2*R*)-6-methoxy-4-(3-methylindol-5-yloxy)-7-(oxiran-2-ylmethoxy)quinazoline (350 mg, 0.93 mmol), (prepared as described in Example 278), and diethylamine (0.29 ml, 2.78 mmol) in DMF (5 ml) was stirred at 60 °C for 24 hours and

allowed to cool to ambient temperature. The solvents were removed *in vacuo* and the residue purified by silica column chromatography using gradient elution (dichloromethane, 5% methanol/95% dichloromethane, methanol/dichloromethane/0.880 saturated aqueous ammonia (100/8/1)) to give **(2*R*)-7-(2-hydroxy-3-((N,N-diethylamino)propoxy))-6-methoxy-4-(3-methylindol-5-yloxy)quinazoline** (338 mg, 81 %).

$^1$H NMR Spectrum: (DMSO-$d_6$) 0.95 (t, 6H), 2.11 (s, 3H), 2.40 (m, 6H), 3.98 (s, 3H), 4.13 (m, 3H), 4.84 (br s, 1H), 6.98 (dd, 1H), 7.18 (s, 1H), 7.35 (m, 3H), 7.60 (s, 1H), 8.42 (s, 1H) and 10.82 (br s, 1H)

MS (ESI) : 451 $(MH)^+$

| | | | | | |
|---|---|---|---|---|---|
| Elemental analysis: | Found | C 64.4 | H 6.6 | N 12.0 | |
| $C_{25}H_{30}N_4O_4$ 1.0$H_2O$. | Requires | C 64.1 | H 6.9 | N 12.0% | |

**Example 285**

A mixture of (2*R*)-6-methoxy-4-(3-methylindol-5-yloxy)-7-(oxiran-2-ylmethoxy)quinazoline (350 mg, 0.93 mmol), (prepared as described in Example 278), and isopropylamine (0.29 ml, 4.65 mmol) in DMF (5 ml) was stirred at 100 °C for 24 hours and allowed to cool to ambient temperature. The solvents were removed *in vacuo* and the residue purified by silica column chromatography using gradient elution (dichloromethane, 5% methanol/95% dichloromethane, methanol/dichloromethane/0.880 saturated aqueous ammonia (100/8/1)) to give **(2*R*)-7-(2-hydroxy-3-(isopropylamino)propoxy)-6-methoxy-4-(3-methylindol-5-yloxy)quinazoline** (307 mg, 75 %).

$^1$H NMR Spectrum: (DMSO-$d_6$) 0.98 (d, 6H), 2.20 (s, 3H), 2.55-2.80 (m, 3H), 3.98 (s, 3H), 4.02-4.20 (m, 3H), 4.98 (br s, 1H), 6.98 (dd, 1H), 7.18 (s, 1H), 7.30-7.40 (m, 3H), 7.60 (s, 1H), 8.42 (s, 1H) and 10.82 (br s, 1H)

MS (ESI) : 437 $(MH)^+$

| | | | | | |
|---|---|---|---|---|---|
| Elemental analysis: | Found | C 63.3 | H 6.3 | N 12.4 | |
| $C_{24}H_{28}N_4O_4$ 1.0$H_2O$. | Requires | C 63.4 | H 6.7 | N 12.3% | |

**Example 286**

A mixture of (2*R*)-6-methoxy-4-(3-methylindol-5-yloxy)-7-(oxiran-2-ylmethoxy)quinazoline (350 mg, 0.93 mmol), (prepared as described in Example 278), and diisopropylamine (0.78 ml, 5.58 mmol) in DMF (10 ml) was stirred at 130 °C for 24 hours

and allowed to cool to ambient temperature. The solvents were removed *in vacuo* and the residue purified by silica column chromatography using gradient elution (dichloromethane, 5% methanol/95% dichloromethane, methanol/dichloromethane/0.880 saturated aqueous ammonia (100/8/1)) to give **(2*R*)-7-(2-hydroxy-3-((N,N-diisopropyl)amino)propoxy)-6-methoxy-4-(3-methylindol-5-yloxy)quinazoline** (398 mg, 93 %).

$^1$H NMR Spectrum: (DMSO-$d_6$) 0.98 (d, 12H), 2.20 (s, 3H), 2.72 (m, 2H), 3.00 (m, 2H), 3.98 (s, 3H), 4.11 (m, 3H), 6.98 (dd, 1H), 7.18 (s, 1H), 7.35 (m, 3H), 7.60 (s, 1H), 8.42 (s, 1H) and 10.82 (br s, 1H)

MS (ESI) : 479 $(MH)^+$

| | | | | | |
|---|---|---|---|---|---|
| Elemental analysis: | Found | C 65.4 | H 6.8 | N 11.3 | |
| $C_{27}H_{34}N_4O_4$ 0.8$H_2O$. | Requires | C 55.8 | H 7.2 | N 11.4% | |

**Example 287**

A mixture of (2*R*)-6-methoxy-4-(3-methylindol-5-yloxy)-7-(oxiran-2-ylmethoxy)quinazoline (100 mg, 0.28 mmol), (prepared as described in Example 278), and 4-(3-aminopropyl)morpholine (0.12 ml, 0.84 mmol) in DMF (5 ml) was heated to 70 °C for 3 hours. The solvents were removed *in vacuo* and the residue taken up in dichloromethane. This was washed with water, dried ($MgSO_3$), filtered and evaporated. The residue was purified by silica column chromatography using gradient elution (dichloromethane, 5% methanol/95% dichloromethane, 20% methanolic ammonia (7M)/80% dichloromethane) to give **(2*R*)-7-(2-hydroxy-3-(3-morpholinopropylamino)propoxy)-6-methoxy-4-(3-methylindol-5-yloxy)quinazoline** (67 mg, 46 %).

$^1$H NMR Spectrum: (DMSO-$d_6$) 1.28 (m, 2H), 2.30 (t, 4H), 2.56 (t, 2H), 2.650 (m, 4H), 3.55 (t, 4H), 3.98 (s, 3H), 4.15 (m, 3H), 6.42 (s, 1H), 6.98 (dd, 1H), 7.42 (m, 4H), 7.60 (s, 1H), 8.45 (s, 1H), and 11.19 (br s, 1H)

MS (ESI) : 508 $(MH)^+$

| | | | | | |
|---|---|---|---|---|---|
| Elemental analysis: | Found | C 59.7 | H 6.6 | N 13.4 | |
| $C_{27}H_{33}N_5O_5$ 1.8$H_2O$ | Requires | C 60.1 | H 6.8 | N 13.0% | |

**Example 288**

A mixture of (2*R*)-6-methoxy-4-(3-methylindol-5-yloxy)-7-(oxiran-2-ylmethoxy)quinazoline (100 mg, 0.28 mmol), (prepared as described in Example 278), and 1-

(3-aminopropyl)-4-methylpiperazine (132 mg, 0.84 mmol) in DMF (5 ml) was heated to 70 °C for 3 hours. The solvents were removed *in vacuo* and the residue taken up in dichloromethane. This was washed with water, dried ($MgSO_4$), filtered and evaporated. The residue was purified by silica column chromatography using gradient elution (dichloromethane, 5% methanol/95% dichloromethane, 20% methanolic ammonia (7M)/80% dichloromethane) to give **(2*R*)-7-(2-hydroxy-3-(3-(4-methylpiperazin-1-yl)propylamino)propoxy)-6-methoxy-4-(3-methylindol-5-yloxy)quinazoline** (44 mg, 31 %).

$^1$H NMR Spectrum: (DMSO-$d_6$) 1.55 (m, 2H), 2.10 (s, 3H), 2.30 (t, 8H), 2.62 (m, 6H), 3.98 (s, 3H), 4.12 (m, 3H), 6.42 (s, 1H), 6.98 (dd, 1H), 7.42 (m, 4H), 7.60 (s, 1H), 8.45 (s, 1H), and 11.19 (br s, 1H)

MS (ESI) : 521 $(MH)^+$

| | | | | | |
|---|---|---|---|---|---|
| Elemental analysis: | Found | C 61.3 | H 7.3 | N 16.1 | |
| $C_{28}H_{36}N_6O_4$ 1.6$H_2O$ | Requires | C 61.2 | H 7.2 | N 16.3% | |

**Example 289**

A mixture of (2*R*)-6-methoxy-4-(3-methylindol-5-yloxy)-7-(oxiran-2-ylmethoxy)quinazoline (70 mg, 0.19 mmol), (prepared as described in Example 278), and 1-(3-aminopropyl)pyrrolidine (74 mg, 0.58 mmol) in DMF (5 ml) was heated to 60 °C overnight. The solvents were removed *in vacuo* and the residue purified by column chromatography using gradient elution (dichloromethane, 5% methanol/95% dichloromethane, 20% methanolic ammonia (7M)/80% dichloromethane) to give **(2*R*)-7-(2-hydroxy-3-(3-(pyrrolidin-1-yl)propylamino)propoxy)-6-methoxy-4-(3-methylindol-5-yloxy)quinazoline** (64 mg, 68 %).

$^1$H NMR Spectrum: (DMSO-$d_6$) 1.60 (m, 6H), 2.25 (m, 4H), 2.60 (m, 4H), 3.08 (m, 2H), 3.98 (s, 3H), 4.12 (m, 3H), 6.42 (s, 1H), 6.98 (dd, 1H), 7.34 (m, 4H), 7.58 (s, 1H), 8.42 (s, 1H), and 11.80 (br s, 1H)

MS (ESI) : 492 $(MH)^+$

**Example 290**

A mixture of 4-chloro-6-methoxy-7-(3-piperidinopropoxy)quinazoline (380 mg, 1.13 mmol), (prepared as described for the starting material in Example 67), potassium carbonate

(469 mg, 3.4 mmol), 4-bromo-5-hydroxyindole (240 mg, 1.13 mmol) and DMA (4.0 ml) were stirred at 90°C for 3 hours and allowed to cool to ambient temperature. The reaction mixture was filtered and the filtrate evaporated under vacuum. The residue was purified by column chromatography eluting with dichloromethane/methanolic ammonia (7M) (95/5) to give an oil. This oil was further purified by column chromatography eluting with dichloromethane/methanol (60/40) to give **4-(4-bromoindol-5-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline** (256 mg, 44%).

$^1$H NMR Spectrum: ($CDCl_3$) 1.47 (m, 2H), 1.60 (m, 4H), 2.14 (m, 2H), 2.44 (m, 4H), 2.54 (t, 2H), 4.08 (s, 3H), 4.27 (t, 2H), 6.67 (m, 1H), 7.15 (d, 1H), 7.32 (t, 1H), 7.36 (s, 1H), 7.42 (d, 1H), 7.69 (s, 1H) 8.55 (br s, 1H) and 8.62 (s, 1H)

MS (ESI) : 511, 513 $(MH)^+$

| | | | | |
|---|---|---|---|---|
| Elemental analysis | Found | C 58.2 | H 5.3 | N 10.8 |
| $C_{25}H_{27}BrN_4O_3$ 0.25 $H_2O$, | Requires | C 58.2 | H 5.4 | N 10.9% |

The starting material was prepared as follows:

Ethyl 4-bromo-5-hydroxyindole-2-carboxylate (1.49 g, 5 mmol.), (Jnl. Org. Chem. 1984, 49, 4761), was dissolved in ethanol (10 ml) and water (3.5 ml). Potassium hydroxide (840 mg) was added and the mixture stirred at 50 °C under an atmosphere of nitrogen for 1 hour then cooled to ambient temperature. The solvent was evaporated and the residue re-dissolved in water (25 ml). 2M Aqueous hydrochloric acid was added until the reaction mixture was at pH4, giving a precipitate which was filtered off, washed with water and dried under vacuum to give 4-bromo-5-methoxyindole-2-carboxylic acid (1.30, 96%).

$^1$H NMR Spectrum: (DMSO-$d_6$) 3.83 (s, 3H), 6.90 (d, 1H), 7.16 (d, 1H), 7.40 (d, 1H). 11.88 (br s, 1H) and 13.19 (br s, 1H)

MS (ESI) : 268, 270 (M-H)

4-Bromo-5-methoxyindole-2-carboxylic acid (1.25 g, 4.19 mmol), quinoline (15ml) and copper chromite (313 mg) were mixed together. Nitrogen was gently bubbled through the mixture for 5 minutes, then the mixture heated quickly to 245°C under an atmosphere of nitrogen. After 90 minutes the mixture was cooled to ambient temperature diluted with ethyl acetate (100ml) and washed with 2M aqueous hydrochloric acid (60ml). The ethyl acetate layer was filtered, the filtrate dried ($MgSO_4$) and the solvent evaporated. The residue was

purified by silica column chromatography eluting with dichloromethane/hexane (1/1) to give 4-bromo-5-methoxyindole (635mg, 60%).

$^1$H NMR Spectrum ($CDCl_3$) 3.94 (s, 3H), 6.55 (m, 1H), 6.93 (d, 1H), 7.27 (m, 2H). 8.18 (br s, 1H)

MS (ESI) : 224, 226 $(M-H)^-$

A solution of 4-bromo-5-methoxyindole (540 mg, 2.4 mmol) in dichloromethane (12ml) was cooled to - 40°C under an atmosphere of nitrogen. Boron tribromide (4.8 ml of a 1M solution in dichloromethane, 4.8 mmol) was added dropwise then the mixture warmed to ambient temperature and stirred for 1 hour. The mixture was diluted with dichloromethane (5ml) and washed with 2M aqueous hydrochloric acid (3ml). The organic layer was separated, dried ($MgSO_4$) and evaporated to give a dark oil. This was purified by silica column chromatography eluting with dichloromethane/ethyl acetate (8/2) to give 4-bromo-5-hydroxyindole (295 mg, 55%).

$^1$H NMR Spectrum: ($CDCl_3$) 6.46 (m, 1H), 7.92 (d, 1H), 7.22 (m, 2H), 8.80 (br s, 1H)

MS (ESI) : 210, 212 $(M-H)^-$

**Example 291**

Nitrogen was bubbled through a mixture of 4-chloro-6-methoxy-7-(3-piperidinopropoxy)quinazoline (335 mg, 0.68 mmol), (prepared as described for the starting material in Example 67), potassium carbonate (281.5 mg, 2.04 mmol), 5-hydroxy-1-methylindole (100 mg, 0.68 mmol) and DMA (4.0 ml) for 5 minutes. The mixture was then stirred at 90°C for 4 hours under an atmosphere of nitrogen and allowed to cool to ambient temperature. The reaction mixture was filtered and the filtrate evaporated under vacuum. The residue was purified by trituration with methanol then water to give **6-methoxy-4-(1-methylindol-5-yloxy)-7-(3-piperidinopropoxy)quinazoline** (148 mg, 49%).

$^1$H NMR Spectrum: (DMSO-$d_6$) 1.38 (m, 2H), 1.51 (m, 4H), 1.93 (m, 2H), 2.35 (m, 4H), 2.41 (t, 2H), 3.83 (s, 3H), 3.97 (s, 3H), 4.24 (t, 2H), 6.42 (d, 1H), 7.06 (dd, 1H), 7.33 (s, 1H), 7.42 (m, 2H), 7.50 (d, 1H), 7.59 (s, 1H) and 8.47 (s, 1H)

MS (ESI) : 447 $(MH)^+$

| | | | | |
|---|---|---|---|---|
| Elemental analysis | Found | C 69.5 | H 6.8 | N 12.5 |
| $C_{26}H_{30}N_4O_3$ | Requires | C 69.9 | H 6.8 | N 12.6% |

The starting material was prepared as follows:

A solution of 5-benzyloxy-1-methylindole (3.5 g, 15.7 mmol), in ethanol (100 ml) was hydrogenated at ambient temperature and 1atmosphere pressure hydrogen for 4 hours using 10% palladium on carbon (0.5 g) as catalyst. The catalyst was filtered off and the filtrate evaporated *in vacuo*. The residue was purified by silica column chromatography eluting with ethyl acetate/dichloromethane (10/90) to give 5-hydroxy-1-methylindole (2.1 g, 97%).

MS (ESI) : 146 $(M-H)^-$

$^1H$ NMR Spectrum: ($CDCl_3$) 3.74 (s, 3H), 4.50 (S, 1H), 6.33 (d, 1H), 6.79 (dd, 1H), 7.00 (m, 2H), 7.17 (d, 1H)

**Example 292**

A mixture of (2*R*)-4-(indol-5-yloxy)-6-methoxy-7-(oxiran-2-ylmethoxy)quinazoline (300 mg, 0.83 mmol), and pyrrolidine (176 mg, 2.48 mmol) in DMF (5 ml) was stirred at 75°C for 3 hours under an atmosphere of nitrogen and allowed to cool to ambient temperature. The solvents were removed *in vacuo* and the residue purified on silica gel, gradient elution with dichloromethane, dichloromethane/methanol (95/5), dichloromethane/methanolic ammonia (7M) (98/2 to 90/10), to give **(2*R*)-7-(2-hydroxy-3-(pyrrolidin-1-yl)propoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline** (326 mg, 87%).

$^1H$ NMR Spectrum: ($CDCl_3$) 1.80 (m, 4H), 2.56 (m, 3H), 2.71 (m, 2H), 2.87 (m, 1H), 4.04 (s, 3H), 4.23 (m, 3H), 6.59 (m, 1H), 7.07 (dd, 1H), 7.25 (m, 1H), 7.32 (s, 1H), 7.45 (d, 1H), 7.50 (d, 1H), 7.61 (s, 1H), 8.30 (br s, 1H) and 8.60 (s, 1H)

MS (ESI) : 435$(MH)^+$

| | | | | |
|---|---|---|---|---|
| Elemental analysis | Found | C 63.4 | H 5.9 | N 12.3 |
| $C_{24}H_{26}N_4O_4.1H_2O$ | Requires | C 63.7 | H 6.2 | N 12.4% |

The starting material was prepared as follows:

Nitrogen was bubbled through a mixture of 7-hydroxy-4-(indol-5-yloxy)-6-methoxyquinazoline (3.07 g, 10 mmol), (prepared as described for the starting material in Example 107), potassium carbonate (4.14 g, 30 mmol) and (2*R*)-(-)- glycidyl tosylate (4.57 g, 20 mmol) in DMA (35 ml) for 5 minutes. The mixture was then stirred at 60 °C for 2 hours under an atmosphere of nitrogen and allowed to cool to ambient temperature. The reaction mixture was filtered and the filtrate evaporated *in vacuo*. The residue was purified by column

chromatography on silica by gradient elution with dichloromethane/methanol (100/0 to 95/5), to give (2*R*)-4-(indol-5-yloxy)-6-methoxy-7-(oxiran-2-ylmethoxy)quinazoline as a yellow solid (1.92g, 53%).

$^1$H NMR Spectrum: ($DMSOd_6$) 2.75 (m, 1H), 2.89 (m, 1H), 3.44 (m, 1H), 3.97 (s, 3H), 4.06 (m, 1H), 4.58 (dd, 1H), 6.44 (m, 1H), 6.95 (dd, 1H), 7.40 (m, 4H) 7.62 (s, 1H), 8.47 (s, 1H), 11.19 (br s 1H)

MS (ESI) : 364 $(MH)^+$

**Example 293**

Using an analogous procedure to that described in Example 292, (2*R*)-4-(indol-5-yloxy)-6-methoxy-7-(oxiran-2-ylmethoxy)quinazoline (300 mg, 0.83 mmol), (prepared as described for the starting material in Example 292), was reacted with morpholine (211 mg, 2.49 mmol) to give **(2*R*)-7-(2-hydroxy-3-morpholinopropoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline** (338 mg, 85%).

