MS (ESI): 433 [MH]+

Example 12

To a solution of 4-chloro-6-methoxy-7-((1-(2-methylsulphonylethyl)piperidin-4-yl)methoxy)quinazoline (115mg, 0.28mmol) and 7-hydroxyquinoline (50mg, 0.33mmol) in DMF (1.5ml) was added potassium carbonate (60mg, 0.42mmol). The mixture was stirred for 2 hours at 100°C. After cooling, and removal of the volatiles by evaporation, the residue was partitioned between ethyl acetate and water. The organic layer was washed with water, brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography eluting with ethylacetate/methylene chloride/methanol (1/1/0 followed by 40/50/10 and 0/9/1). After removal of the volatiles by evaporation, the residue was triturated with pentane, filtered and dried under vacuum to give **6-methoxy-7-((1-(2-methylsulphonylethyl)piperidin-4-yl)methoxy)-4-(quinolin-7-yloxy)quinazoline** (110mg, 76%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.3-1.45(m, 2H); 1.75-1.9(m, 3H); 2.05(t, 2H); 2.72(t, 2H); 2.95(d, 2H); 3.05(s, 3H); 3.35-3.45(m, 2H); 4.00(s, 3H); 4.1(d, 2H); 7.41(s, 1H); 7.57(dd, 1H); 7.62(dd, 1H); 7.65(s, 1H); 7.93(s, 1H); 8.12(d, 1H); 8.45(d, 1H); 8.55(s, 1H); 8.95(d, 1H)

MS (ESI): 523 $[MH]^+$

G00002

Elemental analysis:	Found	C 61.3	H 6.0	N 10.6	
$C_{27}H_{30}N_4O_5S$ $0.4H_2O$	Requires	C 61.2	H 5.9	N 10.6%	

The starting material was prepared as follows:

Sodium hydride (1.44g of a 60% suspension in mineral oil, 36mmol) was added in portions over 20 minutes to a solution of 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (8.46g, 30mmol), (prepared as described for the starting material in Example 1), in DMF (70ml) and the mixture was stirred for 1.5 hours. Chloromethyl pivalate (5.65g, 37.5mmol) was added dropwise and the mixture stirred for 2 hours at ambient temperature. The mixture was diluted with ethyl acetate (100ml) and poured onto ice/water (400ml) and 2M hydrochloric acid (4ml). The organic layer was separated and the aqueous layer extracted with ethyl acetate, the combined extracts were washed with brine, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was triturated with a mixture of ether and petroleum ether, the solid was collected by filtration and dried under vacuum to give 7-

benzyloxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (10g, 84%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.11(s, 9H); 3.89(s, 3H); 5.3(s, 2H); 5.9(s, 2H); 7.27(s, 1H); 7.35(m, 1H); 7.47(t, 2H); 7.49(d, 2H); 7.51(s, 1H); 8.34(s, 1H)

A mixture of 7-benzyloxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (7g, 17.7mmol) and 10% palladium-on-charcoal catalyst (700mg) in ethyl acetate (250ml), DMF (50ml), methanol (50ml) and acetic acid (0.7ml) was stirred under hydrogen at atmospheric pressure for 40 minutes. The catalyst was removed by filtration and the solvent removed from the filtrate by evaporation. The residue was triturated with ether, collected by filtration and dried under vacuum to give 7-hydroxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (4.36g, 80%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.1(s, 9H); 3.89(s, 3H); 5.89(s, 2H); 7.0(s, 1H); 7.48(s, 1H); 8.5(s, 1H)

A suspension of 7-hydroxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (6.12g, 20mmol) potassium carbonate (5.52g, 40mmol) in DMF (60ml) was stirred at ambient temperature for 30 minutes. 4-(4-Methylphenylsulphonyloxymethyl)-1-tert-butyloxycarbonylpiperidine (8.86g, 24mmol), (prepared as described for the starting material in Example 10), was added and the mixture was stirred at 100°C for 2 hours. After cooling, the mixture was poured onto water/ice (400ml, 1/1) containing 2M hydrochloric acid (10ml). The precipitate was collected by filtration, washed with water and dried under vacuum over phophorus pentoxide. The solid was triturated in a mixture of ether/pentane (1/1), collected by filtration and dried to give 6-methoxy-3-((pivaloyloxy)methyl)-7-((1-tert-butyloxycarbonylpiperidin-4-yl)methoxy)-3,4-dihydroquinazolin-4-one (7.9g, 78.5%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.1(s, 9H); 1.1-1.3(m, 2H); 1.42(s, 9H); 1.73(d, 2H); 1.93-2.1(br s, 1H); 2.65-2.9(br s, 2H); 3.9(s, 3H); 3.9-4.1(m, 4H); 5.9(s, 2H); 7.2(s, 1H); 7.5(s, 1H); 8.35(s, 1H)

MS (ESI): 526 [MNa]+

A solution of 6-methoxy-3-((pivaloyloxy)methyl)-7-((1-tert-butyloxycarbonylpiperidin-4-yl)methoxy)-3,4-dihydroquinazolin-4-one (7.9g, 16mmol) in methylene chloride (80ml) containing 5.5M hydrogen chloride in isopropanol (80ml) was stirred for 1 hour at ambient temperature. Ether was added and the solid was collected by

filtration, washed with ether and dried under vacuum at 60°C to give 6-methoxy-7-((piperidin-4-yl)methoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one hydrochloride (6.9g, 100%).

^{1}H NMR Spectrum: ($DMSOd_6$, CF_3CO_2D) 1.15(s, 9H); 1.5-1.7(m, 2H); 2.0(d, 2H); 2.2-2.3(br s, 1H); 3.0(t, 2H); 3.4(d, 2H); 3.94(s, 3H); 4.15(d, 2H); 5.97(s, 2H); 7.3(s, 1H); 7.6(s, 1H); 8.65(s, 1H)

MS (ESI): 404 $[MH]^+$

To a solution of 6-methoxy-7-((piperidin-4-yl)methoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one hydrochloride (0.88g, 2mmol) and triethylamine (0.3ml, 2.1mmol) in methanol (10ml) and methylene chloride (10ml) was added potassium carbonate (280mg, 2mmol) and methyl vinyl sulfone (0.4ml, 2.1mmol). After stirring for 2 hours at ambient temperature, the volatiles were removed under vacuum. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to give 6-methoxy-7-((1-(2-methylsulphonylethyl)piperidin-4-yl)methoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (0.55g, 54%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.09(s, 9H); 1.25-1.4(m, 2H); 1.7-1.9(m, 3H); 2.0(t, 2H); 2.7(t, 2H); 2.95(d, 2H); 3.02(s, 3H); 3.25-3.45(m, 2H); 3.9(s, 3H); 4.0(d, 2H); 5.9(s, 2H); 7.15(s, 1H); 7.49(s, 1H); 8.35(s, 1H)

MS (ESI): 510 $[MH]^+$.

To a suspension of 6-methoxy-7-((1-(2-methylsulphonylethyl)piperidin-4-yl)methoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (90mg, 0.18mmol) in methanol (3ml) was added 2M aqueous sodium hydroxide (180µl, 0.35mmol). After stirring for 2 hours at ambient temperature, the mixture was adjusted to pH10 with 2M hydrochloric acid. The volatiles were removed under vacuum and the residue was suspended in water, filtered, washed with water followed by ether and dried under vacuum at 60°C to give 6-methoxy-7-((1-(2-methylsulphonylethyl)piperidin-4-yl)methoxy)-3,4-dihydroquinazolin-4-one (55mg, 79%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.2-1.4(m, 2H); 1.7-1.85(m, 3H); 2.0(t, 2H); 2.7(t, 2H); 2.9(d, 2H); 3.02(s, 3H); 3.3-3.5(m, 2H); 3.9(s, 3H); 4.0(d, 2H); 7.11(s, 1H); 7.45(s, 1H); 7.97(s, 1H)

MS (ESI): 396 $[MH]^+$

A solution of 6-methoxy-7-((1-(2-methylsulphonylethyl)piperidin-4-yl)methoxy)-3,4-dihydroquinazolin-4-one (335mg, 0.85mmol) in thionyl chloride (5ml) containing DMF

(50µl) was refluxed for 1 hour. After cooling, the volatiles were removed under vacuum and the residue was triturated with ether and filtered. The solid was suspended in methylene chloride and sodium hydrogen carbonate was added. The organic layer was washed with water, brine, dried ($MgSO_4$) and evaporated. The residue was triturated with ether, filtered and dried under vacuum to give 4-chloro-6-methoxy-7-((1-(2-methylsulphonylethyl)piperidin-4-ylmethoxy)quinazoline (335mg, 95%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.25-1.45(m, 2H); 1.75-1.90(m, 3H); 2.0(t, 2H); 2.7(t, 2H); 2.92(d, 2H); 3.03(s, 3H); 3.2-3.35(m, 2H); 4.0(s, 3H); 4.1(d, 2H); 7.40(s, 1H); 7.45(s, 1H); 8.9(s, 1H)

MS (ESI): 414 $[MH]^+$

Example 13

Using a procedure analogous to that described for Example 10, 4-chloro-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline (130mg, 0.4mmol), (prepared as described for the starting material in Example 10), was reacted with 4-methyl-7-hydroxyquinoline (80mg, 0.5mol), (Chem. Ber. 1967, 100, 2077), to give **6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)-4-(4-methylquinolin-7-yloxy)quinazoline** (160mg, 90%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.3-1.5(m, 2H); 1.7-1.95(m, 3H); 1.9(t, 2H); 2.17(s, 3H); 2.74(s, 3H); 2.8(d, 2H); 4.07(s, 3H); 4.1(d, 2H); 7.4(m, 2H); 7.65(dd, 1H); 7.65(s, 1H); 7.9(s, 1H); 8.21(d, 1H); 8.54(s, 1H); 8.78(d, 1H)

MS (ESI): 445 $[MH]^+$

Example 14

A solution of 4-chloro-6-methoxy-7-((1-(2-methylsulphonylethyl)piperidin-4-yl)methoxy)quinazoline (115mg, 0.28mmol), (prepared as described for the starting material in Example 12), 5-hydroxy-2-methylindole (50mg, 0.33mmol) and potassium carbonate (60mg, 0.42mmol) in DMF (1.5ml) was stirred at 100°C for 2 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 purified by chromatography eluting with ethyl acetate/methylene chloride (1/1) followed by methanol/ethyl acetate/methylene chloride (1/4/5 and 1/0/9) to give **6-methoxy-4-(2-methylindol-5-yloxy)-7-((1-(2-methylsulphonylethyl)piperidin-4-yl)methoxy)quinazoline** (60mg, 41%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.3-1.45(m, 2H); 1.75-1.92(m, 3H); 2.02(t, 2H); 2.4(s, 3H); 2.7(t, 2H); 2.95(d, 2H); 3.05(s, 3H); 4.0(s, 3H); 4.05(d, 2H); 6.15(s, 1H); 6.85(dd, 1H); 7.25(s, 1H); 7.3(d, 1H); 7.38(s, 1H); 7.6(s, 1H); 8.45(s, 1H)

MS (ESI): 525 $[MH]^+$

Elemental analysis:	Found	C 60.7	H 6.2	N 10.5	
$C_{27}H_{32}O_5S$ $0.5H_2O$	Requires	C 60.8	H 6.2	N 10.5%	

Example 15

Using a procedure analogous to that described for Example 9, 4-chloro-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline (0.13g, 0.4mmol), (prepared as described for the starting material in Example 9), was reacted with 7-hydroxy-4-methylquinoline (80mg, 0.5mol), (Chem. Berich. 1967, 100, 2077), to give **6-methoxy-4-(4-methylquinolin-7-yloxy)-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline** (155mg, 87%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.7(br s, 4H); 2.05(m, 2H); 2.5(br s, 4H); 2.6(t, 2H); 2.75(s, 3H); 4.02(s, 3H); 4.3(t, 2H); 7.41(s, 1H); 7.45(d, 1H); 7.65(s, 1H); 7.65(d, 1H); 7.95(s, 1H); 8.25(d, 1H); 8.55(s, 1H); 8.8(d, 1H)

MS (ESI): 445 $[MH]^+$

Example 16

Using a procedure analogous to that described for Example 9, 4-chloro-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline (0.13g, 0.4mmol), (prepared as described for the starting material in Example 9), was reacted with 2,2,4-trimethyl-1,2-dihydroquinolin-6-ol (95mg, 0.5mmol), (IZV. ACAD. NAVK. SSSR. Ser. Khim. 1981, 9, 2008), to give **6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)-4-(2,2,4-trimethyl-1,2-dihydroquinolin-6-yloxy)quinazoline** (90mg, 47%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.23(s, 6H); 1.7(br s, 4H); 1.85(s, 3H); 2.0(m, 2H); 2.45(br s, 4H); 2.57(t, 2H); 3.95(s, 3H); 4.25(t, 2H); 5.35(s, 1H); 5.9(s, 1H); 6.5(d, 1H); 6.8(dd, 1H); 6.85(s, 1H); 7.32(s, 1H); 7.52(s, 1H); 8.5(s, 1H)

MS (ESI): 475 $[MH]^+$

Example 17

Using a procedure analogous to that described for Example 9, 4-chloro-6-methoxy-7-

((1-methylpiperidin-4-yl)methoxy)quinazoline (0.13g, 0.4mmol), (prepared as described for the starting material in Example 10), was reacted with 2,2,4-trimethyl-1,2-dihydroquinolin-6-ol (95mg, 0.5mmol), (IZV. ACAD. NAVK. SSSR. Ser. Khim. 1981, 9, 2008), to give **6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)-4-(2,2,4-trimethyl-1,2-dihydroquinolin-6-yloxy)quinazoline** (140mg, 74%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.15(s, 6H); 1.3-1.45(m, 2H); 1.7-2.0(m, 8H); 2.16(s, 3H); 2.65-2.85(d, 2H); 4.0(s, 3H); 4.05(d, 2H); 5.35(s, 1H); 5.9(s, 1H); 6.5(d, 1H); 6.80(d, 1H); 6.82(s, 1H); 7.33(s, 1H); 7.5(s, 1H); 8.52(s, 1H)

MS (ESI): 475 $[MH]^+$

Example 18

Using a procedure analogous to that described for Example 9, 4-chloro-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline (0.13g, 0.4mmol), (prepared as described for the starting material in Example 10), was reacted with 2,4-dimethyl-7-hydroxyquinoline (87mg, 0.5mmol), (Chem. Berichte, 1903, 36, 4016), to give **4-(2,4-dimethylquinolin-7-yloxy)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline** (61mg, 33%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.3-1.5(m, 2H); 1.7-1.95(m, 5H); 2.2(s, 3H); 2.65(s, 3H); 2.7(s, 3H); 2.75-2.9(br d, 2H); 4.05(s, 3H); 4.1(d, 2H); 7.3(s, 1H); 7.4(s, 1H); 7.52(d, 1H); 7.65(s, 1H); 7.8(s, 1H); 8.15(d, 1H); 8.55(s, 1H)

MS (ESI): 459 $[MH]^+$

Example 19

Using a procedure analogous to that described for Example 9, 4-chloro-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline (0.13g, 0.4mmol), (prepared as described for the starting material in Example 10), was reacted with 6-hydroxy-2*H*-4*H*-1,4-benzoxazin-3-one (83mg, 0.5mmol), (J. Chem. Soc. C, 1971, 2696), to give **6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)-4-(3-oxo-2*H*-4*H*-1,4-benzoxazin-6-yloxy)quinazoline** (158mg, 88%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.25-1.45(m, 2H); 1.8(d, 2H); 1.7-1.9(m, 1H); 1.9(t, 2H); 2.2(s, 3H); 2.8(d, 2H); 3.97(s, 3H); 4.05(d, 2H); 4.65(s, 2H); 6.8(s, 1H); 6.85(d, 1H); 7.05(d, 1H); 7.35(s, 1H); 7.52(s, 1H); 8.55(s, 1H)

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

Example 20

Using a procedure analogous to that described for Example 9, 4-chloro-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline (0.13g, 0.4mmol), (prepared as described for the starting material in Example 9), was reacted with 6-hydroxy-2*H*-4*H*-1,4-benzoxazin-3-one (83mg, 0.5mmol), (J. Chem. Soc. C, 1971, 2696), to give **6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)-4-(3-oxo-2*H*-4*H*-1,4-benzoxazin-6-yloxy)quinazoline** (170mg, 94%).

^{1}H NMR Spectrum: ($DMSOd_6$, CF_3CO_2D) 1.8-2.0(m, 2H); 2.0-2.15(m, 2H); 2.2-2.35(m, 2H); 3.0-3.2(m, 2H); 3.4(t, 2H); 3.6-3.75(m, 2H); 4.05(s, 3H); 4.35(t, 2H); 4.65(s, 2H); 6.85(s, 1H); 6.9(d, 1H); 7.1(d, 1H); 7.5(s, 1H); 7.7(s, 1H); 8.9(s, 1H)

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

Example 21

Using a procedure analogous to that described for Example 10, 4-chloro-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline (74mg, 0.23mmol), (prepared as described for the starting material in Example 10), was reacted with 6-hydroxyquinoline (41mg, 0.28mol) to give **6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)-4-(quinolin-6-yloxy)quinazoline** (89mg, 94%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.3-1.5(m, 2H); 1.8(d, 2H); 1.9(t, 2H); 1.8-1.9(m, 1H); 2.2(s, 3H); 2.82(d, 2H); 4.02(s, 3H); 4.1(d, 2H); 7.4(s, 1H); 7.6(dd, 1H); 7.65(s, 1H); 7.75(d, 1H); 7.95(s, 1H); 8.15(d, 1H); 8.4(d, 1H); 8.55(s, 1H); 8.95(d, 1H)

MS (ESI): 431 $[MH]^+$

Example 22

To 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (250mg, 0.74mmol), (prepared as described for the starting material in Example 1), in suspension in DMF (4ml) were successively added 4-chloro-7-hydroxyquinoline (133mg, 0.74mmol) and potassium carbonate (153mg, 1mmol) and the reaction mixture heated to 100°C. More 4-chloro-7-hydroxyquinoline (27mg, 0.15mmol) was added after one hour and heating was continued for a further 30 minutes. The product precipitated upon cooling to ambient temperature. The reaction mixture was diluted with water, the product was collected by filtration and washed with more water. The dried solid was triturated with ether and filtered to give **4-(4-chloroquinolin-7-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline** (166mg, 47%).

^{1}H NMR Spectrum: (DMSOd_6, CF_3CO_2D) 2.3(m, 2H); 3.2(m, 2H); 3.4(m, 2H); 3.5(m, 2H); 3.7(m, 2H); 4.0(m, 2H); 4.1(s, 3H); 4.4(m, 2H); 7.55(s, 1H); 7.75(s, 1H); 7.90(dd, 1H); 7.95(d, 1H); 8.15(d, 1H); 8.45 (d, 1H); 8.80(s, 1H); 9.05(d, 1H)

MS - ESI: 481 $[MH]^+$

Elemental analysis:	Found	C 61.8	H 5.1 N 11.5
$C_{25}H_{25}ClN_4O_4$	Requires	C 62.4	H 5.2 N 11.7%

The starting material was prepared as follows:

A solution of 7-benzyloxy-4-chloroquinoline (17g, 56mmol), (Konishi et al. WO 96/11187), in TFA (170ml) was heated at reflux for 2 hours. The solvent was removed under vacuum and the residue was triturated with ether, filtered and washed with ether. The solid was suspended in an aqueous solution of sodium hydrogen carbonate (5.5g, 65mmol in 200ml of water) and stirred at ambient temperature for 30 minutes. The solid was collected by filtration, washed with water and dried overnight under vacuum and over phosphorus pentoxide to give 4-chloro-7-hydroxyquinoline (9.85g, 98%).

^{1}H NMR Spectrum: (DMSOd_6) 7.37(s, 1H); 7.39(d, 1H); 7.62(d, 1H); 8.15(d, 1H); 8.8(d, 1H)

MS - EI: m/z 179 [M.]+

Example 23

A solution of 4-chloro-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline (74mg, 0.23mmol), (prepared as described for the starting material in Example 10), and 2-hydroxynaphthalene (40mg, 0.28mmol) in DMF (1.5ml) containing potassium carbonate (48mg, 0.35mmol) was stirred at 100°C for 3.5 hours. After cooling, methylene chloride (4.5ml) was added and the mixture was poured onto a column of silica (SiO2 Isolute®) and eluted with, successively, methylene chloride, methylene chloride/methanol (9/1), methylene chloride/methanol/3M ammonia in methanol (75/20/5). The fractions containing the product were evaporated under vacuum. The residues was triturated with ether, filtered and dried under vacuum to give **6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)-4-(2-naphthyloxy)quinazoline** (80mg, 83%).

MS - ESI: 430 [MH]+

^{1}H NMR Spectrum: (DMSOd_6) 1.35-1.45 (m, 2H), 1.8 (d, 2H), 2.0 (t, 1H), 2.2 (s, 3H), 2.85

(d, 2H), 3.3-3.4 (m, 2H), 4.02 (s, 3H), 4.1 (d, 2H), 7.4 (s, 1H), 7.5 (dd, 1H), 7.55 (m, 2H), 7.65 (s, 1H), 7.88 (s, 1H), 7.98 (d, 1H), 8.0 (d, 1H), 8.1 (d, 1H), 8.55 (s, 1H)

Example 24

A solution of 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (74mg, 0.23mmol), (prepared as described for the starting material in Example 1), and 3,4-(methylenedioxy)aniline (53mg, 0.24mmol) in a solution of isopropanol (3.5ml) containing 5.5M hydrogen chloride in isopropanol (42µl) was heated for 3 hours. After cooling to ambient temperature, the reaction mixture was cooled to 0°C and maintained at this temperature overnight. The precipitate was collected by filtration, washed with ethyl acetate and dried under vacuum to give **4-(1,3-benzodioxol-5-ylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline** (82mg, 76%).

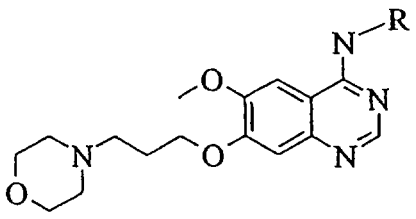
MS - ESI: 439 $[MH]^+$

^1H NMR Spectrum: ($DMSOd_6$) 2.3-2.4 (m, 2H), 3.05-3.2 (m,2H), 3.25-3.35 (m, 2H), 3.5 (d, 2H), 3.82 (t, 2H), 4.0 (d, 2H), 4.05 (s, 3H), 4.32 (t, 2H), 6.1 (s, 2H), 7.02 (d, 1H), 7.1 (dd, 1H), 7.3 (s, 1H), 7.4 (s, 1H), 8.32 (s, 1H), 8.8 (s, 1H)

Examples 25-29

Using an analogous procedure to that described in Example 24, 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline, (prepared as described for the starting material in Example 1), was used in the synthesis of the compounds described in Table I hereinafter as detailed in the notes a)-e) to Table I.

Table I



Example No.	Weight (mg)	yield %	MS-ESI [MH]+	note	R
25	104	90	435.1	a	1-*H*-indazol-6-yl

26	102	89	435.1	b	1-*H*-indazol-5-yl
27	99	84	452	c	1,3-benzothiazol-6-yl
28	108	91	466	d	2-methyl-1,3-benzothiazol-5-yl
29	102	95	435.1	e	2,3-dihydro-1*H*-inden-5-yl

Notes

a) 4-Chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (74mg) was reacted with 6-aminoindazole (32mg) to give **4-(1-*H*-indazol-6-ylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline**.

^{1}H NMR Spectrum: ($DMSOd_6$) 2.3-2.4 (m, 2H), 3.05-3.2 (m, 2H), 3.2-3.3 (m, 2H), 3.52 (d, 2H), 3.85 (t, 2H), 4.0 (d, 2H), 4.05 (s, 3H), 4.32 (t, 2H), 7.42 (s, 1H), 7.45 (d, 1H), 7.85 (d, 1H), 7.98 (s, 1H), 8.1 (s, 1H), 8.42 (s, 1H), 8.85 (s, 1H)

b) 4-Chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (74mg) was reacted with 5-aminoindazole (32mg) to give **4-(1-*H*-indazol-5-ylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline**.