$^1$H NMR Spectrum: ($CDCl_3$) 2.48 (m, 2H), 2.624 (m, 2H), 2.68 (m, 2H), 3.78 (m, 4H), 4.04 (s, 3H), 4.24 (m, 3H), 6.58 (m, 1H), 7.08 (dd, 1H), 7.29 (m, 1H), 7.34 (s, 1H), 7.46 (d, 1H), 7.50 (d, 1H), 7.62 (s, 1H), 8.31 (br s, 1H) and 8.62 (s, 1H)

MS (ESI) : 451$(MH)^+$

| | | | | | |
|---|---|---|---|---|---|
| Elemental analysis | Found | C 60.3 | H 5.9 | N 12.3 | |
| $C_{24}H_{26}N_4O_5.1.5H_2O$ | Requires | C 60.4 | H 6.1 | N 11.7% | |

**Example 294**

Using an analogous procedure to that described in Example 292, (2*R*)-4-(indol-5-yloxy)-6-methoxy-7-(oxiran-2-ylmethoxy)quinazoline (300 mg, 0.83 mmol), (prepared as described for the starting material in Example 292), was reacted with piperidine (211 mg, 2.49 mmol) to give **(2*R*)-7-(2-hydroxy-3-piperidinopropoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline** (325 mg, 86%).

$^1$H NMR Spectrum: ($CDCl_3$) 1.47 (m, 2H), 1.61 (m, 4H), 2.39 (m, 2H), 2.54 (d, 2H), 2.64 (m, 2H), 4.04 (s, 3H), 4.24 (m, 3H), 6.58 (m, 1H), 7.08 (dd, 1H), 7.29 (m, 1H), 7.32 (s, 1H), 7.45 (d, 1H), 7.48 (d, 1H), 7.62 (s, 1H), 8.28 (br s, 1H) and 8.60 (s, 1H)

MS (ESI) : 449 $(MH)^+$

| | | | | | |
|---|---|---|---|---|---|
| Elemental analysis | Found | C 65.9 | H 6.3 | N 12.3 | |

| | | |
|---|---|---|
| $C_{25}H_{28}N_4O_4.0.5H_2O$ | Requires | C 65.6 H 6.4 N 12.3% |

**Example 295**

A mixture of (2*R*)-4-(indol-5-yloxy)-6-methoxy-7-(oxiran-2-ylmethoxy)quinazoline (300 mg, 0.83 mmol), (prepared as described for the starting material in Example 292), and dimethylamine (1.24 ml of a 2M solution in THF, 2.48 mmol) in DMF (5 ml) was stirred at 75°C for 3 hours under an atmosphere of nitrogen then allowed to cool to ambient temperature. The solvents were removed *in vacuo* and the residue purified by trituration with methanol to give **(2*R*)-7-(2-hydroxy-3-dimethylaminopropoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline** (265 mg, 63%).

$^1$H NMR Spectrum: ($DMSOd_6$) 2.21 (s, 6H), 2.38 (m, 2H), 3.97 (s, 3H), 4.073 (m, 2H), 4.21 (m, 1H), 4.96 (d, 1H), 6.43 (m, 1H), 6.97 (dd, 1H), 7.37 (s, 1H), 7.43 (m, 3H), 7.62 (s, 1H), 8.48 (s, 1H) and 11.20 (br s, 1H)

MS (ESI) : 409$(MH)^+$

| | | |
|---|---|---|
| Elemental analysis | Found | C 62.8 H 5.8 N 13.2 |
| $C_{22}H_{24}N_4O_4.0.7H_2O$ | Requires | C 62.8 H 6.1 N 13.3% |

**Example 296**

A mixture of (2*R*)-4-(indol-5-yloxy)-6-methoxy-7-(oxiran-2-ylmethoxy)quinazoline (300 mg, 0.83 mmol), (prepared as described for the starting material in Example 292), and diisopropylamine (1.35 ml, 9.7 mmol) in DMF (5 ml) was stirred at 70°C for 19 hours under an atmosphere of nitrogen then allowed to cool to ambient temperature. The solvents were removed *in vacuo* and the residue purified on silica gel using gradient elution with dichloromethane, dichloromethane/methanol (95/5), dichloromethane/methanolic ammonia (7M) (98/2 to 90/10) to give **(2*R*)-7-(2-hydroxy-3-((N,N-diisopropyl)amino)propoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline** (343 mg, 86%).

$^1$H NMR Spectrum: ($CDCl_3$) 1.08 (m, 12H), 1.57 (m, 1H), 1.75 (m, 1H), 3.10 (m, 2H), 4.04 (s, 3H), 4.16 (m, 3H), 6.58 (m, 1H), 7.08 (dd, 1H), 7.26 (m, 1H), 7.32 (s, 1H), 7.45 (d, 1H), 7.50 (d, 1H), 7.61 (s, 1H), 8.32 (br s, 1H) and 8.61 (s, 1H)

MS (ESI) : 465$(MH)^+$

| | | |
|---|---|---|
| Elemental analysis | Found | C 64.8 H 6.8 N 11.9 |
| $C_{26}H_{32}N_4O_4.1.0H_2O$ | Requires | C 64 6 H 7.0 N 11.6% |

**Example 297**

A mixture of (2*S*)-4-(indol-5-yloxy)-6-methoxy-7-(oxiran-2-ylmethoxy)quinazoline (100 mg, 0.28 mmol), and pyrrolidine (60 mg, 0.84 mmol) in DMF (5 ml) was stirred at 75°C for 3 hours under an atmosphere of nitrogen and then allowed to cool to ambient temperature. The solvents were removed *in vacuo* and the residue purified on silica gel, gradient elution with dichloromethane, dichloromethane/methanol (95/5), dichloromethane/methanolic ammonia (7M) (98/2 to 90/10), to give **(2*S*)-7-(2-hydroxy-3-(pyrrolidin-1-yl)propoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline** (114 mg, 92%).

$^1$H NMR Spectrum: ($CDCl_3$) 1.80 (m, 4H), 2.56 (m, 3H), 2.71 (m, 2H), 2.86 (m, 1H), 4.04 (s, 3H), 4.23 (m, 3H), 6.59 (m, 1H), 7.07 (dd, 1H), 7.25 (m, 1H), 7.32 (s, 1H), 7.45 (d, 1H), 7.50 (d, 1H), 7.61 (s, 1H), 8.30 (br s, 1H) and 8.60 (s, 1H)

MS (ESI) : 435$(MH)^+$

| | | | | | |
|---|---|---|---|---|---|
| Elemental analysis | Found | C 64.7 | H 6.0 | N 12.6 | |
| $C_{24}H_{26}N_4O_4.0.5H_2O$ | Requires | C 64.9 | H 6.1 | N 12.7% | |

The starting material was prepared as follows:

Nitrogen was bubbled through a mixture of 7-hydroxy-4-(indol-5-yloxy)-6-methoxyquinazoline (3.07 g, 10 mmol), (prepared as described for the starting material in Example 107), potassium carbonate (4.14 g, 30 mmol) and (2*S*)-(+)-glycidyl tosylate (4.57 g, 20 mmol) in DMA (35 ml) for 5 minutes. This mixture was then stirred at 60 °C for 2 hours under an atmosphere of nitrogen and allowed to cool to ambient temperature. The reaction mixture was filtered and the filtrate evaporated *in vacuo*. The residue was purified by column chromatography on silica by gradient elution with dichloromethane/methanol (100/0 to 95/5), to give after removal of the solvents *in vacuo* and trituration of the residue with ether, (2*S*)-4-(indol-5-yloxy)-6-methoxy-7-(oxiran-2-ylmethoxy)quinazoline (1.88g, 52%) as a yellow solid:

$^1$H NMR Spectrum: ($DMSOd_6$) 2.75 (m, 1H), 2.89 (m, 1H), 3.44 (m, 1H), 3.97 (s, 3H), 4.06 (m, 1H), 4.58 (dd, 1H), 6.44 (m, 1H), 6.95 (dd, 1H), 7.46 (m, 4H) 7.62 (s, 1H), 8.47 (s, 1H) and 11.19 (br s 1H)

MS (ESI) : 364 $(MH)^+$

**Example 298**

Using an analogous procedure to that described in Example 297, (2*S*)-4-(indol-5-yloxy)-6-methoxy-7-(oxiran-2-ylmethoxy)quinazoline (100 mg, 0.28 mmol), (prepared as described for the starting material in Example 297), was reacted with morpholine (73.2 mg, 0.84 mmol) to give **(2*S*)-7-(2-hydroxy-3-morpholinopropoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline** (82 mg, 63%).

$^1$H NMR Spectrum: ($CDCl_3$) 2.48 (m, 2H), 2.62 (m, 2H), 2.68 (m, 2H), 3.78 (m, 4H), 4.04 (s, 3H), 4.29 (m, 3H), 6.58 (m, 1H), 7.08 (dd, 1H), 7.29 (m, 1H), 7.34 (s, 1H), 7.46 (d, 1H), 7.50 (d, 1H), 7.62 (s, 1H), 8.31 (br s, 1H) and 8.62 (s, 1H)

MS (ESI) : 451$(MH)^+$

| | | |
|---|---|---|
| Elemental analysis | Found | C 61.7 H 5.7 N 11.8 |
| $C_{24}H_{26}N_4O_5.1.0H_2O$ | Requires | C 61.5 H 6.0 N 12.0% |

**Example 299**

Using an analogous procedure to that described in Example 297, (2*S*)-4-(indol-5-yloxy)-6-methoxy-7-(oxiran-2-ylmethoxy)quinazoline (100 mg, 0.28 mmol), (prepared as described for the starting material in Example 297), was reacted with piperidine (70 mg, 0.83 mmol), to give **(2*S*)-7-(2-hydroxy-3-piperidinopropoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline** (93 mg, 73%).

$^1$H NMR Spectrum: ($CDCl_3$) 1.47 (m, 2H), 1.61 (m, 4H), 2.39 (m, 2H), 2.54 (d, 2H), 2.64 (m, 2H), 4.04 (s, 3H), 4.29 (m, 3H), 6.58 (m, 1H), 7.08 (dd, 1H), 7.29 (m, 1H), 7.32 (s, 1H), 7.45 (d, 1H), 7.48 (d, 1H), 7.62 (s, 1H), 8.28 (br s, 1H) and 8.60 (s, 1H)

MS (ESI) : 449 $(MH)^+$

| | | |
|---|---|---|
| Elemental analysis | Found | C 65.8 H 6.2 N 12.2 |
| $C_{25}H_{28}N_4O_4.0.5H_2O$ | Requires | C 65.6 H 6.4 N 12.3% |

**Example 300**

A mixture of (2*S*)-4-(indol-5-yloxy)-6-methoxy-7-(oxiran-2-ylmethoxy)quinazoline (100 mg, 0.28 mmol), (prepared as described for the starting material in Example 297), and dimethylamine (0.42 ml of a 2M solution in THF, 0.84 mmol) in DMF (5 ml) was stirred at 75°C for 3 hours under an atmosphere of nitrogen and then allowed to cool to ambient temperature. The solvents were removed *in vacuo* and the residue purified by trituration with

methanol to give **(2*S*)-7-(2-hydroxy-3-dimethylaminopropoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline** (100 mg, 85%).

$^1$H NMR Spectrum: ($DMSOd_6$) 2.21 (s, 6H), 2.38 (m, 2H), 3.97 (s, 3H), 4.083 (m, 2H), 4.21 (m, 1H), 4.96 (d, 1H), 6.43 (m, 1H), 6.97 (dd, 1H), 7.37 (s, 1H), 7.43 (m, 3H), 7.62 (s, 1H), 8.48 (s, 1H) and 11.20 (br s, 1H)

MS (ESI) : 409$(MH)^+$

| | | |
|---|---|---|
| Elemental analysis | Found | C 63.6 H 6.0 N 13.3 |
| $C_{22}H_{24}N_4O_4.0.5H_2O$ | Requires | C 63.3 H 6.0 N 13.4% |

**Example 301**

A mixture of (2*S*)-4-(indol-5-yloxy)-6-methoxy-7-(oxiran-2-ylmethoxy)quinazoline (100 mg, 0.28 mmol), (prepared as described for the starting material in Example 297), and diisopropylamine (0.45 ml, 3.2 mmol) in DMF (5 ml) was stirred at 70°C for 19 hours under an atmosphere of nitrogen and then allowed to cool to ambient temperature. The solvents were removed *in vacuo* and the residue purified on silica gel, using gradient elution with dichloromethane/methanol (100/0 to 95/5), dichloromethane/methanolic ammonia (7M) (98/2 to 90/10) to give **(2*S*)-7-(2-hydroxy-3-((N,N-diisopropyl)amino)propoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline** (43 mg, 33%).

$^1$H NMR Spectrum: ($CDCl_3$) 1.08 (m, 12H), 1.57 (m, 1H), 1.759 (m, 1H), 3.10 (m, 2H), 4.04 (s, 3H), 4.16 (m, 3H), 6.58 (m, 1H), 7.08 (dd, 1H), 7.26 (m, 1H), 7.32 (s, 1H), 7.45 (d, 1H), 7.50 (d, 1H), 7.61 (s, 1H), 8.32 (br s, 1H) and 8.61 (s, 1H)

MS (ESI) : 465$(MH)^+$

| | | |
|---|---|---|
| Elemental analysis | Found | C 67.2 H 7.0 N 11.9 |
| $C_{26}H_{32}N_4O_4$ | Requires | C 67.2 H 6.9 N 12.1% |

**Example 302**

A mixture of (2*R*)-4-(indol-5-yloxy)-6-methoxy-7-(oxiran-2-ylmethoxy)quinazoline (100 mg, 0.28 mmol), (prepared as described for the starting material in Example 292), and isopropylamine (1.0 ml) in THF (10 ml) was stirred at 75°C for 18 hours under an atmosphere of nitrogen and then allowed to cool to ambient temperature. The mixture was filtered and the filtrate evaporated *in vacuo*. The residue was purified by silica gel chromatography, gradient elution with dichloromethane/methanolic ammonia (7M) (100/0 to 90/10) to give **(2*R*)-7-(2-**

**hydroxy-3-(isopropylamino)propoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline** (82 mg, 68%).

$^1$H NMR Spectrum: ($DMSOd_6$) 0.98 (m, 6H), 2.68 (m, 3H), 3.96 (m, 4H), 4.13 (m, 2H), 5.06 (br s, 1H), 6.44 (s, 1H), 6.98 (dd, 1H), 7.439 (m, 4H), 7.60 (s, 1H), 8.46 (s, 1H) and 11.22 (s, 1H)

MS (ESI) : 423$(MH)^+$

| | | | | |
|---|---|---|---|---|
| Elemental analysis | Found | C 63.6 | H 6.4 | N 12.9 |
| $C_{23}H_{26}N_4O_4.0.6H_2O$ | Requires | C 63.8 | H 6.3 | N 12.9% |

**Example 303**

A mixture of (2*S*)-4-(indol-5-yloxy)-6-methoxy-7-(oxiran-2-ylmethoxy)quinazoline (100 mg, 0.28 mmol), (prepared as described for the starting material in Example 297), and isopropylamine (1.0 ml) in THF (10 ml) was stirred at 75°C for 18 hours under an atmosphere of nitrogen and then allowed to cool to ambient temperature. The mixture was filtered and the filtrate evaporated *in vacuo*. The residue was purified by silica gel chromatography using gradient elution with dichloromethane/methanolic ammonia (7M) (100/0 to 90/10) to give **(2*S*)-7-(2-hydroxy-3-(isopropylamino)propoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline** (66 mg, 56%).

$^1$H NMR Spectrum: ($DMSOd_6$) 0.985 (m, 6H), 2.68 (m, 3H), 3.96 (m, 4H), 4.13 (m, 2H), 5.06 (br s, 1H), 6.44 (s, 1H), 6.98 (dd, 1H), 7.43 (m, 4H), 7.60 (s, 1H), 8.46 (s, 1H) and 11.22 (s, 1H)

MS (ESI) : 423$(MH)^+$

| | | | | |
|---|---|---|---|---|
| Elemental analysis | Found | C 63.1 | H 6.3 | N 12.7 |
| $C_{23}H_{26}N_4O_4.0.9\ H_2O$ | Requires | C 63.0 | H 6.4 | N 12.8% |

**Example 304**

A mixture of (2*S*)-6-methoxy-4-(2-methylindol-5-yloxy)-7-(oxiran-2-ylmethoxy)quinazoline (250 mg, 0.66 mmol), and pyrrolidine (1.5 ml) in THF (10 ml) was stirred at 75°C for 3 hours under an atmosphere of nitrogen and then allowed to cool to ambient temperature. The mixture was filtered and the filtrate evaporated *in vacuo*. The residue was purified by silica gel chromatographyusing gradient elution with dichloromethane/methanolic ammonia (7M) (100/0 to 90/10) to give (2*S*)-7-(2-hydroxy-3-

**(pyrrolidin-1-yl)propoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline** (106 mg, 36%).

$^1$H NMR Spectrum: ($DMSOd_6$) 1.60 (s, 4H), 2.38 (s, 3H), 2.57 (m, 6H), 4.11 (m, 6H), 4.95 (d, 1H), 6.14 (s, 1H), 6.88 (dd, 1H), 7.29 (m, 2H), 7.37 (s, 1H), 7.59 (s, 1H), 8.48 (s, 1H) and 11.00 (s, 1H)

MS (ESI) : 450 $(MH)^+$

| | | | | |
|---|---|---|---|---|
| Elemental analysis | Found | C 67.0 | H 6.5 | N 12.0 |
| $C_{25}H_{28}N_4O_4 .0.1\ H_2O$ | Requires | C 66.7 | H 6.3 | N 12.4% |

The starting material was prepared as follows:

A mixture of 7-hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (300 mg, 0.93 mmol), (prepared as described in Example 49), potassium carbonate (385 mg, 2.79 mmol) and (2*S*)-(-)- glycidyl tosylate (426 mg, 2.79 mmol) in DMF (15 ml) was stirred at 60°C for 2 hours and allowed to cool to ambient temperature. The reaction mixture was filtered and the filtrate evaporated *in vacuo*. The residue was dissolved in dichloromethane and washed with saturated sodium hydrogen carbonate solution. The organic layer was then dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a yellow solid. This was triturated with ether, filtered off and dried to give (2*S*)-6-methoxy-4-(2-methylindol-5-yloxy)-7-(oxiran-2-ylmethoxy)quinazoline as a yellow solid (277 mg, 78 %).

$^1$H NMR Spectrum: (DMSO) 2.40 (s, 3H), 2.75 (m, 1H), 2.90 (m, 1H), 3.40 (m, 1H), 3.98 (s, 3H), 4.05 (m, 1H), 4.60 (m, 1H), 6.15 (s, 1H), 6.85 (dd, 1H), 7.30 (m, 2H) 7.40 (s, 1H), 7.60 (s, 1H), 8.45 (s, 1H) and 10.98 (s, 1H)

MS (ESI) : 378 $(MH)^+$

**Example 305**

A mixture of the (2*R*)-6-methoxy-4-(2-methylindol-5-yloxy)-7-(oxiran-2-ylmethoxy)quinazoline (250 mg, 0.66 mmol), (prepared as described for the starting material in Example 269), and pyrrolidine (1.5 ml) in THF (10 ml) was stirred at 75°C for 3 hours under an atmosphere of nitrogen and then allowed to cool to ambient temperature. The mixture was filtered and the filtrate evaporated *in vacuo*. The residue was purified by silica gel chromatography using gradient elution with dichloromethane/methanolic ammonia (7M)

(100/0 to 90/10) to give **(2*R*)-7-(2-hydroxy-3-(pyrrolidin-1-yl)propoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline** (165 mg, 55%).