^{1}H NMR Spectrum: ($DMSOd_6$) 2.3-2.4 (m, 2H), 3.05-3.2 (m, 2H), 3.25-3.3 (m, 2H), 3.45-3.55 (m, 2H), 3.8-3.9 (m, 2H), 3.9-4.02 (m, 2H), 4.05 (s, 3H), 4.32 (t, 2H), 7.42 (s, 1H), 7.65 (m, 2H), 8.05 (s, 1H), 8.15 (s, 1H), 8.4 (s, 1H), 8.75 (s, 1H)

c) 4-Chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (74mg) was reacted with 6-aminothiazole (36mg) to give **4-(1,3-benzothiazol-6-ylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline**.

^{1}H NMR Spectrum: ($DMSOd_6$) 2.3-2.4 (m, 2H), 3.05-3.2 (m, 2H), 3.2-3.3 (m, 2H), 3.55 (d, 2H), 3.8 (t, 2H), 4.0 (d, 2H), 4.08 (s, 3H), 4.32 (t, 2H), 7.4 (s, 1H), 7.88 (dd, 1H), 8.2 (d, 1H), 8.4 (s, 1H), 8.55 (s, 1H), 8.85 (s, 1H), 9.42 (s, 1H)

d) 4-Chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (74mg) was reacted with 6-amino-2-methylthiazole (57mg) to give **6-methoxy-4-(2-methyl-1,3-benzothiazol-5-ylamino)-7-(3-morpholinopropoxy)quinazoline**.

^{1}H NMR Spectrum: ($DMSOd_6$) 2.3-2.4 (m, 2H), 2.85 (s, 3H), 3.05-3.2 (m, 2H), 3.3 (t, 2H), 3.4-3.5 (m, 2H), 3.85 (t, 2H), 4.0 (d, 2H), 4.05 (s, 3H), 4.35 (t, 2H), 7.42 (s, 1H), 7.75 (dd,

1H), 8.15 (d, 1H), 8.3 (s, 1H), 8.42 (s, 1H), 8.85 (s, 1H)

e) 4-Chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (74mg) was reacted with 5-aminoindan (32mg) to give **4-(2,3-dihydro-1*H*-inden-5-ylamino)-6-methoxy-7-(3-morpholinopropoxy)quinazoline**.

^{1}H NMR Spectrum: ($DMSOd_6$) 2.08 (m, 2H), 2.3-2.4 (m, 2H), 2.9 (m, 4H), 3.05-3.2 (m, 2H), 3.2-3.3 (m, 2H), 3.5 (d, 2H), 3.82 (t, 2H), 4.0 (d, 2H), 4.05 (s, 3H), 4.3 (t, 2H), 7.32 (d, 1H), 7.4 (m, 2H), 7.55 (s, 1H), 8.32 (s, 1H), 8.8 (s, 1H)

Example 30

A suspension of 4-chloro-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (130mg, 0.4mmol), (prepared as described for the starting material in Example 10), 7-hydroxy-2-methylchromone (88mg, 0.5 mmol), (Bull Soc. Chim. Fr. 1995, 132, 233), and potassium carbonate (83mg, 0.6 mmol) was heated at 100°C for 1.5 hours. After cooling, the mixture was partitioned between water and ethyl acetate. The organic layer was washed with water, brine, dried ($MgSO_4$), and the volatiles were removed by evaporation. The residue was triturated with ether, collected by filtration, washed with ether and dried under vacuum to give **6-methoxy-4-(2-methyl-4-oxo-4*H*-chromen-7-yloxy)-7-(1-methylpiperidin-4-ylmethoxy)quinazoline** (170mg, 92%).

MS - ESI: 462 [MH]+

^{1}H NMR Spectrum: ($DMSOd_6$) 1.3-1.5 (m, 2H); 1.75-1.95 (m, 5H); 2.2 (s, 3H), 2.42 (s, 3H); 4.0 (s, 3H); 4.1 (d, 2H); 6.3 (s, 2H); 7.4 (s, 1H); 7.45 (dd, 1H); 7.6 (s, 1H); 7.7 (s, 1H); 8.15 (d, 1H); 8.61 (s, 1H)

Examples 31-33

Using an analogous procedure to that described in Example 30, the compounds described in Table II hereinafter and detailed in the notes a)-c) to Table II, were made.

Table II

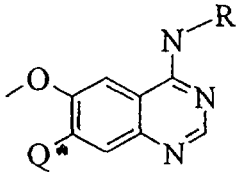


Table II

Example No.	Weight (mg)	yield %	MS-ESI [MH]+	note	Q	R
31	180	85	451	a	1-methylpiperidin-4-ylmethoxy	4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-6-yloxy
32	160	87	462	b	3-pyrrolidin-1-ylpropoxy	2-methyl-4-oxo-4*H*-chromen-7-yloxy
33	100	56	451	c	3-pyrrolidin-1-ylpropoxy	4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-6-yloxy

a) 4-Chloro-6-methoxy-7-(1-methylpiperidin-4-yloxy)quinazoline (130mg), (prepared as described for the starting material in Example 10), was reacted with 3,4-dihydro-4-methyl-2*H*-1,4-benzoxazin-6-ol (83mg), (J. Org. Chem. 1971, 36 (1)), to give **6-methoxy-4-(4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-6-yloxy)-7-(1-methylpiperidin-4-ylmethoxy)quinazoline**

^{1}H NMR Spectrum: ($DMSOd_6$) 1.6-1.75 (m, 2H); 1.9-2.3 (m, 5H); 2.8 (s, 3H); 2.9 (s, 3H); 3.0-3.15 (m,2H); 3.3 (br s, 2H); 3.5-3.6 (d, 2H); 4.1 (s, 3H); 4.2 (d, 2H); 4.3 (t, 2H); 6.55 (m, 1H); 6.75 (s, 1H); 6.8 (d, 1H); 7.6 (s, 1H); 7.75 (s, 1H); 9.15 (s, 1H)

b) 4-Chloro-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (130mg), (prepared as described for the starting material in Example 9), was reacted with 7-hydroxy-2-methylchromone (88mg), (Bull Soc. Chim Fr. 1995, 132, 233). After cooling, water was added (20ml) and the precipitate was collected by filtration and dried under vacuum over phosphorus pentoxide at 60°C to give **6-methoxy-4-(2-methyl-4-oxo-4*H*-chromen-7-yloxy)-7-(3-pyrrolidin-1-ylpropoxy)quinazoline**.

^{1}H NMR Spectrum: ($DMSOd_6$, CF_3COOD) 1.8-2.0 (m, 2H); 2.0-2.15 (m, 2H); 2.2-2.3 (m, 2H); 2.4 (s, 3H); 3.05-3.15 (m, 2H); 3.3-3.4 (m, 2H); 3.6-3.7 (m, 2H); 4.05 (s, 3H); 4.35 (t, 2H); 6.3 (s, 1H); 7.45 (d, 1H); 7.5 (s, 1H); 7.65 (s, 1H); 7.72 (s, 1H); 8.15 (d, 1H); 8.75 (s, 1H)

c) 4-Chloro-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (130mg), (prepared as described for the starting material in Example 9), was reacted with 3,4-dihydro-4-methyl-2*H*-1,4-benzoxazin-6-ol (83mg), (J. Org. Chem. 1971, 36 (1)), to give **6-methoxy-4-(4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-6-yloxy)-7-(3-pyrrolidin-1-ylpropoxy)quinazoline**.

^{1}H NMR Spectrum: ($DMSOd_6$) 1.85-2.0 (m, 2H); 2.0-2.15 (m, 2H); 2.25-2.35 (m, 2H); 2.83 (s, 3H); 3.05-3.15 (m, 2H); 3.3 (t, 2H); 3.4 (t, 2H); 3.7 (br m, 2H); 4.1 (s, 3H); 4.3 (t, 2H); 4.4 (t, 2H); 6.52 (d, 1H); 6.7 (s, 1H); 6.8 (d, 1H); 7.55 (s, 1H); 7.75 (s, 1H); 9.1 (s, 1H)

Example 34

A solution of 4-chloro-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (110mg, 0.34mmol), (prepared as described for the starting material in Example 10), and 5-hydroxyindole (55mg, 0.41mmol) in DMF (1.5ml) containing potassium carbonate (70mg, 0.51mmol) was heated at 100°C for 2 hours. After cooling, water was added and the precipitate was collected by filtration, washed with water followed by ether, and dried under vacuum over phosphorus pentoxide to give **4-(indol-5-yloxy)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline** (90mg, 64%).

MS - ESI: 419 [MH]+

^{1}H NMR Spectrum: ($DMSOd_6$) 1.35-1.5 (m, 2H); 1.8 (d, 2H); 1.95 (t, 2H); 1.7-2.0 (m, 1H); 2.2 (s, 3H); 2.85 (d, 2H); 4.02 (s, 3H); 4.1 (d, 2H); 6.45 (s, 1H); 7.0 (d, 1H); 7.35 (s, 1H); 7.4-7.5 (m, 3H); 7.6 (s, 1H); 8.5 (s, 1H)

Elemental analysis:	Found	C 67.4	H 6.5	N 13.1	
$C_{24}H_{26}N_4O_3$ $0.5H_2O$	Requires	C 67.4	H 6.4	N 13.1%	

Example 35

Using an analogous procedure to that described in Example 34, 4-chloro-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (110mg, 0.34mmol), (prepared as described for the starting material in Example 10), was reacted with 2,3-dimethyl-5-hydroxyindole (66mg, 0.41mmol), (Arch. Pharm. 1972, 305, 159). The crude product was purified by column chromatography eluting with methanol/methylene chloride (1/9) followed by 3M ammonia in methanol/methanol/methylene chloride (5/15/80) to give **4-(2,3-dimethylindol-5-yloxy)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline** (60mg, 40%).

MS - ESI: 447 [MH]+

^{1}H NMR Spectrum: ($DMSOd_6$) 1.2-1.4 (m, 2H); 1.7 (d, 2H); 1.8 (t, 2H); 1.7-1.9 (m, 1H); 2.05 (s, 3H); 2.12 (s, 3H); 2.25 (s, 3H); 2.75 (d, 2H); 3.9 (s, 3H); 4.0 (d, 2H); 6.8 (d, 1H); 7.15 (s, 1H); 7.2 (d, 1H); 7.3 (s, 1H); 7.52 (s, 1H); 8.45 (s, 1H)

Elemental analysis:	Found	C 68.6	H 6.9	N 12.5	
$C_{26}H_{30}N_4O_3$ 0.4H_2O	Requires	C 68.8	H 6.8	N 12.4%	

Example 36

Using an analogous procedure to that described in Example 34, 4-chloro-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (110mg, 0.34mmol), (prepared as described for the starting material in Example 9), was reacted with 5-hydroxyindole (55mg, 0.41mmol). The crude product was purified by chromatography on alumina, eluting with methanol/ethyl acetate/methylene chloride (5/45/50) to give **4-(indol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline** (70mg, 50%).

MS - ESI 419 [MH]+

^{1}H NMR Spectrum: ($DMSOd_6$, CF_3COOD) 1.9-2.0 (m, 2H); 2.1 (m, 2H); 2.3 (t, 2H); 3.0-3.15 (m, 2H); 3.4 (t, 2H); 3.6-3.75 (m, 2H); 4.1 (s, 3H); 4.4 (t, 2H); 6.5 (s, 1H); 7.05 (d, 1H); 7.5 (s, 1H); 7.5-7.6 (m, 2H); 7.85 (s, 1H); 9.11 (s, 1H)

Elemental analysis:	Found	C 63.7	H 6.4	N 12.1	
$C_{24}H_{26}N_4O_3$ 1.9H_2O	Requires	C 63.7	H 6.6	N 12.4%	

Example 37

A suspension of 4-chloro-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (100mg, 0.31mmol), (prepared as described for the starting material in Example 10), and 5-amino-2,3-dimethylindole (55mg, 0.34mmol) in isopropanol (6ml) containing 5.5M hydrogen choride in isopropanol (60μL) was heated for 30 minutes at 70°C. After cooling, the solid was collected by filtration, washed with isopropanol, followed by ether and dried under vacuum to give **4-(2,3-dimethylindol-5-ylamino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline** hydrochloride (118mg, 74%).

MS - ESI: 446 [MH]+

^{1}H NMR Spectrum: ($DMSOd_6$): 1.8-1.9 (m, 2H); 2.0 (d, 2H); 2.1-2.2 (m, 1H); 2.16 (s, 3H); 2.33 (s, 3H); 2.75 (br s, 3H); 2.95-3.05 (m, 2H); 3.5 (d, 2H); 4.0 (s, 3H); 4.07 (d, 2H); 7.25 (d, 1H); 7.4 (d, 1H); 7.42 (s, 1H); 7.52 (s, 1H); 8.25 (s, 1H); 8.75 (s, 1H); 10.0 (br s, 1H); 10.9 (s,

1H); 11.25 (br s, 1H)

Elemental analysis:	Found	C 58.5	H 6.8	N 12.9	
$C_{26}H_{31}N_5O_2$ $1H_2O$ 1.9HCl	Requires	C 58.6	H 6.6	N 13.1%	

Example 38

Using an analogous procedure to that described in Example 37, 4-chloro-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (100mg, 0.31mmol), (prepared as described for the starting material in Example 9), was reacted with 5-amino-2,3-dimethylindole (55mg, 0.34mmol) to give **4-(2,3-dimethylindol-5-ylamino)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline** hydrochloride (114mg, 72%).

MS - ESI: 446 [MH]+

^{1}H NMR Spectrum: (DMSOd_6, CF_3COOD) 1.85-2.0 (m, 2H); 2.05-2.15 (m, 2H); 2.1 (s, 3H); 2.2 (s, 3H); 2.25-2.35 (m, 2H); 2.35 (s, 3H); 3.0-3.15 (m, 2H); 3.32-3.42 (m, 2H); 3.6-3.7 (m, 2H); 4.05 (s, 3H); 4.3 (t, 2H); 7.2 (d, 1H); 7.3 (s, 1H); 7.35 (d, 1H); 7.57 (s, 1H); 8.2 (s, 1H); 8.8 (s, 1H)

Elemental analysis:	Found	C 58.8	H 7.0	N 12.5	
$C_{26}H_{31}N_5O$ $1.9H_2O$ 1.9HCl 0.1isopropanol	Requires	C 58.6	H 7.1	N 12.9%	

Examle 39

Using an analogous procedure to that described in Example 38, 4-chloro-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (100mg, 0.31mmol), (prepared as described for the starting material in Example 9), was reacted with 5-amino-2-methylindole (50mg, 0.34mmol) to give **6-methoxy-4-(2-methylindol-5-ylamino)-7-(3-pyrrolidin-1-ylpropoxy)quinazoline** hydrochloride (138mg, 89%).

MS - ESI: 432 [MH]+

^{1}H NMR Spectrum: (DMSOd_6) 1.8-1.9 (m, 2H); 2.0-2.1 (m, 2H); 2.15-2.35 (m, 2H); 2.4 (s, 3H); 3.0-3.1 (m, 2H); 3.2-3.3 (m, 2H); 3.5-3.6 (m, 2H); 4.0 (s, 3H); 4.32 (t, 2H); 6.2 (s, 1H); 7.2 (d, 1H); 7.3 (m, 2H); 7.65 (s, 1H); 8.25 (s, 1H); 8.75 (s, 1H); 10.75 (br s, 1H); 11.15 (s, 1H); 11.25 (br s, 1H)

Elemental analysis:	Found	C 58.9	H 6.6	N 13.5	
$C_{25}H_{29}N_5O_2$ 2.2HCl 0.1isopropanol	Requires	C 58.7	H 6.2	N 13.5%	

Example 40

A mixture of 4-chloro-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (100mg, 0.31mmol), (prepared as described for the starting material in Example 9), and 7-hydroxy-2,4-dimethylquinoline (64mg, 0.36mmol), (Chem. Berichte, 1903, 36, 4016), in DMF (3ml) containing potassium carbonate (86mg, 0.62mmol) was heated at 90°C for 3 hours. After cooling, the mixture was poured onto a column of silica and eluted with 2.5M ammonia in methanol/methylene chloride (5/95) to give **4-(2,4-dimethylquinolin-7-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline** (50mg, 35%).

MS - ESI: 459 [MH]+

^{1}H NMR Spectrum: ($CDCl_3$) 1.8 (br s, 4H); 2.2 (m, 4H); 2.55 (br s, 4H); 2.7 (2s, 6H); 2.68 (m, 2H); 4.05 (s, 3H); 4.3 (t, 2H); 7.15 (s, 1H); 7.35 (s, 1H); 7.45 (d, 1H); 7.6 (s, 1H); 7.9 (s, 1H); 8.05 (d, 1H); 8.6 (s, 1H)

Elemental analysis:	Found	C 70.4	H 7.1	N 12.1
$C_{27}H_{30}N_4O_3$ 0.2ether	Requires	C 70.5	H 6.8	N 11.8%

Example 41

Using an analogous procedure to that described in Example 37, 4-chloro-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (50mg, 0.155mmol), (prepared as described for the starting material in Example 10), was reacted with 5-amino-2-methylindole (0.171mmol) to give **6-methoxy-4-(2-methylindol-5-ylamino)-7-(1-methylpiperidin-4-ylmethoxy)quinazoline** hydrochloride (72mg, quant.).

MS - ESI: 432 [MH]+

^{1}H NMR Spectrum: ($DMSOd_6$, CF_3COOD) 1.5-1.7 (m, 2H); 2.05 (d, 2H); 2.1-2.2 (m, 1H); 2.45 (s, 3H); 2.8 (s, 3H); 3.05 (t, 2H); 3.5 (d, 2H); 4.0 (s, 3H); 4.1 (d, 2H); 6.2 (s, 1H); 7.2 (d, 1H); 7.32 (d, 1H); 7.4 (d, 1H); 7.6 (s, 1H); 8.2 (s, 1H); 8.85 (s, 1H)

Elemental analysis:	Found	C 53.9	H 6.8	N 12.4
$C_{25}H_{29}N_5O_2$ 2.6H_2O 2.07HCl	Requires	C 54.2	H 6.6	N 12.6%

Example 42

A suspension of 4-chloro-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (100mg, 0.31 mmol), (prepared as described for the starting material in Example 9), and 7-hydroxy-2-methylquinoline (54mg, 0.34mmol), (J. Med. Chem. 1998, 41, 4062), in DMF

(3ml) containing potassium carbonate (86mg, 0.62mmol) was heated at 90°C for 2 hours. After cooling, the mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with water, brine, dried and the volatiles were removed by evaporation. The residue was triturated with minimal ether, collected by filtration and dried under vacuum to give **6-methoxy-4-(2-methylquinolin-7-yloxy)-7-(3-pyrrolidin-1-ylpropoxy)quinazoline** (95mg, 69%).

MS - ESI: 445 [MH]+

^{1}H NMR Spectrum: ($CDCl_3$) 1.8 (br s, 4H); 2.2 (m, 2H); 2.5 (br s, 4H); 2.7 (t, 2H); 2.8 (s, 3H); 4.1 (s, 3H); 4.3 (t, 2H); 7.3 (d, 1H); 7.35 (s, 1H); 7.45 (dd, 1H); 7.6 (s, 1H); 7.85 (d, 1H); 7.9 (s, 1H); 8.1 (d, 1H); 8.6 (s, 1H)

Example 43

Using an analogous procedure to that described in Example 42, 4-chloro-6-methoxy-7-(1-(2-methylsulphonylethyl)piperidin-4-ylmethoxy)quinazoline (156mg, 0.38mmol), (prepared as described for the starting material in Example 12), was reacted with 7-hydroxy-2-methylquinoline (66mg, 0.4 mmol), (J. Med. Chem. 1998, 41, 4062), to give **6-methoxy-7-(1-(2-methylsulphonylethyl)piperidin-4-ylmethoxy)-4-(2-methylquinolin-7-yloxy)quinazoline** (166mg, 82%).

MS - ESI: 537 [MH]+

^{1}H NMR Spectrum: ($DMSOd_6$) 1.3-1.5 (m, 2H); 1.75-1.95 (m, 3H); 1.95-2.15 (m, 2H); 2.7 (s, 3H); 2.7-2.8 (m, 2H); 2.9-3.0 (m, 2H); 3.05 (s, 3H); 3.2-3.35 (m, 2H); 4.02 (s, 3H); 4.1 (d, 2H); 7.4 (s, 1H); 7.45 (d, 1H); 7.55 (d, 1H); 7.65 (s, 1H); 7.8 (s, 1H); 8.05 (d, 1H); 8.35 (d, 1H); 8.55 (s, 1H)

Elemental analysis:	Found	C 62.2	H 6.3	N 10.4	
$C_{28}H_{32}N_4O_5S$ 0.35ether 0.2DMF	Requires	C 62.4	H 6.4	N 10.2%	

Example 44

A suspension of 4-chloro-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (50mg, 0.155mmol), (prepared as described for the starting material in Example 10), and 5-hydroxy-2-trifluoromethylindole (34mg, 0.17mmol) in DMF (1.5ml) containing potassium carbonate (43mg, 0.31mmol) was heated at 90°C for 2 hours. After cooling, the mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with

brine, dried ($MgSO_4$) and the volatiles were removed by evaporation. The residue was purified by column chromatography eluting with methanol/ethyl acetate/methylene chloride (10/50/40) followed by 2.5M ammonia in methanol/ethyl acetate/methylene chloride (10/50/40) to give **6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)-4-(2-trifluoromethylindol-5-yloxy)quinazoline** (35mg, 48%).

MS - ESI: 487 [MH]+

^{1}H NMR Spectrum: ($DMSOd_6$) 1.25-1.4 (m, 2H); 1.75 (d, 2H); 1.8 (t, 2H); 1.7-2.0 (m, 1H); 2.2 (s, 3H); 2.75 (d, 2H); 4.0 (s, 3H); 4.1 (d, 2H); 7.0 (s, 1H); 7.25 (d, 1H); 7.4 (s, 1H); 7.6 (d, 1H); 7.8 (s, 1H); 8.5 (s, 1H); 12.5 (s, 1H)

Elemental analysis:	Found	C 60.2	H 5.8	N 10.9	
$C_{25}H_{25}F_3N_4O_3$ 0.7H_2O 0.2ether	Requires	C 60.3	H 5.6	N 10.9%	

The starting material was prepared as follows:

A solution of (4-methoxy-2-methylphenyl)-carbamic acid-1,1-dimethylethyl ester (2g, 8.43mmol), (J. Med. Chem. 1996, 39, 5119), in dry THF (25ml) was cooled to -40°C and sec-butyllithium (15ml, 19.5mmol) was added. After stirring for 15 minutes at this temperature, N-methyl-N-methoxytrifluoroacetamide (1.32g, 8.43mmol) in THF (20ml) was added in portions. Stirring was continued for 1 hour at -40°C and then the mixture was allowed to warm to ambient temperature. The mixture was poured onto ether/1M hydrochloric acid. The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and the volatiles were removed by evaporation.

The crude residue (1.4g) was dissolved in methylene chloride (8ml) and TFA was added (1.5ml). After stirring for 3 hours at ambient temperature, the volatiles were removed under vacuum. The crude product was partitoned between methylene chloride and water. The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and the volatiles were removed by evaporation. The residue was purified by column chromatography, eluting with ether/petroleum ether (1/9) to give 5-methoxy-2-trifluoromethylindole (845mg, 47% over 2 steps).

^{1}H NMR Spectrum: ($CDCl_3$) 3.83 (s, 3H), 6.82 (s, 1H), 7.0 (dd, 1H), 7.1 (s, 1H), 7.3 (d, 1H), 8.15 (br s, 1H)

A solution of 5-methoxy-2-trifluoromethylindole (800mg, 3.7mmol) in methylene chloride (6ml) was cooled to -15°C and a solution of 1M boron tribromide in methylene

chloride (7.44 ml, 7.4mmol) was added in portions. The mixture was allowed to warm to ambient temperature and was stirred for 45 minutes. After cooling to 0°C, saturated aqueous sodium hydrogen carbonate (25ml) was added. The mixture was extracted with ethyl acetate. The organic layer was dried ($MgSO_4$) and the volatiles were removed by evaporation. The residue was purified by column chromatography eluting with ethyl acetate/petroleum ether. After removal of the volatiles by evaporation, the solid was triturated with pentane, collected by filtration and dried under vacuum to give 5-hydroxy-2-trifluoromethylindole (290mg, 39%).

MS - EI: 201 [M.]+

^{1}H NMR Spectrum: ($CDCl_3$) 4.64 (s, 1H), 6.8 (s, 1H), 6.92 (dd, 1H), 7.1 (s, 1H), 7.3 (d, 1H), 8.3 (br s, 1H)

Elemental analysis:	Found	C 53.3	H 2.9	N 6.8	
$C_9H_6F_3NO$ 0.1 H_2O	Requires	C 53.3	H 3.1	N 6.9%	

Example 45

Using an analogous procedure to that described in Example 44, 4-chloro-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (100mg, 0.3mmol), (prepared as described for the starting material in Example 9), was reacted with 5-hydroxy-2-trifluoromethylindole (75mg, 0.37 mmol), (prepared as described for the starting material in Example 44), to give **6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)-4-(2-trifluoromethylindol-5-yloxy)quinazoline** (105mg, 70%).

MS - ESI: 487 [MH]+

^{1}H NMR Spectrum: ($CDCl_3$) 1.8 (m, 4H); 2.1-2.3 (m, 2H); 2.55 (br s, 4H); 2.7 (t, 2H); 4.1 (s, 3H); 4.3 (t, 2H); 6.95 (s, 1H); 7.2 (dd, 1H); 7.35 (s, 1H); 7.5 (d, 1H); 7.55 (s, 1H); 7.6 (s, 1H); 8.6 (s, 1H); 8.8 (s, 1H)

Elemental analysis:	Found	C 61.7	H 5.5	N 11.5	
$C_{25}H_{25}F_3N_4O_3$	Requires	C 61.7	H 5.2	N 11.5%	

Example 46

Using an analogous procedure to that described in Example 42, 4-chloro-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (100mg, 0.31mmol), (prepared as described for the starting material in Example 10), was reacted with 7-hydroxy-2-methylquinoline (54mg,

0.34mmol), (J. Med. Chem. 1998, 41, 4062), to give **6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)-4-(2-methylquinolin-7-yloxy)quinazoline** (86mg, 63%).

MS - ESI: 445 [MH]+

^{1}H NMR Spectrum: ($CDCl_3$) 1.4-1.6 (m, 2H); 1.95 (d, 2H); 2.05 (t, 2H); 1.9-2.1 (m, 1H); 2.35 (s, 3H); 2.8 (s, 3H); 2.95 (d, 2H); 4.1 (s, 3H); 4.15 (d, 2H); 7.3 (m, 2H); 7.45 (dd, 1H); 7.6 (s, 1H); 7.9 (d, 1H); 7.95 (s, 1H); 8.1 (d, 1H); 8.6 (s, 1H)

Elemental analysis:	Found	C 69.7	H 6.5	N 12.8	
$C_{26}H_{28}N_4O_3$ 0.2H_2O	Requires	C 69.7	H 6.4	N 12.5%	

Example 47

A suspension of 4-chloro-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (110mg, 0.34 mmol), (prepared as described for the starting material in Example 9), and 2,3-dimethyl-5-hydroxyindole (66mg, 0.41mmol), (Arch. Pharm. 1972, 305, 159), in DMF (1.5ml) containing potassium carbonate (70mg, 0.51mmol) was heated at 100°C for 2 hours. After cooling, the residue was purified by chromatography, eluting with methanol/methylene chloride (1/9) followed by 2.5M ammonia in methanol/methanol/methylene chloride (5/10/85) to give **4-(2,3-dimethylindol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline** (50mg, 33%).

MS - ESI: 447 [MH]+

^{1}H NMR Spectrum: ($DMSOd_6$, CF_3COOD) 1.9-2.0 (m, 2H); 2.05-2.15 (m, 2H); 2.15 (s, 3H); 2.3-2.4 (m, 2H); 2.4 (s, 3H), 3.05-3.15 (m, 2H); 3.35-3.45 (t, 2H); 3.7 (br s, 2H); 4.1 (s, 3H); 4.4 (t, 2H); 6.95 (d, 1H); 7.3 (s, 1H); 7.35 (d, 1H); 7.55 (s, 1H); 7.85 (s, 1H); 9.15 (s, 1H)

Elemental analysis:	Found	C 67.7	H 6.8	N 12.2	
$C_{26}H_{30}N_4O_3$ 0.8H_2O	Requires	C 67.8	H 6.9	N 12.2%	

Example 48

Using an analogous procedure to that described in Example 32, 7-benzyloxy-4-chloro-6-methoxyquinazoline (1g, 3.33mmol), (prepared as described for the starting material in Example 1), was reacted with 5-hydroxy-2-methylindole (0.59g, 4mmol) to give **7-benzyloxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline** (1.25g, 91%).

MS - ESI: 412 [MH]+

^{1}H NMR Spectrum: ($DMSOd_6$) 2.4 (s, 3H); 4.0 (s, 3H); 5.35 (s, 2H); 6.15 (s, 1H); 6.85 (s,

1H); 7.2-7.6 (m, 9H); 8.5 (s, 1H)

Elemental analysis:	Found	C 72.2	H 5.1	N 10.2	
$C_{25}H_{21}N_3O_3$ $0.2H_2O$	Requires	C 72.3	H 5.2	N 10.1%	

The starting material may be prepared as follows:

A solution of boron tribromide (32.5ml, 341mmol) in methylene choride (60ml) was added in portions to a solution of 5-methoxy-2-methylindole (25g, 155mmol) in methylene chloride (250ml) cooled at -45°C. After stirring for 15 minutes at -30°C, the mixture was warmed up to ambient temperature and stirred for 1 hour. Methylene chloride (300ml) was added in portions and the mixture was cooled to 0°C. Water was added in portions and the mixture was adjusted to pH6 with 4N sodium hydroxide. The organic layer was separated. The aqueous layer was extracted with methylene chloride and the organic layers were combined, washed with water, brine, dried ($MgSO_4$) and the volatiles were removed by evaporation. The residue was purified by column chromatography eluting with ethyl acetate/methylene chloride (1/9 followed by 15/85) to give 5-hydroxy-2-methylindole (21.2g, 93%).

^{1}H NMR Spectrum: ($DMSOd_6$) 2.35 (s, 3H) ; 5.95 (s, 1H) ; 6.5 (dd, 1H) ; 6.7 (s, 1H) ; 7.05 (d, 1H) ; 8.5 (s, 1H)

Example 49

A solution of 7-benzyloxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (0.2g, 0.5mmol), (prepared as described in Example 48), in a mixture of methylene chloride (5ml) and DMF (2ml) containing 10% palladium-on-charcoal (50mg) was treated with hydrogen at 1.8 atmospheres pressure for 2 hours. The suspension was filtered and the catalyst was washed with methanol followed by methylene chloride. The volatiles were removed from the filtrate by evaporation. The residue was triturated with water. The resulting solid was washed with water and dried under vacuum over phosphorus pentoxide at 60°C to give **7-hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline** (140mg, 89%).

MS - ESI: 322 [MH]+

^{1}H NMR Spectrum: ($DMSOd_6$) 2.4 (s, 3H); 4.0 (s, 3H); 6.15 (s, 1H); 6.9 (d, 1H); 7.2 (s, 1H); 7.25 (s, 1H); 7.3 (d, 1H); 7.6 (s, 1H); 8.4 (s, 1H)

Example 50

A suspension of 4-chloro-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline (150mg, 0.45mmol) and 5-hydroxy-2-trifluoromethylindole (109mg, 0.54mmol), (prepared as described for the starting material in Example 44), in DMF (1.5ml) containing potassium carbonate (94mg, 0.67mmol) was heated at 100°C for 1 hour. After cooling, the precipitate was collected by filtration, washed with ether, and dried under vacuum to give **6-methoxy-7-(3-methylsulphonylpropoxy)-4-(2-trifluoromethylindol-5-yloxy)quinazoline** (195mg, 87%).

MS - ESI: 496 $[MH]^+$

^1H NMR Spectrum: ($DMSOd_6$, CF_3COOD) 2.25-2.4 (m, 2H), 3.1 (s, 3H), 3.35 (t, 2H), 4.1 (s, 3H), 4.4 (t, 2H), 7.1 (s, 1H), 7.3 (d, 1H), 7.5 (s, 1H), 7.6 (d, 1H), 7.7 (s, 1H), 7.78 (s, 1H), 8.9 (s, 1H)

The starting material was prepared as follows:

A solution of 3-(methylthio)-1-propanol (5.3g, 50mmol) in methanol (500ml) was added to a solution of OXONE, (trade mark of E.I. du Pont de Nemours & Co.,Inc), (30g) in water (150ml) and the mixture stirred at ambient temperature for 24 hours. The precipitated solid was removed by filtration and the methanol removed from the filtrate by evaporation. The aqueous residue was saturated with sodium chloride and extracted with methylene chloride (4x25ml). The aqueous residue was then saturated with ammonium chloride and extracted with ethyl acetate (4x25ml). The extracts were combined, dried ($MgSO_4$) and the solvent removed by evaporation to give 3-(methylsulphonyl)-1-propanol (610mg, 9%) as an oil.

^1H NMR Spectrum: ($CDCl_3$) 2.10(m, 2H); 2.96(s, 3H); 3.20(t, 2H); 3.80(t, 2H)

MS - ESI: 139 $[MH]^+$

Alternatively the 3-(methylsulphonyl)-1-propanol may be prepared as follows:

m-Chloroperoxybenzoic acid (67%, 25 g, 97.2 mmol) was added in portions to 3-(methylthio)-1-propanol (5 ml, 48.6 mmol) in solution in dichloromethane. Some m-chlorobenzoic acid precipitated out and was removed by filtration. The filtrate was evaporated and the residue was purified over alumina using first dichloromethane (100%) then dichloromethane/methanol (95/5) to give 3-(methylsulphonyl)-1-propanol (4.18 g, 62%) as an oil.

Triphenylphosphine (8.9g, 35.2mmol) was added to a suspension of 7-hydroxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (6g, 19.6mmol), (prepared as described for the starting material in Example 12), in methylene chloride (150ml). This was followed by the addition of 3-(methylsulphonyl)-1-propanol (3.5g, 25.4mmol) and diethyl azodicarboxylate (5.55ml, 35.2mmol) in portions. The reaction was complete once the reaction became homogeneous. Silica was added and the volatiles were removed by evaporation. The free flowing powder was placed on the top of a flash chromatography column pre-equilibrated with ethyl acetate (100%). Elution was done using ethyl acetate (100%) followed by methylene chloride/ethyl acetate/methanol (60/35/5). The volatiles were removed by evaporation to give 6-methoxy-7-(3-methylsulphonylpropoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (7.58 g, 91%) as a white solid.

^{1}H NMR Spectrum: ($CDCl_3$) 1.2(s, 9H); 2.4-2.5(m, 2H); 3.0(s, 3H); 3.25-3.35(t, 2H); 5.95(s, 1H); 7.1(s, 1H); 7.65(s, 1H); 8.2(s, 1H)

6-Methoxy-7-(3-methylsulphonylpropoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (7g, 17mmol) was suspended in methanol and 2M sodium hydroxide (3.3ml, 6.6mmol) was added with continuous stirring. The reaction mixture became homogeneous after 15 minutes. After a further 45 minutes water was added (7ml) and the reaction mixture was adjusted to pH10 with 2M hydrochloric acid. The precipitate (a white solid) was collected by filtration, washed with water and dried over phosphorus pentoxide under vacuum to give 6-methoxy-7-(3-methylsulphonylpropoxy)-3,4-dihydroquinazolin-4-one (5 g, 90%).

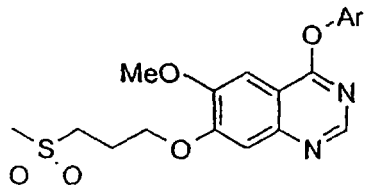
^{1}H NMR Spectrum: ($DMSOd_6$) 2.2-2.3(m, 2H); 3.05(s, 3H); 3.35(t, 2H); 3.9(s, 3H); 4.25(t, 2H); 7.15(s, 1H); 7.5(s, 1H); 8.0(s, 1H)

6-Methoxy-7-(3-methylsulphonylpropoxy)-3,4-dihydroquinazolin-4-one (3.6g, 11.5mmol) was suspended in thionyl chloride (40ml). DMF (1.8ml) was added under argon and the mixture was heated at reflux for 1.5 hours. The thionyl chloride was eliminated by several azeotropic distillations using toluene. The solid residue was suspended in ice/water and a saturated solution of sodium hydrogen carbonate was added to adjust the mixture to pH7. The solid was collected by filtration, washed with water and dried in a vacuum dessicator over phosphorus pentoxide to give 4-chloro-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline (3.35g, 88%).

Examples 51-52

Using an analogous procedure to that described in Example 50, 4-chloro-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline, (prepared as described for the starting material in Example 50), was reacted with the appropriate phenol to give the compounds described in Table III:

Table III



Example No.	Weight (mg)	Yield %	MS-ESI $[MH]^+$	Ar	Note
51	189	92	454	2-methylquinolin-7-yl	a
52	175	90	428	indol-5-yl	b

a) 4-Chloro-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline (150mg, 0.45mmol) was reacted with 7-hydroxy-2-methylquinoline (86.6mg, 0.54mmol), (J. Med. Chem. 1998, 41, 4062). After cooling, water was added and the precipitate was collected by filtration, washed with water, followed by ether and dried under vacuum to give **6-methoxy-7-(3-methylsulphonylpropoxy)-4-(2-methylquinolin-7-yloxy)quinazoline**.

^{1}H NMR Spectrum: ($DMSOd_6$, CF_3COOD) 2.2-2.35 (m, 2H), 2.95 (s, 3H), 3.1 (s, 3H), 3.35 (m, 2H), 4.05 (s, 3H), 4.4 (t, 2H), 7.5 (s, 1H), 7.7 (s, 1H), 7.95 (dd, 1H), 8.02 (d,; 1H), 8.2 (s, 1H), 8.48 (d, 1H), 8.7 (s, 1H), 9.12 (d, 1H)

b) Using an analogous procedure to that described in note a), 4-chloro-6-methoxy-7-(3-(methylsulphonyl)propoxy)quinazoline (150mg, 0.45mmol) was reacted with 5-hydroxyindole (72.4mg, 0.54mmol) to give **4-(indol-5-yloxy)-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline**.

^{1}H NMR Spectrum: ($DMSOd_6$) 2.2-2.35 (m, 2H), 3.1 (s, 3H), 3.3-3.4 (t, 2H), 4.0 (s, 3H), 4 4 (t, 2H), 6.5 (s, 1H), 7.0 (dd, 1H), 7.4 (s, 1H), 7.4-7.5 (m, 3H), 7.6 (s, 1H), 8.5 (s, 1H), 11.25

(s, 1H)

Example 53

0.5M Triphenylphosphine in methylene chloride and diisopropyl azodicarboxylate (150µl, 0.75mmol) were added in portions to a suspension of 7-hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (112mg, 0.35mmol), (prepared as described in Example 49), and N,N-dimethylethanolamine (62mg, 0.7mmol) in methylene chloride (2ml). After stirring for 2 hours at ambient temperature, the reaction mixture was poured onto an isolute® column (10g of silica) and eluted with ethyl acetate/methylene chloride (1/1) followed by methanol/ethyl acetate/methylene chloride (10/40/50), methanol/methylene chloride (10/90), and 3M ammonia in methanol/methanol/methylene chloride (5/15/80). After removal of the volatiles by evaporation, the residue was dissolved in the minimum amount of methylene chloride (about 3ml) and ether and petroleum ether (about 10ml) was added. The resulting precipitate was collected by filtration and dried under vacuum to give **7-(2-(N,N-dimethylamino)ethoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline** (52mg, 38%).

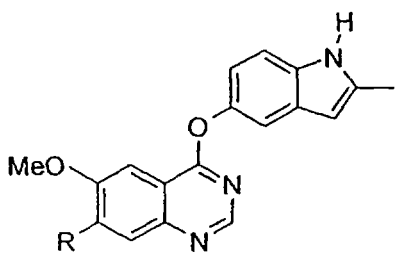
MS - ESI: 393 $[MH]^+$

^1H NMR Spectrum: ($DMSOd_6$) 2.25 (s, 6H), 2.4 (s, 3H), 2.75 (t, 2H), 4.0 (s, 3H), 4.3 (t, 2H), 6.15 (s, 1H), 6.87 (d, 1H), 7.25 (s, 1H), 7.3 (d, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 7.5 (s, 1H)

Examples 54-56

Using an analogous procedure to that described in Example 53, the appropriate alcohols were reacted with 7-hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline, (prepared as described in Example 49), in analogous proportions to give the compounds described in Table IV:

Table IV



Example	Weight	Yield	MS-ESI	R	Note

No.	(mg)	%	$[MH]^+$		
54	25	17	419	2-pyrrolidin-1-ylethoxy	a
55	112	74	433	1-methylpiperidin-3-ylmethoxy	b
56	115	72	456	2-(N-methyl-N-(4-pyridyl)amino)ethoxy	c

a) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline was reacted with 1-(2-hydroxyethyl)pyrrolidine (81mg) to give **6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-pyrrolidin-1-ylethoxy)quinazoline**.

^{1}H NMR Spectrum: ($DMSOd_6$) 1.65-1.8 (m, 4H), 2.4 (s, 3H), 2.6 (br s, 4H), 2.9 (t, 2H), 4.0 (s, 3H), 4.3 (t, 2H), 6.15 (s, 1H), 6.9 (d, 1H), 7.25 (s, 1H), 7.3 (d, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 8.5 (s, 1H)

b) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline was reacted with 1-methyl-3-piperidinemethanol (90mg) to give **6-methoxy-4-(2-methylindol-5-yloxy)-7-(1-methylpiperidin-3-ylmethoxy)quinazoline**.

^{1}H NMR Spectrum: ($DMSOd_6$) 1.45-2.2 (m, 7H), 2.18 (s, 3H), 2.4 (s, 3H), 2.6 (br d, 1H), 2.85 (br d, 1H), 4.0 (s, 3H), 4.1 (d, 2H), 6.15 (s, 1H), 6.9 (d, 1H), 7.25 (d, 1H), 7.3 (d, 1H), 7.35 (s, 1H), 7.6 (s, 1H), 8.5 (s, 1H)

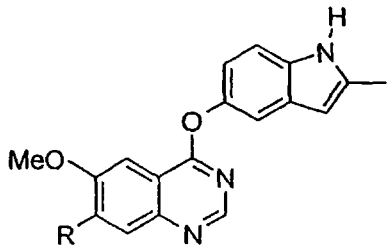
c) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline was reacted with 2-(N-methyl-N-(4-pyridyl)amino)ethanol (106mg), (EP 0359389), to give **6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(N-methyl-N-(4-pyridyl)amino)ethoxy)quinazoline**.

^{1}H NMR Spectrum: ($DMSOd_6$) 2.4 (s, 3H), 3.1 (s, 3H), 3.9 (t, 2H), 3.97 (s, 3H), 4.4 (t, 2H), 6.15 (s, 1H), 6.75 (d, 2H), 6.87 (dd, 1H), 7.25 (s, 1H), 7.3 (d, 1H), 7.35 (s, 1H), 7.6 (s, 1H), 8.15 (d, 2H), 8.5 (s, 1H)

Examples 57-66

Using an analogous procedure to that described in Example 53, except that ammonia in methanol was not necessary during the column chromatography, the appropriate alcohols were reacted with 7-hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline, (prepared as described in Example 49), in analogous proportions to give the compounds described in Table V:

Table V



Example No.	Weight (mg)	Yield %	MS-ESI [MH]$^+$	R	Note
57	115	76	435	2-morpholinoethoxy	a
58	64	42	433	2-piperidinoethoxy	b
59	66	43	437	2-(N-(2-methoxyethyl)-N-methylamino)ethoxy	c
60	118	75	449	3-morpholinopropoxy	d
61	101	68	424	2-(2-methoxyethoxy)ethoxy	e
62	81	57	407	3-(N,N-dimethylamino)propoxy	f
63	160	92	497	3-(1,1-dioxothiomorpholino)propoxy	g
64	121	83	417	2-(1*H*-1,2,4-triazol-1-yl)ethoxy	h
65	38	22	492	2-(2-(4-methylpiperazin-1-yl)ethoxy)ethoxy	i
66	80	48	479	2-(2-morpholinoethoxy)ethoxy	j

a) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline was reacted with 4-(2-hydroxyethyl)morpholine (92mg) to give **6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-morpholinoethoxy)quinazoline**.

^{1}H NMR Spectrum: ($DMSOd_6$) 2.4 (s, 3H), 2.5-2.7 (m, 4H), 2.8 (t, 2H), 3.6 (t, 4H), 4.0 (s, 3H), 4.35 (t, 2H), 6.15 (s, 1H), 6.87 (dd, 1H), 7.25 (s, 1H), 7.32 (d, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 8.5 (s, 1H)

b) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline was reacted with 1-(2-hydroxyethyl)piperidine (90mg) to give **6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-**

piperidinoethoxy)quinazoline.

^{1}H NMR Spectrum: ($DMSOd_6$) 1.3-1.45 (m, 2H), 1.4-1.6 (m, 4H), 2.4 (s, 3H), 2.4-2.5 (m, 4H), 2.75 (t, 2H), 3.97 (s, 3H), 4.3 (t, 2H), 6.15 (s, 1H), 6.9 (d, 1H), 7.25 (s, 1H), 7.3 (d, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 8.5 (s, 1H)

c) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline was reacted with 2-(N-(2-methoxyethyl)-N-methylamino)ethanol (93mg) to give **6-methoxy-7-(2-(N-(2-methoxyethyl)-N-methylamino)ethoxy)-4-(2-methylindol-5-yloxy)quinazoline.**

^{1}H NMR Spectrum: ($DMSOd_6$) 2.35 (s, 3H), 2.4 (s, 3H), 2.65 (t, 2H), 2.85 (t, 2H), 3.25 (s, 3H), 3.45 (t, 2H), 3.97 (s, 3H), 4.25 (t, 2H), 6.15 (s, 1H), 6.9 (dd, 1H), 7.25 (s, 1H), 7.32 (d, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 8.5 (s, 1H)

The starting material was prepared as follows:

A mixture of 2-(methylamino)ethanol (5.4g, 72 mmol), 2-bromoethyl methyl ether (10g, 72 mmol) and triethylamine (10ml, 72 mmol) in acetonitrile (70ml) was refluxed overnight. After cooling, the solid was filtered and the filtrate was evaporated. The residue was triturated with ether. The ether layer was separated and evaporated to give 2-(N-(2-methoxyethyl)-N-methylamino)ethanol (3g, 31%).

MS-EI : 134 [MH]+

^{1}H NMR Spectrum: ($CDCl_3$) 2.35 (s, 3H) ; 2.6 (t, 2H) ; 2.65 (t, 2H) ; 3.35 (s, 3H) ; 3.5 (t, 2H) ; 3.6 (t, 2H)

d) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline was reacted with 4-(3-hydroxypropyl)morpholine (102mg) to give **6-methoxy-4-(2-methylindol-5-yloxy)-7-(3-morpholinopropoxy)quinazoline.**

^{1}H NMR Spectrum: ($DMSOd_6$) 1.9-2.1 (m, 2H), 2.4 (s, 3H), 2.45 (t, 2H), 2.45-2.6 (s, 4H), 3.6 (t, 4H), 4.0 (s, 3H), 4.25 (t, 2H), 6.15 (s, 1H), 6.9 (d, 1H), 7.25 (s, 1H), 7.3 (d, 1H), 7.38 (s, 1H), 7.6 (s, 1H), 8.5 (s, 1H)

The starting material was prepared as follows:

Morpholine (94g, 1.08mol) was added dropwise to a solution of 3-bromo-1-propanol (75g, 0.54mol) in toluene (750ml) and the reaction then heated at 80°C for 4 hours. The

mixture was allowed to cool to ambient temperature and the precipitated solid was removed by filtration. The volatiles were removed from the filtrate and the resulting yellow oil was purified by distillation at 0.4-0.7 mmHg to give 4-(3-hydroxypropyl)morpholine (40g, 50%) as a colourless oil.

b.p. 68-70°C (~0.5mmHg)

^{1}H NMR Spectrum: ($DMSOd_6$) 1.65-1.78(m, 2H); 2.50(t, 4H); 2.60(t, 2H); 3.68(t, 4H); 3.78(t, 2H); 4.90(br d, 1H)

e) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline was reacted with 2-(2-methoxyethoxy)ethanol (84mg) to give **6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)-4-(2-methylindol-5-yloxy)quinazoline**.