$^1$H NMR Spectrum: ($DMSOd_6$) 1.60 (s, 4H), 2.38 (s, 3H), 2.57 (m, 6H), 4.11 (m, 6H), 4.95 (d, 1H), 6.14 (s, 1H), 6.88 (dd, 1H), 7.29 (m, 2H), 7.37 (s, 1H), 7.59 (s, 1H), 8.48 (s, 1H) and 11.00 (s, 1H)

MS (ESI) : 450 $(MH)^+$

| | | |
|---|---|---|
| Elemental analysis | Found | C 66.8 H 6.3 N 12.4 |
| $C_{25}H_{28}N_4O_4.0.1\ H_2O$ | Requires | C 66.7 H 6.3 N 12.4% |

**Example 306**

A mixture of (2*S*)-6-methoxy-4-(2-methylindol-5-yloxy)-7-(oxiran-2-ylmethoxy)quinazoline (250 mg, 0.66 m.mol), (prepared as described for the starting material in Example 304), and isopropylamine (1.5 ml) in THF (10 ml) was stirred at 75°C for 18 hours under an atmosphere of nitrogen and then allowed to cool to ambient temperature. The mixture was filtered and the filtrate evaporated *in vacuo*. The residue was purified by silica gel chromatography using gradient elution with dichloromethane/methanolic ammonia (7M) (100/0 to 90/10) to give **(2*S*)-7-(2-hydroxy-3-(isopropylamino)propoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline** (210 mg, 73%).

$^1$H NMR Spectrum: ($DMSOd_6$) 0.99 (d, 6H), 2.39 (s, 3H), 2.66 (m, 3H), 4.07 (m, 6H), 5.08 (d, 1H), 6.14 (s, 1H), 6.88 (dd, 1H), 7.29 (m, 2H), 7.37 (s, 1H), 7.58 (s, 1H), 8.49 (s, 1H) and 11.03 (s, 1H)

MS (ESI) : 437 $(MH)^+$

| | | |
|---|---|---|
| Elemental analysis | Found | C 64.3 H 6.4 N 12.3 |
| $C_{24}H_{28}N_4O_4.0.5\ H_2O$ | Requires | C 64.7 H 6.6 N 12.6% |

**Example 307**

A mixture of (2*R*)-6-methoxy-4-(2-methylindol-5-yloxy)-7-(oxiran-2-ylmethoxy)quinazoline (250 mg, 0.66 mmol), (prepared as described for the starting material in Example 269), and isopropylamine (1.5 ml) in THF (10 ml) was stirred at 75°C for 18 hours under an atmosphere of nitrogen and then allowed to cool to ambient temperature. The mixture was filtered and the filtrate evaporated *in vacuo*. The residue was purified by silica gel chromatography using gradient elution with dichloromethane/methanolic ammonia (7M)

(100/0 to 90/10) to give **(2*R*)-7-(2-hydroxy-3-(isopropylamino)propoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline** (243 mg, 84%).

$^1$H NMR Spectrum: ($DMSOd_6$): 0.99 (d, 6H), 2.39 (s, 3H), 2.66 (m, 3H), 4.07 (m, 6H), 5.08 (d, 1H), 6.14 (s, 1H), 6.88 (dd, 1H), 7.29 (m, 2H), 7.37 (s, 1H), 7.58 (s, 1H), 8.49 (s, 1H) and 11.03 (s, 1H)

MS (ESI) : 437 $(MH)^+$

| | | |
|---|---|---|
| Elemental analysis | Found | C 64.3 H 6.5 N 12.3 |
| $C_{24}H_{28}N_4O_4.0.5\ H_2O$ | Requires | C 64.7 H 6.6 N 12.6% |

**Example 308**

Nitrogen was bubbled through a mixture of 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (400 mg, 1.19 mmol), (prepared as described for the starting material in Example 1), potassium carbonate (476 mg, 3.45 mmol), 5-hdyroxy-1-methylindole (220 mg, 1.5 mmol), (prepared as described for the starting material in Example 291), and DMA (5.0 ml) for 5 minutes. The mixture was then stirred at 90°C for 3 hours under an atmosphere of nitrogen and allowed to cool to ambient temperature. The reaction mixture was filtered and the filtrate evaporated *in vacuo*. The residue was purified by trituration with methanol to give **6-methoxy-4-(1-methylindol-5-yloxy)-7-(3-morpholinopropoxy)quinazoline** (312 mg, 59%).

$^1$H NMR Spectrum: ($CDCl_3$) 2.13 (m, 2H), 1.48 (t, 4H), 1.57 (t, 2H), 3.72 (t, 4H), 3.84 (s, 3H), 4.05 (s, 3H), 4.3 (t, 2H), 6.50 (d, 1H), 7.08-7.13 (m, 2H), 7.32 (s, 1H), 7.37 (s, 1H), 7.47 (d, 1H), 7.62 (s, 1H) 8.59 (s, 1H)

MS (ESI) : 449 $(MH)^+$

| | | |
|---|---|---|
| Elemental analysis | Found | C 66.5 H 6.4 N 12.3 |
| $C_{25}H_{28}N_4O_4.0.1\ H_2O$ | Requires | C 66.7 H 6.3 N 12.4% |

**Example 309**

Nitrogen was bubbled through a mixture of 4-chloro-6-methoxy-7-(2-piperidinoethoxy)quinazoline (400 mg, 1.24 mmol), (prepared as described for the starting material in Example 180), potassium carbonate (500 mg, 3.62 mmol), 5-hydroxy-1-methylindole (231 mg, 1.57 mmol), (prepared as described for the starting material in Example 291), and DMA (5.0 ml) for 5 minutes. The mixture was then stirred at 90°C for 3

hours under an atmosphere of nitrogen and then allowed to cool to ambient temperature. The reaction mixture was filtered and the filtrate evaporated *in vacuo*. The residue was purified by trituration with methanol to give **6-methoxy-4-(1-methylindol-5-yloxy)-7-(2-piperidinopropoxy)quinazoline** (447 mg, 83%).

$^1$H NMR Spectrum: ($CDCl_3$) 1.47 (m, 2H), 1.64 (m, 4H), 2.57 (t, 4H) 2.94 (t, 2H), 3.83 (s, 3H), 4.05 (s, 3H), 4.34 (t, 2H), 6.49 (d, 1H), 7.10 (m, 2H), 7.32 (s, 1H), 7.38 (d, 1H), 7.45 (d, 1H), 7.62 (s, 1H) 8.60 (s, 1H)

MS (ESI) : 433 $(MH)^+$

| | | |
|---|---|---|
| Elemental analysis | Found | C 69.2 H 6.7 N 12.7 |
| $C_{25}H_{28}N_4O_3$ | Requires | C 69.4 H 6.5 N 13.0% |

**Example 310**

Nitrogen was bubbled through a mixture of 4-chloro-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline (400 mg, 1.24 mmol), (prepared as described for the starting material in Example 9), potassium carbonate (500 mg, 3.62 mmol), 5-hydroxy-1-methylindole (231 mg, 1.57 mmol), (prepared as described for the starting material in Example 291), and DMA (5.0 ml) for 5 minutes. The mixture was then stirred at 90°C for 3 hours under an atmosphere of nitrogen and allowed to cool to ambient temperature. The reaction mixture was filtered and the filtrate evaporated *in vacuo*. The residue was purified by column chromatography, gradient elution, with dichloromethane/methanolic ammonia (7M), (100/0 to 90/10) to give **6-methoxy-4-(1-methylindol-5-yloxy)-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline** (247 mg, 44%).

$^1$H NMR Spectrum: ($CDCl_3$) 1.81 (m, 4H), 2.18 (m, 2H), 2.56 (m, 4H), 2.69 (t, 2H), 3.82 (s, 3H), 4.05 (s, 3H), 4.30 (t, 2H), 6.45 (d, 1H), 7.09 (dd, 2H), 7.31 (s, 1H), 7.38 (d, 1H), 7.47 (d, 1H), 7.62 (s, 1H) and 8.59 (s, 1H)

MS (ESI) : 433 $(MH)^+$

| | | |
|---|---|---|
| Elemental analysis | Found | C 66.5 H 6.3 N 12.4 |
| $C_{25}H_{28}N_4O_3$ 0.1dichloromethane+0.7 $H_2O$ | Requires | C 66.7 H 6.6 N 12.4% |

**Example 311**

Nitrogen was bubbled through a mixture of 4-chloro-6-methoxy-7-(3-piperidinopropoxy)quinazoline (114 mg, 0.34 mmol), (prepared as described for the starting

material in Example 67), potassium carbonate (141 mg, 1.02 mmol), 5-hydroxy-4-nitroindole (60.5 mg, 0.34 mmol) and DMA (8.5 ml) for 5 minutes at ambient temperature. This mixture was then stirred at 90°C for 4 hours under an atmosphere of nitrogen and allowed to cool to ambient temperature. The reaction mixture was filtered and the filtrate evaporated *in vacuo*. The residue was purified by silica column chromatography using gradient elution with dichloromethane/methanol (100/0 to 95/5) followed by dichloromethane/methanolic ammonia (7M) (95/5) to give a partially purified oil. This oil was further purified by silica column chromatography, gradient elution with ethyl acetate/methanolic ammonia (95/5 to 80/20) to give **6-methoxy-(4-nitroindol-5-yloxy)-7-(3-piperidinopropoxy)quinazoline** (63 mg, 39%).

$^1$H NMR Spectrum: ($CDCl_3$) 1.46 (m, 2H), 1.60 (m, 4H), 2.16 (m, 2H), 2.43 (m, 4H), 2.54 (t, 2H), 3.85 (s, 3H), 4.33 (t, 2H), 7.04 (d, 1H), 7.10 (s, 1H), 7.47 (s, 1H), 7.57 (d, 1H), 7.83 (d, 1H), 7.95 (d, 1H) and 9.09 (s, 1H)

MS (ESI) : 478 $(MH)^+$

| | | | |
|---|---|---|---|
| Elemental analysis | Found | C 62.5 | H 5.8 N 14.7 |
| $C_{25}H_{27}N_5O_5$ | Requires | C 62.9 | H 5.7 N 14.7% |

The starting material was prepared as follows:

A mixture of ethyl 5-methoxyindole-2-carboxylate (8.15 g, 37.2 mmol), (prepared by the method described in Heterocycles Vol. 43, No. 2, p. 263-266), nitric acid adsorbed on silica gel (24g) and dichloromethane (150 ml) was stirred at ambient temperature for 18 hours. The dichloromethane was removed *in vacuo* and the product washed off the silica with acetone. The acetone was evaporated *in vacuo*. The residue was treated again with nitric acid on silica (1g) as above and the work up procedure repeated to give ethyl 5-hydroxy-4-nitroindole-2-carboxylate (5.8 g, 59%).

$^1$H NMR Spectrum: ($DMSOd_6$) 1.33 (t, 3H), 3.95 (s, 3H), 4.35 (q, 2H), 7.19 (d, 1H), 7.35 (d, 1H), 7.75 (d, 1H) and 12.45 (br s, 1H)

Ethyl 5-hydroxy-4-nitroindole-2-carboxylate (1.0 g, 3.8 mmol.) was suspended in a mixture of ethanol (20 ml) and water (5 ml). Potassium hydroxide (840 mg) was added and the mixture stirred at 50 °C under an atmosphere of nitrogen for 1 hour then cooled to ambient temperature. The solvent was evaporated *in vacuo* and the residue re-dissolved in water (25 ml). The pH was adjusted to pH2 using aqueous hydrochloric acid (2M ). The resulting

precipitate was filtered off, washed with water and dried *in vacuo* to give 5-methoxy-4-nitroindole-2-carboxylic acid (790 mg). This was used without further purification.

The crude 5-methoxy-4-nitroindole-2-carboxylic acid (720 mg, 3.05 mmol), quinoline (9 ml) and copper chromite (180 mg) were stirred together. Nitrogen was gently bubbled through the mixture for 5 minutes, then the mixture was heated quickly to 225°C, and stirred at this temperature for 40 minutes under an atmosphere of nitrogen. The mixture was cooled to ambient temperature diluted with ethyl acetate (80ml) and the insoluble material filtered off. The filtrate was extracted twice with aqueous hydrochloric acid (2M) and then with saturated aqueous sodium hydrogen carbonate solution. The ethyl acetate layer was dried ($MgSO_4$), evaporated and the residue purified by silica column chromatography eluting with dichloromethane to give 5-methoxy-4-nitroindole (129mg, 22%).

$^1$H NMR Spectrum: ($CDCl_3$) 3.99 (s, 3H), 6.88 (t, 1H), 6.97 (d, 1H), 7.37 (t, 1H). 7.55 (d, 1H) and 8.38 (br s, 1H)

MS (ESI) : 193 $(MH)^+$

A solution of 5-methoxy-4-nitroindole (110 mg, 0.57 mmol) in dichloromethane (12 ml) was cooled to - 30°C under an atmosphere of nitrogen. Boron tribromide (0.74 ml of a 1M solution in dichloromethane, 0.74 mmol) was added dropwise then the mixture warmed to ambient temperature and stirred for 1 hour. The mixture was cooled to 5°C, diluted with dichloromethane (5ml), and water (10 ml). After stirring for 5 minutes the insoluble material was filtered off and the dichloromethane layer separated, dried ($MgSO_4$), and evaporated to give a dark oil which was and purified by silica column chromatography eluting with dichloromethane to give 5-hydroxy-4-nitroindole (68 mg, 67%).

$^1$H NMR Spectrum: ($CDCl_3$) 6.95 (d, 1H), 7.29 (m, 1H), 7.43 (t, 1H), 7.63 (d, 1H) and 11.60 (br s, 1H)

MS (ESI) : 177 $(M-H)^-$

**Example 312**

6-Methoxy-(4-nitroindol-5-yloxy)-7-(3-piperidinopropoxy)quinazoline (45 mg 0.094 mmol), (prepared as described in Example 311), ethanol (20 ml) and 10% palladium on charcoal were hydrogenated at 45°C and 1 atmosphere pressure of hydrogen for 3.5 hours. The mixture was cooled to ambient temperature, the catalyst filtered off and the filtrate evaporated *in vacuo*. The residue was purified

by silica column chromatography using gradient elution with dichloromethane/methanolic ammonia (7M) (100/0 to 95/5), to give **4-(4-amino-indol-5-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline** (39 mg, 87%).

$^1$H NMR Spectrum: ($CDCl_3$) 1.39(m, 2H), 1.50 (m, 4H), 1.96 (m, 2H), 2.35 (m, 4H), 2.43 (t, 2H), 3.80 (s, 3H), 4.28 (t, 2H), 4.84 (br s, 2H), 6.68 (d, 1H), 6.78 (d, 1H), 6.94 (s, 1H), 7.28 (s, 1H), 7.45 (s, 1H), 7.69 (s, 1H), 8.45 (br s, 1H) and 8.98 (s, 1H)

MS (ESI) : 448 $(MH)^+$

| | | | | |
|---|---|---|---|---|
| Elemental analysis | Found | C 64.0 | H 6.4 | N 14.4 |
| $C_{25}H_{29}N_5O_3$.0.3 $H_2O$+ 0.4 dichloromethane | Requires | C 63.6 | H 6.3 | N 14.4% |

**Example 313**

A mixture of 4-chloro-6-methoxy-7-(3-piperidinopropoxy)quinazoline (227 mg, 0.68 mmol), (prepared as described for the starting material in Example 67), 5-hydroxy-1*H*-pyrrolo[2,3-*b*]pyridine (100 mg, 0.75 mmol), (prepared as described for the starting material in Example 182), and potassium carbonate (350 mg, 2.5mmol) in DMF (4 ml) was stirred at 95°C for 6 hours and allowed to cool to ambient temperature. The reaction mixture was treated with 1.0 N aqueous sodium hydroxide solution and allowed to stir at ambient temperature for a few minutes. The resulting precipitate was filtered off, washed with water and air dried to give a crude product. This was purified by column chromatography, eluting initially with dichloromethane/methanol (85/15) to isolate a less polar impurity and then with dichloromethane/methanol/0.88 ammonia (100/8/1) to isolate the target compound. The relevant fractions were combined and evaporated *in vacuo* to give a white solid which was triturated with acetone, filtered and dried to give **6-methoxy-7-(3-piperidinopropoxy)-4-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)quinazoline** (58 mg, 20%).

$^1$H NMR Spectrum: (DMSO-$d_6$) 1.38 (m, 2H), 1.50 (m, 4H), 1.95 (m, 2H), 2.15 (m, 4H), 2.42 (t, 2H), 3.99 (s, 3H), 4.22 (t, 2H), 6.47 (m, 1H), 7.36 (s, 1H), 7.55 (m, 1H), 7.60 (s, 1H), 7.90 (d, 1H), 8.18 (d, 1H), 8.49 (s, 1H) and 11.76 (br s, 1H)

MS (ESI) : 434 $(MH)^+$

| | | | | |
|---|---|---|---|---|
| Elemental analysis | Found | C 63.9 | H 6.4 | N 15.4 |
| $C_{24}H_{27}N_5O_3$ 1.0 $H_2O$ | Requires | C 63.8 | H 6.5 | N 15.5% |

**Example 314**

To a solution of 7-(3-bromopropoxy)-4-(1*H*-indol-5-yloxy)-6-methoxyquinazoline (200mg, 0.47 mmol) in methylene chloride was added 4-piperidinopiperidine (237mg, 1.41mmol) and the reaction heated at 40° C for 1 hour. A further portion of 4-piperidinopiperidine (100mg, 0.59mmol) was added and reaction heated for a further 2 hours. The reaction was purified by flash chromatography eluting from methylene chloride to 15% methanol/methylene chloride (+ 1% ammonium hydroxide). The product was evaporated, triturated with ether and filtered to give **4-(indol-5-yloxy)-6-methoxy-7-(3-(4-piperidino)piperidinopropoxy)quinazoline** (200mg, 83%) as a yellow solid.

$^1$H NMR Spectrum: ($CDCl_3$) 1.48-2.18 (m, 19H), 2.58 (t, 2H), 3.06 (d, 2H), 4.05 (s, 3H), 4.26 (t, 2H), 6.59 (s, 1H), 7.08 (dd, 1H), 7.28 (d, 1H), 7.36 (s, 1H), 7.50 (d, 1H), 7.63 (s, 1H), 8.30 (s, 1H), 8.59 (s, 1H)

M S: 516 [MH]+

The starting material was prepared as follows:

To a solution of 7-hydroxy-4-(1*H*-indol-5-yloxy)-6-methoxyquinazoline (1g, 3.2 mmol), (prepared as described for the starting material in Example 107), in DMF (50ml) was added powdered potassium carbonate (1.32g, 9.6mmol) and 1,3-dibromopropane (6.43g, 32mmol). The reaction was heated at 50°C for 2 hours. The inorganic material was filtered off and then the DMF removed. The residue was partitioned between methylene chloride/water. The organics were separated, dried over $MgSO_4$, filtered, evaporated in vacuo and purified by flash chromatography eluting from methylene chloride to 5% methanol/95% methylene chloride. The product was concentrated *in vacuo*, triturated with ether and the resulting solid filtered to give 7-(3-bromopropoxy)-4-(1*H*-indol-5-yloxy)-6-methoxyquinazoline (900mg, 66%) as a white solid.

$^1$H NMR Spectrum: ($CDCl_3$) 2.46-2.57 (m, 2H), 3.68 (t, 2H), 4.08 (s, 3H), 4.38 (t, 2H), 6.58 (s, 1H), 7.09 (d, 1H), 7.27 (s, 1H), 7.35 (s, 1H), 7.46 (d, 1H), 7.50 (s, 1H), 7.63 (s, 1H), 8.30 (s, 1H), 8.62 (s, 1H)

M S: 428 [MH] +

**Example 315**

To a solution of 7-hydroxy-6-methoxy-4-(2-methyl-1*H*-indol-5-yloxy)quinazoline (225mg, 0.7 mmol), (prepared as described in Example 49), in DMF was added powdered

potassium carbonate (290mg, 2.1 mmol) and (5*S*)-5-(*p*-toluenesulphonylmethyl)-1-methyl-2-pyrrolidinone (340mg, 1.2mmol). The reaction was then heated at 95°C for 5 hours. The inorganic material was filtered off and the DMF removed by evaporation. The residue was then purified by chromatography eluting from methylene chloride to 12 % methanol/88% methylene chloride (+1% ammonium hydroxide). The product was evaporated, triturated with ether and filtered to give **(5*S*)-6-methoxy-4-(2-methyl-1*H*-indol-5-yloxy)-7-(1-methyl-2-oxopyrrolidin-5-ylmethoxy)quinazoline** (100mg, 33%) as a white solid.