^{1}H NMR Spectrum: ($DMSOd_6$) 2.42 (s, 3H), 3.27 (s, 3H), 3.5 (t, 2H), 3.65 (t, 2H), 3.85 (t, 2H), 4.0 (s, 3H), 4.32 (t, 2H), 6.15 (s, 1H), 6.9 (d, 1H), 7.3 (s, 1H), 7.35 (d, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 8.5 (s, 1H)

f) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline was reacted with 3-(N,N-dimethylamino)propanol (72mg) to give **7-(3-N,N-dimethylaminopropoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline**.

^{1}H NMR Spectrum: ($DMSOd_6$) 1.9-2.0 (m, 2H), 2.17 (s, 6H), 2.4 (s, 3H), 3.98 (s, 3H), 4.22 (t, 2H), 6.14 (s, 1H), 6.88 (dd, 1H), 7.25 (s, 1H), 7.3 (d, 1H), 7.35 (s, 1H), 7.6 (s, 1H), 8.47 (s, 1H)

g) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline was reacted with 3-(1,1-dioxothiomorpholino)-1-propanol (135mg), (prepared as described for the starting material in Example 5), to give **7-(3-(1,1-dioxothiomorpholino)propoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline**.

^{1}H NMR Spectrum: ($DMSOd_6$) 1.9-2.0 (m, 2H), 2.38 (s, 3H), 2.65 (t, 2H), 2.9 (br s, 4H), 3.1 (br s, 4H), 3.96 (s, 3H), 4.25 (t, 2H), 6.12 (s, 1H), 6.85 (dd, 1H), 7.25 (s, 1H), 7.3 (d, 1H), 7.37 (s, 1H), 7.56 (s, 1H), 8.46 (s, 1H)

h) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline was reacted with 2-(1*H*-1,2,4-triazol-1-yl)ethanol (79mg), (Ann. Phar. Fr. 1977, 35, 503-508), to give **6-methoxy-4-**

(2-methylindol-5-yloxy)-7-(2-(1*H*-1,2,4-triazol-1-yl)ethoxy)quinazoline.

^{1}H NMR Spectrum: ($DMSOd_6$) 2.42 (s, 3H), 3.96 (s, 3H), 4.62 (m, 2H), 4.75 (m, 2H), 6.15 (s, 1H), 6.9 (dd, 1H), 7.27 (s, 1H), 7.32 (d, 1H), 7.47 (s, 1H), 7.63 (s, 1H), 8.03 (s, 1H), 8.51 (s, 1H), 8.60 (s, 1H)

i) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline was reacted with 2-(2-(4-methylpiperazin-1-yl)ethoxy)ethanol (132mg), (Arzneim. Forsch. 1966, 16, 1557-1560), to give **6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(2-(4-methylpiperazin-1-yl)ethoxy)ethoxy)quinazoline.**

^{1}H NMR Spectrum: ($DMSOd_6$) 2.15 (s, 3H), 2.2-2.6 (m, 10H), 2.4 (s, 3H), 3.65 (t, 2H), 3.85 (t, 2H), 4.03 (s, 3H), 4.35 (m, 2H), 6.16 (s, 1H), 6.9 (dd, 1H), 7.3 (s, 1H), 7.35 (d, 1H), 7.4 (s, 1H), 7.61 (s, 1H), 8.5 (s, 1H)

j) 7-Hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline was reacted with 2-(2-morpholinoethoxy)ethanol (123mg) to give **6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(2-morpholinoethoxy)ethoxy)quinazoline.**

^{1}H NMR Spectrum: ($DMSOd_6$) 2.40 (s, 3H), 2.4-2.5 (m, 4H), 2.4-2.6 (m, 2H), 3.55 (t, 4H), 3.6 (t, 2H), 3.85 (t, 2H), 3.97 (br s, 3H), 4.15 (br s, 2H), 6.15 (s, 1H), 6.9 (d, 1H), 7.25 (s, 1H), 7.3 (d, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 8.48 (s, 1H)

The starting material was prepared as follows:

2-(2-Chloroethoxy)ethanol (1.25g, 10mmol) was added to a mixture of morpholine (2.58g, 30mmol) and potassium carbonate (5.5g, 40mmol) in acetonitrile (50ml). The mixture was heated at reflux for 6 hours and then stirred for 18 hours at ambient temperature. The insolubles were removed by filtration and the volatiles were removed from the filtrate by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol (95/5 followed by 90/10 and then 80/20) to give 2-(2-morpholinoethoxy)ethanol (600mg, 34%).

MS - (EI): 175 $[M.]^+$

^{1}H NMR Spectrum: ($CDCl_3$) 2.5(br s, 4H); 2.59(t, 2H); 3.6-3.85(m, 10H)

Example 67

A solution of 4-chloro-6-methoxy-7-(3-piperidinopropoxy)quinazoline (100mg, 0.29mmol), 5-hydroxy-2-methylindole (53mg, 0.36mmol), (prepared as described for the starting material in Example 48), and potassium carbonate (62mg, 0.44mmol) in DMF (2ml) was heated at 85°C for 3 hours, followed by heating at 95°C for 2 hours. After cooling, ice/water (15ml) was added and the precipitate was collected by filtration and dried under vacuum. The solid was purified by column chromatography eluting with methylene chloride/methanol (95/5) followed by methylene chloride/methanol/3M ammonia in methanol (95/3/2) to give **6-methoxy-4-(2-methylindol-5-yloxy)-7-(3-piperidinopropoxy)quinazoline** (71mg, 54%).

MS - ESI: 447 $[MH]^+$

^1H NMR Spectrum: ($DMSOd_6$) 1.35-1.4 (m, 2H), 1.45-1.55 (m, 4H), 1.92-2.0 (m, 2H), 2.3-2.4 (m, 4H), 2.40 (s, 3H), 2.4-2.5 (m, 2H), 3.97 (s, 3H), 4.22 (t, 2H), 6.15 (s, 1H), 6.9 (d, 1H), 7.27 (s, 1H), 7.8 (d, 1H), 7.35 (s, 1H), 7.58 (s, 1H), 8.48 (s, 1H)

The starting material was prepared as follows:

Diethyl azodicarboxylate (3.9ml, 24.5mmol) was added in portions to a suspension of 7-hydroxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (5g, 16.3mmol), (prepared as described for the starting material in Example 12), 3-bromo-1-propanol (2.21ml, 24.5mmol) and triphenylphosphine (6.42g, 24.5mmol) in methylene chloride (50ml). 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 followed by methylene chloride/methanol (95/5) to give 7-(3-bromopropoxy)-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (6g, 86%).

MS - ESI: 427-429 $[MH]^+$

^1H NMR Spectrum: ($DMSOd_6$) 1.12 (s, 9H), 2.32 (t, 2H), 3.7 (t, 2H), 3.9 (s, 3H), 4.25 (t, 2H), 5.9 (s, 2H), 7.20 (s, 1H), 7.51 (s, 1H), 8.36 (s, 1H)

Elemental analysis:	Found	C 50.1 H 5.4 N 6.4
$C_{18}H_{23}BrN_2O_5$ $0.2H_2O$	Requires	C 50.2 H 5.5 N 6.5%

A solution of 7-(3-bromopropoxy)-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (2.89g, 6.78mmol) in piperidine (10ml) was heated at 100°C for 1 hour. After cooling, the volatiles were removed under vacuum. The residue was dissolved in methylene chloride, and washed with saturated ammonium chloride and brine. The organic

layer was dried ($MgSO_4$) and the volatiles were removed by evaporation. The residue was dried under vacuum to give 6-methoxy-7-(3-piperidinopropoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (2.4g, 83%).

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

^1H NMR Spectrum: ($DMSOd_6$) 1.15 (s, 9H), 1.35-1.5 (m, 1H), 1.6-1.8 (m, 3H), 1.8-1.9 (d, 2H), 2.2-2.3 (m, 2H), 2.95 (t, 2H), 3.25 (t, 2H), 3.55 (d, 2H), 3.95 (s, 3H), 4.25 (t, 2H), 5.94 (s, 2H), 7.24 (s, 1H), 7.56 (s, 1H), 8.46 (s, 1H)

A solution of 6-methoxy-7-(3-piperidinopropoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (2.35g, 5.45mmol) in 7M ammonia in methanol (50ml) was stirred overnight at ambient temperature. The volatiles were removed under vacuum and the residue was triturated with ether, filtered and washed with ether followed by ether/methylene chloride (1/1) and dried under vacuum to give 6-methoxy-7-(3-piperidinopropoxy)-3,4-dihydroquinazolin-4-one (1.65g, 95%).

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

^1H NMR Spectrum: ($DMSOd_6$) 1.3-1.4 (m, 2H), 1.4-1.55 (m, 4H), 1.85-1.95 (m, 2H), 2.35 (br s, 4H), 2.4 (t, 2H), 3.9 (s, 3H), 4.15 (t, 2H), 7.11 (s, 1H), 7.44 (s, 1H), 7.9 (s, 1H)

Elemental analysis:	Found	C 63.5 H 7.4 N 13.1
$C_{17}H_{23}N_3O_3$ $0.2H_2O$	Requires	C 63.6 H 7.4 N 13.0%

A solution of 6-methoxy-7-(3-piperidinopropoxy)-3,4-dihydroquinazolin-4-one (1.5g, 4.7mmol) in thionyl chloride (15ml) containing DMF (1.5ml) was heated at reflux for 3 hours. After cooling, the volatiles were removed under vacuum. The residue was azeotroped with toluene. The solid was partitioned between methylene chloride and sodium hydrogen carbonate. The aqueous layer was adjusted to pH10 with 6M aqueous sodium hydroxide. The organic layer was separated, washed with brine, dried ($MgSO_4$) and the volatiles were removed by evaporation. The residue was purified by column chromatography to give 4-chloro-6-methoxy-7-(3-piperidinopropoxy)quinazoline (1.21g, 76%).

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

^1H NMR Spectrum: ($DMSOd_6$) 1.35-1.45 (m, 2H), 1.5-1.6 (m, 4H), 1.9-2.05 (m, 2H), 2.4 (br s, 4H), 2.45 (t, 2H), 4.0 (s, 3H), 4.29 (t, 2H), 7.41 (s, 1H), 7.46 (s, 1H), 8.9 (s, 1H)

Example 68

Using an analogous procedure to that described in Example 67, 4-chloro-6-methoxy-7-

(3-piperidinopropoxy)quinazoline (100mg), (prepared as described for the starting material in Example 67), was reacted with 5-hydroxyindole (48mg, 0.36mmol) to give **4-(indol-5-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline** (57mg, 45%).

MS - ESI: 433 $[MH]^+$

^1H NMR Spectrum: ($DMSOd_6$) 1.4 (br s, 2H), 1.45-1.6 (br s, 4H), 1.9-2.1 (m, 2H), 2.4 (br s, 4H), 2.45 (t, 2H), 4.0 (s, 3H), 4.25 (t, 2H), 6.47 (s, 1H), 7.0 (d, 1H), 7.35 (s, 1H), 7.45 (s, 2H), 7.47 (d, 1H), 7.61 (s, 1H), 8.49 (s, 1H)

Example 69

A solution of 7-hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (161mg, 0.5mmol), (prepared as described in Example 49), 4-(4-methylphenylsulphonyloxymethyl)-1-tert-butoxycarbonylpiperidine (222mg, 0.6mmol), (prepared as described for the starting material in Example 10), and potassium carbonate (188mg, 1mol) in DMF (1.6ml) was heated at 100°C for 2 hours. After cooling, water was added. The precipitate was collected by filtration, washed with water, and dried under vacuum over phosphorus pentoxide at 60°C. The solid was triturated with petroleum ether, collected by filtration, washed with a mixture of ether/petroleum ether (1/1) and dried under vacuum to give **6-methoxy-4-(2-methylindol-5-yloxy)-7-(1-*tert*-butoxycarbonylpiperidin-4-ylmethoxy)quinazoline** (200mg, 77%).

MS - ESI: 541 $[MNa]^+$

^1H NMR Spectrum: ($DMSOd_6$) 1.1-1.3 (m, 2H), 1.4 (s, 9H), 1.8 (d, 2H), 1.95-2.1 (m, 1H), 2.4 (s, 1H), 2.7-2.85 (br s, 2H), 3.95 (s, 3H), 4.05 (d, 2H), 6.12 (s, 1H), 6.85 (d, 1H), 7.25 (s, 1H), 7.3 (d, 1H), 7.35 (s, 1H), 7.55 (s, 1H), 8.45 (s, 1H)

Example 70

A solution of 6-methoxy-4-(2-methylindol-5-yloxy)-7-(1-*tert*-butoxycarbonylpiperidin-4-ylmethoxy)quinazoline (155mg, 0.3mmol), (prepared as described in Example 69), in methylene chloride (5ml) containing TFA (1ml) was stirred at ambient temperature for 30 minutes. The volatiles were removed under vacuum and the residue was treated with water and adjusted to pH12 with 2M sodium hydroxide. The mixture was extracted with methylene chloride. The organic layer was dried ($MgSO_4$), and the volatiles were removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/ethyl acetate/methanol (5/4/1) followed by methylene

chloride/methanol (9/1) and by 3M ammonia in methanol/methanol/methylene chloride (5/15/80). After removal of the solvent by evaporation, the residue was dissolved in the minimum of methylene chloride, ether was added followed by petroleum ether. The precipitate was collected by filtration, washed with ether and dried under vacuum to give **6-methoxy-4-(2-methylindol-5-yloxy)-7-(piperidin-4-ylmethoxy)quinazoline** (120mg, 96%).

MS - ESI: 419 $[MH]^+$

^1H NMR Spectrum: ($DMSOd_6$, CF_3COOD) 1.5-1.7 (m, 2H), 2.05 (br d, 2H), 2.3-2.4 (m, 1H), 2.4 (s, 3H), 3.05 (t, 2H), 3.4 (d, 2H), 4.09 (s, 3H), 4.25 (d, 2H), 6.95 (dd, 1H), 7.35 (s, 1H), 7.4 (d, 1H), 7.6 (s, 1H), 7.85 (s, 1H), 9.15 (s, 1H)

Example 71

Methoxyacetaldehyde (368mg, 3.47mmol) (freshly distilled) followed by sodium triacetoxyborohydride (552mg, 2.6mmol) were added to a solution of 6-methoxy-4-(2-methylindol-5-yloxy)-7-(piperidin-4-ylmethoxy)quinazoline (726mg, 1.74mmol), (prepared as described in Example 70), in a mixture of methylene chloride (15ml) and methanol (15ml). After stirring for 1.5 hours at ambient temperature, saturated sodium hydrogen carbonate was added. The volatiles were removed under vacuum and the residue was partitioned between methylene chloride and water. The organic layer, was separated, washed with water, brine, dried ($MgSO_4$) and the volatiles were removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol (80/20). After removal of the solvent, the residue was triturated with ether, collected by filtration, washed with ether and dried under vacuum at 60°C to give **6-methoxy-7-(1-(2-methoxyethyl)piperidin-4-ylmethoxy)-4-(2-methylindol-5-yloxy)quinazoline** (392mg, 47%).

MS - ESI 477 $[MH]^+$

^1H NMR Spectrum: ($DMSOd_6$, CF_3COOD) 1.6-1.8 (m, 2H), 2.05 (br d, 2H), 2.15-2.3 (m, 1H), 2.4 (s, 3H), 3.05 (t, 2H), 3.3 (br s, 2H), 3.32 (s, 3H), 3.58 (d, 2H), 3.65 (br s, 2H), 4.05 (s, 3H), 4.18 (d, 2H), 6.2 (s, 0.5 H (partly exchanged)), 6.92 (dd, 1H), 7.32 (s, 1H), 7.35 (d, 1H), 7.55 (s, 1H), 7.8 (s, 1H), 9.15 (s, 1H)

Elemental analysis:	Found	C 68.0	H 6.8	N 11.8	
$C_{27}H_{32}N_4O_4$	Requires	C 68.1	H 6.8	N 11.8%	

The starting material was prepared as follows :

A solution of 1,1,2-trimethoxyethane (90g, 750mmol) in water (570ml) containing 12 N hydrochloric acid (3.75ml) was stirred at 40°C for 1.5 hours. After cooling, solid sodium chloride was added and the mixture was extracted with ether. The organic layer was dried ($MgSO_4$). The organic layer was distilled and the fraction from 70-90°C was collected to give methoxyacetaldehyde (20.3g) which was used directly in the next step.

Example 72

Diphenylphosphoryl azide (83mg, 0.3mmol) was added in portions to a solution of 7-(2-carboxyvinyl)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (75mg, 0.2mmol), triethylamine (40mg, 0.4mmol) and 1-(2-aminoethyl)pyrrolidine (46mg, 0.4mmol) in DMF (1.5ml). After stirring for 5 hours at ambient temperature, the mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and the volatiles were removed by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol (9/1) followed by methylene chloride/3M ammonia in methanol (9/1). After removal of the solvent, the solid was triturated with ether, collected by filtration, washed with ether and dried under vacuum to give **6-methoxy-4-(2-methylindol-5-yloxy)-7-((2-(2-pyrrolidin-1-ylethyl)carbamoyl)vinyl)quinazoline** (25mg, 26%).

MS - ESI: 472 $[MH]^+$

^1H NMR Spectrum: ($DMSOd_6$, CF_3COOD) 1.8-1.95 (m, 2H), 1.95-2.1 (m, 2H), 2.48 (s, 3H), 3.0-3.2 (m, 2H), 3.35 (t, 2H), 3.6 (t, 2H), 3.65 (br s, 2H), 4.11 (s, 3H), 6.18 (s, 0.5H, partially exchanged), 6.95 (dd, 1H), 7.05 (d, 1H), 7.35 (s, 1H), 7.37 (d, 1H), 7.8 (s, 1H), 7.86 (d, 1H), 8.2 (s, 1H), 8.76 (s, 1H)

The starting material was prepared as follows:

Trifluoromethanesulphonic anhydride (338mg, 1.2mmol) was added to a suspension of 4-(4-chloro-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline (320mg, 1mmol), (prepared as described for the starting material in Example 5), in methylene chloride (2ml) containing pyridine (2ml) cooled at 5°C. When the addition was complete, the mixture was left to warm to ambient temperature and stirred for 1 hour. After removal of the volatiles by evaporation, the residue was partitioned between ethyl acetate/ether and water. The organic layer was separated, washed with 0.5M hydrochloric acid, followed by water, brine, dried

($MgSO_4$) and evaporated to give 4-(4-chloro-2-fluorophenoxy)-6-methoxy-7-(trifluoromethylsulphonyloxy)quinazoline (400mg, 88%).

MS - ESI: 453 - 455 $[MH]^+$

^1H NMR Spectrum: ($DMSOd_6$) 4.15 (s, 3H), 7.5 (d, 1H), 7.62 (t, 1H), 7.78 (d, 1H), 8.02 (s, 1H), 8.27 (s, 1H), 8.77 (s, 1H)

Triethylamine (33mg, 0.33mmol) and *tert*-butyl acrylate (77mg, 0.6mmol) followed by diphenylpropylphosphine (3.4mg, 0.008mmol) and palladium(II) acetate (1.7mg, 0.0075mmol) were added to a solution of 4-(4-chloro-2-fluorophenoxy)-6-methoxy-7-(trifluoromethylsulphonyloxy)quinazoline (136mg, 0.3mmol) in DMF (1.5ml) under argon. When the addition was complete the reaction flask was purged with argon. The mixture was stirred at 80-85°C for 6 hours. After cooling, the mixture was partitioned between ethyl acetate and water. The aqueous layer was adjusted to pH6 with 2M hydrochloric acid. The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography eluting with methylene chloride followed by methylene chloride/ether (95/5). After removal of the solvent under vacuum, the solid was triturated with pentane/ether, collected by filtration and dried under vacuum to give 4-(4-chloro-2-fluorophenoxy)-6-methoxy-7-(2-(tert-butoxycarbonyl)vinyl)quinazoline (63mg, 49%).

MS - ESI: 431 $[MH]^+$

^1H NMR Spectrum: ($DMSOd_6$) 1.51 (s, 9H), 4.07 (s, 3H), 6.87 (d, 1H), 7.45 (d, 1H), 7.6 (t, 1H), 7.7 (s, 1H), 7.75 (d, 1H), 7.91 (d, 1H), 8.39 (s, 1H), 8.65 (s, 1H)

Elemental analysis: Found C 61.1 H 4.8 N 6.6

$C_{22}H_{20}ClFN_2O_3$ Requires C 61.3 H 4.7 N 6.5%

A solution of 4-(4-chloro-2-fluorophenoxy)-6-methoxy-7-(2-(tert-butoxycarbonyl)vinyl)quinazoline (581mg, 1.31mmol) in a mixture of methylene chloride/TFA (2.5ml/2.5ml) was stirred at ambient temperature for 1.5 hours. After removal of the volatiles under vacuum, the residue was partitioned between ethyl acetate and water. The aqueous layer was adjusted to pH3 with 0.5M sodium hydroxide. The organic layer was separated and the aqueous layer was further extracted with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated to give 7-(2-carboxyvinyl)-4-(4-chloro-2-fluorophenoxy)-6-methoxyquinazoline (430mg, 85%).

^1H NMR Spectrum: ($DMSOd_6$) 4.08 (s, 3H), 6.9 (d, 1H), 7.45 (s, 1H), 7.6 (t, 1H), 7.70 (s,

1H), 7.73 (d, 1H), 7.95 (d, 1H), 8.39 (s, 1H), 8.66 (s, 1H)

1M Sodium HMDS in THF (0.84ml, 8.4mmol) was added to a suspension of 7-(2-carboxyvinyl)-4-(4-chloro-2-fluorophenoxy)-6-methoxyquinazoline (105mg, 0.28mmol) and 5-hydroxy-2methylindole (82mg, 0.56mmol), (prepared as described for the starting material in Example 48), in DMSO (1.5ml). After stirring for 2 hours at ambient temperature, the mixture was partitioned between ethyl acetate and water. The aqueous layer was adjusted to pH3 with 2M hydrochloric acid. The organic layer was washed with water, brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography eluting with methylene chloride/methanol (95/5 followed by 90/10 and 70/30) to give 7-(2-carboxyvinyl)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (75mg, 71%).

^{1}H NMR Spectrum: ($DMSOd_6$) 2.4 (s, 3H), 4.06 (s, 3H), 6.15 (s, 1H), 6.82 (d, 1H), 6.9 (dd, 1H), 7.3 (s, 1H), 7.35 (d, 1H), 7.68 (s, 1H), 7.84 (d, 1H), 8.25 (s, 1H), 8.55 (s, 1H)

Example 73

A suspension of 7-hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (321mg, 1mmol), (prepared as described in Example 49), 1-bromo-3-chloropropane (120µl, 1.2mmol) and potassium carbonate (359mg, 2.6mmol) in DMF (5ml) was stirred at ambient temperature overnight. After addition of water, the precipitate was collected by filtration, washed with water and dried over phosphorus pentoxide at 60°C to give **7-(3-chloropropoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline** (280mg, 70%).

MS - ESI: 398 $[MH]^+$

^{1}H NMR Spectrum: ($DMSOd_6$) 2.2-2.35 (m, 2H), 2.4 (s, 3H), 3.85 (t, 2H), 4.0 (s, 3H), 4.32 (t, 2H), 6.15 (s, 1H), 6.88 (d, 1H), 7.27 (s, 1H), 7.3 (d, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 8.5 (s, 1H)

Example 74

A solution of 7-(3-chloropropoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (150mg, 0.38mmol), (prepared as described in Example 73), in 1-methylpiperazine (2ml) was heated at 100°C for 2 hours. After cooling, the mixture was partitioned between ethyl acetate and aqueous 5% sodium hydrogen carbonate. The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on an isolute column eluting with methanol/ethyl acetate/methylene chloride (1/4/5 followed by 1/9/0) and 3M ammonia in methanol/methanol/methylene chloride

(5/10/80). After removal of the solvent under vacuum, the solid was dissolved in the minimum of methylene chloride and ether/petroleum ether was added. The precipitate was collected by filtration, and dried under vacuum to give **6-methoxy-4-(2-methylindol-5-yloxy)-7-(3-(4-methypiperazin-1-yl)propoxy)quinazoline** (55mg, 32%).

MS - ESI: 462 $[MH]^+$

^1H NMR Spectrum: ($DMSOd_6$, CF_3COOD, 60°C) 2.2-2.3 (m, 2H), 2.4 (s, 3H), 2.9 (s, 3H), 3.4-3.5 (m, 4H), 3.5-3.8 (m, 6H), 4.07 (s, 3H), 4.4 (t, 2H), 6.95 (d, 1H), 7.35 (s, 1H), 7.4 (d, 1H), 7.55 (s, 1H), 7.8 (s, 1H), 8.95 (s, 1H)

Example 75

Triphenylphosphine (262mg, 1mmol) and N,N-diethylethanolamine (88mg, 0.75mmol) were added to a suspension of 7-hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (160mg, 0.5mmol), (prepared as described in Example 49), in methylene chloride (5ml), followed by the addition, in portions, of diethyl azodicarboxylate (165µl, 1mmol). After stirring for 1 hour at ambient temperature, the volatiles were removed under vacuum. The residue was purified by column chromatography eluting with methylene chloride/methanol (95/5) followed by methylene chloride/3M ammonia in methanol (90/10) to give **7-(2-(N,N-diethylamino)ethoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline** (147mg, 70%).

MS - ESI 421 $[MH]^+$

^1H NMR Spectrum: ($DMSOd_6$) 1.0 (t, 6H), 2.41 (s, 3H), 2.6 (q, 4H), 2.88 (t, 2H), 3.97 (s, 3H), 4.24 (t, 2H), 6.14 (s, 1H), 6.89 (dd, 1H), 7.25 (s, 1H), 7.32 (d, 1H), 7.38 (s, 1H), 7.58 (s, 1H), 8.48 (s, 1H)

Elemental analysis:	Found	C 66.2 H 6.9 N 13.1
$C_{24}H_{28}N_4O_3$ $0.8H_2O$	Requires	C 66.3 H 6.9 N 12.9%

Example 76

Using an analogous procedure to that described in Example 75, 7-hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (321mg, 1mmol), (prepared as described in Example 49), was reacted with 2-((1-*tert*butoxycarbonyl)piperidin-4-yloxy)ethanol (294mg, 1.2mmol) to give **6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-((1-*tert*butoxycarbonyl)piperidin-4-yloxy)ethoxy)quinazoline** (420mg, 76%).

MS - ESI: 549 $[MH]^+$

^{1}H NMR Spectrum: ($DMSOd_6$) 1.4 (s, 9H), 1.3-1.5 (m, 2H), 1.7-1.9 (m, 2H), 2.38 (s, 3H), 3.0 (br t, 2H), 3.5-3.7 (m, 3H), 3.85 (m, 2H), 3.98 (s, 3H), 4.3 (t, 2H), 6.12 (s, 1H), 6.85 (d, 1H), 7.22 (s, 1H), 7.3 (d, 1H), 7.4 (s, 1H), 7.55 (s, 1H), 8.48 (s, 1H)

The starting material was prepared as follows:

tert-Butoxycarbonyl anhydride (1.52g, 7mmol) in acetone (3.5ml) was added to a solution of 4,4-(ethylenedioxy)piperidine (1g, 7mmol) in acetone/trichloromethane (3.5ml/3.5ml) cooled at 0°C. After stirring for 4 hours at ambient temperature, the volatiles were removed under vacuum. The residue was dissolved in ether and the ether solution was washed with water, brine, dried ($MgSO_4$) and evaporated to give 4,4-(ethylenedioxy)-1-*tert*butoxycarbonylpiperidine (1.7g, quant.).

^{1}H NMR Spectrum: ($CDCl_3$): 1.46 (s, 9H), 1.65 (t, 4H), 3.5 (t, 4H), 3.97 (s, 4H)

Freshly distilled boron trifluoride etherate (52µl, 0.41mmol), followed by sodium cyanoborohydride (38mg, 0.6mmol) were added to a solution of 4,4-(ethylenedioxy)-1-tertbutoxycarbonylpiperidine (100mg, 0.41mmol) in THF (1.4ml) cooled at 0°C. After stirring for 6 hours at ambient temperature, boron trifluoride etherate (52µl) and sodium cyanoborohydride (26mg, 0.41mmol) were added. After stirring overnight at ambient temperature, the mixture was partitioned between ethyl acetate and 2M sodium hydroxide. The organic layer was washed with water, brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography eluting with methylene chloride/methanol (95/5) followed by methylene chloride/methanol/3M ammonia in methanol (80/15/5) to give 2-((1-*tert*butoxycarbonyl)piperidin-4-yloxy)ethanol (42mg, 42%).

MS - ESI: 268 $[MNa]^+$

^{1}H NMR Spectrum: ($CDCl_3$) 1.48 (s, 9H), 1.5-1.6 (m, 2H), 1.8-1.9 (m, 2H), 2.0 (t, 1H), 3.05-3.15 (m, 2H), 3.5 (m, 1H), 3.57 (t, 2H), 3.7-3.9 (m, 4H)

Example 77

A solution of 6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-((1-*tert*butoxycarbonyl)piperidin-4-yloxy)ethoxy)quinazoline (379 mg, 0.69 mmol), (prepared as described in Example 76), in methylene chloride (7ml) containing TFA (2.5ml) was stirred for 1.5 hours at ambient temperature. After removal of the volatiles under vacuum, the residue

was partitioned between ethyl acetate and water. Solid sodium hydrogen carbonate and 2N sodium hydroxide were added to adjust the aqueous layer to about pH10. The organic layer was washed with water, followed by brine, dried ($MgSO_4$) and evaporated. The residue was triturated with ether, filtered, washed with ether and dried under vacuum to give **6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(piperidin-4-yloxy)ethoxy)quinazoline** (164 mg, 53 %).

^{1}HNMR Spectrum: ($DMSOd_6$) 1.2-1.4 (m, 2H), 1.8-1.9 (m, 2H), 2.47 (s, 3H), 2.4-2.5 (m, 2H), 2.9-3.0 (d, 2H), 3.3-3.5 (m, 1H), 3.95 (s, 2H), 4.0 (s, 3H), 4.35 (s, 2H), 6.15 (s, 1H), 6.9 (dd, 1H), 7.28 (s, 1H), 7.32 (d, 1H), 7.41 (s, 1H), 7.60 (s, 1H), 8.49 (s, 1H)

MS-ESI : 448 $[M.]^+$

Example 78

A solution of 7-hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (193 mg, 0.6 mmol), (prepared as described in Example 49), 4-(2-hydroxyethoxy)pyridine (166 mg, 1.2 mmol), (J. Chem. Soc. Perkin II, 1987, 1867), in methylene chloride (5 ml) containing triphenylphosphine (330 mg, 1.26 mmol) and diisopropyl azodicarboxylate (255 mg, 1.26 mmol) was stirred at ambient temperature for 2 hours. The precipitate was filtered, triturated with ether followed by ethyl acetate, and dried under vacuum to give **6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(4-pyridyloxy)ethoxy)quinazoline** (142 mg, 54 %).

^{1}HNMR Spectrum: ($DMSOd_6$) 2.40 (s, 3H), 3.97 (s, 3H), 4.52 (t, 2H), 4.58 (t, 2H), 6.14 (s, 1H), 6.89 (dd, 1H), 7.07 (d, 2H), 7.26 (s, 1H), 7.31 (d, 1H), 7.46 (s, 1H), 7.61 (s, 1H), 8.41 (d, 2H), 8.5 (s, 1H)

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

Elemental analysis	Found	C 66.6 H 5.0 N 12.5
$C_{25}H_{22}N_4O_4$ 0.12 CH_2Cl_2	Requires	C 66.9 H 5.0 N 12.4%

Example 79

A suspension of 6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(N-methyl-N-*tert*-butoxycarbonylamino)ethoxy)quinazoline (148 mg, 0.31 mmol), (prepared as described in Example 149), in methylene chloride (4 ml) containing TFA (1 ml) was stirred for 1 hour. After removing the volatiles under vacuum, the residue was azeotroped with toluene. The residue was dissolved in methylene chloride (3 ml) and triethylamine (215 µl, 1.5 mmol) was added followed by methanesulphonyl chloride (48 µl, 0.62 mmol). After stirring for 1 hour at

ambient temperature, the mixture was partitioned between methylene chloride 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 ethylacetate/methanol (99/1 followed by 97/3). After evaporation of the solvent, the solid was triturated with ether, filtered, washed with ether and dried under vacuum to give **6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(N-methyl-N-methylsulphonylamino)ethoxy)quinazoline** (54 mg, 38 %).

^{1}H NMR Spectrum: ($DMSOd_6$) 2.4 (s, 3H), 2.93 (s, 3H), 3.0 (s, 3H), 3.62 (t, 2H), 4.0 (s, 3H), 4.38 (t, 2H), 6.14 (s, 1H), 6.88 (dd, 1H), 7.26 (s, 1H), 7.3 (d, 1H), 7.43 (s, 1H), 7.61 (s, 1H), 8.49 (s, 1H)

MS-ESI : 457 $[MH]^+$

Example 80

A solution of 6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(piperidin-4-yloxy)ethoxy)quinazoline (76 mg, 0.17 mmol), (prepared as described in Example 77), in acrylonitrile (0.5 ml), methylene chloride (1 ml) and methanol (1 ml) was stirred overnight at ambient temperature. After removal of the volatiles under vacuum the residue was purified by column chromatography eluting with methylene chloride/methanol (98/2 followed by 95/5 and 90/10). The residue was triturated with ethyl acetate and ether. The resulting solid was filtered and dried under vacuum to give **7-(2-(1-(2-cyanoethyl)piperidin-4-yloxy)ethoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline** (73 mg, 86 %).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.4-1.55 (m, 2H), 1.8-1.9 (m, 2H), 2.15 (t, 2H), 2.4 (s, 3H), 2.55 (t, 2H), 2.65 (t, 2H), 2.7-2.8 (m, 2H), 3.4-3.5 (m, 1H), 3.85 (m, 2H), 4.0 (s, 3H), 4.3 (t, 2H), 6.15 (s, 1H), 6.9 (dd, 1H), 7.25 (s, 1H), 7.3 (d, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 8.5 (s, 1H)

MS-ESI : 502 $[MH]^+$

Elemental analysis	Found	C 67.0	H 6.2 N 14.0
$C_{28}H_{31}N_5O_4$	Requires	C 67.1	H 6.2 N 14.0%

Example 81

A solution of 4-chloro-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (100 mg, 0.31 mmol), (prepared as described for the starting material in Example 9), 6-hydroxyindole (50 mg, 0.37 mmol) and potassium carbonate (64 mg, 0.466 mmol) in DMF (1 ml) was heated at 95°C for 4 hours. After cooling, the mixture was diluted with methylene chloride and

poured onto a silica column. The product was eluted with methylene chloride, followed by methylene chloride/methanol (80/20 followed by 70/30 and 50/50). After removal of the solvent by evaporation, the precipitate was triturated with ether, filtered and dried under vacuum to give **6-methoxy-4-(indol-6-yloxy)-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline** (90 mg, 69 %).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.85 (br s, 4H), 2.15-2.25 (m, 2H), 2.85-3.15 (m, 6H), 4.01 (s, 3H), 4.32 (t, 2H), 6.5 (s, 1H), 6.95 (dd, 1H), 7.32 (s, 1H), 7.4 (s, 2H), 7.6 (d, 1H), 7.65 (s, 1H), 8.52 (s, 1H)

MS-ESI : 419 $[MH]^+$

Example 82

Diisopropyl azodicarboxylate (146 mg, 0.72 mmol) was added to a solution of 7-hydroxy-4-(2-methylindol-5-yloxy)quinazoline (100 mg, 0.34 mmol), triphenyl phosphine (189 mg, 0.72 mol), and 3-pyrrolidinopropan-1-ol (89 mg, 0.686 mmol), (J. Org. Chem. 1988, 53, 3164), in methylene chloride (2.5 ml). After stirring overnight at ambient temperature, the solid was filtered. The filtrate was purified by column chromatography eluting with ethyl acetate/methylene chloride (1/1) followed by ethyl acetate/methylene chloride/methanol (4/5/1), methylene chloride/methanol (9/1) and 3N ammonia in methanol/methylene chloride (1/9). After removal of the solvent, the residue was triturated with ether, filtered, and dried under vacuum to give **4-(2-methylindol-5-yloxy)-7-(3-(pyrrolidin-yl)propoxy)quinazoline** (49 mg, 35 %).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.8-2.0 (m, 2H), 2.0-2.15 (m, 2H), 2.2-2.32 (m, 2H), 2.41 (s, 3H), 3.0-3.2 (m, 2H), 3.4 (t, 2H), 3.6-3.7 (m, 2H), 4.35 (t, 2H), 6.2 (s, 1H), 6.95 (dd, 1H), 7.3 (s, 1H), 7.35 (d, 1H), 7.5 (s, 1H), 7.57 (dd, 1H), 8.5 (d, 1H), 9.15 (s, 1H)

MS-ESI : 403 $[MH]^+$

The starting material was prepared as follows:

Sodium (368mg, 16mmol) was added to benzyl alcohol (10ml, 96mmol) and the mixture was heated at 148°C for 30 minutes. 7-Fluoro-3,4-dihydroquinazolin-4-one (656mg, 4mmol), (J. Chem. Soc. section B 1967, 449), was added and the mixture maintained at 148°C for 24 hours. The reaction mixture was allowed to cool, the solution was poured on to water (170ml) and the aqueous mixture adjusted to pH3 with concentrated hydrochloric acid. The

precipitate was collected by filtration, washed with water, ether and dried under vacuum to give 7-benzyloxy-3,4-dihydroquinazolin-4-one (890mg, 89%) as a white solid.

m.p. 267-269°C

^{1}H NMR Spectrum: (DMSOd_6; CF_3COOD) 5.32(s, 2H); 7.25(d, 1H); 7.32-7.52(m, 6H); 8.12(d, 1H); 8.99(s, 1H)

MS - ESI: 252 $[MH]^+$

Elemental analysis:	Found	C 71.4	H 4.9	N 10.7
$C_{15}H_{12}N_2O_2$ 0.04H_2O	Requires	C 71.2	H 4.8	N 11.1%

A mixture of 7-benzyloxy-3,4-dihydroquinazolin-4-one (11g, 43.6mmol) and DMF (1ml) in thionyl chloride (100ml) was heated at reflux for 1.5 hours. Excess thionyl chloride was removed by evaporation and the residue azeotroped with toluene. The residue was partitioned between methylene chloride and water and saturated aqueous sodium hydrogen carbonate was added until the aqueous layer was at about pH9. The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and evaporated to give 7-benzyloxy-4-chloroquinazoline (10.5g, 89%).

^{1}H NMR Spectrum: (DMSOd_6) 5.4 (s, 2H); 7.35-7.65 (m, 6H); 8.2 (d, 1H); 9.0 (s, 1H)

MS - ESI: 270 $[MH]^+$

A solution of 7-benzyloxy-4-chloroquinazoline (2g, 7.4mmol), 5-hydroxy-2-methylindole (1.3 g, 8.9 mmol), (prepared as described for the starting material in Example 48), in DMF (20 ml) containing potassium carbonate (1.53 g, 11.1 mmol) was stirred at 80°C for 3 hours. After cooling, the mixture was poured in portions into ice/water. The precipitate was filtered and washed with water and dried under vacuum. The solid was dissolved in methylene chloride and was purified by column chromatography eluting with ethyl acetate and methylene chloride (1/1) to give 7-benzyloxy-4-(2-methylindol-5-yloxy)quinazoline (2.28 g, 81 %).

MS-ESI : 382 $[MH]^+$.

^{1}H NMR Spectrum: (DMSOd_6) 2.41 (s, 3H), 5.4 (s, 2H), 6.15 (s, 1H), 6.9 (dd, 1H), 7.3 (s, 1H), 7.35 (d, 1H), 7.4 (d, 1H), 7.4-7.5 (m, 4H), 7.55 (d, 2H), 8.32 (d, 1H), 8.6 (s, 1H).

10% Palladium on charcoal (200 mg) followed by ammonium formate (4.34 g, 69 mmol) were added to a solution of 7-benzyloxy-4-(2-methylindol-5-yloxy)quinazoline (1.75 g, 4.58 mmol) in DMF (60 ml). After stirring for 1 hour at ambient temperature, the mixture

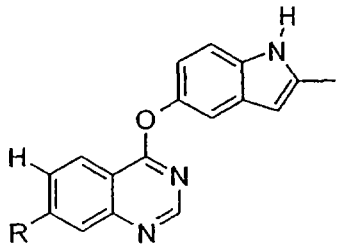
was filtered. The filtrate was evaporated. The residue was triturated with water, filtered, washed with ethyl acetate, and dried under vacuum to give 7-hydroxy-4-(2-methylindol-5-yloxy)quinazoline (1.24 g, 93 %).

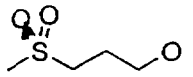
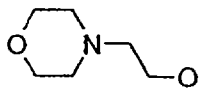
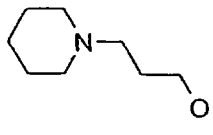
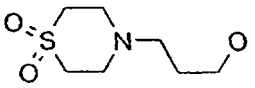
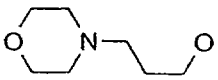
^{1}H NMR Spectrum: ($DMSOd_6$) 2.4 (s, 3H), 6.14 (s, 1H), 6.88 (dd, 1H), 7.17 (s, 1H), 7.25-7.3 (m, 2H), 7.30 (d, 1H), 8.24 (d, 1H), 8.5 (s, 1H)

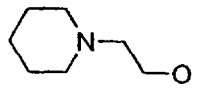
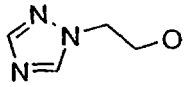
Examples 83-89

Using an analogous procedure to that described in Example 82, the appropriate alcohols were reacted with 7-hydroxy-4-(2-methylindol-5-yloxy)quinazoline, (prepared as described for the starting material in Example 82), to give the compounds described in Table VI below.

Table VI



Example number	Weight (mg)	Yield %	MS-ESI $[MH]^+$	R	Note
83	34	24	412		a
84	45	32	405		b
85	5	3	417		c
86	56	35	467		d
87	63	44	419		e

88	24	17	403		f
89	84	63	387		g

a) 7-Hydroxy-4-(2-methylindol-5-yloxy)quinazoline (100 mg) was reacted with 3-(methylsulphonyl)-1-propanol (95 mg), (prepared as described for the starting material in Example 50), to give **7-(3-(methylsulphonyl)propoxy)-4-(2-methylindol-5-yloxy)quinazoline.**

^{1}H NMR Spectrum: (DMSOd_6, CF_3COOD) 2.2-2.3 (m, 2H), 2.4 (s, 3H), 3.05 (s, 3H), 3.3-3.45 (m, 2H), 4.4 (t, 2H), 6.2 (s, 1H), 6.95 (dd, 1H), 7.38 (s, 1H), 7.4 (d, 1H), 7.5 (s, 1H), 7.6 (dd, 1H), 8.5 (d, 1H), 9.2 (s, 1H)

Elemental analysis Found C 60.2 H 5.3 N 10.6

$C_{21}H_{21}N_3O_4S$ 0.4 DMF Requires C 60.5 H 5.4 N 10.8%

b) 7-Hydroxy-4-(2-methylindol-5-yloxy)quinazoline (100 mg) was reacted with 4-(2-hydroxyethyl)morpholine (90 mg) to give **4-(2-methylindol-5-yloxy)-7-(2-morpholinoethoxy)quinazoline.**

^{1}H NMR Spectrum: (DMSOd_6, CF_3COOD) 2.4 (s, 3H), 3.1-3.3 (m, 2H), 3.62 (d, 2H), 3.7-3.9 (m, 4H), 4.05 (d, 2H), 4.7 (t, 2H), 6.2 (s, 0.5 H, partially exchanged), 6.95 (dd, 1H), 7.35 (s, 1H), 7.39 (d, 1H), 7.6 (s, 1H), 7.65 (dd, 1H), 8.55 (d, 1H), 9.15 (s, 1H)

Elemental analysis Found C 67.2 H 6.0 N 13.5

$C_{23}H_{24}N_4O_3$ 0.3 H_2O Requires C 67.4 H 6.1 N 13.7%

c) 7-Hydroxy-4-(2-methylindol-5-yloxy)quinazoline (100 mg) was reacted with 1-(3-hydroxypropyl)piperidine (98 mg) to give **4-(2-methylindol-5-yloxy)-7-(3-(piperidin-1-yl)propoxy)quinazoline.**

^{1}H NMR Spectrum: (DMSOd_6, CF_3COOD) 1.2-1.5 (m, 2H), 1.6-1.8 (m, 2H), 1.8-1.9 (m, 2H), 2.25-2.35 (m, 2H), 2.45 (s, 3H), 2.95 (t, 2H), 3.25-3.3 (m, 2H), 3.55 (d, 2H), 4.4 (t, 2H), 6.95 (dd, 1H), 7.4 (s, 1H), 7.45 (d, 1H), 7.5 (s, 1H), 7.6 (d, 1H), 8.55 (d, 1H), 9.15 (s, 1H)

d) 7-Hydroxy-4-(2-methylindol-5-yloxy)quinazoline (100 mg) was reacted with 3-(1,1-dioxothiomorpholino)-1-propanol (133 mg), (prepared as described for the starting material in Example 5), to give **4-(2-methylindol-5-yloxy)-7-(3-(1,1-dioxothiomorpholino)propoxy)quinazoline.**

^{1}H NMR Spectrum: ($DMSOd_6$) 1.9-2.0 (m, 2H), 2.4 (s, 3H), 1.6-1.7 (m, 2H), 2.9 (br s, 4H), 3.1 (br s, 4H), 4.25 (t, 2H), 6.12 (s, 1H), 6.85 (d, 1H), 7.22 (s, 1H), 7.3 (d, 1H), 7.3-7.4 (m, 2H), 8.25 (d, 1H), 8.55 (s, 1H)

e) 7-Hydroxy-4-(2-methylindol-5-yloxy)quinazoline (100 mg) was reacted with 4-(3-hydroxypropyl)morpholine (100 mg), (prepared as described for the starting material in Example 60), to give **4-(2-methylindol-5-yloxy)-7-(3-morpholinopropoxy)quinazoline.**

^{1}H NMR Spectrum: ($DMSOd_6$) 1.95-2.05 (m, 2H), 2.42 (s, 3H), 2.5 (t, 2H), 2.55 (t, 4H), 3.6 (t, 4H), 4.3 (t, 2H), 6.18 (s, 1H), 6.9 (dd, 1H), 7.3 (s, 1H), 7.35 (d, 1H), 7.3-7.4 (m, 2H), 8.3 (d, 1H), 8.6 (s, 1H)

Elemental analysis	Found	C 66.5 H 6.2 N 12.7
$C_{24}H_{26}N_4O_3$ 0.14 CH_2Cl_2 0.7 H_2O	Requires	C 66.7 H 6.4 N 13.0%

f) 7-Hydroxy-4-(2-methylindol-5-yloxy)quinazoline (100 mg) was reacted with 1-(2-hydroxyethyl)piperidine (89 mg) to give **4-(2-methylindol-5-yloxy)-7-(2-(piperidin-1-yl)ethoxy)quinazoline.**