$^1$H NMR Spectrum: (DMSO-$d_6$) 1.84-1.96 (m, 1H), 2.10-2.30 (m, 2H), 2.39 (s, 3H), 2.43-2.53 (m, 1H), 2.80 (s, 3H), 3.98 (s, 4H), 4.22 (dd, 1H), 4.40 (dd, 1H), 6.10 (s, 1H), 6.84 (dd, 1H), 7.23 (d, 1H), 7.30 (d, 1H), 7.40 (s, 1H), 7.59 (s, 1H), 8.49 (s, 1H), 10.98 (br s, 1H)

M S: 429 [MH]+

| | | | | | |
|---|---|---|---|---|---|
| Elemental Analysis: | Found | C 64.4 | H 5.4 | N 12.6 | |
| $C_{24}H_{24}N_4O_4$ 0.8$H_2O$ | Requires | C 64.5 | H 5.8 | N 12.5% | |

The starting material was prepared as follows:

(5*S*)-5-(*p*-Toluenesulphonylmethyl)-2-pyrrolidinone (0.8g, 3mmol) was dissolved in dry THF and cooled to –70°C. Lithium diisopropylamide was slowly added and the reaction stirred for 20 minutes before addition of methyl iodide (2ml, excess). The reaction was allowed to warm to ambient temperature for over 2 hours. The reaction was partitioned between ethyl acetate and water, the organic layer separated, dried over $MgSO_4$, filtered, and evaporated *in vacuo*. The residue was purified by flash chromatography eluting from methylene chloride to 5% methanol/95% methylene chloride and the product evaporated to give (5*S*)-5-(*p*-toluenesulphonyl-methyl)-1-methyl-2-pyrrolidinone (340 mg, 40%) as a brown oil.

$^1$H NMR Spectrum: ($CDCl_3$) 2.10-2.44 (m, 4H), 2.48 (s, 3H), 2.76 (s, 3H), 3.30-3.54 (m, 1H), 4.04 (dd, 1H), 4.15 (dd, 1H), 7.38 (d, 2H), 7.78 (d, 2H)

M S: 284 [MH] +

**Example 316**

To a solution of 7-hydroxy-4-(1*H*-indol-5-yloxy)-6-methoxyquinazoline (600mg, 1.95 mmol), (prepared as described for the starting material in Example 107), in DMF (20ml) was added powdered potassuim carbonate (540mg, 3.9 mmol) and (5*S*)-5-(*p*-toluene-

sulphonylmethyl)-2-pyrrolidinone (580mg, 2.16mmol). The reaction was then heated at 100°C for 4 hours. The inorganic material was filtered off and the DMF removed by evaporation. The residue was then purified by chromatography eluting from methylene chloride to 12 % methanol/88% methylene chloride (+1% ammonium hydroxide). The product was evaporated, triturated with ether, and filtered to give **(5*S*)-4-(1*H*-indol-5-yloxy)-6-methoxy-7-(2-oxopyrrolidin-5-ylmethoxy)quinazoline** (240mg, 31%) as a white solid.

$^1$H NMR Spectrum: (DMSO-$d_6$) 1.87-2.48 (m, 4H), 3.97 (s, 3H), 4.17 (m, 2H), 6.45 (s, 1H), 6.96 (dd, 1H), 7.38-7.49 (m, 4H), 7.60 (s, 1H), 7.81 (s, 1H), 8.50 (s, 1H)

M S: 405 [MH]+

**Example 317**

To a solution of 7-hydroxy-4-(1*H*-indol-5-yloxy)-6-methoxyquinazoline (800mg, 2.6 mmol), (prepared as described for the starting material in Example 107), in DMF (20ml) was added powdered potassuim carbonate (1.08g, 7.8mmol) and (5*R*)-5-(*p*-toluenesulphonylmethyl)-2-pyrrolidinone (1.13g, 4.2mmol). The reaction was then heated at 90°C for 4 hours. The inorganic material was filtered off and the DMF removed by evaporation. The residue was then purified by chromatography eluting from methylene chloride to 12% methanol/88% methylene chloride (+1% ammonium hydroxide). A small portion was recolumned using the same gradient. The product was evaporated, triturated with ether and filtered to give **(5*R*)-4-(1*H*-indol-5-yloxy)-6-methoxy-7-(2-oxopyrrolidin-5-ylmethoxy)quinazoline** (70mg, 6.5%) as a white solid.

$^1$H NMR Spectrum: (DMSO-$d_6$) 1.64-2.45 (m, 4H), 3.78 (m, 1H), 3.99 (s, 3H), 4.18 (t, 2H), 6.42 (s, 1H), 6.97 (dd, 1H), 7.38 -7.48 (m, 3H), 7.60 (s, 1H), 7.73 (s, 2H), 8.48 (s, 1H), 11.18 (br s, 1H)

M S: 405 [MH]+

The starting material was prepared as follows:

To a solution of (5*R*)-5-hydroxymethyl-2-pyrrolidinone (5.0g, 43mmol) in methylene chloride (100 ml) was added 4-dimethylaminopyridine (15.7g, 129mmol) and *p*-toluenesulphonyl chloride (9.0g, 47mmol). The reaction was stirred at ambient temperature for 16 hours. The reaction was then washed with 1M hydrochloric acid and the organic layer

separated. This was then dried over $MgSO_4$, filtered and evaporated to give (5*R*)-5-(*p*-toluenesulphonylmethyl)-2-pyrrolidinone (10.3g, 89%) as a white solid.

$^1$H NMR Spectrum: ($CDCl_3$) 1.68-1.86 (m, 1H), 2.16-2.38 (m, 3H), 2.48 (s, 3H), 3.86-3.96 (m, 2H), 4.08 (dd, 1H), 6.20 (br s, 1H), 7.38 (d, 2H), 7.80 (d, 2H)

M S: 270 [MH]+

**Example 318**

To a suspension of 7-hydroxy-6-methoxy-4-(2-methyl-1*H*-indol-5-yloxy)quinazoline (1.36g, 4.24mmol), (prepared as described in Example 49), in DMF (70ml), was added potassium carbonate (2.34g, 17.0mmol, 4eq.) followed by (5*R*)-5-(*p*-toluenesulphonylmethyl)-2-pyrrolidinone (1.25g, 4.66mmol, 1.1eq.), (prepared as described for the starting material in Example 317), and the resulting yellow suspension heated at reflux. After 4 hours, some starting material remained, and a further addition of (5*R*)-5-(*p*-toluenesulphonylmethyl)-2-pyrrolidinone (0.57g, 2.12mmol, 0.5eq.) was made. The reaction was heated at reflux for a further 2 hours resulting in consumption of starting material. The reaction was cooled to ambient temperature, the inorganic residue filtered off and the filtrate evaporated *in vacuo* to leave a brown oil which was purified by column chromatography (methylene chloride/methanol, (100/0 to 90/10)) to give a light brown oil. Trituration with ether afforded a thick oil, which upon chromatography eluting as above gave a yellow oil. Trituration of this oil with ether gave an initial crop of **(5*R*)-6-methoxy-4-(2-methyl-1*H*-indol-5-yloxy)-7-(2-oxopyrrolidin-5-ylmethoxy)quinazoline** (5mg) as an off-white solid (ca. 90% pure by nmr). Chromatography of the residues (eluting as above) followed by ether trituration gave further crops of **(5*R*)-6-methoxy-4-(2-methyl-1*H*-indol-5-yloxy)-7-(2-oxopyrrolidin-5-ylmethoxy)quinazoline** as a white solid (180mg, >95% pure by nmr), as an off-white solid (800mg, ca. 95% pure by nmr).

$^1$H NMR Spectrum: ($DMSOd_6$) 1.8-2.2 (m, 5H), 2.4 (s, 3H), 4.0 (br s, 3H), 4.1-4.2 (m, 2H), 6.1 (br s, 1H), 6.9 (dd, 1H), 7.2 (d, 1H), 7.3 (d, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 7.8 (s, 1H), 8.5 (s, 1H), 11.0 (br s, 1H)

M S: 419 $[MH]^+$

| | | | | | |
|---|---|---|---|---|---|
| Elemental analysis: | Found | C 60.8 | H 5.3 | N 12.1 | |
| $C_{21}H_{22}N_4O_4$ $2H_2O$ | Requires | C 60.8 | H 5.7 | N 12.3% | |

**Example 319**

To a solution of 7-hydroxy-6-methoxy-4-(2-methyl-1*H*-indol-5-yloxy)quinazoline (4.8g, 15.7mmol), (prepared as described in Example 49), in DMF (100 ml), was added potassuim carbonate (6.5g, 47mmol) and 3-chloropropyl piperidine (3.3g, 20.4mmol). The reaction was then heated to 100°C for 4 hours. The inorganic material was filtered off and the DMF removed by evaporation. The residue was then purified by chromatography eluting from methylene chloride to 10 % methanol/90% methylene chloride (+1% ammonium hydroxide). The relevant fractions were concentrated and the residue dissolved in ethyl acetate. Hexane was added and the precipitae was filtered off. The filtrate was evaporated and the residue was triturated with ether and filtered to give **6-methoxy-4-(1-(3-piperidinopropyl)-1*H*-indol-5-yloxy)-7-(3-piperidinopropoxy)quinazoline** (170mg, 1.9%) as a white solid.

$^1$H NMR Spectrum: (DMSO-$d_6$) 1.38 (br s, 4H), 1.50 (br s, 8H), 1.92 (m, 4H), 2.14-2.48 (m, 12H), 3.98 (s, 3H), 4.24 (t, 4H), 6.43 (s, 1H), 7.02 (d, 1H), 7.38 (s, 1H), 7.42 (s, 2H), 7.53 (d, 1H), 7.58 (s, 1H), 8.44 (s, 1H)

M S: 558 [MH]+

**Example 320**

A mixture of (2*R*)-6-methoxy-4-(2-methylindol-5-yloxy)-7-(oxiran-2-ylmethoxy)quinazoline (6.201g, 16.4 mmol), (prepared as described for the starting material in Example 269), and piperidine (4.8 ml, 49.3 mmol) in DMF (100 ml) was stirred at 60°C for 24 hours and allowed to cool to ambient temperature. The solvents were removed *in vacuo* and the residue purified on silica gel, eluting with dichloromethane, dichloromethane/methanol (95/5) then dichloromethane/methanol/0.880 aqueous ammonia (89:10:1). The product was then recrystallised from acetonitrile to give **(2*R*)-6-methoxy-(2-methyl-1*H*-indol-5-yloxy)-7-(2-hydroxy-3-piperidinopropoxy)quinazoline** (3.33g, 44 %) as an off-white solid.

$^1$H NMR Spectrum: ($DMSO_6$) 1.35 (m, 2H), 1.51 (m, 4H), 2.30-2.40 (m, 9H), 3.98 (s, 3H), 4.08 (m, 2H), 4.21 (m, 1H), 4.86 (m, 1H), 6.10 (s, 1H), 6.87 (dd, 1H), 7.25 (d, 1H) 7.30 (d, 1H), 7.40 (s, 1H), 7.60 (s, 1H), 8.45 (s, 1H) and 10.98 (br s, 1H)

MS (ESI) : 463 $(MH)^+$

Elemental analysis: Found C 66.5 H 6.6 N 12.0

| | | | | | |
|---|---|---|---|---|---|
| $C_{26}H_{30}N_4O_4$ 0.4$H_2O$ | Requires | C 66.5 | H 6.6 | N 11.9% | |

**Example 321**

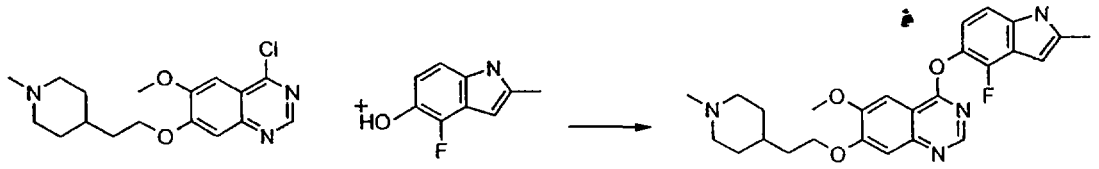
A mixture of (2*S*)-6-methoxy-4-(2-methylindol-5-yloxy)-7-(oxiran-2-ylmethoxy)quinazoline (175 mg 0.46 mmol), (prepared as described for the starting material in Example 304), and piperidine (0.14 ml, 1.39 mmol) in DMF (5 ml) was stirred at 60°C for 24 hours and allowed to cool to ambient temperature. The solvents were removed *in vacuo* and the residue purified on silica gel, gradient elution eluting with dichloromethane, dichloromethane/methanol (95/5) then dichloromethane/methanol/0.880 aqueous ammonia (89:10:1). The product was then recrystallised from acetonitrile to give **(2*S*)-6-methoxy-(2-methyl-1*H*-indol-5-yloxy)-7-(2-hydroxy-3-piperidinopropoxy)quinazoline** (88 mg, 41 %) as an off-white solid.

$^1$H NMR Spectrum: ($DMSO_6$) 1.35 (m, 2H), 1.51 (m, 4H), 2.30-2.40 (m, 9H), 3.98 (s, 3H), 4.08 (m, 2H), 4.21 (m, 1H), 4.86 (m, 1H), 6.10 (s, 1H), 6.87 (dd, 1H), 7.25 (d, 1H) 7.30 (d, 1H), 7.40 (s, 1H), 7.60 (s, 1H), 8.45 (s, 1H) and 10.98 (br s, 1H)

MS (ESI) : 463 $(MH)^+$

| | | | | | |
|---|---|---|---|---|---|
| Elemental analysis: | Found | C 66.2 | H 6.8 | N 11.9 | |
| $C_{26}H_{30}N_4O_4$ 0.5$H_2O$ | Requires | C 66.2 | H 6.6 | N 11.9% | |

**Example 322**



A solution of 4-chloro-6-methoxy-7-(2-(1-methylpiperidin-4-yl)ethoxy)quinazoline (1.22g, 3.65 mmol), (prepared as described for the starting material in Example 241), 4-fluoro-5-hydroxy-2-methylindole (723mg, 4.38 mmol), (prepared as described for the starting material in Example 237), in DMF (20ml) containing potassium carbonate (756mg, 5.48 mmol) was stirred at 95°C for 3 hours. After cooling, the mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography eluting with methylene chloride/methanol (9/1) followed by methylene chloride/methanol/methanol saturated with ammonia (90/5/5). The fractions containing the expected product were combined and evvaporated. The residue was triturated with ether, filtered, washed with ether and dried

under vacuum. The solid was dissolved in methylene chloride/ethyl acetate and the minimum of methanol, filtered and the volatiles were removed under vacuum. The solid was triturated with ether, filtered, washed with ether and dried under vacuum at 50°C to give **4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(2-(1-methylpiperidin-4-yl)ethoxy)quinazoline** (1.06g, 62%).

MS-ESI : 465 [MH]+

$^1$H NMR Spectrum: ($DMSOd_6$) 1.1-1.3 (m, 2H) ; 1.35-1.5 (m, 1H) ; 1.6-1.9 (m, 6H) ; 2.12 (s, 3H) ; 2.4 (s, 3H) ; 2.75 (d, 2H) ; 3.95 (s, 3H) ; 4.22 (t, 2H) ; 6.2 (s, 1H) ; 6.95 (dd, 1H) ; 7.15 (d, 1H) ; 7.4 (s, 1H) ; 7.6 (s, 1H) ; 8.5 (s, 1H)

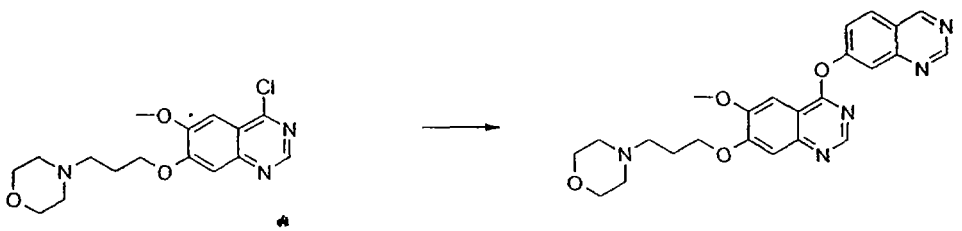
**Example 323**

Sodium hydride (71 mg, 1.8 mmol) was added to 5-hydroxy-2-methylbenzimidazole (204 mg, 0.89 mmol) in anhydrous DMF (2.5 ml) under an argon atmosphere. The mixture was stirred at ambient temperature for 10 minutes. 4-Chloro-6,7-dimethoxyquinazoline (200 mg, 0.89 mmol) was added and the reaction mixture stirred at 95 °C for 2 hours. Upon cooling to ambient temperature the mixture was poured in water and extracted with ethyl acetate. The organic phase was washed with brine, dried ($MgSO_4$), silica was added and the solvent evaporated off. The obtained powder was placed on the top of a disposable silica column (ISOLUTE) and the product eluted off using a gradient of methanol/dichloromethane (3/97, 5/95, 8/92). Evaporation of the solvent gave **6,7-dimethoxy-4-(2-methyl-1*H*-benzimidazol-6-yloxy)quinazoline** (145 mg, 48%).

$^1$H NMR Spectrum: ($DMSOd_6$) 2.50 (s, 3H); 3.95 (s, 3H); 4.0 (s, 3H); 7.05 (d, 1H); 7.38 (s, 1H); 7.39 (d, 1H); 7.51 (d, 1H); 7.60 (s,1H); 8.50 (s,1H)

MS (ESI) : 337 $[MH]^+$

**Example 324**



7-Hydroxyquinazoline (87 mg, 0.6 mmol) and potassium carbonate (110 mg, 0.8 mmol) were added to 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (180 mg, 0.53 mmol), (prepared as described for the starting material in Example 1), in suspension in DMF (3 ml) under an argon atmosphere. The reaction mixture was heated to 100 °C for 90 minutes. Upon cooling to ambient temperature the reaction was diluted with ethyl acetate and a saturated ammonium chloride solution. The aqueous phase was re-extracted with ethyl acetate, the organic phases combined, dried ($MgSO_4$) and the solvent evaporated. The residue was purified by flash chromatography using a gradient of methanol/dichloromethane (3/97, 4/96, 5/95). Evaporation of the solvent and trituration of the solid with ether gave **6-methoxy-7-(3-morpholinopropoxy)-4-(quinazolin-7-yloxy)quinazoline** (197 mg, 83%).

$^1$H NMR Spectrum ($DMSOd_6$) 2.01 (t, 2H); 2.47 (m, 4H); 2.49 (m, 2H); 3.60 (m, 4H); 4.01 (s, 3H); 4.29 (t, 2H); 7.45 (s, 1H); 7.65 (s, 1H); 7.80 (d, 1H); 8.01 (d, 1H); 8.32 (d, 1H); 8.60 (s, 1H); 9.34 (s, 1H); 9.69 (s, 1H)

MS (ESI) : 448 $[MH]^+$

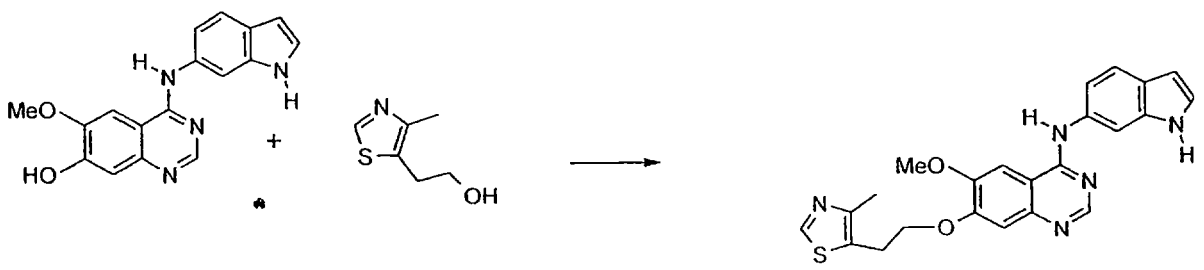
Elemental analysis: Found C 63.4 H 5.7 N 15.6

$C_{24}H_{25}N_5O_4$; 0.4 $H_2O$ Requires C 63.4 H 5.7 N 15.4%

The starting material was prepared as follows:

Raney Nickel (about 200 mg), (prewashed several times with ethanol), was added to a solution of 7-hydroxy-4-thiomethylquinazoline (400mg, 2.08 mmol), (Tet. Lett. 1999, 40. 3881), and the solution was refluxed for 1 hour. Raney Nickel (100 mg) was added and the mixture was refluxed for a further 1 hour. The mixture was filtered, washed with ethanol and the volatiles were removed under vacuum. The residue was purified by column chromatography eluting with methylene chloride/methanol (97/3 followed by 96/4) to give 7-hydroxyquinazoline (62mg, 20%).

**Example 325**



Using an analogous procedure to that described in Example 201, 7-hydroxy-4-(indol-6-ylamino)-6-methoxyquinazoline (98 mg, 0.32 mmol), (prepared as described for the starting material in Example 217), was reacted with 5-(2-hydroxyethyl)-4-methylthiazole (69 mg, 0.48 mmol) to give **6-methoxy-4-(indol-6-ylamino)-7-(2-(4-methylthiazol-5-yl)ethoxy)quinazoline** (47 mg, 34 %).

MS - ESI : 432 $[MH]^+$

$^1H$ NMR Spectrum: ($DMSOd_6$) 2.4 (s, 3H) ; 3.3 (t, 2H) ; 4.0 (s, 3H) ; 4.35 (t, 2H) ; 6.45 (s, 1H) ; 7.2 (s, 1H) ; 7.25-7.4 (m, 2H) ; 7.55 (d, 1H) ; 7.9 (s, 1H) ; 8.05 (s, 1H) ; 8.45 (s, 1H) ; 8.87 (s, 1H) ; 9.45 (s, 1H)

**Example 326**

The following illustrate representative pharmaceutical dosage forms containing the compound of formula I, or a pharmaceutically acceptable salt thereof (hereafter compound X), for therapeutic or prophylactic use in humans:

| (a) Tablet I | mg/tablet |
|---|---|
| Compound X | 100 |
| Lactose Ph.Eur | 182.75 |
| Croscarmellose sodium | 12.0 |
| Maize starch paste (5% w/v paste) | 2.25 |
| Magnesium stearate | 3.0 |

| (b) Tablet II | mg/tablet |
|---|---|
| Compound X | 50 |
| Lactose Ph.Eur | 223.75 |
| Croscarmellose sodium | 6.0 |
| Maize starch | 15.0 |
| Polyvinylpyrrolidone (5% w/v paste) | 2.25 |
| Magnesium stearate | 3.0 |

| (c) Tablet III | mg/tablet |
|---|---|
| Compound X | 1.0 |

| | |
|---|---|
| Lactose Ph.Eur | 93.25 |
| Croscarmellose sodium | 4.0 |
| Maize starch paste (5% w/v paste) | 0.75 |
| Magnesium stearate | 1.0 |

(d) Capsule — mg/capsule

| | |
|---|---|
| Compound X | 10 |
| Lactose Ph.Eur | 488.5 |
| Magnesium stearate | 1.5 |

(e) Injection I — (50 mg/ml)

| | |
|---|---|
| Compound X | 5.0% w/v |
| 1N Sodium hydroxide solution | 15.0% v/v |
| 0.1N Hydrochloric acid (to adjust pH to 7.6) | |
| Polyethylene glycol 400 | 4.5% w/v |
| Water for injection to 100% | |

(f) Injection II — 10 mg/ml)

| | |
|---|---|
| Compound X | 1.0% w/v |
| Sodium phosphate BP | 3.6% w/v |
| 0.1N Sodium hydroxide solution | 15.0% v/v |
| Water for injection to 100% | |

(g) Injection III — (1mg/ml,buffered to pH6)

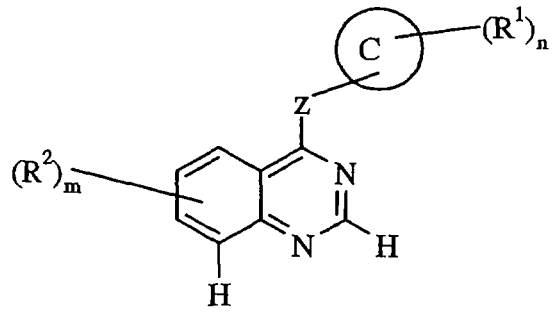
| | |
|---|---|
| Compound X | 0.1% w/v |
| Sodium phosphate BP | 2.26% w/v |
| Citric acid | 0.38% w/v |
| Polyethylene glycol 400 | 3.5% w/v |
| Water for injection to 100% | |

Note

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

**Claims:**

1. The use of a compound of the formula I:



(I)

wherein:

ring C is an 8, 9, 10, 12 or 13-membered bicyclic or tricyclic moiety which moiety may be saturated or unsaturated, which may be aromatic or non-aromatic, and which optionally may contain 1-3 heteroatoms selected independently from O, N and S;

Z is -O-, -NH-, or -S-;

n is an integer from 0 to 5;

m is an integer from 0 to 3;

$R^2$ represents hydrogen, hydroxy, halogeno, cyano, nitro, trifluoromethyl, $C_{1-3}$alkyl, $C_{1-3}$alkoxy, $C_{1-3}$alkylsùlphanyl, $-NR^3R^4$ (wherein $R^3$ and $R^4$, which may be the same or different, each represents hydrogen or $C_{1-3}$alkyl), or $R^5X^1$- (wherein $X^1$ represents a direct bond, -O-, $-CH_2$-, -OC(O)-, -C(O)-, -S-, -SO-, $-SO_2$-, $-NR^6C(O)$-, $-C(O)NR^7$-; $-SO_2NR^8$-, $-NR^9SO_2$- or $-NR^{10}$- (wherein $R^6$, $R^7$, $R^8$, $R^9$ and $R^{10}$ each independently represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl), and $R^5$ is selected from one of the following twenty-two groups:

1) hydrogen, oxiranyl$C_{1-4}$alkyl or $C_{1-5}$alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, chloro, bromo and amino;

2) $C_{1-5}$alkyl$X^2C(O)R^{11}$ (wherein $X^2$ represents -O- or $-NR^{12}$- (in which $R^{12}$ represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{11}$ represents $C_{1-3}$alkyl, $-NR^{13}R^{14}$ or $-OR^{15}$ (wherein $R^{13}$, $R^{14}$ and $R^{15}$ which may be the same or different each represents hydrogen, $C_{1-5}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl));

3) $C_{1-5}$alkyl$X^3R^{16}$ (wherein $X^3$ represents -O-, -S-, -SO-, -$SO_2$-, -OC(O)-, -$NR^{17}$C(O)-, -C(O)$NR^{18}$-, -$SO_2NR^{19}$-, -$NR^{20}SO_2$- or -$NR^{21}$- (wherein $R^{17}$, $R^{18}$, $R^{19}$, $R^{20}$ and $R^{21}$ each independently represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{16}$ represents hydrogen, $C_{1-3}$alkyl, cyclopentyl, cyclohexyl or a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which $C_{1-3}$alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and $C_{1-4}$alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, $C_{1-4}$cyanoalkyl, $C_{1-4}$alkyl, $C_{1-4}$hydroxyalkyl, $C_{1-4}$alkoxy, $C_{1-4}$alkoxy$C_{1-4}$alkyl, $C_{1-4}$alkylsulphonyl$C_{1-4}$alkyl, $C_{1-4}$alkoxycarbonyl, $C_{1-4}$aminoalkyl, $C_{1-4}$alkylamino, di($C_{1-4}$alkyl)amino, $C_{1-4}$alkylamino$C_{1-4}$alkyl, di($C_{1-4}$alkyl)amino$C_{1-4}$alkyl, $C_{1-4}$alkylamino$C_{1-4}$alkoxy, di($C_{1-4}$alkyl)amino$C_{1-4}$alkoxy and a group -(-O-)$_f$($C_{1-4}$alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from $C_{1-4}$alkyl));

4) $C_{1-5}$alkyl$X^4C_{1-5}$alkyl$X^5R^{22}$ (wherein $X^4$ and $X^5$ which may be the same or different are each -O-, -S-, -SO-, -$SO_2$-, -$NR^{23}$C(O)-, -C(O)$NR^{24}$-, -$SO_2NR^{25}$-, -$NR^{26}SO_2$- or -$NR^{27}$- (wherein $R^{23}$, $R^{24}$, $R^{25}$, $R^{26}$ and $R^{27}$ each independently represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{22}$ represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl);

5) $R^{28}$ (wherein $R^{28}$ is a 4-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, $C_{1-4}$cyanoalkyl, $C_{1-4}$alkyl, $C_{1-4}$hydroxyalkyl, $C_{1-4}$alkoxy, $C_{1-4}$alkoxy$C_{1-4}$alkyl, $C_{1-4}$alkylsulphonyl$C_{1-4}$alkyl, $C_{1-4}$alkoxycarbonyl, $C_{1-4}$aminoalkyl, $C_{1-4}$alkylamino, di($C_{1-4}$alkyl)amino, $C_{1-4}$alkylamino$C_{1-4}$alkyl, di($C_{1-4}$alkyl)amino$C_{1-4}$alkyl, $C_{1-4}$alkylamino$C_{1-4}$alkoxy, di($C_{1-4}$alkyl)amino$C_{1-4}$alkoxy and a group -(-O-)$_f$($C_{1-4}$alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from $C_{1-4}$alkyl));

6) $C_{1-5}$alkyl$R^{28}$ (wherein $R^{28}$ is as defined herein);

7) $C_{2-5}$alkenyl$R^{28}$ (wherein $R^{28}$ is as defined herein);

8) $C_{2-5}$alkynyl$R^{28}$ (wherein $R^{28}$ is as defined herein);

9) $R^{29}$ (wherein $R^{29}$ represents a pyridone group, a phenyl group or a 5-6-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-3 heteroatoms selected from O, N and S, which pyridone, phenyl or aromatic heterocyclic group may carry up to 5 substituents selected from hydroxy, halogeno, amino, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, $C_{1-4}$hydroxyalkyl, $C_{1-4}$aminoalkyl, $C_{1-4}$alkylamino, $C_{1-4}$hydroxyalkoxy, carboxy, trifluoromethyl, cyano, -$C(O)NR^{30}R^{31}$, -$NR^{32}C(O)R^{33}$ (wherein $R^{30}$, $R^{31}$, $R^{32}$ and $R^{33}$, which may be the same or different, each represents hydrogen, $C_{1-4}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and a group -(-O-)$_f$($C_{1-4}$alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from $C_{1-4}$alkyl));

10) $C_{1-5}$alkyl$R^{29}$ (wherein $R^{29}$ is as defined herein);

11) $C_{2-5}$alkenyl$R^{29}$ (wherein $R^{29}$ is as defined herein);

12) $C_{2-5}$alkynyl$R^{29}$ (wherein $R^{29}$ is as defined herein);

13) $C_{1-5}$alkyl$X^6R^{29}$ (wherein $X^6$ represents -O-, -S-, -SO-, -$SO_2$-, -$NR^{34}C(O)$-, -$C(O)NR^{35}$-, -$SO_2NR^{36}$-, -$NR^{37}SO_2$- or -$NR^{38}$- (wherein $R^{34}$, $R^{35}$, $R^{36}$, $R^{37}$ and $R^{38}$ each independently represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{29}$ is as defined herein);

14) $C_{2-5}$alkenyl$X^7R^{29}$ (wherein $X^7$ represents -O-, -S-, -SO-, -$SO_2$-, -$NR^{39}C(O)$-, -$C(O)NR^{40}$-, -$SO_2NR^{41}$-, -$NR^{42}SO_2$- or -$NR^{43}$- (wherein $R^{39}$, $R^{40}$, $R^{41}$, $R^{42}$ and $R^{43}$ each independently represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{29}$ is as defined herein);

15) $C_{2-5}$alkynyl$X^8R^{29}$ (wherein $X^8$ represents -O-, -S-, -SO-, -$SO_2$-, -$NR^{44}C(O)$-, -$C(O)NR^{45}$-, -$SO_2NR^{46}$-, -$NR^{47}SO_2$- or -$NR^{48}$- (wherein $R^{44}$, $R^{45}$, $R^{46}$, $R^{47}$ and $R^{48}$ each independently represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{29}$ is as defined herein);

16) $C_{1-4}$alkyl$X^9C_{1-4}$alkyl$R^{29}$ (wherein $X^9$ represents -O-, -S-, -SO-, -$SO_2$-, -$NR^{49}C(O)$-, -$C(O)NR^{50}$-, -$SO_2NR^{51}$-, -$NR^{52}SO_2$- or -$NR^{53}$- (wherein $R^{49}$, $R^{50}$, $R^{51}$, $R^{52}$ and $R^{53}$ each independently represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{29}$ is as defined herein);

17) $C_{1-4}$alkyl$X^9C_{1-4}$alkyl$R^{28}$ (wherein $X^9$ and $R^{28}$ are as defined herein);

18) $C_{2-5}$alkenyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, $C_{1-4}$alkylamino, N,N-di($C_{1-4}$alkyl)amino, aminosulphonyl, N-$C_{1-4}$alkylaminosulphonyl and N,N-di($C_{1-4}$alkyl)aminosulphonyl;

19) $C_{2-5}$alkynyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, $C_{1-4}$alkylamino, N,N-di($C_{1-4}$alkyl)amino, aminosulphonyl, N-$C_{1-4}$alkylaminosulphonyl and N,N-di($C_{1-4}$alkyl)aminosulphonyl;

20) $C_{2-5}$alkenyl$X^9C_{1-4}$alkyl$R^{28}$ (wherein $X^9$ and $R^{28}$ are as defined herein);

21) $C_{2-5}$alkynyl$X^9C_{1-4}$alkyl$R^{28}$ (wherein $X^9$ and $R^{28}$ are as defined herein); and

22) $C_{1-4}$alkyl$R^{54}(C_{1-4}alkyl)_q(X^9)_rR^{55}$ (wherein $X^9$ is as defined herein, q is 0 or 1, r is 0 or 1, and $R^{54}$ and $R^{55}$ are each independently selected from hydrogen, $C_{1-3}$alkyl, cyclopentyl, cyclohexyl and a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which $C_{1-3}$alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and $C_{1-4}$alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, $C_{1-4}$cyanoalkyl, $C_{1-4}$alkyl, $C_{1-4}$hydroxyalkyl, $C_{1-4}$alkoxy, $C_{1-4}$alkoxy$C_{1-4}$alkyl, $C_{1-4}$alkylsulphonyl$C_{1-4}$alkyl, $C_{1-4}$alkoxycarbonyl, $C_{1-4}$aminoalkyl, $C_{1-4}$alkylamino, di($C_{1-4}$alkyl)amino, $C_{1-4}$alkylamino$C_{1-4}$alkyl, di($C_{1-4}$alkyl)amino$C_{1-4}$alkyl, $C_{1-4}$alkylamino$C_{1-4}$alkoxy, di($C_{1-4}$alkyl)amino$C_{1-4}$alkoxy and a group -(-O-)$_f$($C_{1-4}$alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from $C_{1-4}$alkyl), with the proviso that $R^{54}$ cannot be hydrogen);

and additionally wherein any $C_{1-5}$alkyl, $C_{2-5}$alkenyl or $C_{2-5}$alkynyl group in $R^5X^1$- may bear one or more substituents selected from hydroxy, halogeno and amino);

$R^1$ represents hydrogen, oxo, halogeno, hydroxy, $C_{1-4}$alkoxy, $C_{1-4}$alkyl, $C_{1-4}$alkoxymethyl, $C_{1-4}$alkanoyl, $C_{1-4}$haloalkyl, cyano, amino, $C_{2-5}$alkenyl, $C_{2-5}$alkynyl, $C_{1-3}$alkanoyloxy, nitro, $C_{1-4}$alkanoylamino, $C_{1-4}$alkoxycarbonyl, $C_{1-4}$alkylsulphanyl, $C_{1-4}$alkylsulphinyl, $C_{1-4}$alkylsulphonyl, carbamoyl, N-$C_{1-4}$alkylcarbamoyl, N,N-di($C_{1-4}$alkyl)carbamoyl, aminosulphonyl, N-$C_{1-4}$alkylaminosulphonyl, N,N-di($C_{1-4}$alkyl)aminosulphonyl, N-($C_{1-4}$alkylsulphonyl)amino, N-($C_{1-4}$alkylsulphonyl)-N-($C_{1-4}$alkyl)amino, N,N-di($C_{1-4}$alkylsulphonyl)amino, a $C_{3-7}$alkylene chain joined to two ring C carbon atoms, $C_{1-4}$alkanoylamino$C_{1-4}$alkyl, carboxy or a group $R^{56}X^{10}$ (wherein $X^{10}$ represents a direct bond, -O-, -$CH_2$-, -OC(O)-, -C(O)-, -S-, -SO-, -$SO_2$-, -$NR^{57}$C(O)-, -C(O)$NR^{58}$-, -$SO_2NR^{59}$-, -$NR^{60}SO_2$- or -$NR^{61}$- (wherein $R^{57}$, $R^{58}$, $R^{59}$, $R^{60}$ and $R^{61}$ each independently represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl), and $R^{56}$ is selected from one of the following twenty-two groups:

1) hydrogen, oxiranyl$C_{1-4}$alkyl or $C_{1-5}$alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, chloro, bromo and amino;

2) $C_{1-5}$alkyl$X^{11}C(O)R^{62}$ (wherein $X^{11}$ represents -O- or -$NR^{63}$- (in which $R^{63}$ represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{62}$ represents $C_{1-3}$alkyl, -$NR^{64}R^{65}$ or -$OR^{66}$ (wherein $R^{64}$, $R^{65}$ and $R^{66}$ which may be the same or different each represents hydrogen, $C_{1-5}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl));

3) $C_{1-5}$alkyl$X^{12}R^{67}$ (wherein $X^{12}$ represents -O-, -S-, -SO-, -$SO_2$-, -OC(O)-, -$NR^{68}$C(O)-, -C(O)$NR^{69}$-, -$SO_2NR^{70}$-, -$NR^{71}SO_2$- or -$NR^{72}$- (wherein $R^{68}$, $R^{69}$, $R^{70}$, $R^{71}$ and $R^{72}$ each independently represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{67}$ represents hydrogen, $C_{1-3}$alkyl, cyclopentyl, cyclohexyl or a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which $C_{1-3}$alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and $C_{1-4}$alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, $C_{1-4}$cyanoalkyl, $C_{1-4}$alkyl, $C_{1-4}$hydroxyalkyl, $C_{1-4}$alkoxy, $C_{1-4}$alkoxy$C_{1-4}$alkyl, $C_{1-4}$alkylsulphonyl$C_{1-4}$alkyl, $C_{1-4}$alkoxycarbonyl, $C_{1-4}$aminoalkyl, $C_{1-4}$alkylamino, di($C_{1-4}$alkyl)amino, $C_{1-4}$alkylamino$C_{1-4}$alkyl, di($C_{1-4}$alkyl)amino$C_{1-4}$alkyl, $C_{1-4}$alkylamino$C_{1-4}$alkoxy, di($C_{1-4}$alkyl)amino$C_{1-4}$alkoxy and a group -(-O-)$_f$($C_{1-4}$alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from $C_{1-4}$alkyl));