^{1}H NMR Spectrum: ($DMSOd_6$) 1.4-1.5 (br s, 2H), 1.5-1.7 (br s, 4H), 2.42 (s, 3H), 2.5-2.7 (br s, 4H), 2.8-3.0 (br s, 2H), 4.35 (br s, 2H), 6.18 (s, 1H), 6.9 (dd, 1H), 7.3 (s, 1H), 7.35 (d, 1H), 7.4 (d, 1H), 7.42 (s, 1H), 8.3 (d, 1H), 8.6 (s, 1H)

Elemental analysis	Found	C 69.0 H 6.6 N 13.4
$C_{24}H_{26}N_4O_2$ 0.8 H_2O	Requires	C 69.1 H 6.7 N 13.4%

g) 7-Hydroxy-4-(2-methylindol-5-yloxy)quinazoline (100 mg) was reacted with 2-(1*H*-1,2,4-triazol-1-yl)ethanol (78 mg), (Ann. Phar. Fr. 1977, 35, 503-508), to give **4-(2-methylindol-5-yloxy)-7-(2-(1*H*-1,2,4-triazol-1-yl)ethoxy)quinazoline.**

^{1}H NMR Spectrum: ($DMSOd_6$) 2.4 (s, 3H), 4.6 (m, 2H), 4.7 (m, 2H), 6.15 (s, 1H), 6.9 (dd, 1H), 7.28 (s, 1H), 7.3 (d, 2H), 7.4 (s, 1H), 8.02 (s, 1H), 8.3 (d, 1H), 8.6 (s, 1H), 8.65 (s, 1H)

Elemental analysis	Found	C 63.7 H 4.8 N 21.5

$C_{21}H_{18}N_6O_2$ 0.5 H_2O	Requires	C 63.8 H 4.8 N 21.3%

Example 90

A solution of 7-hydroxy-4-(2-methylindol-5-yloxy)quinazoline (423 mg, 1.45 mmol), (prepared as described for the starting material in Example 82), triphenylphosphine (685 mg, 2.61 mmol), 4-hydroxymethyl-1-*tert*-butoxycarbonylpiperidine (500 mg, 2.32 mmol), (prepared as described for the starting material in Example 10), and diisopropyl azodicarboxylate (528 mg, 2.61 mmol) in methylene chloride (18 ml) was stirred overnight at ambient temperature. The mixture was then poured onto a column of silica and eluted with ethyl acetate. After evaporation of the solvent, the residue was triturated with ether, filtered, and dried under vacuum to give **7-(1-*tert*-butoxycarbonylpiperidin-4-ylmethoxy)-4-(2-methylindol-5-yloxy)quinazoline** (478 mg, 68 %).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.3-1.4 (m, 2H), 1.42 (s, 9H), 1.85 (d, 2H), 2.0-2.1 (m, 1H), 2.42 (s, 3H), 2.7-2.9 (br s, 2H), 3.95-4.05 (m, 2H), 4.1 (d, 2H), 6.15 (s, 1H), 6.9 (dd, 1H), 7.3 (s, 1H), 7.33 (d, 1H), 7.38 (s, 1H), 7.35-7.4 (m, 1H), 8.3 (d, 1H), 8.6 (s, 1H)

MS-ESI : 489 $[MH]^+$

Elemental analysis	Found	C 68.7 H 6.7 N 11.3
$C_{28}H_{32}N_4O_4$	Requires	C 68.8 H 6.6 N 11.5%

Example 91

To a suspension of 4-(2,3-dimethylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline (124 mg, 0.32 mmol) in methylene chloride (2.5 ml) was added triphenylphosphine (179 mg, 0.628 mmol), 1-(2-hydroxyethyl)pyrrolidine (75 mg, 0.65 mmol) followed by diisopropyl azodicarboxylate (134 µl, 0.68 mmol) in portions. After stirring overnight at ambient temperature the mixture was poured onto a column of silica and eluted with ethyl acetate/methylene chloride (1/1) followed by ethyl acetate/methylene chloride/methanol (4/5/1) followed by methylene chloride/methanol (9/1). After removal of the solvent, the solid was triturated with ether, filtered, washed with ether and dried under vacuum to give **4-(2,3-dimethylindol-5-yloxy)-6-methoxy-7-(2-(pyrrolidin-1-yl)ethoxy)quinazoline** (51 mg, 37 %).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.6-1.75 (m, 4H), 2.12 (s, 3H), 2.28 (s, 3H), 2.52 (br s, 4H), 3.85 (t, 2H), 3.93 (s, 3H), 4.25 (t, 2H), 6.8 (d, 1H), 7.17 (s, 1H), 7.22 (d, 1H), 7.33 (s, 1H),

7.54 (s, 1H), 8.43 (s, 1H)

The starting material was prepared as follows:

To a solution of 2,3-dimethyl-5-methoxyindole (175mg, 1 mmol), (J. Chem. Soc. 1957, 3175-3180) in methylene (5 ml) cooled at -60°C was added boron tribromide (210 µl, 2.2 mmol) dropwise. After completion of addition, the mixture was left to warm up to ambient temperature and was stirred for 1 hour. Water was added and the pH was adjusted to 6 with 2N sodium hydroxide. The mixture was extracted with ethyl acetate and the organic layer was separated, washed with brine, dried ($MgSO_4$) and evaporated to give 2,3-dimethyl-5-hydroxyindole (124mg, 77%).

^{1}H NMR Spectrum: ($DMSOd_6$) 2.1 (s, 3H) ; 2.3 (s, 3H) ; 6.5 (dd, 1H) ; 6.65 (d, 1H) ; 7.0 (d, 1H) ; 8.45 (s, 1H)

Under nitrogen, to a solution of 2,3-dimethyl-5-hydroxyindole (643mg, 4 mmol), in DMF (10 ml) was added potassium carbonate (690mg, 5 mmol). After stirring for 15 minutes at ambient temperature, 7-benzyloxy-4-chloro-6-methoxyquinazoline (1g, 3.33 mmol), (prepared as described for the starting material in Example 1), was added. The mixture was heated at 90°C for 2 hours followed by 30 minutes at 95°C. After cooling , the mixture was poured onto water (100ml) cooled at 5 °C. The precipitate was filtered, washed with water, followed by ether and dried under vacuum to give 7-benzyloxy-4-(2,3-dimethylindol-5-yloxy)-6-methoxyquinazoline (1.4 g, 95%).

^{1}H NMR Spectrum: ($DMSOd_6$) 2.15 (s, 3H) ; 2.35 (s, 3H) ; 4.02 (s, 3H) ; 5.4 (s, 2H) ; 6.9 (dd, 1H) ; 7.22 (d, 1H) ; 7.3 (d, 1H) ; 7.35-7.6 (m, 6H) ; 7.65 (s, 1H) ; 8.5 (s, 1H)

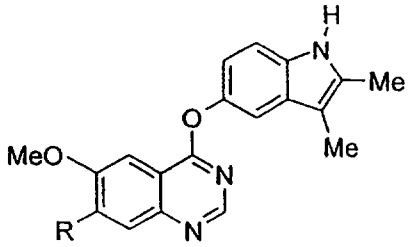
A solution of 7-benzyloxy-4-(2,3-dimethylindol-5-yloxy)-6-methoxyquinazoline (2g, 4.7 mmol) in DMF (120 ml) containing ammonium formate (11gr, 174 mmol) and 10% palladium on charcoal (200mg) was stirred for 2.5 hours at ambient temperature. The mixture was filtered, and the filtrate was evaporated under vacuum. The residue was triturated with ether and the solid was filtered, washed with water followed by ether and dried under vacuum at 50°C to give 4-(2,3-dimethylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline (1.1 g, 69%).

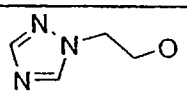
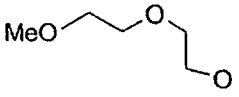
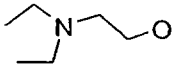
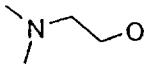
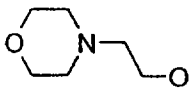
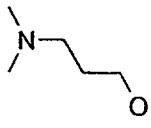
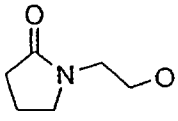
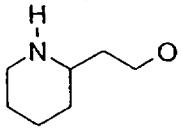
^{1}H NMR Spectrum: ($DMSOd_6$) 2.1 (s, 3H) ; 2.32 (s, 3H) ; 3.97 (s, 3H) ; 7.85 (dd, 1H) ; 7.2 (bs, 2H) ; 7.25 (d, 1H) ; 7.58 (s, 1H) ; 8.4 (s, 1H)

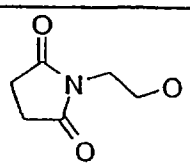
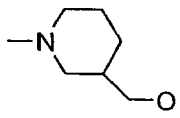
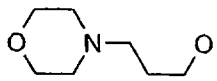
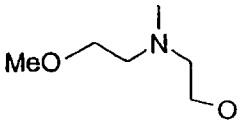
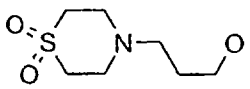
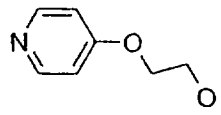
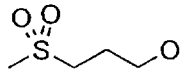
Examples 92-106

Using an analogous procedure to that described in Example 91, the appropriate alcohol was reacted with 4-(2,3-dimethylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline, (prepared as described for the starting material in Example 91), to give the compounds described in the Table VII below.

Table VII



Example number	Weight (mg)	Yield %	MS-ESI $[MH]^+$	R	HPLC* RT (min)	Note
92	91	65	431		-	a
93	78	55	438		-	b
94	34	27	435		-	c
95	39	33	407		-	d
96	58	44	449		-	e
97	58	47	421		-	f
98	85	66	447		-	g
99	24	18	447		-	h

100	110	82	461		-	i
101	9	7	447		-	j
102	81	62	463		3.4	k
103	75	57	451		-	l
104	96	65	511		-	m
105	103	78	457		-	n
106	64	49	456		-	o

* HPLC conditions 2) as described hereinbefore.

a) 4-(2,3-Dimethylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline (124 mg) was reacted with 2-(1*H*-1,2,4-triazol-1-yl)ethanol (74 mg), (Ann. Phar. Fr. 1977, 35, 503-508), to give **4-(2,3-dimethylindol-5-yloxy)-6-methoxy-7-(2-(1H-1,2,4-triazol-1-yl)ethoxy)quinazoline**.

^{1}H NMR Spectrum: ($DMSOd_6$) 2.10 (s, 3H), 2.30 (s, 3H), 3.93 (s, 3H), 4.52 (m, 2H), 4.55-4.65 (m, 2H), 6.85 (d, 1H), 7.2 (s, 1H), 7.25 (d, 1H), 7.4 (d, 1H), 7.58 (s, 1H), 8.0 (s, 1H), 8.48 (s, 1H), 8.58 (s, 1H)

b) 4-(2,3-Dimethylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline (124 mg) was reacted with 2-(2-methoxyethoxy)ethanol (78 mg) to give **4-(2,3-dimethylindol-5-yloxy)-6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)quinazoline**.

^{1}H NMR Spectrum: ($DMSOd_6$) 2.14 (s, 3H), 2.35 (s, 3H), 3.3 (s, 3H), 3.5 (t, 2H), 3.65 (t, 2H), 3.85 (t, 2H), 4.0 (s, 3H), 4.32 (t, 2H), 6.9 (d, 1H), 7.25 (d, 1H), 7.28 (d, 1H), 7.4 (s, 1H), 7.6

(s, 1H), 8.5 (s, 1H)

c) 4-(2,3-Dimethylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline (97 mg) was reacted with N,N-diethylethanolamine (68 mg) to give **7-(2-(N,N-diethylamino)ethoxy)-4-(2,3-dimethylindol-5-yloxy)-6-methoxyquinazoline**.

^{1}H NMR Spectrum: ($DMSOd_6$) 1.05 (t, 6H), 2.15 (s, 3H), 2.35 (s, 3H), 2.6-2.7 (m, 4H), 2.92 (br s, 2H), 4.0 (s, 3H), 4.25 (t, 2H), 6.9 (dd, 1H), 7.25 (s, 1H), 7.3 (d, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 8.5 (s, 1H)

d) 4-(2,3-Dimethylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline (97 mg) was reacted with N,N-dimethylethanolamine (52 mg) to give **7-(2-(N,N-dimethylamino)ethoxy)-4-(2,3-dimethylindol-5-yloxy)-6-methoxyquinazoline**.

^{1}H NMR Spectrum: ($DMSOd_6$) 2.15 (s, 3H), 2.35 (s, 9H), 2.85 (br s, 2H), 4.0 (s, 3H), 4.35 (t, 2H), 6.87 (dd, 1H), 7.22 (s, 1H), 7.3 (d, 1H), 7.42 (s, 1H), 7.6 (s, 1H), 8.5 (s, 1H)

e) 4-(2,3-Dimethylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline (97 mg) was reacted with 4-(2-hydroxyethyl)morpholine (59 mg) to give **4-(2,3-dimethylindol-5-yloxy)-6-methoxy-7-(2-morpholinoethoxy)quinazoline**.

^{1}H NMR Spectrum: ($DMSOd_6$) 2.15 (s, 3H), 2.35 (s, 3H), 3.25-3.4 (m, 2H), 3.65 (d, 2H), 3.7-3.8 (m, 4H), 4.0-4.1 (m, 2H), 4.1 (s, 3H), 4.7 (t, 2H), 6.95 (dd, 1H), 7.3 (s, 1H), 7.35 (d, 1H), 7.6 (s, 1H), 7.8 (s, 1H), 9.0 (s, 1H)

f) 4-(2,3-Dimethylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline (97 mg) was reacted with 3-(N,N-dimethylamino)propan-1-ol (60 mg) to give **7-(3-(N,N-dimethylamino)propoxy)-4-(2,3-dimethylindol-5-yloxy)-6-methoxyquinazoline**.

^{1}H NMR Spectrum: ($DMSOd_6$) 1.95-2.05 (m, 2H), 2.15 (s, 3H), 2.2 (s, 6H), 2.35 (s, 3H), 2.45 (t, 2H), 4.0 (s, 3H), 4.25 (t, 2H), 6.9 (dd, 1H), 7.22 (d, 1H), 7.3 (d, 1H), 7.37 (s, 1H), 7.6 (s, 1H), 8.5 (s, 1H)

g) 4-(2,3-Dimethylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline (97 mg) was reacted with 1-(2-hydroxyethyl)-2-pyrrolidinone (75 mg) to give **4-(2,3-dimethylindol-5-yloxy)-6-methoxy-7-(2-(2-oxopyrrolidin-1-yl)ethoxy)quinazoline**.

^{1}H NMR Spectrum: ($DMSOd_6$) 1.9-2.05 (m, 4H), 2.15 (s, 3H), 2.25 (t, 2H), 2.35 (s, 3H), 3.65 (t, 2H), 4.0 (s, 3H), 4.35 (t, 2H), 6.9 (d, 1H), 7.25 (s, 1H), 7.3 (d, 1H), 7.45 (s, 1H), 7.62 (s, 1H), 8.5 (s, 1H)

h) 4-(2,3-Dimethylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline (97 mg) was reacted with 2-(2-hydroxyethyl)piperidine (75 mg) to give **4-(2,3-dimethylindol-5-yloxy)-6-methoxy-7-(2-(piperidin-2-yl)ethoxy)quinazoline**.

^{1}H NMR Spectrum: ($DMSOd_6$) 1.0-1.15 (m, 1H), 1.25-1.4 (m, 2H), 1.5 (br s , 1H), 1.65 (d, 1H), 1.7-1.8 (m, 1H), 1.8-1.9 (m, 2H), 2.15 (s, 3H), 2.35 (s, 3H), 2.5 (d, 1H), 2.6-2.7 (m, 1H), 2.9-3.0 (m, 1H), 4.0 (s, 3H), 4.2-4.35 (m, 2H), 6.88 (dd, 1H), 7.2 (s, 1H), 7.27 (d, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 8.5 (s, 1H)

i) 4-(2,3-Dimethylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline (97 mg) was reacted with 1-(2-hydroxyethyl)pyrrolidin-2,5-dione (83 mg) to give **4-(2,3-dimethylindol-5-yloxy)-7-(2-(2,5-dioxopyrrolidin-1-yl)ethoxy)-6-methoxyquinazoline**.

^{1}H NMR Spectrum: ($DMSOd_6$) 2.12 (s, 3H), 2.35 (s, 3H), 2.68 (s, 4H), 3.85 (t, 2H), 3.95 (s, 3H), 4.35 (t, 2H), 6.88 (dd, 1H), 7.22 (s, 1H), 7.25 (d, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 8.5 (s, 1H)

j) 4-(2,3-Dimethylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline (97 mg) was reacted with 1-methyl-3-piperidinemethanol (75 mg) to give **4-(2,3-dimethylindol-5-yloxy)-6-methoxy-7-(1-methylpiperidin-3-ylmethoxy)quinazoline**.

k) 4-(2,3-Dimethylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline (97 mg) was reacted with 4-(3-hydroxypropyl)morpholine (75 mg), (prepared as described for the starting material in Example 60), to give **4-(2,3-dimethylindol-5-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline**.

^{1}H NMR Spectrum: ($DMSOd_6$) 1.95-2.05 (m, 2H), 2.15 (s, 3H), 2.35 (s, 3H), 2.42 (br s, 4H), 2.5 (t, 2H), 3.6 (m, 4H), 4.0 (s, 3H), 4.25 (t, 2H), 6.85 (dd, 1H), 7.25 (d, 1H), 7.3 (d, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 8.5 (s, 1H).

l) 4-(2,3-Dimethylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline (97 mg) was reacted with 2-(N-(2-methoxyethyl)-N-methylamino)ethanol (77 mg), (prepared as described for the

starting material in Example 59), to give **4-(2,3-dimethylindol-5-yloxy)-6-methoxy-7-(2-(N-(2-methoxyethyl)-N-methylamino)ethoxy)quinazoline.**

^{1}H NMR Spectrum: ($DMSOd_6$) 2.15 (s, 3H), 2.35 (s, 6H), 2.65 (t, 2H), 2.9 (t, 2H), 3.25 (s, 3H), 3.45 (t, 2H), 4.0 (s, 3H), 4.3 (t, 2H), 6.9 (dd, 1H), 7.22 (s, 1H), 7.3 (d, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 8.5 (s, 1H)

m) 4-(2,3-Dimethylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline (97 mg) was reacted with 3-(1,1-dioxothiomorpholino)-1-propanol (112 mg), (prepared as described for the starting material in Example 5), to give **4-(2,3-dimethylindol-5-yloxy)-7-(3-(1,1-dioxothiomorpholino)propoxy)-6-methoxyquinazoline.**

^{1}H NMR Spectrum: ($DMSOd_6$) 1.95-2.05 (m, 2H), 2.15 (s, 3H), 2.35 (s, 3H), 2.7 (t, 2H), 2.95 (br s, 4H), 3.15 (br s, 4H), 4.0 (s, 3H), 4.29 (t, 2H), 6.9 (dd, 1H), 7.25 (s, 1H), 7.3 (d, 1H), 7.4 (s, 1H), 7.61 (s, 1H), 8.5 (s, 1H)

n) 4-(2,3-Dimethylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline (97 mg) was reacted with 2-(4-pyridyloxy)ethanol (81 mg), (J. Chem. Soc. Perkin Trans 2, 1987, 12, 1867), to give **4-(2,3-dimethylindol-5-yloxy)-6-methoxy-7-(2-(4-pyridyloxy)ethoxy)quinazoline.**

^{1}H NMR Spectrum: ($DMSOd_6$) 2.15 (s, 3H), 2.35 (s, 3H), 4.0 (s, 3H), 4.55 (m, 2H), 4.6 (m, 2H), 6.88 (dd, 1H), 7.08 (d, 2H), 7.22 (s, 1H), 7.28 (d, 1H), 7.48 (s, 1H), 7.6 (s, 1H), 8.42 (d, 2H), 8.5 (s, 1H), 10.78 (s, 1H)

o) 4-(2,3-Dimethylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline (97 mg) was reacted with 3-(methylsulphonyl)-1-propanol (80 mg), (prepared as described for the starting material in Example 50), to give **4-(2,3-dimethylindol-5-yloxy)-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline.**

^{1}H NMR Spectrum: ($DMSOd_6$) 1.8-1.9 (m, 2H), 2.15 (s, 3H), 2.25-2.35 (m, 2H), 2.35 (s, 3H), 3.0 (s, 3H), 4.02 (s, 3H), 4.35 (t, 2H), 6.9 (dd, 1H), 7.25 (s, 1H), 7.3 (d, 1H), 7.4 (s, 1H), 7.7 (s, 1H), 8.52 (s, 1H)

Example 107

Using an analogous procedure to that described in Example 91, 7-hydroxy-4-(indol-5-yloxy)-6-methoxyquinazoline (89mg) was reacted with 2-(2-methoxyethoxy)ethanol (70mg)

to give **4-(indol-5-yloxy)-6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)quinazoline** (50mg, 42%).

^{1}H NMR Spectrum: ($DMSOd_6$) 3.3 (s, 3H), 3.5 (m, 2H), 3.65 (m, 2H), 3.85 (m, 2H), 4.02 (s, 3H), 4.35 (t, 2H), 6.58 (s, 1H), 7.0 (dd, 1H), 7.4 (s, 1H), 7.45 (br s, 2H), 7.47 (d, 1H), 7.61 (s, 1H), 8.5 (s, 1H)

MS-ESI : 410 [MH]+

The starting material was prepared as follows:

A mixture of 7-benzyloxy-4-chloro-6-methoxyquinazoline (3g, 10 mmol), (prepared as described for the starting material in Example 1), 5-hydroxyindole (1.46g, 11 mmol) in DMF (30ml) containing potassium carbonate (2.75g, 20 mmol) was heated at 95°C for 2 hours. After cooling the mixture was poured onto water (100ml). The precipitate was filtered, washed with water and dried under vacuum at 50°C over phosphorus pentoxide. The solid was triturated with ether, filtered, washed with ether and dried under vacuum to give 7-benzyloxy-4-(indol-5-yloxy)-6-methoxyquinazoline (3.5g, 88%).

^{1}H NMR Spectrum: ($DMSOd_6$) 4.02 (s, 3H), 5.4 (s, 2H), 6.5 (s, 1H), 7.0 (dd, 1H), 7.4-7.6 (m, 9H), 7.65 (s, 1H), 8.5 (s, 1H), 11.23 (s, 1H)

MS-ESI : 398 [MH]+

A solution of 7-benzyloxy-4-(indol-5-yloxy)-6-methoxyquinazoline (8 g, 20 mmol) in DMF (50 ml) and methylene chloride (100 ml) containing 10% palladium on charcoal (2 g) was hydrogenated at 1.8 atmospheres pressure until uptake of hydrogen had ceased. The solution was filtered, the catalyst was washed with DMF and the filtrate was evaporated. The residue was purified by column chromatography eluting with methylene chloride, followed by methylene chloride/methanol (95/5 and 90/10). After evaporation of the solvent, the residue was triturated with ether, filtered and dried under vacuum to give 7-hydroxy-4-(indol-5-yloxy)-6-methoxyquinazoline (2.7 g; 44 %).