4) $C_{1-5}$alkyl$X^{13}C_{1-5}$alkyl$X^{14}R^{73}$ (wherein $X^{13}$ and $X^{14}$ which may be the same or different are each -O-, -S-, -SO-, -$SO_2$-, -$NR^{74}$C(O)-, -C(O)$NR^{75}$-, -$SO_2NR^{76}$-, -$NR^{77}SO_2$- or -$NR^{78}$- (wherein $R^{74}$, $R^{75}$, $R^{76}$, $R^{77}$ and $R^{78}$ each independently represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{73}$ represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl);

5) $R^{79}$ (wherein $R^{79}$ is a 4-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, $C_{1-4}$cyanoalkyl, $C_{1-4}$alkyl, $C_{1-4}$hydroxyalkyl, $C_{1-4}$alkoxy, $C_{1-4}$alkoxy$C_{1-4}$alkyl, $C_{1-4}$alkylsulphonyl$C_{1-4}$alkyl, $C_{1-4}$alkoxycarbonyl, $C_{1-4}$aminoalkyl, $C_{1-4}$alkylamino, di($C_{1-4}$alkyl)amino, $C_{1-4}$alkylamino$C_{1-4}$alkyl, di($C_{1-4}$alkyl)amino$C_{1-4}$alkyl, $C_{1-4}$alkylamino$C_{1-4}$alkoxy, di($C_{1-4}$alkyl)amino$C_{1-4}$alkoxy and a group -(-O-)$_f$($C_{1-4}$alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected

independently from O, S and N, which cyclic group may bear one or more substituents selected from $C_{1-4}$alkyl));

6) $C_{1-5}$alkyl$R^{79}$ (wherein $R^{79}$ is as defined herein);

7) $C_{2-5}$alkenyl$R^{79}$ (wherein $R^{79}$ is as defined herein);

8) $C_{2-5}$alkynyl$R^{79}$ (wherein $R^{79}$ is as defined herein);

9) $R^{80}$ (wherein $R^{80}$ represents a pyridone group, a phenyl group or a 5-6-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-3 heteroatoms selected from O, N and S, which pyridone, phenyl or aromatic heterocyclic group may carry up to 5 substituents selected from hydroxy, halogeno, amino, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, $C_{1-4}$hydroxyalkyl, $C_{1-4}$aminoalkyl, $C_{1-4}$alkylamino, $C_{1-4}$hydroxyalkoxy, carboxy, trifluoromethyl, cyano, -$C(O)NR^{81}R^{82}$, -$NR^{83}C(O)R^{84}$ (wherein $R^{81}$, $R^{82}$, $R^{83}$ and $R^{84}$, which may be the same or different, each represents hydrogen, $C_{1-4}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and a group -(-O-)$_f$($C_{1-4}$alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from $C_{1-4}$alkyl));

10) $C_{1-5}$alkyl$R^{80}$ (wherein $R^{80}$ is as defined herein);

11) $C_{2-5}$alkenyl$R^{80}$ (wherein $R^{80}$ is as defined herein);

12) $C_{2-5}$alkynyl$R^{80}$ (wherein $R^{80}$ is as defined herein);

13) $C_{1-5}$alkyl$X^{15}R^{80}$ (wherein $X^{15}$ represents -O-, -S-, -SO-, -$SO_2$-, -$NR^{85}C(O)$-, -$C(O)NR^{86}$-, -$SO_2NR^{87}$-, -$NR^{88}SO_2$- or -$NR^{89}$- (wherein $R^{85}$, $R^{86}$, $R^{87}$, $R^{88}$ and $R^{89}$ each independently represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{80}$ is as defined herein);

14) $C_{2-5}$alkenyl$X^{16}R^{80}$ (wherein $X^{16}$ represents -O-, -S-, -SO-, -$SO_2$-, -$NR^{90}C(O)$-, -$C(O)NR^{91}$-, -$SO_2NR^{92}$-, -$NR^{93}SO_2$- or -$NR^{94}$- (wherein $R^{90}$, $R^{91}$, $R^{92}$, $R^{93}$ and $R^{94}$ each independently represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{80}$ is as defined herein);

15) $C_{2-5}$alkynyl$X^{17}R^{80}$ (wherein $X^{17}$ represents -O-, -S-, -SO-, -$SO_2$-, -$NR^{95}C(O)$-, -$C(O)NR^{96}$-, -$SO_2NR^{97}$-, -$NR^{98}SO_2$- or -$NR^{99}$- (wherein $R^{95}$, $R^{96}$, $R^{97}$, $R^{98}$ and $R^{99}$ each independently represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{80}$ is as defined herein);

16) $C_{1-4}$alkyl$X^{18}C_{1-4}$alkyl$R^{80}$ (wherein $X^{18}$ represents -O-, -S-, -SO-, -$SO_2$-, -$NR^{100}C(O)$-, -$C(O)NR^{101}$-, -$SO_2NR^{102}$-, -$NR^{103}SO_2$- or -$NR^{104}$- (wherein $R^{100}$, $R^{101}$, $R^{102}$, $R^{103}$ and $R^{104}$ each independently represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{80}$ is as defined herein);

17) $C_{1-4}$alkyl$X^{18}C_{1-4}$alkyl$R^{79}$ (wherein $X^{18}$ and $R^{79}$ are as defined herein);

18) $C_{2-5}$alkenyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, $C_{1-4}$alkylamino, N,N-di($C_{1-4}$alkyl)amino, aminosulphonyl, N-$C_{1-4}$alkylaminosulphonyl and N,N-di($C_{1-4}$alkyl)aminosulphonyl;

19) $C_{2-5}$alkynyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, $C_{1-4}$alkylamino, N,N-di($C_{1-4}$alkyl)amino, aminosulphonyl, N-$C_{1-4}$alkylaminosulphonyl and N,N-di($C_{1-4}$alkyl)aminosulphonyl;

20) $C_{2-5}$alkenyl$X^{18}C_{1-4}$alkyl$R^{79}$ (wherein $X^{18}$ and $R^{79}$ are as defined herein);

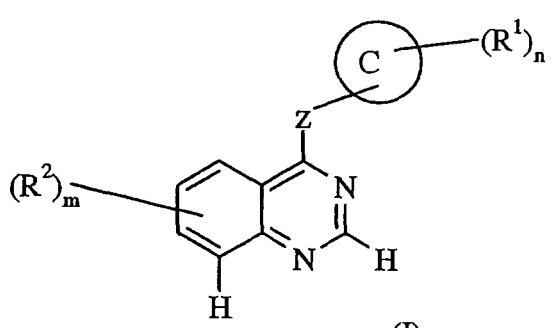
21) $C_{2-5}$alkynyl$X^{18}C_{1-4}$alkyl$R^{79}$ (wherein $X^{18}$ and $R^{79}$ are as defined herein); and

22) $C_{1-4}$alkyl$R^{105}(C_{1-4}alkyl)_x(X^{18})_yR^{106}$ (wherein $X^{18}$ is as defined herein, x is 0 or 1, y is 0 or 1, and $R^{105}$ and $R^{106}$ are each independently selected from hydrogen, $C_{1-3}$alkyl, cyclopentyl, cyclohexyl and a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which $C_{1-3}$alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and $C_{1-4}$alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, $C_{1-4}$cyanoalkyl, $C_{1-4}$alkyl, $C_{1-4}$hydroxyalkyl, $C_{1-4}$alkoxy, $C_{1-4}$alkoxy$C_{1-4}$alkyl, $C_{1-4}$alkylsulphonyl$C_{1-4}$alkyl, $C_{1-4}$alkoxycarbonyl, $C_{1-4}$aminoalkyl, $C_{1-4}$alkylamino, di($C_{1-4}$alkyl)amino, $C_{1-4}$alkylamino$C_{1-4}$alkyl, di($C_{1-4}$alkyl)amino$C_{1-4}$alkyl, $C_{1-4}$alkylamino$C_{1-4}$alkoxy, di($C_{1-4}$alkyl)amino$C_{1-4}$alkoxy and a group -(-O-)$_f$($C_{1-4}$alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from $C_{1-4}$alkyl) with the proviso that $R^{105}$ cannot be hydrogen);

and additionally wherein any $C_{1-5}$alkyl, $C_{2-5}$alkenyl or $C_{2-5}$alkynyl group in $R^{56}X^{10}$- may bear one or more substituents selected from hydroxy, halogeno and amino);

or a salt thereof in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals such as humans.

2. The use of a compound of the formula I according to claim 1:



(I)

wherein:

ring C is a 9-10-membered bicyclic moiety which may be saturated or unsaturated, which may be aromatic or non-aromatic, and which optionally may contain 1-3 heteroatoms selected independently from O, N and S;

Z is -O-, -NH-, or –S–;

$R^1$ represents hydrogen, oxo, halogeno, hydroxy, $C_{1-4}$alkoxy, $C_{1-4}$alkyl, $C_{1-4}$alkoxymethyl, $C_{1-4}$alkanoyl, $C_{1-4}$haloalkyl, cyano, amino, $C_{2-5}$alkenyl, $C_{2-5}$alkynyl, $C_{1-3}$alkanoyloxy, nitro, $C_{1-4}$alkanoylamino, $C_{1-4}$alkoxycarbonyl, $C_{1-4}$alkylsulphanyl, $C_{1-4}$alkylsulphinyl, $C_{1-4}$alkylsulphonyl, carbamoyl, N-$C_{1-4}$alkylcarbamoyl, N,N-di($C_{1-4}$alkyl)carbamoyl, aminosulphonyl, N-$C_{1-4}$alkylaminosulphonyl, N,N-di($C_{1-4}$alkyl)aminosulphonyl, N-($C_{1-4}$alkylsulphonyl)amino, N-($C_{1-4}$alkylsulphonyl)-N-($C_{1-4}$alkyl)amino, N,N-di($C_{1-4}$alkylsulphonyl)amino or a $C_{3-7}$alkylene chain joined to two ring C carbon atoms;

n is an integer from 0 to 5;

m is an integer from 0 to 3;

$R^2$ represents hydrogen, hydroxy, halogeno, cyano, nitro, trifluoromethyl, $C_{1-3}$alkyl, $C_{1-3}$alkoxy, $C_{1-3}$alkylsulphanyl, $-NR^3R^4$ (wherein $R^3$ and $R^4$, which may be the same or different, each represents hydrogen or $C_{1-3}$alkyl), or $R^5X^1$- (wherein $X^1$ represents a direct bond, -O-, $-CH_2$-, -OC(O)-, -C(O)-, -S-, -SO-, $-SO_2$-, $-NR^6C(O)$-, $-C(O)NR^7$-, $-SO_2NR^8$-, $-NR^9SO_2$- or $-NR^{10}$- (wherein $R^6$, $R^7$, $R^8$, $R^9$ and $R^{10}$ each independently represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl), and $R^5$ is selected from one of the following twenty-one groups:

1) hydrogen or $C_{1-5}$alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro and amino;

2) $C_{1-5}$alkyl$X^2C(O)R^{11}$ (wherein $X^2$ represents -O- or $-NR^{12}$- (in which $R^{12}$ represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{11}$ represents $C_{1-3}$alkyl, $-NR^{13}R^{14}$ or $-OR^{15}$

(wherein $R^{13}$, $R^{14}$ and $R^{15}$ which may be the same or different each represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl));

3) $C_{1-5}$alkyl$X^3R^{16}$ (wherein $X^3$ represents -O-, -S-, -SO-, -$SO_2$-, -OC(O)-, -$NR^{17}$C(O)-, -C(O)$NR^{18}$-, -$SO_2NR^{19}$-, -$NR^{20}SO_2$- or -$NR^{21}$- (wherein $R^{17}$, $R^{18}$, $R^{19}$, $R^{20}$ and $R^{21}$ each independently represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{16}$ represents hydrogen, $C_{1-3}$alkyl, cyclopentyl, cyclohexyl or a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which $C_{1-3}$alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and $C_{1-4}$alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, $C_{1-4}$alkyl, $C_{1-4}$hydroxyalkyl and $C_{1-4}$alkoxy);

4) $C_{1-5}$alkyl$X^4C_{1-5}$alkyl$X^5R^{22}$ (wherein $X^4$ and $X^5$ which may be the same or different are each -O-, -S-, -SO-, -$SO_2$-, -$NR^{23}$C(O)-, -C(O)$NR^{24}$-, -$SO_2NR^{25}$-, -$NR^{26}SO_2$- or -$NR^{27}$- (wherein $R^{23}$, $R^{24}$, $R^{25}$, $R^{26}$ and $R^{27}$ each independently represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{22}$ represents hydrogen or $C_{1-3}$alkyl);

5) $R^{28}$ (wherein $R^{28}$ is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, $C_{1-4}$cyanoalkyl, $C_{1-4}$alkyl, $C_{1-4}$hydroxyalkyl, $C_{1-4}$alkoxy, $C_{1-4}$alkoxy$C_{1-4}$alkyl and $C_{1-4}$alkylsulphonyl$C_{1-4}$alkyl);

6) $C_{1-5}$alkyl$R^{28}$ (wherein $R^{28}$ is as defined herein);

7) $C_{2-5}$alkenyl$R^{28}$ (wherein $R^{28}$ is as defined herein);

8) $C_{2-5}$alkynyl$R^{28}$ (wherein $R^{28}$ is as defined herein);

9) $R^{29}$ (wherein $R^{29}$ represents a pyridone group, a phenyl group or a 5-6-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-3 heteroatoms selected from O, N and S, which pyridone, phenyl or aromatic heterocyclic group may carry up to 5 substituents on an available carbon atom selected from hydroxy, halogeno, amino, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, $C_{1-4}$hydroxyalkyl, $C_{1-4}$aminoalkyl, $C_{1-4}$alkylamino, $C_{1-4}$hydroxyalkoxy, carboxy, trifluoromethyl, cyano, -C(O)$NR^{30}R^{31}$ and -$NR^{32}$C(O)$R^{33}$ (wherein $R^{30}$, $R^{31}$, $R^{32}$ and $R^{33}$, which may be the same or different, each represents hydrogen, $C_{1-4}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl));

10) $C_{1-5}$alkyl$R^{29}$ (wherein $R^{29}$ is as defined herein);

11) $C_{2-5}$alkenyl$R^{29}$ (wherein $R^{29}$ is as defined herein);

12) $C_{2-5}$alkynyl$R^{29}$ (wherein $R^{29}$ is as defined herein);

13) $C_{1-5}$alkyl$X^6R^{29}$ (wherein $X^6$ represents -O-, -S-, -SO-, $-SO_2-$, $-NR^{34}C(O)-$, $-C(O)NR^{35}-$, $-SO_2NR^{36}-$, $-NR^{37}SO_2-$ or $-NR^{38}-$ (wherein $R^{34}$, $R^{35}$, $R^{36}$, $R^{37}$ and $R^{38}$ each independently represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{29}$ is as defined herein);

14) $C_{2-5}$alkenyl$X^7R^{29}$ (wherein $X^7$ represents -O-, -S-, -SO-, $-SO_2-$, $-NR^{39}C(O)-$, $-C(O)NR^{40}-$, $-SO_2NR^{41}-$, $-NR^{42}SO_2-$ or $-NR^{43}-$ (wherein $R^{39}$, $R^{40}$, $R^{41}$, $R^{42}$ and $R^{43}$ each independently represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{29}$ is as defined herein);

15) $C_{2-5}$alkynyl$X^8R^{29}$ (wherein $X^8$ represents -O-, -S-, -SO-, $-SO_2-$, $-NR^{44}C(O)-$, $-C(O)NR^{45}-$, $-SO_2NR^{46}-$, $-NR^{47}SO_2-$ or $-NR^{48}-$ (wherein $R^{44}$, $R^{45}$, $R^{46}$, $R^{47}$ and $R^{48}$ each independently represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{29}$ is as defined herein);

16) $C_{1-3}$alkyl$X^9C_{1-3}$alkyl$R^{29}$ (wherein $X^9$ represents -O-, -S-, -SO-, $-SO_2-$, $-NR^{49}C(O)-$, $-C(O)NR^{50}-$, $-SO_2NR^{51}-$, $-NR^{52}SO_2-$ or $-NR^{53}-$ (wherein $R^{49}$, $R^{50}$, $R^{51}$, $R^{52}$ and $R^{53}$ each independently represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{29}$ is as defined herein);

17) $C_{1-3}$alkyl$X^9C_{1-3}$alkyl$R^{28}$ (wherein $X^9$ and $R^{28}$ are as defined herein);

18) $C_{2-5}$alkenyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, $C_{1-4}$alkylamino, N,N-di($C_{1-4}$alkyl)amino, aminosulphonyl, N-$C_{1-4}$alkylaminosulphonyl and N,N-di($C_{1-4}$alkyl)aminosulphonyl;

19) $C_{2-5}$alkynyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, $C_{1-4}$alkylamino, N,N-di($C_{1-4}$alkyl)amino, aminosulphonyl, N-$C_{1-4}$alkylaminosulphonyl and N,N-di($C_{1-4}$alkyl)aminosulphonyl;

20) $C_{2-5}$alkenyl$X^9C_{1-4}$alkyl$R^{28}$ (wherein $X^9$ and $R^{28}$ are as defined herein); and

21) $C_{2-5}$alkynyl$X^9C_{1-4}$alkyl$R^{28}$ (wherein $X^9$ and $R^{28}$ are as defined herein);

and salts thereof, and prodrugs thereof for example esters, amides and sulphides, in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals such as humans.

3. The use of a compound of the formula I according to claim 1, wherein $R^2$ represents hydroxy, halogeno, cyano, nitro, trifluoromethyl, $C_{1-3}$alkyl, amino or $R^5X^1-$ [wherein $X^1$ is as defined in claim 1 and $R^5$ is selected from one of the following twenty-two groups:

1) $C_{1-4}$alkyl which may be unsubstituted or which may be substituted with one or more groups selected from fluoro, chloro and bromo, or $C_{2-5}$alkyl which may be unsubstituted or substituted with one or more groups selected from hydroxy and amino;

2) $C_{2-3}$alkyl$X^2$C(O)$R^{11}$ (wherein $X^2$ is as defined in claim 1 and $R^{11}$ represents -$NR^{13}R^{14}$ or -$OR^{15}$ (wherein $R^{13}$, $R^{14}$ and $R^{15}$ which may be the same or different are each $C_{1-4}$alkyl or $C_{1-2}$alkoxyethyl));

3) $C_{2-4}$alkyl$X^3R^{16}$ (wherein $X^3$ is as defined in claim 1 and $R^{16}$ is a group selected from $C_{1-3}$alkyl, cyclopentyl, cyclohexyl, pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl and tetrahydropyranyl, which $C_{1-3}$alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and $C_{1-2}$alkoxy and which cyclopentyl, cyclohexyl, pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl or tetrahydropyranyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, $C_{1-3}$cyanoalkyl, $C_{1-3}$alkyl, $C_{1-3}$hydroxyalkyl, $C_{1-3}$alkoxy, $C_{1-2}$alkoxy$C_{1-3}$alkyl, $C_{1-2}$alkylsulphonyl$C_{1-3}$alkyl, $C_{1-3}$alkoxycarbonyl, $C_{1-3}$alkylamino, di($C_{1-3}$alkyl)amino, $C_{1-3}$alkylamino$C_{1-3}$alkyl, di($C_{1-3}$alkyl)amino$C_{1-3}$alkyl, $C_{1-3}$alkylamino$C_{1-3}$alkoxy, di($C_{1-3}$alkyl)amino$C_{1-3}$alkoxy and a group -(-O-)$_f$($C_{1-3}$alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino and thiomorpholino, which cyclic group may bear one or more substituents selected from $C_{1-3}$alkyl));

4) $C_{2-3}$alkyl$X^4C_{2-3}$alkyl$X^5R^{22}$ (wherein $X^4$ and $X^5$ are as defined in claim 1 and $R^{22}$ represents hydrogen or $C_{1-3}$alkyl);

5) $R^{28}$ (wherein $R^{28}$ is as defined in claim 1);

6) $C_{1-4}$alkyl$R^{110}$ (wherein $R^{110}$ is a group selected from pyrrolidinyl, piperazinyl, piperidinyl, imidazolidin-1-yl, azetidinyl, 1,3-dioxolan-2-yl, 1,3-dioxan-2-yl, 1,3-dithiolan-2-yl and 1,3-dithian-2-yl, which group is linked to $C_{1-4}$alkyl through a carbon atom and which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, $C_{1-3}$cyanoalkyl, $C_{1-3}$alkyl, $C_{1-3}$hydroxyalkyl, $C_{1-3}$alkoxy, $C_{1-2}$alkoxy$C_{1-3}$alkyl, $C_{1-2}$alkylsulphonyl$C_{1-3}$alkyl, $C_{1-3}$alkoxycarbonyl, $C_{1-3}$alkylamino, di($C_{1-3}$alkyl)amino, $C_{1-3}$alkylamino$C_{1-3}$alkyl, di($C_{1-3}$alkyl)amino$C_{1-3}$alkyl, $C_{1-3}$alkylamino$C_{1-3}$alkoxy, di($C_{1-3}$alkyl)amino$C_{1-3}$alkoxy and a group -(-O-)$_f$($C_{1-3}$alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino and thiomorpholino, which cyclic group may bear one or more substituents selected from $C_{1-}$

$_3$alkyl)) or $C_{2-4}$alkyl$R^{111}$ (wherein $R^{111}$ is a group selected from morpholino, thiomorpholino, azetidin-1-yl, pyrrolidin-1-yl, piperazin-1-yl and piperidino which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, $C_{1-3}$cyanoalkyl, $C_{1-3}$alkyl, $C_{1-3}$hydroxyalkyl, $C_{1-3}$alkoxy, $C_{1-2}$alkoxy$C_{1-3}$alkyl, $C_{1-2}$alkylsulphonyl$C_{1-3}$alkyl, $C_{1-3}$alkoxycarbonyl, $C_{1-3}$alkylamino, di($C_{1-3}$alkyl)amino, $C_{1-3}$alkylamino$C_{1-3}$alkyl, di($C_{1-3}$alkyl)amino$C_{1-3}$alkyl, $C_{1-3}$alkylamino$C_{1-3}$alkoxy, di($C_{1-3}$alkyl)amino$C_{1-3}$alkoxy and a group -(-O-)$_f$($C_{1-3}$alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino and thiomorpholino, which cyclic group may bear one or more substituents selected from $C_{1-3}$alkyl));

7) $C_{3-4}$alkenyl$R^{112}$ (wherein $R^{112}$ represents $R^{110}$ or $R^{111}$ as defined herein);

8) $C_{3-4}$alkynyl$R^{112}$ (wherein $R^{112}$ represents $R^{110}$ or $R^{111}$ as defined herein);

9) $R^{29}$ (wherein $R^{29}$ is as defined in claim 1);

10) $C_{1-4}$alkyl$R^{29}$ (wherein $R^{29}$ is as defined in claim 1);

11) 1-$R^{29}$prop-1-en-3-yl or 1-$R^{29}$but-2-en-4-yl (wherein $R^{29}$ is as defined in claim 1 with the proviso that when $R^5$ is 1-$R^{29}$prop-1-en-3-yl, $R^{29}$ is linked to the alkenyl group via a carbon atom);

12) 1-$R^{29}$prop-1-yn-3-yl or 1-$R^{29}$but-2-yn-4-yl (wherein $R^{29}$ is as defined in claim 1 with the proviso that when $R^5$ is 1-$R^{29}$prop-1-yn-3-yl, $R^{29}$ is linked to the alkynyl group via a carbon atom);

13) $C_{1-5}$alkyl$X^6R^{29}$ (wherein $X^6$ and $R^{29}$ are as defined in claim 1);

14) 1-($R^{29}X^7$)but-2-en-4-yl (wherein $X^7$ and $R^{29}$ are as defined in claim 1);

15) 1-($R^{29}X^8$)but-2-yn-4-yl (wherein $X^8$ and $R^{29}$ are as defined in claim 1);

16) $C_{2-3}$alkyl$X^9C_{1-3}$alkyl$R^{29}$ (wherein $X^9$ and $R^{29}$ are as defined in claim 1);

17) $C_{2-3}$alkyl$X^9C_{1-3}$alkyl$R^{28}$ (wherein $X^9$ and $R^{28}$ are as defined in claim 1);

18) $C_{2-5}$alkenyl which may be unsubstituted or which may be substituted with one or more fluorine atoms or with one or two groups selected from hydroxy, fluoro, amino, $C_{1-4}$alkylamino, N,N-di($C_{1-4}$alkyl)amino, aminosulphonyl, N-$C_{1-4}$alkylaminosulphonyl and N,N-di($C_{1-4}$alkyl)aminosulphonyl;

19) $C_{2-5}$alkynyl which may be unsubstituted or which may be substituted with one or more fluorine atoms or with one or two groups selected from hydroxy, fluoro, amino, $C_{1-}$

$_4$alkylamino, N,N-di($C_{1-4}$alkyl)amino, aminosulphonyl, N-$C_{1-4}$alkylaminosulphonyl and N,N-di($C_{1-4}$alkyl)aminosulphonyl;

20) $C_{2-4}$alkenyl$X^9C_{1-3}$alkyl$R^{28}$ (wherein $X^9$ and $R^{28}$ are as defined in claim 1);

21) $C_{2-4}$alkynyl$X^9C_{1-3}$alkyl$R^{28}$ (wherein $X^9$ and $R^{28}$ are as defined in claim 1); and

22) $C_{1-3}$alkyl$R^{54}(C_{1-3}alkyl)_q(X^9)_rR^{55}$ (wherein $X^9$, q, r, $R^{54}$ and $R^{55}$ are as defined in claim 1);

and additionally wherein any $C_{1-5}$alkyl, $C_{2-5}$alkenyl or $C_{2-5}$alkynyl group in $R^5X^1$- may bear one or more substituents selected from hydroxy, halogeno and amino].

4. The use of a compound of the formula I according to any one of the preceding claims wherein Z is –O–, –NH– or –S–.

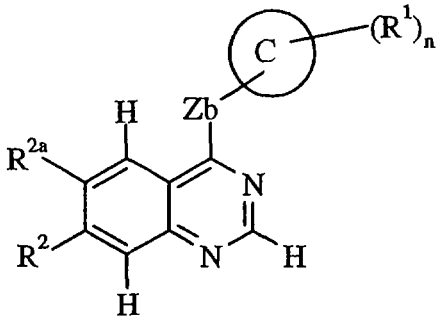
5. 4. The use of a compound of the formula I according to any one of the preceding claims wherein ring C is a 9-10-membered heteroaromatic bicyclic moiety which contains 1-3 heteroatoms selected independently from O, N and S.

6. 5. The use of a compound of the formula I according to any one of the preceding claims wherein $R^1$ represents oxo, halogeno, hydroxy, $C_{1-2}$alkoxy, $C_{1-2}$alkyl, $C_{1-2}$alkoxymethyl, $C_{2-3}$alkanoyl, $C_{1-2}$haloalkyl, cyano, amino, $C_{2-4}$alkenyl, $C_{2-4}$alkynyl, $C_{2-3}$alkanoyloxy, nitro, $C_{2-3}$alkanoylamino, $C_{1-2}$alkoxycarbonyl, $C_{1-2}$alkylsulphanyl, $C_{1-2}$alkylsulphinyl, $C_{1-2}$alkylsulphonyl, carbamoyl, N-$C_{1-2}$alkylcarbamoyl, N,N-di($C_{1-2}$alkyl)carbamoyl, aminosulphonyl, N-$C_{1-2}$alkylaminosulphonyl, N,N-di($C_{1-2}$alkyl)aminosulphonyl, N-($C_{1-2}$alkylsulphonyl)amino, N-($C_{1-2}$alkylsulphonyl)-N-($C_{1-2}$alkyl)amino or a $C_{3-7}$alkylene chain joined to two ring C carbon atoms.

7. 6. The use of a compound of the formula I according to any one of the preceding claims wherein n is 0, 1 or 2.

8. 7. The use of a compound of the formula I according to any one of the preceding claims wherein m is 1 or 2.

9. 8. A compound of the formula II:



(II)

[wherein:

ring C, $R^1$, $R^2$ and n are as defined in claim 1, Zb is -O- or -S- and $R^{2a}$ represents hydrogen, halogeno, $C_{1-3}$alkyl, trifluoromethyl, $C_{1-3}$alkoxy, $C_{1-3}$alkylsulphanyl, $-NR^{3a}R^{4a}$ (wherein $R^{3a}$ and $R^{4a}$, which may be the same or different, each represents hydrogen or $C_{1-3}$alkyl), or $R^{5a}(CH_2)_{za}X^{1a}$ (wherein $R^{5a}$ is a 4-, 5- or 6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, $C_{1-4}$cyanoalkyl, $C_{1-4}$alkyl, $C_{1-4}$hydroxyalkyl, $C_{1-4}$alkoxy, $C_{1-4}$alkoxy$C_{1-4}$alkyl, $C_{1-4}$alkylsulphonyl$C_{1-4}$alkyl, $C_{1-4}$alkoxycarbonyl, $C_{1-4}$aminoalkyl, $C_{1-4}$alkylamino, di($C_{1-4}$alkyl)amino, $C_{1-4}$alkylamino$C_{1-4}$alkyl, di($C_{1-4}$alkyl)amino$C_{1-4}$alkyl, $C_{1-4}$alkylamino$C_{1-4}$alkoxy, di($C_{1-4}$alkyl)amino$C_{1-4}$alkoxy and a group -(-O-)$_f$($C_{1-4}$alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from $C_{1-4}$alkyl), za is an integer from 0 to 4 and $X^{1a}$ represents a direct bond, -O-, $-CH_2-$, -S-, -SO-, $-SO_2-$, $-NR^{6a}C(O)-$, $-C(O)NR^{7a}-$, $-SO_2NR^{8a}-$, $-NR^{9a}SO_2-$ or $-NR^{10a}-$ (wherein $R^{6a}$, $R^{7a}$, $R^{8a}$, $R^{9a}$ and $R^{10a}$ each independently represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl));

with the proviso that $R^2$ is not hydrogen and excluding the compounds:

6,7-dimethoxy-4-(1-naphthylsulphanyl)quinazoline, 6,7-dimethoxy-4-(2-naphthylsulphanyl)quinazoline, 6,7-dimethoxy-4-(1-naphthyloxy)quinazoline, 6,7-dimethoxy-4-(2-naphthyloxy)quinazoline and 6,7-dimethyl-4-(1-naphthylsulphanyl)quinazoline;

or a salt thereof.

10 9. A compound of the formula II according to claim 8 wherein $R^2$ represents hydroxy, halogeno, cyano, nitro, trifluoromethyl, $C_{1-3}$alkyl, amino or $R^5X^1$- [wherein $X^1$ is as defined in claim 1 and $R^5$ is selected from one of the following twenty-two groups:

1) $C_{1-4}$alkyl which may be unsubstituted or which may be substituted with one or more groups selected from fluoro, chloro and bromo, or $C_{2-5}$alkyl which may be unsubstituted or substituted with one or more groups selected from hydroxy and amino;

2) $C_{2-3}$alkyl$X^2$C(O)$R^{11}$ (wherein $X^2$ is as defined in claim 1 and $R^{11}$ represents -$NR^{13}R^{14}$ or -$OR^{15}$ (wherein $R^{13}$, $R^{14}$ and $R^{15}$ which may be the same or different are each $C_{1-4}$alkyl or $C_{1-2}$alkoxyethyl));

3) $C_{2-4}$alkyl$X^3R^{16}$ (wherein $X^3$ is as defined in claim 1 and $R^{16}$ is a group selected from $C_{1-3}$alkyl, cyclopentyl, cyclohexyl, pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl and tetrahydropyranyl, which $C_{1-3}$alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and $C_{1-2}$alkoxy and which cyclopentyl, cyclohexyl, pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl or tetrahydropyranyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, $C_{1-3}$cyanoalkyl, $C_{1-3}$alkyl, $C_{1-3}$hydroxyalkyl, $C_{1-3}$alkoxy, $C_{1-2}$alkoxy$C_{1-3}$alkyl, $C_{1-2}$alkylsulphonyl$C_{1-3}$alkyl, $C_{1-3}$alkoxycarbonyl, $C_{1-3}$alkylamino, di($C_{1-3}$alkyl)amino, $C_{1-3}$alkylamino$C_{1-3}$alkyl, di($C_{1-3}$alkyl)amino$C_{1-3}$alkyl, $C_{1-3}$alkylamino$C_{1-3}$alkoxy, di($C_{1-3}$alkyl)amino$C_{1-3}$alkoxy and a group -(-O-)$_f$($C_{1-3}$alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino and thiomorpholino, which cyclic group may bear one or more substituents selected from $C_{1-3}$alkyl));

4) $C_{2-3}$alkyl$X^4C_{2-3}$alkyl$X^5R^{22}$ (wherein $X^4$ and $X^5$ are as defined in claim 1 and $R^{22}$ represents hydrogen or $C_{1-3}$alkyl);

5) $R^{28}$ (wherein $R^{28}$ is as defined in claim 1);

6) $C_{1-4}$alkyl$R^{110}$ (wherein $R^{110}$ is a group selected from pyrrolidinyl, piperazinyl, piperidinyl, imidazolidin-1-yl, azetidinyl, 1,3-dioxolan-2-yl, 1,3-dioxan-2-yl, 1,3-dithiolan-2-yl and 1,3-dithian-2-yl, which group is linked to $C_{1-4}$alkyl through a carbon atom and which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, $C_{1-3}$cyanoalkyl, $C_{1-3}$alkyl, $C_{1-3}$hydroxyalkyl, $C_{1-3}$alkoxy, $C_{1-2}$alkoxy$C_{1-3}$alkyl, $C_{1-2}$alkylsulphonyl$C_{1-3}$alkyl, $C_{1-3}$alkoxycarbonyl, $C_{1-3}$alkylamino, di($C_{1-3}$alkyl)amino, $C_{1-3}$alkylamino$C_{1-3}$alkyl, di($C_{1-3}$alkyl)amino$C_{1-3}$alkyl, $C_{1-3}$alkylamino$C_{1-3}$alkoxy, di($C_{1-3}$alkyl)amino$C_{1-3}$alkoxy and a group -(-

O-)$_f$($C_{1-3}$alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino and thiomorpholino, which cyclic group may bear one or more substituents selected from $C_{1-3}$alkyl)) or $C_{2-4}$alkyl$R^{111}$ (wherein $R^{111}$ is a group selected from morpholino, thiomorpholino, azetidin-1-yl, pyrrolidin-1-yl, piperazin-1-yl and piperidino which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, $C_{1-3}$cyanoalkyl, $C_{1-3}$alkyl, $C_{1-3}$hydroxyalkyl, $C_{1-3}$alkoxy, $C_{1-2}$alkoxy$C_{1-3}$alkyl, $C_{1-2}$alkylsulphonyl$C_{1-3}$alkyl, $C_{1-3}$alkoxycarbonyl, $C_{1-3}$alkylamino, di($C_{1-3}$alkyl)amino, $C_{1-3}$alkylamino$C_{1-3}$alkyl, di($C_{1-3}$alkyl)amino$C_{1-3}$alkyl, $C_{1-3}$alkylamino$C_{1-3}$alkoxy, di($C_{1-3}$alkyl)amino$C_{1-3}$alkoxy and a group -(-O-)$_f$($C_{1-3}$alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, azetidinyl, morpholino and thiomorpholino, which cyclic group may bear one or more substituents selected from $C_{1-3}$alkyl));

7) $C_{3-4}$alkenyl$R^{112}$ (wherein $R^{112}$ represents $R^{110}$ or $R^{111}$ as defined herein);

8) $C_{3-4}$alkynyl$R^{112}$ (wherein $R^{112}$ represents $R^{110}$ or $R^{111}$ as defined herein);

9) $R^{29}$ (wherein $R^{29}$ is as defined in claim 1);

10) $C_{1-4}$alkyl$R^{29}$ (wherein $R^{29}$ is as defined in claim 1);

11) 1-$R^{29}$prop-1-en-3-yl or 1-$R^{29}$but-2-en-4-yl (wherein $R^{29}$ is as defined in claim 1 with the proviso that when $R^5$ is 1-$R^{29}$prop-1-en-3-yl, $R^{29}$ is linked to the alkenyl group via a carbon atom);

12) 1-$R^{29}$prop-1-yn-3-yl or 1-$R^{29}$but-2-yn-4-yl (wherein $R^{29}$ is as defined in claim 1 with the proviso that when $R^5$ is 1-$R^{29}$prop-1-yn-3-yl, $R^{29}$ is linked to the alkynyl group via a carbon atom);

13) $C_{1-5}$alkyl$X^6R^{29}$ (wherein $X^6$ and $R^{29}$ are as defined in claim 1);

14) 1-($R^{29}X^7$)but-2-en-4-yl (wherein $X^7$ and $R^{29}$ are as defined in claim 1);

15) 1-($R^{29}X^8$)but-2-yn-4-yl (wherein $X^8$ and $R^{29}$ are as defined in claim 1);

16) $C_{2-3}$alkyl$X^9C_{1-3}$alkyl$R^{29}$ (wherein $X^9$ and $R^{29}$ are as defined in claim 1);

17) $C_{2-3}$alkyl$X^9C_{1-3}$alkyl$R^{28}$ (wherein $X^9$ and $R^{28}$ are as defined in claim 1);

18) $C_{2-5}$alkenyl which may be unsubstituted or which may be substituted with one or more fluorine atoms or with one or two groups selected from hydroxy, fluoro, amino, $C_{1-4}$alkylamino, N,N-di($C_{1-4}$alkyl)amino, aminosulphonyl, N-$C_{1-4}$alkylaminosulphonyl and N,N-di($C_{1-4}$alkyl)aminosulphonyl;

19) $C_{2-5}$alkynyl which may be unsubstituted or which may be substituted with one or more fluorine atoms or with one or two groups selected from hydroxy, fluoro, amino, $C_{1-4}$alkylamino, N,N-di($C_{1-4}$alkyl)amino, aminosulphonyl, N-$C_{1-4}$alkylaminosulphonyl and N,N-di($C_{1-4}$alkyl)aminosulphonyl;

20) $C_{2-4}$alkenyl$X^9C_{1-3}$alkyl$R^{28}$ (wherein $X^9$ and $R^{28}$ are as defined in claim 1);

21) $C_{2-4}$alkynyl$X^9C_{1-3}$alkyl$R^{28}$ (wherein $X^9$ and $R^{28}$ are as defined in claim 1); and

22) $C_{1-3}$alkyl$R^{54}(C_{1-3}alkyl)_q(X^9)_rR^{55}$ (wherein $X^9$, q, r, $R^{54}$ and $R^{55}$ are as defined in claim 1);

and additionally wherein any $C_{1-5}$alkyl, $C_{2-5}$alkenyl or $C_{2-5}$alkynyl group in $R^5X^1$- may bear one or more substituents selected from hydroxy, halogeno and amino].

9 and 10

11. 10. A compound according to any one of claims 8 and 9 wherein Zb is -O-.

9, 10 and 11

12. 11. A compound according to any one of claims 8, 9 and 10 wherein ring C is a 9-10-membered heteroaromatic bicyclic moiety which contains 1-3 heteroatoms selected independently from O, N and S.