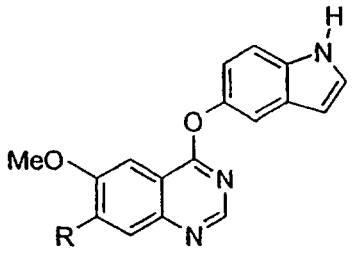
^{1}H NMR Spectrum: ($DMSOd_6$) 4.0 (s, 3H), 6.46 (s, 1H), 7.01 (dd, 1H); 7.2 (s, 1H), 7.4-7.5 (m, 3H), 7.6 (s, 1H), 8.41 (s, 1H)

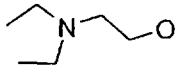
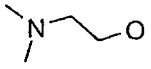
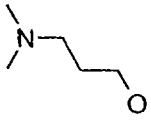
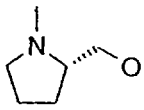
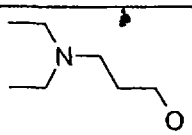
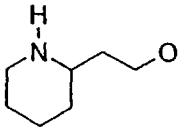
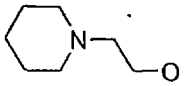
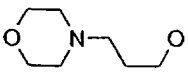
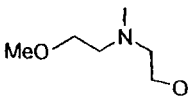
Examples 108-118

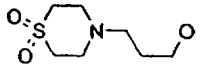
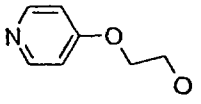
Using an analogous procedure to that described in Example 107, the appropriate alcohol was reacted with 7-hydroxy-4-(indol-5-yloxy)-6-methoxyquinazoline, (prepared as

described for the starting material in Example 107), to give the compounds described in the Table VIII below.

Table VIII



Example number	Weight (mg)	Yield %	MS-ESI $[MH]^+$	R	Note
108	58	49	407		r
109	14	13	379		s
110	55	48	393		t
111	27	23	405		u
112	58	47	421		v
113	63	52	419		w
114	64	53	419		x
115	106	84	435		y
116	76	62	423		z

117	113	81	483		aa
118	24	19	429		bb

r) 7-Hydroxy-4-(indol-5-yloxy)-6-methoxyquinazoline (89 mg) was reacted with N,N-diethylethanolamine (68 mg) to give **7-(2-(N,N-diethylamino)ethoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline.**

s) 7-Hydroxy-4-(indol-5-yloxy)-6-methoxyquinazoline (89 mg was reacted with N,N-dimethylethanolamine (52 mg) to give **7-(2-(N,N-dimethylamino)ethoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline.**

^{1}H NMR Spectrum: ($DMSOd_6$) 2.3 (s, 6H), 2.8 (t, 2H), 4.0 (s, 3H), 4.3 (t, 2H), 6.45 (s, 1H), 7.0 (dd, 1H), 7.4-7.5 (m, 4H), 7.6 (s, 1H), 8.5 (s, 1H)

t) 7-Hydroxy-4-(indol-5-yloxy)-6-methoxyquinazoline (89 mg) was reacted with 3-(N,N-dimethylamino)propan-1-ol (60 mg) to give **7-(3-(N,N-dimethylamino)propoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline.**

^{1}H NMR Spectrum: ($DMSOd_6$) 1.9-2.05 (m, 2H), 2.21 (s, 6H), 2.45 (t, 2H), 4.02 (s, 3H), 4.25 (t, 2H), 6.47 (s, 1H), 7.0 (dd, 1H), 7.38 (s, 1H), 7.35-7.4 (m, 2H), 7.45 (d, 1H), 7.6 (s, 1H), 8.5 (s, 1H)

u) 7-Hydroxy-4-(indol-5-yloxy)-6-methoxyquinazoline (89 mg) was reacted with (2*S*)-2-(hydroxymethyl)-1-methylpyrrolidine (67 mg) to give **(2*S*)-4-(indol-5-yloxy)-6-methoxy-7-(1-methylpyrrolidin-2-yl)quinazoline.**

v) 7-Hydroxy-4-(indol-5-yloxy)-6-methoxyquinazoline (89 mg) was reacted with 3-(N,N-diethylamino)-1-propanol (76 mg) to give **7-(3-(N,N-diethylamino)propoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline.**

^{1}H NMR Spectrum: ($DMSOd_6$) 0.95 (t, 6H), 1.9-2.0 (m, 2H), 2.5 (m, 4H), 2.6 (t, 2H), 4.0 (s, 3H), 4.25 (t, 2H), 6.48 (s, 1H), 7.0 (dd, 1H), 7.38 (s, 1H), 7.42-7.5 (m, 3H), 7.6 (s, 1H), 8.5 (s, 1H)

w) 7-Hydroxy-4-(indol-5-yloxy)-6-methoxyquinazoline (89 mg) was reacted with 2-(2-hydroxyethyl)piperidine (75 mg) to give **4-(indol-5-yloxy)-6-methoxy-7-(2-(piperidin-2-yl)ethoxy)quinazoline.**

^{1}H NMR Spectrum: ($DMSOd_6$) 1.45-1.75 (m, 3H), 1.75-1.85 (m, 2H), 2.0-2.1 (m, 1H), 2.1-2.2 (m, 1H), 2.25-2.35 (m, 1H), 2.95 (t, 1H), 3.3-3.4 (m, 2H), 4.1 (s, 3H), 4.4-4.5 (m, 2H), 6.5 (s, 1H), 7.05 (dd, 1H), 7.45-7.6 (m, 4H), 7.75 (s, 1H), 9.0 (s, 1H)

x) 7-Hydroxy-4-(indol-5-yloxy)-6-methoxyquinazoline (89 mg) was reacted with 1-(2-hydroxyethyl)piperidine (75 mg) to give **4-(indol-5-yloxy)-6-methoxy-7-(2-(piperidin-1-yl)ethoxy)quinazoline.**

^{1}H NMR Spectrum: ($DMSOd_6$) 1.1-1.3 (m, 1H), 1.35-1.5 (m, 1H), 1.65-1.8 (m, 2H), 1.8-1.9 (m, 2H), 3.1 (t, 2H), 3.6 (d, 2H), 3.65 (t,2H), 4.1 (s, 3H), 4.7 (t, 2H), 6.5 (d, 1H), 7.05 (dd, 1H), 7.45 (s, 1H), 7.5-7.55 (m, 2H), 7.61 (s, 1H), 7.8 (s, 1H), 9.0 (m, 1H)

y) 7-Hydroxy-4-(indol-5-yloxy)-6-methoxyquinazoline (89 mg) was reacted with 4-(3-hydroxypropyl)morpholine (84 mg), (prepared as described for the starting material in Example 60), to give **4-(indol-5-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline.**

^{1}H NMR Spectrum: ($DMSOd_6$) 1.9-2.1 (m, 2H), 2.4 (br s, 4H), 2.5 (t, 2H), 3.6 (t, 4H), 4.0 (s, 3H), 4.25 (t, 2H), 6.45 (s, 1H), 7.0 (dd, 1H), 7.4 (s, 1H), 7.4-7.45 (m, 2H), 7.47 (d, 1H), 7.6 (s, 1H), 8.5 (s, 1H)

z) 7-Hydroxy-4-(indol-5-yloxy)-6-methoxyquinazoline (89 mg) was reacted with 2-(N-(2-methoxyethyl)-N-methylamino)ethanol (77 mg), (prepared as described for the starting material in Example 59), to give **4-(indol-5-yloxy)-6-methoxy-7-(2-(N-(2-methoxyethyl)-N-methylamino)ethoxy)quinazoline.**

^{1}H NMR Spectrum: ($DMSOd_6$) 2.35 (s, 3H), 2.65 (t, 2H), 2.9 (t, 2H), 3.25 (s, 3H), 3.45 (t, 2H), 4.0 (s, 3H), 4.3 (t, 2H), 6.45 (s, 1H), 7.05 (dd, 1H), 7.4-7.5 (m, 4H), 7.6 (s, 1H), 8.5 (s, 1H)

aa) 7-Hydroxy-4-(indol-5-yloxy)-6-methoxyquinazoline (89 mg) was reacted with 3-(1,1-dioxothiomorpholino)-1-propanol (112 mg), (prepared as described for the starting material in

Example 5), to give **7-(3-(1,1-dioxothiomorpholino)propoxy)-4-(indol-5-yloxy)-6-methoxyquinazoline.**

^{1}H NMR Spectrum: ($DMSOd_6$) 2.0 (m, 2H), 2.65 (m, 2H), 2.9 (br s, 4H), 3.15 (br s, 4H), 4.0 (s, 3H), 4.25 (t, 2H), 6.5 (s, 1H), 7.0 (dd, 1H), 7.35-7.5 (m, 4H), 7.65 (s, 1H), 8.5 (s, 1H)

bb) 7-Hydroxy-4-(indol-5-yloxy)-6-methoxyquinazoline (89 mg) was reacted with 2-(4-pyridyloxy)ethanol (81 mg), (J. Chem. Soc. Perkin Trans 2, 1987, 12, 1867), to give **4-(indol-5-yloxy)-6-methoxy-7-(2-(4-pyridyloxy)ethoxy)quinazoline.**

Example 119

A solution of 4-chloro-6-methoxy-7-(3-piperidinopropoxy)quinazoline (200 mg, 0.59 mmol), (prepared as described for the starting material in Example 67), 6-hydroxyindole (96 mg, 0.715 mmol) in DMF (3 ml) containing cesium carbonate (291 mg, 0.894 mmol) was heated at 90°C for 4 hours. After cooling, the mixture was diluted with water, the precipitate was filtered, washed with water and dried under vacuum. The solid was purified by column chromatography eluting with methylene chloride/methanol (90/10 increasing to 50/50) to give **4-(indol-6-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline** (240 mg, 93 %).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.35-1.45 (m, 2H), 1.45-1.55 (m, 4H), 1.9-2.05 (m, 2H), 2.3-2.4 (m, 4H), 2.45 (t, 2H), 4.0 (s, 3H), 4.22 (t, 2H), 6.5 (s, 1H), 6.9 (dd, 1H), 7.3 (s, 1H), 7.35-7.40 (m, 2H), 7.55-7.65 (m, 2H), 8.5 (s, 1H)

MS-ESI : 433 $[MH]^+$

Elemental analysis	Found	C 68.4	H 6.4	N 12.8
$C_{25}H_{28}N_4O_3$ 0.4 H_2O	Requires	C 68.3	H 6.6	N 12.7%

Example 120

A solution of 4-chloro-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline (200 mg, 0.6 mmol), (prepared as described for the starting material in Example 50), and 6-hydroxyindole (97 mg, 0.73 mmol) in DMF (3 ml) containing potassium carbonate (125 mg, 0.91 mmol) was heated at 90°C for 2.5 hours. After cooling, water was added. The precipitate was filtered, washed with water and dried under vacuum. The residue was triturated with ether, filtered, washed with ether and dried under vacuum to give **4-(indol-6-yloxy)-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline** (130 mg, 50 %).

^{1}H NMR Spectrum: ($DMSOd_6$) 2.2-2.35 (m, 2H), 3.05 (s, 3H), 3.3 (m, 2H), 4.0 (s, 3H), 4.35 (t, 2H), 6.48 (s, 1H), 6.9 (dd, 1H), 7.3 (s, 1H), 7.4 (2s, 2H), 7.6 (d, 1H), 7.65 (s, 1H), 7.9 (s, 1H)

MS-ESI : 428 $[MH]^+$

Elemental analysis	Found	C 56.2	H 4.9 N 9.3
$C_{21}H_{21}N_3O_5S$ 1.1 H_2O	Requires	C 56.4	H 5.2 N 9.4%

Example 121

Using an analogous procedure to that described for Example 120, 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (200 mg, 0.59 mmol), (prepared as described for the starting material in Example 1), was reacted with 6-hydroxyindole (95 mg, 0.71 mmol) to give **4-(indol-6-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline** (155 mg, 60 %).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.95-2.05 (m, 2H), 2.4 (br s, 4H), 2.48 (t, 2H), 3.6 (t, 4H), 4.0 (s, 3H), 4.27 (t, 2H), 6.5 (s, 1H), 6.93 (dd, 1H), 7.3 (s, 1H), 7.4 (br s, 2H), 7.6 (d, 1H), 7.61 (s, 1H), 8.5 (s, 1H)

MS-ESI : 435 $[MH]^+$

Elemental analysis	Found	C 62.0	H 6.2 N 12.1
$C_{24}H_{26}N_4O_4$ 1.6 H_2O	Requires	C 62.2	H 6.4 N 12.1%

Example 122

A suspension of 7-(1-*tert*-butoxycarbonylpiperidin-4-ylmethoxy)-4-(2-methylindol-5-yloxy)quinazoline (150 mg, 0.31 mmol), (prepared as described in Example 90), in methylene chloride (2 ml) and TFA (1.5 ml) was stirred for 1 hour at ambient temperature. After removal of the volatiles under vacuum the residue was azeotroped with toluene. The residue was partitioned between methylene chloride and water and the aqueous layer was adjusted to pH11. The organic layer was separated, washed with brine, dried ($MgSO_4$), and evaporated. The residue was triturated with ether, filtered, washed with ether and dried under vacuum to give **4-(2-methylindol-5-yloxy)-7-(piperidin-4-ylmethoxy)quinazoline** (80 mg, 67 %).

^{1}H NMR Spectrum: ($DMSOd_6$, CF_3COOD) 1.5-1.65 (m, 2H), 2.0 (d, 2H), 2.15-2.3 (m, 1H), 2.4 (s, 3H), 2.95 (t, 2H), 3.38 (d, 2H), 4.2 (d, 2H), 6.2 (s, 0.5H, partially exchanged), 6.9 (dd, 1H), 7.35 (s, 1H), 7.4 (d, 1H), 7.5 (s, 1H), 7.58 (dd, 1H), 8.5 (d, 1H), 9.1 (s, 1H)

MS-ESI : 389 $[MH]^+$

Elemental analysis	Found	C 68.9 H 6.2 N 13.7
$C_{23}H_{24}N_4O_2$ 0.2 H_2O 0.12 CH_2Cl_2	Requires	C 69.0 H 6.2 N 13.9%

Example 123

Using an analogous procedure to that described for Example 71, 4-(2-methylindol-5-yloxy)-7-(piperidin-4-ylmethoxy)quinazoline (150 mg, 0.386 mmol), (prepared as described in Example 122), was reacted with methoxyacetaldehyde (83 mg, 0.772 mmol), (prepared as described for the starting material in Example 71), to give **7-(1-(2-methoxyethyl)piperidin-4-ylmethoxy)-4-(2-methylindol-5-yloxy)quinazoline** (80 mg, 46 %).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.3-1.42 (m, 2H), 1.7-1.9 (m, 3H), 2.0 (t, 2H), 2.4 (s, 3H), 2.48 (t, 2H), 2.92 (d, 2H), 3.22 (s, 3H), 3.42 (t, 2H), 4.05 (d, 2H), 6.15 (s, 1H), 6.88 (dd, 1H), 7.25 (s, 1H), 7.3 (d, 1H), 7.35 (s, 1H), 7.37 (d, 1H), 8.28 (d, 1H), 8.6 (s, 1H)

MS-ESI : 447 $[MH]^+$

Elemental analysis	Found	C 68.4 H 6.7 N 12.2
$C_{26}H_{30}N_4O_3$ 0.5 H_2O	Requires	C 68.6 H 6.9 N 12.3%

Example 124

Diethyl azodicarboxylate (117 mg, 0.67 mmol) was added in portions to a solution of 7-hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (120 mg, 0.37 mmol), (prepared as described in Example 49), and 3-(ethylsulphonyl)-1-propanol (74 mg, 0.48 mmol) in methylene chloride (3.5 ml) and triphenylphosphine (176 mg, 0.67 mmol). After stirring for 2 hours at ambient temperature, the residue was poured onto a column of silica and eluted with ethyl acetate/methylene chloride (1/1) followed by methylene chloride/methanol (97/3 followed by 95/5). After removal of the solvent under vacuum, the residue was triturated with ether, filtered and dried under vacuum to give **7-(3-(ethylsulphonyl)propoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline** (93 mg, 55 %).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.25 (t, 3H), 2.2-2.3 (m, 2H), 2.4 (s, 3H), 3.2 (q, 2H), 3.3 (t, 2H), 4.0 (s, 3H), 4.35 (t, 2H), 6.15 (s, 1H), 6.9 (dd, 1H), 7.28 (s, 1H), 7.32 (d, 1H), 7.4 (s, 1H), 7.62 (s, 1H), 8.5 (s, 1H)

MS-ESI : 456 $[MH]^+$

Elemental analysis	Found	C 60.3 H 5.6 N 9.2
$C_{23}H_{25}N_3O_5S$	Requires	C 60.6 H 5.5 N 9.2%

The starting material was prepared as follows:

A solution of ethylthiopropanol (1.2 g, 10 mmol) in methylene chloride (30 ml) containing 3-chloroperoxybenzoic acid (5 g, 20 mmol) was stirred at ambient temperature for 30 minutes. The precipitate was filtered, washed with methylene chloride and the filtrate was poured onto a column of aluminium oxide and eluted with methylene chloride, followed by methylene chloride/methanol (95/5 and 90/10). After removal of the solvent, the residue was dissolved in methylene chloride, dried ($MgSO_4$) and evaporated to give 3-(ethylsulphonyl)-1-propanol (1.05 g, 69 %).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.25 (t, 3H), 1.75-1.9 (m, 2H), 3.0-3.2 (m, 4H), 3.5 (q, 2H), 4.7 (t, 1H)

MS-ESI : 153 $[MH]^+$

Example 125

Using an analogous procedure to that described for Example 124, 4-(2,3-dimethylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline (120 mg, 0.36 mol), (prepared as described for the starting material in Example 91), was reacted with 3-(ethylsulphonyl)-1-propanol (71 mg, 0.46 mol), (prepared as described for the starting material in Example 124), to give **4-(2,3-dimethylindol-5-yloxy)-7-(3-ethylsulphonylpropoxy)-6-methoxyquinazoline** (96 mg, 57 %).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.25 (t, 3H), 2.15 (s, 3H), 2.2-2.3 (m, 2H), 2.35 (s, 3H), 3.2 (q, 2H), 3.3 (t, 2H), 4.02 (s, 3H), 4.35 (t, 2H), 6.9 (dd, 1H), 7.22 (s, 1H), 7.3 (d, 1H), 7.4 (s, 1H), 7.63 (s, 1H), 8.51 (s, 1H)

MS-ESI : 470 $[MH]^+$

Elemental analysis	Found	C 60.6	H 6.0	N 8.8
$C_{24}H_{27}N_3O_5S$ 0.4 H_2O	Requires	C 60.5	H 5.9	N 8.8%

Example 126

Using an analogous procedure to that described for Example 124, 7-hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (128 mg, 0.4 mmol), (prepared as described in Example 49), was reacted with 4-(2-hydroxyethyl)-(1-*tert*-butoxycarbonyl)piperidine (119 mg, 0.52 mmol) overnight to give **7-(2-(1-tert-butoxycarbonylpiperidin-4-yl)ethoxy)-6-**

methoxy-4-(2-methylindol-5-yloxy)quinazoline (34 mg, 16 %).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.05-1.2 (m, 2H), 1.42 (s, 9H), 1.62-1.85 (m, 5H), 2.42 (s, 3H), 2.62-2.82 (m, 2H), 3.9-4.0 (m, 2H), 4.0 (s, 3H), 4.25 (t, 2H), 6.17 (s, 1H), 6.9 (dd, 1H), 7.3 (d, 1H), 7.32 (d, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 8.5 (s, 1H)

MS-ESI : 533 $[MH]^+$

Elemental analysis	Found	C 67.8	H 6.9	N 10.5
$C_{30}H_{36}N_4O_5$	Requires	C 67.7	H 6.8	N 10.5%

The starting material was prepared as follows:

A solution of 4-(2-hydroxyethyl)pyridine (1.8 g, 14.6 mol) in acetic acid (15 ml) containing platinum oxide (200 mg) was hydrogenated for 20 hours at 3.3-4 atmospheres pressure. After filtration, the filtrate was evaporated and azeotroped twice with toluene. The residue was triturated with 2N sodium hydroxide and solid sodium hydroxide was added to adjust the pH to 13. The volatiles were removed under vacuum and the residue was triturated with ether, filtered, washed with methylene chloride, and dried under vacuum to give 2-(piperidin-4-yl)-1-ethanol (860 mg, 46 %).

^{1}H NMR Spectrum: ($DMSOd_6$, CF_3COOD) 1.3-1.5 (m, 4H), 1.6-1.7 (m, 1H), 1.7-1.9 (d, 2H), 1.75 (t, 2H), 3.25 (d, 2H), 3.55 (t, 2H)

A solution of 2-(piperidin-4-yl)-1-ethanol (830 mg, 6.4 mmol) in DMF (5 ml) containing tertbutyl dicarbonate anhydride (1.4 g, 6.4 mmol) was stirred at ambient temperature for 48 hours. After removal of the volatiles under vacuum, the residue was partitioned between ether and water. The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and evaporated to give 4-(2-hydroxyethyl)-(1-*tert*-butoxycarbonyl)piperidine (1 g, 68 %).

^{1}H NMR Spectrum: ($DMSOd_6$) 0.9-1.1 (m, 2H), 1.3-1.6 (m, 3H), 1.4 (s, 9H), 1.6 (d, 2H), 2.5-2.8 (br s, 2H), 3.45 (dd, 2H), 3.9 (d, 2H), 4.35 (t, 1H)

Example 127

Using an analogous procedure to that described for Example 121, 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (160 mg, 0.47 mol), (prepared as described for the starting material in Example 1), was reacted with 6-hydroxy-2-methylindole (84 mg, 0.57 mol), (Eur. J. Med. Chem. 1975, 10, 187), to give **6-methoxy-4-(2-methylindol-6-yloxy)-7-**

(3-morpholinopropoxy)quinazoline (157 mg, 73 %).

^{1}H NMR Spectrum: ($DMSOd_6$, CF_3COOD) 2.25-2.35 (m, 2H), 2.38 (s, 3H), 3.15 (t, 2H), 3.35 (t, 2H), 3.5 (d, 2H), 3.68 (t, 2H), 4.0 (d, 2H), 4.05 (s, 3H), 4.35 (t, 2H), 6.18 (s, 1H), 6.9 (d, 1H), 7.22 (s, 1H), 7.45 (d, 1H), 7.52 (s, 1H), 7.8 (s, 1H), 9.05 (s, 1H)

MS-ESI : 449 $[MH]^+$

Elemental analysis	Found	C 66.4	H 6.4	N 12.4
$C_{25}H_{28}N_4O_4$ 0.2 H_2O	Requires	C 66.4	H 6.3	N 12.4%

Example 128

Using an analogous procedure to that described for the synthesis of 4-(2-methylindol-5-yloxy)-7-(piperidin-4-ylmethoxy)quinazoline, (prepared as described in Example 122), 7-(2-(1-*tert*-butoxycarbonylpiperidin-4-yl)ethoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (400 mg, 0.75 mmol), (prepared as described in Example 126), was used to give **6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(piperidin-4-yl)ethoxy)quinazoline** (284 mg, 87 %).

^{1}H NMR Spectrum: ($DMSOd_6$, CF_3COOD) 1.3-1.5 (m, 2H), 1.8-2.0 (m, 5H), 2.4 (s, 3H), 2.9 (t, 2H), 3.3 (d, 2H), 4.05 (s, 3H), 4.35 (t, 2H), 6.2 (s, 1H), 6.95 (dd, 1H), 7.35 (s, 1H), 7.37 (d, 1H), 7.52 (s, 1H), 7.8 (s, 1H), 9.1 (s, 1H)

MS-ESI : 433 $[MH]^+$

Example 129

Diethyl azodicarboxylate (65 µl, 0.4 mmol) was added in portions to a suspension of 4-(2,3-dimethylindol-5-ylamino)-7-hydroxy-6-methoxyquinazoline (68 mg, 0.2 mmol), triphenylphosphine (107 mg, 0.4 mmol), (E)-4-(pyrrolidin-1-yl)but-2-en-1-ol (40 mg, 0.28 mmol) in DMF (0.4 ml) and dichloromethane (1.5 ml) cooled at 0°C. The reaction mixture was left to warm up to ambient temperature and was stirred overnight. The mixture was poured onto a column of silica and was eluted with methylene chloride followed by methylene chloride/methanol (98/2), followed by methylene chloride/3N ammonia in methanol (95/5 and 90/10) to give **4-(2,3-dimethylindol-5-ylamino)-6-methoxy-7-((*E*)4-(pyrrolidin-1-yl)but-2-en-1-yloxy)quinazoline** (51 mg, 55 %).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.6-1.7 (m, 4H), 2.15 (s, 3H), 2.3 (s, 3H), 2.4 (br s, 4H), 3.1 (d, 2H), 3.97 (s, 3H), 4.7 (d, 2H), 5.8-6.0 (m, 2H), 7.15 (s, 1H), 7.22 (d, 1H), 7.3 (d, 1H), 7.55

(s, 1H), 7.87 (s, 1H), 8.3 (s, 1H), 9.4 (s, 1H), 10.62 (s, 1H)

MS-ESI : 458 $[MH]^+$

The starting material was prepared as follows:

Thionyl chloride (9.3ml, 128mmol) was added in portions to a stirred solution of 2-butyne-1,4-diol (10g, 116mmol) in toluene (15ml) and pyridine (10.3ml) cooled at 0°C. The mixture was stirred for 3.5 hours at ambient temperature and then poured onto ice water. The mixture was extracted with ether, the organic layer was washed with saturated aqueous sodium hydrogen carbonate solution and then brine, dried ($MgSO_4$) and the volatiles removed by evaporation. The residue was purified by column chromatography eluting with petroleum ether/ether (7/3) to give 4-chlorobut-2-yn-1-ol (4.74g, 39%).