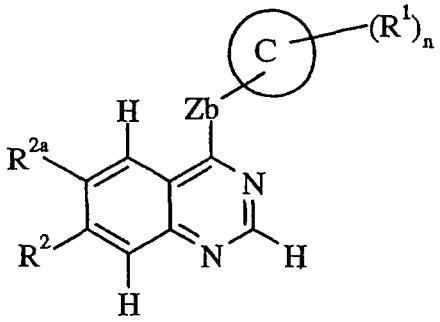
9, 10, 11 and 12

13. 12. A compound according to any one of claims 8, 9, 10 and 11 wherein $R^1$ represents oxo, halogeno, hydroxy, $C_{1-2}$alkoxy, $C_{1-2}$alkyl, $C_{1-2}$alkoxymethyl, $C_{2-3}$alkanoyl, $C_{1-2}$haloalkyl, cyano, amino, $C_{2-4}$alkenyl, $C_{2-4}$alkynyl, $C_{2-3}$alkanoyloxy, nitro, $C_{2-3}$alkanoylamino, $C_{1-2}$alkoxycarbonyl, $C_{1-2}$alkylsulphanyl, $C_{1-2}$alkylsulphinyl, $C_{1-2}$alkylsulphonyl, carbamoyl, N-$C_{1-2}$alkylcarbamoyl, N,N-di($C_{1-2}$alkyl)carbamoyl, aminosulphonyl, N-$C_{1-2}$alkylaminosulphonyl, N,N-di($C_{1-2}$alkyl)aminosulphonyl, N-($C_{1-2}$alkylsulphonyl)amino, N-($C_{1-2}$alkylsulphonyl)-N-($C_{1-2}$alkyl)amino or a $C_{3-7}$alkylene chain joined to two ring C carbon atoms.

9, 10, 11, 12 and 13

14. 13. A compound according to any one of claims 8, 9, 10, 11 and 12 wherein n is 0, 1 or 2.

15. 14. A compound of the formula IIb:



(IIb)

[wherein:

ring C, $R^1$, $R^2$ and n are as defined in claim 1, Zb is -O- and $R^{2a}$ is as defined in claim 9 with the proviso that $R^2$ does not have any of the following values:

hydrogen, substituted or unsubstituted $C_{1-5}$alkyl, halogeno, $C_{1-5}$alkoxy, $C_{2-5}$alkenyl, phenoxy or phenyl$C_{1-5}$alkoxy;

or a salt thereof.

16. 15. A compound according to claim 9 selected from

6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)-4-(2-naphthyloxy)quinazoline,

6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)-4-(quinolin-7-yloxy)quinazoline,

7-(3-(1,1-dioxothiomorpholino)propoxy)-6-methoxy-4-(quinolin-7-yloxy)quinazoline,

6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)-4-(quinolin-7-yloxy)quinazoline,

6-methoxy-7-((1-methylpiperidin-3-yl)methoxy)-4-(quinolin-7-yloxy)quinazoline,

4-(4-chloroquinolin-7-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,

6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)-4-(4-methylquinolin-7-yloxy)quinazoline,

6-methoxy-4-(4-methylquinolin-7-yloxy)-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline,

6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)-4-(quinolin-7-yloxy)quinazoline,

6-methoxy-7-((1-(2-methylsulphonylethyl)piperidin-4-yl)methoxy)-4-(quinolin-7-yloxy)quinazoline,

4-(2,3-dimethylindol-5-yloxy)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline,

4-(2,3-dimethylindol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,

6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)-4-(2-trifluoromethylindol-5-yloxy)quinazoline,

6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)-4-(2-trifluoromethylindol-5-yloxy)quinazoline,

(*R*,*S*)-4-(3-fluoroquinolin-7-yloxy)-6-methoxy-7-((1-methylpiperidin-3-yl)methoxy)quinazoline,

4-(indol-5-yloxy)-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline,

7-(3-N,N-dimethylaminopropoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,

6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(2-morpholinoethoxy)ethoxy)quinazoline,

7-(2-(N,N-diethylamino)ethoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,

6-methoxy-7-(3-piperidinopropoxy)-4-(quinolin-7-yloxy)quinazoline,

4-(2-methylindol-5-yloxy)-7-(3-morpholinopropoxy)quinazoline,

4-(2-methylindol-5-yloxy)-7-(2-(piperidin-1-yl)ethoxy)quinazoline,

4-(2-methylindol-5-yloxy)-7-(2-(1*H*-1,2,4-triazol-1-yl)ethoxy)quinazoline,

6-methoxy-7-(3-piperidinopropoxy)-4-(6-trifluoromethylindol-5-yloxy)quinazoline,

7-(3-(methylsulphonyl)propoxy)-4-(2-methylindol-5-yloxy)quinazoline,

7-(3-(N,N-dimethylamino)propoxy)-4-(2,3-dimethylindol-5-yloxy)-6-methoxyquinazoline,

4-(2,3-dimethylindol-5-yloxy)-6-methoxy-7-(1-methylpiperidin-3-ylmethoxy)quinazoline,

7-(2-(N,N-diethylamino)ethoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline,

4-(indol-5-yloxy)-6-methoxy-7-(2-(piperidin-2-yl)ethoxy)quinazoline,

4-(indol-5-yloxy)-6-methoxy-7-(2-(piperidin-1-yl)ethoxy)quinazoline,

4-(indol-6-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,

7-(3-(ethylsulphonyl)propoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,

6-methoxy-4-(3-methylindol-5-yloxy)-7-(3-piperidinopropoxy)quinazoline,

7-(2-hydroxy-3-piperidinopropoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,

7-(2-hydroxy-3-(4-methylpiperazin-1-yl)propoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,

6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(N-methylamino)ethoxy)quinazoline, and

7-(2-hydroxy-3-(isopropylamino)propoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,

or a salt thereof.

17. ~~16~~. A compound according to claim ~~8~~ 9 selected from

6-methoxy-7-(3-morpholinopropoxy)-4-(quinolin-7-yloxy)quinazoline,

6-methoxy-4-(2-methylindol-5-yloxy)-7-((1-methylpiperidin-4-yl)methoxy)quinazoline,

4-(indol-5-yloxy)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline,

4-(indol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,

6-methoxy-4-(2-methylindol-5-yloxy)-7-(3-methylsulphonylpropoxy)quinazoline,

7-((1-cyanomethyl)piperidin-4-ylmethoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,

6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-morpholinoethoxy)quinazoline,

6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-pyrrolidin-1-ylethoxy)quinazoline,

6-methoxy-4-(2-methylindol-5-yloxy)-7-(1-methylpiperidin-3-ylmethoxy)quinazoline,

6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-piperidinoethoxy)quinazoline,

6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(N-methyl-N-(4-pyridyl)amino)ethoxy)quinazoline,

6-methoxy-4-(2-methylindol-5-yloxy)-7-(3-morpholinopropoxy)quinazoline,

6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)-4-(2-methylindol-5-yloxy)quinazoline,

6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(1*H*-1,2,4-triazol-1-yl)ethoxy)quinazoline,

6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(2-(4-methylpiperazin-1-yl)ethoxy)ethoxy)quinazoline,

6-methoxy-4-(2-methylindol-5-yloxy)-7-(3-piperidinopropoxy)quinazoline,

4-(indol-5-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline

6-methoxy-7-(1-(2-methoxyethyl)piperidin-4-ylmethoxy)-4-(2-methylindol-5-yloxy)quinazoline,

6-methoxy-4-(2-methylindol-5-yloxy)-7-((2-(2-pyrrolidin-1-ylethyl)carbamoyl)vinyl)quinazoline,

6-methoxy-4-(2-methylindol-5-yloxy)-7-(3-(4-methypiperazin-1-yl)propoxy)quinazoline,

6-methoxy-4-(2-methylindol-5-yloxy)-7-(piperidin-4-ylmethoxy)quinazoline,

6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(piperidin-4-yloxy)ethoxy)quinazoline,

6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(N-methyl-N-methylsulphonylamino)ethoxy)quinazoline,

7-(2-(1-(2-cyanoethyl)piperidin-4-yloxy)ethoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,

4-(2-methylindol-5-yloxy)-7-(3-(pyrrolidin-yl)propoxy)quinazoline,

4-(2-methylindol-5-yloxy)-7-(3-(1,1-dioxothiomorpholino)propoxy)quinazoline,

4-(2-methylindol-5-yloxy)-7-(piperidin-4-ylmethoxy)quinazoline,

4-(indol-5-yloxy)-6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)quinazoline,

7-(3-(N,N-dimethylamino)propoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline,

7-(3-(N,N-diethylamino)propoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline,

7-(3-(1,1-dioxothiomorpholino)propoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline,

4-(indol-5-yloxy)-6-methoxy-7-(2-(4-pyridyloxy)ethoxy)quinazoline,

4-(indol-6-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,

7-(1-(2-methoxyethyl)piperidin-4-ylmethoxy)-4-(2-methylindol-5-yloxy)quinazoline,

7-(2-hydroxy-3-morpholinopropoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,

7-(2-(1-(2-methoxyethyl)piperidin-4-yl)ethoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,

7-(2-hydroxy-3-pyrrolidin-1-ylpropoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,

7-(3-(N,N-diethylamino)-2-hydroxypropoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,

7-(3-(1,1-dioxothiomorpholino)propoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,

6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(4-pyridyloxy)ethoxy)quinazoline,

4-(indol-5-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline,

(2*R*)-6-methoxy-(2-methyl-1*H*-indol-5-yloxy)-7-(2-hydroxy-3-piperidinopropoxy)quinazoline,

(5*R*)-6-methoxy-4-(2-methyl-1*H*-indol-5-yloxy)-7-(2-oxopyrrolidin-5-ylmethoxy)quinazoline,

4-(4-bromoindol-5-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,

6-methoxy-4-(2-methylindol-5-yloxy)-7-(1-(2-(pyrrolidin-1-yl)ethyl)-piperidin-4-ylmethoxy)quinazoline,

(2*R*)-7-(2-hydroxy-3-(pyrrolidin-1-yl)propoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline,

(2*R*)-7-(2-hydroxy-3-morpholinopropoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline,

(2*R*)-7-(2-hydroxy-3-piperidinopropoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline,

(2*S*)-7-(2-hydroxy-3-((N,N-diisopropyl)amino)propoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline,

(2*S*)-7-(2-hydroxy-3-piperidinopropoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline,
(2*R*)-7-(2-hydroxy-3-piperidinopropoxy)-6-methoxy-4-(3-methylindol-5-yloxy)quinazoline,
(2*R*)-7-(2-hydroxy-3-(pyrrolidin-1-yl)propoxy)-6-methoxy-4-(3-methylindol-5-yloxy)quinazoline,
(2*R*)-7-(2-hydroxy-3-(pyrrolidin-1-yl)propoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,
(2*R*)-7-(2-hydroxy-3-(4-methylpiperazin-1-yl)propoxy)–6-methoxy-4-(2-methylindol-5-yloxy)quinazoline,
6-methoxy-4-(2-methylindol-5-yloxy)-7-(1-(2-morpholinoethyl)piperidin-4-ylmethoxy)quinazoline,
4-(3-fluoro-quinolin-7-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,
4-(3-fluoro-quinolin-7-yloxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline,
6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)-4-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)quinazoline,
(2*S*)-6-methoxy-(2-methyl-1*H*-indol-5-yloxy)-7-(2-hydroxy-3-piperidinopropoxy)quinazoline,
and
4-(6-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline,
or a salt thereof.

18. 11. A compound according to claim 9 selected from

6-methoxy-4-(2-methylindol-5-yloxy)-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline,
4-(4-fluoroindol-5-yloxy)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline,
4-(4-fluoroindol-5-yloxy)-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline,
4-(6-fluoroindol-5-yloxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline,
4-(4-fluoroindol-5-yloxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline,
4-(4-fluoroindol-5-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,
4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline,
4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,
4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline,
4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline,
4-(4-fluoroindol-5-yloxy)-6-methoxy-7-(2-(1-methylpiperidin-4-yl)ethoxy)quinazoline,

(2*R*)-7-(2-hydroxy-3-(pyrrolidin-1-yl)propoxy)-4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxyquinazoline, and

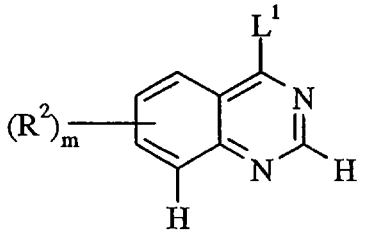
4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(2-(1-methylpiperidin-4-yl)ethoxy)quinazoline,

or a salt thereof.

19 18. A compound according to claim 9 in the form of a pharmaceutically acceptable salt.

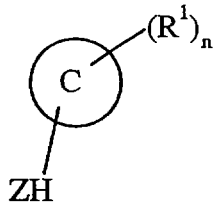
20. 19. A process for the preparation of a compound according to claim 9 of formula II or salt thereof which comprises:

(a) the reaction of a compound of the formula III:



(III)

(wherein $R^2$ and m are as defined in claim 1 and $L^1$ is a displaceable moiety), with a compound of the formula IV:

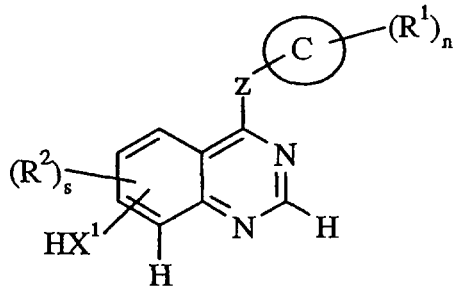


(IV)

(wherein ring C, $R^1$, Z and n are as defined in claim 1);

(b) a compound of formula I or a salt thereof wherein at least one $R^2$ is $R^5X^1$ wherein $R^5$ is as defined in claim 1 and $X^1$ is -O-, -S-, -OC(O)- or -$NR^{10}$- (wherein $R^{10}$ independently

represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) may be prepared by the reaction of a compound of the formula V:



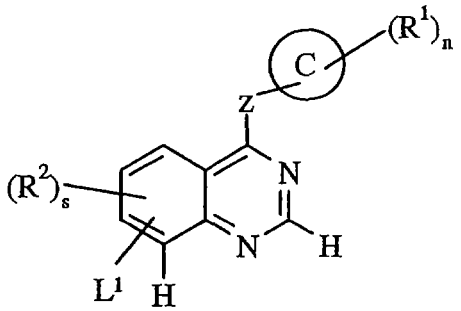
(V)

(wherein ring C, Z, $R^1$, $R^2$ and n are as defined in claim 1 and $X^1$ is as herein defined in this section and s is an integer from 0 to 2) with a compound of formula VI:

$$R^5\text{-}L^1 \qquad \text{(VI)}$$

(wherein $R^5$ is as defined in claim 1 and $L^1$ is as herein defined);

(c) a compound of the formula I or a salt thereof wherein at least one $R^2$ is $R^5X^1$ wherein $R^5$ is as defined in claim 1 and $X^1$ is -O-, -S-, -OC(O)- or -$NR^{10}$- (wherein $R^{10}$ represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) may be prepared by the reaction of a compound of the formula VII:



(VII)

with a compound of the formula VIII:

$R^5$-$X^1$-H (VIII)

(wherein $R^1$, $R^2$, $R^5$, ring C, Z and n are as defined in claim 1 and $L^1$, s and $X^1$ are as herein defined);

(d) a compound of the formula I or a salt thereof wherein at least one $R^2$ is $R^5X^1$ wherein $X^1$ is as defined in claim 1 and $R^5$ is $C_{1-5}$alkyl$R^{113}$, wherein $R^{113}$ is selected from one of the following nine groups:

1) $X^{19}C_{1-3}$alkyl (wherein $X^{19}$ represents -O-, -S-, -$SO_2$-, -$NR^{114}$C(O)- or –$NR^{115}SO_2$- (wherein $R^{114}$ and $R^{115}$ which may be the same or different are each hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl);

2) $NR^{116}R^{117}$ (wherein $R^{116}$ and $R^{117}$ which may be the same or different are each hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl);

3) $X^{20}C_{1-5}$alkyl$X^5R^{22}$ (wherein $X^{20}$ represents -O-, -S-, -$SO_2$-, -$NR^{118}$C(O)-, -$NR^{119}SO_2$- or –$NR^{120}$- (wherein $R^{118}$, $R^{119}$, and $R^{120}$ which may be the same or different are each hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $X^5$ and $R^{22}$ are as defined in claim 1);

4) $R^{28}$ (wherein $R^{28}$ is as defined in claim 1);

5) $X^{21}R^{29}$ (wherein $X^{21}$ represents -O-, -S-, -$SO_2$-, -$NR^{121}$C(O)-, -$NR^{122}SO_2$-, or –$NR^{123}$- (wherein $R^{121}$, $R^{122}$, and $R^{123}$ which may be the same or different are each hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{29}$ is as defined in claim 1); and

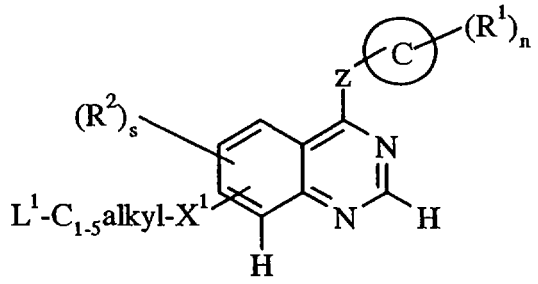
6) $X^{22}C_{1-3}$alkyl$R^{29}$ (wherein $X^{22}$ represents -O-, -S-, -$SO_2$-, -$NR^{124}$C(O)-, -$NR^{125}SO_2$- or –$NR^{126}$- (wherein $R^{124}$, $R^{125}$ and $R^{126}$ each independently represents hydrogen, $C_{1-3}$alkyl or $C_{1-3}$alkoxy$C_{2-3}$alkyl) and $R^{29}$ is as defined in claim 1);

7) $R^{29}$ (wherein $R^{29}$ is as defined in claim 1);

8) $X^{22}C_{1-4}$alkyl$R^{28}$ (wherein $X^{22}$ and $R^{28}$ are as defined in claim 1); and

9) $R^{54}(C_{1-4}\text{alkyl})_q(X^9)_rR^{55}$ (wherein q, r, $X^9$, $R^{54}$ and $R^{55}$ are as defined in claim 1);

may be prepared by reacting a compound of the formula IX:



(IX)

(wherein $X^1$, $R^1$, $R^2$, ring C, Z and n are as defined in claim 1 and $L^1$ and s are as herein defined) with a compound of the formula X:

$$R^{113}\text{-}H \qquad (X)$$

(wherein $R^{113}$ is as defined herein);

(e) a compound of the formula I or a salt thereof wherein one or more of the substituents $(R^2)_m$ is represented by $-NR^{127}R^{128}$, where one (and the other is hydrogen) or both of $R^{127}$ and $R^{128}$ are $C_{1-3}$alkyl, may be effected by the reaction of compounds of formula I wherein the substituent $(R^2)_m$ is an amino group and an alkylating agent; or

(f) a compound of the formula I or a salt thereof wherein $X^1$ is -SO- or $-SO_2-$ may be prepared by oxidation from the corresponding compound in which $X^1$ is -S- or -SO-;

and when a salt of a compound of formula I is required, reaction of the compound obtained with an acid or base whereby to obtain the desired salt.

20. A pharmaceutical composition which comprises as active ingredient a compound of formula II or a pharmaceutically acceptable salt thereof according to claim 9 in association with a pharmaceutically acceptable excipient or carrier.

21. The use of a compound of the formula II, as defined in claim 8, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human being.

22. The use of a compound of the formula II, as defined in claim 9, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human being.

23. The use of a compound of the formula II, as defined in claim 9, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as a human being.

24. The use of a compound of the formula I, as defined in claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in inhibiting the effects of VEGF in a warm-blooded animal such as a human being.

25. A compound 4-fluoro-5-hydroxy-2-methylindole or a salt thereof.

26. A compound 4-fluoro-5-hydroxyindole or a salt thereof.

27. A compound 6-fluoro-5-hydroxy-2-methylindole or a salt thereof.

28. A compound 6-fluoro-5-hydroxyindole or a salt thereof.

29. A process for the preparation of 4-fluoro-5-hydroxy-2-methylindole according to any one of those described in Example 237.

30. A process for the preparation of 4-fluoro-5-hydroxyindole as described in Example 242.

31. A process for the preparation of 6-fluoro-5-hydroxyindole as described in Example 242.

32. A process for the preparation of 6-fluoro-5-hydroxy-2-methylindole as described in Example 250.