^1H NMR Spectrum: ($CDCl_3$) 1.68(t, 1H); 4.18(d, 2H); 4.33(d, 2H)

Pyrrolidine (7.8ml, 94mmol) was added dropwise to a solution of 4-chlorobut-2-yn-1-ol (4.74g, 45mmol) in toluene (40ml) and the mixture stirred and heated at 60°C for 1 hour. The volatiles were removed by evaporation and the residue was purified by chromatography eluting with methylene chloride/methanol (96/4) to give 4-(pyrrolidin-1-yl)but-2-yn-1-ol (4.3g, 69%).

^1H NMR Spectrum: ($CDCl_3$) 1.82(t, 4H); 2.63(t, 4H); 3.44(t, 2H), 4.29(t, 2H)

A solution of 4-(pyrrolidin-1-yl)but-2-yn-1-ol (4.3g, 31mmol) in THF (20ml) was added dropwise to a suspension of lithium aluminium hydride (2.35g, 62mmol) in anhydrous THF (8ml) and the mixture stirred and heated at 60°C for 2 hours. The mixture was cooled to 5°C and 2M aqueous sodium hydroxide solution (28ml) was added dropwise. The resulting suspension was filtered and the volatiles removed from the filtrate by evaporation. The residue was dissolved in a mixture of methylene chloride/ethyl acetate, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by column chromatography on aluminum oxide eluting with methylene chloride/methanol (97/3) to give (E)-4-(pyrrolidin-1-yl)but-2-en-1-ol (3.09g, 70%).

^1H NMR Spectrum: ($CDCl_3$) 1.82(m, 4H); 2.61(m, 4H); 3.17(m, 2H); 4.13(s, 2H); 5.84(m, 2H)

A solution of 4-chloro-6-methoxy-7-benzyloxyquinazoline (7g, 23 mmol), (prepared as described for the starting material in Example 1), and 5-amino-2,3-dimethylindole (4.5g, 28 mmol) in isopropanol (90ml) containing 6.2 N hydrogen chloride in isopropanol (380µl) was

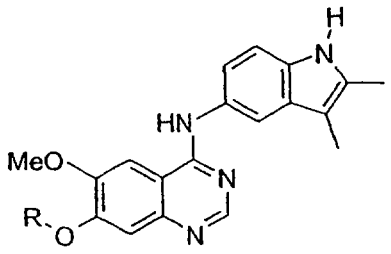
heated at relux for 3hours and stirred overnight at ambient temperature. The mixture was triturated with ether and the solid was filtered, washed with ether and dried under vacuum to give 7-benzyloxy-4-(2,3-dimethylindol-5-ylamino)-6-methoxyquinazoline (10.5 g, quant.).
^{1}H NMR Spectrum: ($DMSOd_6$) 2.16 (s, 3H), 2.33 (s, 3H), 4.0 (s, 3H), 5.34 (s, 2H), 7.2 (d, 1H), 7.32 (d, 1H), 7.35-7.55 (m, 7H), 8.2 (s, 1H), 8.7 (s, 1H), 10.9 (s, 1H), 11.15 (s, 1H)
MS-ESI : 425 [MH]+

Ammonium formate (20g, 326 mmol) and 10% palladium on carbon (1g) were added to a solution of 7-benzyloxy-4-(2,3-dimethylindol-5-ylamino)-6-methoxyquinazoline (10g, 22 mmol) in DMF (100ml) and methanol (300ml). After stirring for 3 hours at ambient temperature, aqueous ammonia (120ml) was added. The precipitate was filtered, washed with water and dried under vacuum. The residue was triturated with ethyl acetate and ether and was filtered, dried under vacuum and purified by column chromatography eluting with methanol/methylene chloride (5/95 followed by 10/90) to give 4-(2,3-dimethylindol-5-ylamino)-7-hydroxy-6-methoxyquinazoline (5.5g, 75%).
^{1}H NMR Spectrum: ($DMSOd_6$) 2.2 (s, 3H), 2.35 (s, 3H), 3.97 (s, 3H), 7.0 (s, 1H), 7.22 (d, 1H), 7.3 (d, 1H), 7.55 (s, 1H), 7.85 (s, 1H), 8.28 (s, 1H), 9.35 (s, 1H), 10.2 (br s, 1H), 10.62 (s, 1H)
MS-ESI : 335 [MH]+

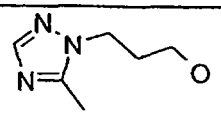
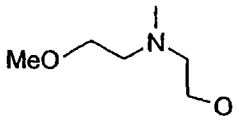
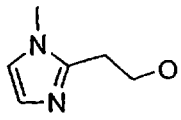
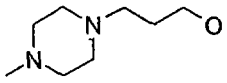
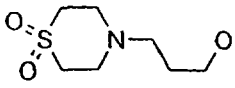
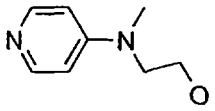
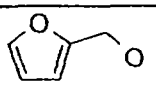
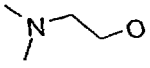
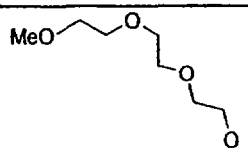
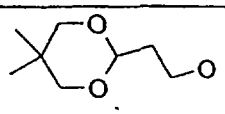
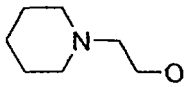
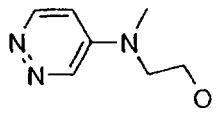
Examples 130-145

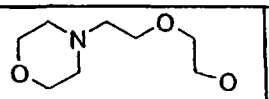
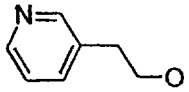
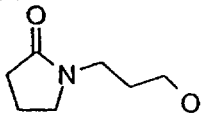
Using an analogous procedure to that described in Example 129, 4-(2,3-dimethylindol-5-ylamino)-7-hydroxy-6-methoxyquinazoline (68 mg, 0.2 mmol), (prepared as described for the starting material in Example 129), was reacted with the appropriate alcohol to give the compounds described in Table IX.

Table IX



Example	Weight (mg)	Yield %	MS-ESI	R	Note

number			[MH]+		
130	10	11	458		a
131	63	69	450		b
132	5	6	443		c
133	35	36	475		d
134	53	51	510		e
135	56	58	469		f
136	4	4.6	415		g
137	29	35	406		h
138	49	56	432		i
139	8	8.6	481		j
140	15	15	477		k
141	38	42	446		l
142	69	72	470		m

143	21	21	492		n
144	36	40	440		o
145	31	33	460		p

a) 4-(2,3-Dimethylindol-5-ylamino)-7-hydroxy-6-methoxyquinazoline (68 mg, 0.2 mmol) was reacted with 3-(5-methyl-[1,2,4]-triazol-1-yl)propan-1-ol (40 mg) to give **4-(2,3-dimethylindol-5-ylamino)-6-methoxy-7-(3-(5-methyl-1*H*-[1,2,4]-triazol-1-yl)propoxy)quinazoline.**

The starting material was prepared as follows:

Under argon, 1,2,4-triazole (13.8g, 200mmol) was added to a solution of sodium ethoxide (freshly prepared from sodium (4.6g) and ethanol (250ml)). After complete dissolution, 3-bromopropan-1-ol (18ml, 200 mmol) was added dropwise. The mixture was refluxed for 18 hours and the solid was filtered and washed with ethanol. The filtrate was evaporated and the residue was purified by column chromatography eluting with methylene chloride/methanol (9/1) to give 3-(1,2,4-triazol-1-yl)propan-1-ol (22.8 g, 90%).

^{1}H NMR Spectrum: ($CDCl_3$): 2.12 (m, 2H) ; 2.6 (br s, 1H) ; 3.65 (t, 2H) ; 4.35 (t, 2H) ; 7.95 (s, 1H) ; 8.1 (s, 1H)

To a solution of 3-(1,2,4-triazol-1-yl)propan-1-ol (7 g, 55 mmol) in DMF (70ml) was added *tert*butyldimethylsilyl chloride (9.1g, 60 mmol) followed by DMAP (336mg, 2.7 mmol) followed by imidazole (4.5gr, 66 mmol). After stirring overnight at ambient temperature, the volatiles were removed under vacuum and the residue was partitioned between water and ethyl acetate/ether. The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography eluting with methylene chloride/ether (6/4) to give 3-(*tert*butyldimethylsilyloxy)-1-(1,2,4-triazol-1-yl)propane (11.1 gr, 84%).

MS-EI : 242 [MH]+

^{1}H NMR Spectrum: ($CDCl_3$) 0.25 (s, 6H) ; 0.9 (s, 9H) ; 2.05 (m, 2H) ; 3.52 (t, 2H) ; 4.25 (t,

2H) ; 7.9 (s, 1H) ; 8.02 (s, 1H)

To a solution of 3-(*tert*butyldimethylsilyloxy)-1-(1,2,4-triazol-1-yl)propane (7 g, 29 mmol) in DMF (100ml) cooled at -70°C was added 2.5M n-butyllithium (17.4 ml) over 45 minutes. After stirring for 90 minutes at -70°C, methyl iodide (3.6ml, 58 mmol) was added. After stirring for 2 hours at ambient temperature, the mixture was poured onto saturated ammonium chloride. The mixture was then diluted with ether and ethyl acetate. The organic layer was separated, washed with aqueous sodium thiosulphate followed by brine, dried ($MgSO_4$) and evaporated to give 3-(*tert*butyldimethylsilyloxy)-1-(5-methyl-[1,2,4]-triazol-1-yl)propane (7.3 g, 98%).

MS-EI : 256 [MH]+

^{1}H NMR Spectrum: ($CDCl_3$) 0.25 (s, 6H) ; 0.85 (s, 9H) ; 2.0 (, 2H) ; 2.4 (s, 3H) ; 3.52 (t, 2H) ; 4.15 (t, 2H) ; 7.72 (s, 1H)

To a solution of ammonium fluoride (10.4 g, 280 mmol) in methanol (110ml) was added a solution of 3-(*tert*butyldimethylsilyloxy)-1-(5-methyl-[1,2,4]-triazol-1-yl)propane (7.2 g, 28 mmol) in methanol (30ml). The mixture was refluxed for 4.5 hours. After cooling, silica (100g) was added and the volatiles were removed under vacuum. The residue was added onto a column of silica and eluted with a mixture of methylene chloride/ethyl acetate (1/1) followed by methylene chloride/methanol (9/1) to give 3-(5-methyl-[1,2,4]-triazol-1-yl)propan-1-ol (3.65 g, 92%).

MS-ESI : 142 [MH]+

^{1}H NMR Spectrum: ($CDCl_3$) 2.05 (m, 2H) ; 2.5 (s, 3H) ; 3.62 (t, 2H) ; 4.25 (t, 2H) ; 7.8 (s, 1H)

b) 4-(2,3-Dimethylindol-5-ylamino)-7-hydroxy-6-methoxyquinazoline (68 mg, 0.2 mmol) was reacted with 2-(N-(2-methoxyethyl)-N-methylamino)ethanol (38 mg), (prepared as described for the starting material in Example 59), to give **4-(2,3-dimethylindol-5-ylamino)-6-methoxy-7-(2-(N-(2-methoxyethyl)-N-methylamino)ethoxy)quinazoline**.

^{1}H NMR Spectrum: ($DMSOd_6$) 2.15 (s, 3H), 2.35 (s, 6H), 2.65 (t, 2H), 2.85 (t, 2H), 3.25 (s, 3H), 3.45 (t, 2H), 3.95 (s, 3H), 4.2 (t, 2H), 7.15 (s, 1H), 7.22 (s, 1H), 7.3 (dd, 1H), 7.55 (s, 1H), 7.85 (s, 1H), 8.3 (s, 1H), 9.4 (s, 1H), 10.62 (s, 1H)

c) 4-(2,3-Dimethylindol-5-ylamino)-7-hydroxy-6-methoxyquinazoline (68 mg, 0.2 mmol) was

reacted with 2-(1-methylimidazol-2-yl)ethanol (36 mg), (EP 06751112 A1), to give **4-(2,3-dimethylindol-5-ylamino)-6-methoxy-7-(2-(1-methylimidazol-2-yl)ethoxy)quinazoline.** ^{1}H NMR Spectrum: ($DMSOd_6$) 2.15 (s, 3H), 2.32 (s, 3H), 3.2 (t, 2H), 3.7 (s, 3H), 3.95 (s, 3H), 4.45 (t, 2H), 6.8 (s, 1H), 7.05 (s, 1H), 7.15 (s, 1H), 7.22 (d, 1H), 7.3 (dd, 1H), 7.55 (s, 1H), 7.88 (s, 1H), 8.32 (s, 1H), 9.4 (s, 1H), 10.62 (s, 1H)

d) 4-(2,3-Dimethylindol-5-ylamino)-7-hydroxy-6-methoxyquinazoline (68 mg, 0.2 mmol) was reacted with 1-(3-hydroxypropyl)-4-methylpiperazine (45 mg) to give **4-(2,3-dimethylindol-5-ylamino)-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline.** ^{1}H NMR Spectrum: ($DMSOd_6$) 1.9-2.0 (m, 2H), 2.15 (2s, 6H), 2.0-2.9 (m, 8H), 2.32 (s, 3H), 2.45 (t, 2H), 3.95 (s, 3H), 4.2 (t, 2H), 7.1 (s, 1H), 7.22 (d, 1H), 7.3 (dd, 1H), 7.55 (s, 1H), 7.85 (s, 1H), 8.3 (s, 1H), 9.4 (s, 1H), 10.62 (s, 1H)

The starting material was prepared as follows:

3-Bromopropan-1-ol (20ml, 20mmol) was added dropwise to a solution of 1-methylpiperazine (29ml, 26 mmol) in ethanol (200ml). Potasium carbonate (83 gr, 60 mmol) was added and the mixture was refluxed for 20 hours. After cooling, the solid was filtered and the filtrate was evaporated. The residue was triturated with ether, filtrate and evaporated. The residue was distilled at about 60-70°C under about 0.2 mm Hg to give 1-(3-hydroxypropyl)-4-methylpiperazine (17g, 53%).
^{1}H NMR Spectrum: ($CDCl_3$) 1.72 (m, 2H) ; 2.3 (s, 3H) ; 2.2-2.8 (m, 8H) ; 2.6 (t, 2H) ; 3.8 (t, 2H) ; 5.3 (br s, 1H)

e) 4-(2,3-Dimethylindol-5-ylamino)-7-hydroxy-6-methoxyquinazoline (68 mg, 0.2 mmol) was reacted with 3-(1,1-dioxothiomorpholino)-1-propanol (55 mg), (prepared as described for the starting material in Example 5), to give **4-(2,3-dimethylindol-5-ylamino)-6-methoxy-7-(3-(1,1-dioxothiomorpholino)propoxy)quinazoline.**
^{1}H NMR Spectrum: ($DMSOd_6$) 1.9-2.0 (m, 2H), 2.5 (s, 9H), 2.65 (t, 2H), 2.9 (br s, 4H), 3.15 (br s, 4H), 3.95 (s, 3H), 4.25 (t, 2H), 7.2 (s, 1H), 7.85 (s, 1H), 8.0 (dd, 1H), 8.15 (d, 1H), 8.2 (s, 1H), 8.45 (s, 1H), 9.6 (s, 1H), 10.95 (s, 1H)

f) 4-(2,3-Dimethylindol-5-ylamino)-7-hydroxy-6-methoxyquinazoline (68 mg, 0.2 mmol) was

reacted with 2-(N-methyl-N-(4-pyridyl)amino)ethanol (43mg), (EP 0359389), to give **4-(2,3-dimethylindol-5-ylamino)-6-methoxy-7-(2-(N-methyl-N-(4-pyridyl)amino)ethoxy)quinazoline**.

^{1}H NMR Spectrum: ($DMSOd_6$) 2.15 (s, 3H), 2.35 (s, 3H), 3.07 (s, 3H), 3.85 (t, 2H), 3.95 (s, 3H), 4.3 (t, 2H), 6.7 (d, 2H), 7.15 (s, 1H), 7.22 (d, 1H), 7.3 (dd, 1H), 7.55 (s, 1H), 7.85 (s, 1H), 8.15 (d, 2H), 8.3 (s, 1H), 9.4 (s, 1H), 10.65 (s, 1H)

g) 4-(2,3-Dimethylindol-5-ylamino)-7-hydroxy-6-methoxyquinazoline (68 mg, 0.2 mmol) was reacted with 2-furanmethanol (28 mg) to give **4-(2,3-dimethylindol-5-ylamino)-6-methoxy-7-(2-furylmethoxy)quinazoline**.

h) 4-(2,3-Dimethylindol-5-ylamino)-7-hydroxy-6-methoxyquinazoline (68 mg, 0.2 mmol) was reacted with 2-N,N-dimethylethanolamine (25 mg) to give **4-(2,3-dimethylindol-5-ylamino)-6-methoxy-7-(2-(N,N-dimethylamino)ethoxy)quinazoline**.

^{1}H NMR Spectrum: ($DMSOd_6$) 2.15 (s, 3H), 2.25 (s, 6H), 2.32 (s, 3H), 2.72 (t, 2H), 3.95 (s, 3H), 4.2 (t, 2H), 7.15 (s, 1H), 7.22 (d, 1H), 7.3 (dd, 1H), 7.55 (s, 1H), 7.85 (s, 1H), 8.32 (s, 1H), 9.4 (s, 1H), 10.6 (s, 1H)

i) 4-(2,3-Dimethylindol-5-ylamino)-7-hydroxy-6-methoxyquinazoline (68 mg, 0.2 mmol) was reacted with 1-(2-hydroxyethyl)pyrrolidine (33 mg) to give **4-(2,3-dimethylindol-5-ylamino)-6-methoxy-7-(2-(pyrrolidin-1-yl)ethoxy)quinazoline**.

^{1}H NMR Spectrum: ($DMSOd_6$) 1.65-1.75 (m, 4H), 2.15 (s, 3H), 2.35 (s, 3H), 2.55-2.65 (m, 4H), 2.9 (t, 2H), 3.95 (s, 3H), 4.25 (t, 2H), 7.15 (s, 1H), 7.22 (d, 1H), 7.3 (dd, 1H), 7.55 (s, 1H), 7.85 (s, 1H), 8.32 (s, 1H), 9.4 (s, 1H), 10.62 (s, 1H)

j) 4-(2,3-Dimethylindol-5-ylamino)-7-hydroxy-6-methoxyquinazoline (68 mg, 0.2 mmol) was reacted with triethylene glycol monomethyl ether (47 mg) to give **4-(2,3-dimethylindol-5-ylamino)-6-methoxy-7-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)quinazoline**.

k) 4-(2,3-Dimethylindol-5-ylamino)-7-hydroxy-6-methoxyquinazoline (68 mg, 0.2 mmol) was reacted with 5,5-dimethyl-1,3-dioxane-2-ethanol (46 mg) to give **7-(2-(5,5-dimethyl-1,3-dioxan-2-yl)ethoxy)-4-(2,3-dimethylindol-5-ylamino)-6-methoxyquinazoline**.

^{1}H NMR Spectrum: ($DMSOd_6$) 0.7 (s, 3H), 1.15 (s, 3H), 2.05-2.1 (m, 2H), 2.1 (s, 3H), 2.6 (s, 3H), 3.42 (d, 2H), 3.57 (d, 2H), 4.0 (s, 3H), 4.22 (t, 2H), 4.7 (t, 1H), 7.2 (s, 1H), 7.82 (s, 1H), 8.0 (dd, 1H), 8.17 (d, 1H), 8.3 (s, 1H), 8.45 (s, 1H), 9.6 (s, 1H), 10.95 (s, 1H)

l) 4-(2,3-Dimethylindol-5-ylamino)-7-hydroxy-6-methoxyquinazoline (68 mg, 0.2 mmol) was reacted with 1-(2-hydroxyethyl)piperidine (37 mg) to give **4-(2,3-dimethylindol-5-ylamino)-6-methoxy-7-(2-piperidinoethoxy)quinazoline.**

^{1}H NMR Spectrum: ($DMSOd_6$) 1.3-1.45 (m, 2H), 1.45-1.6 (m, 4H), 2.15 (s, 3H), 2.35 (s, 3H), 2.45 (br s, 4H), 2.75 (t, 2H), 3.95 (s, 3H), 4.25 (t, 2H), 7.15 (s, 1H), 7.22 (d, 1H), 7.3 (dd, 1H), 7.55 (s, 1H), 7.85 (s, 1H), 8.3 (s, 1H), 9.4 (s, 1H), 10.62 (s, 1H)

m) 4-(2,3-Dimethylindol-5-ylamino)-7-hydroxy-6-methoxyquinazoline (68 mg, 0.2 mmol) was reacted with 2-(N-methyl-N-(pyridazin-4-yl)amino)ethanol (44 mg) to give **4-(2,3-dimethylindol-5-ylamino)-6-methoxy-7-(2-(N-methyl-N-(pyridazin-4-yl)amino)ethoxy)quinazoline.**

^{1}H NMR Spectrum: ($DMSOd_6$) 2.15 (s, 3H), 2.32 (s, 3H), 3.1 (s, 3H), 3.9 (s, 3H), 3.95 (t, 2H), 4.35 (t, 2H), 6.85 (dd, 1H), 7.15 (s, 1H), 7.20 (d, 1H), 7.28 (dd, 1H), 7.55 (s, 1H), 7.85 (s, 1H), 8.3 (s, 1H), 8.58 (d, 1H), 8.9 (d, 1H), 9.4 (s, 1H), 10.62 (s, 1H)

The starting material was prepared as follows:

A solution of 4-bromo-3,6-dichloro-pyridazine (1.11g, 5mmol), (J.Chem. Soc., Perkin Trans I, 1974, 696), and 2-(methylamino)ethanol (0.75g, 10mmol) in isopropanol (10ml) was heated at reflux for 30 minutes. The solvent was removed by evaporation, the residue was partitioned between methylene chloride and water and the aqueous layer was adjusted to pH9 with solid potassium carbonate. The organic layer was separated, washed with brine, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was triturated with ether, collected by filtration and dried under vacuum to give 2-(N-(3,6-dichloropyridazin-4-yl)-N-methylamino)ethanol (1g, 90%).

^{1}H NMR Spectrum: ($CDCl_3$) 2.1(br s, 1H); 3.09(s, 3H); 3.71(t, 2H); 3.93(t, 2H); 6.8(s, 1H)

MS - ESI: 221 $[MH]^+$

A mixture of 2-(N-(3,6-dichloropyridazin-4-yl)-N-methylamino)ethanol (444mg,

2mmol) and 10% palladium-on-charcoal catalyst (150mg) in ethanol (15ml), methanol (5ml) and aqueous ammonia (15ml) was stirred under hydrogen at 3 atmospheres pressure for 4 hours. The catalyst was removed by filtration and the solvent removed from the filtrate by evaporation. The residue was dissolved in methylene chloride, the insoluble material was removed by filtration and the solvent was removed from the filtrate by evaporation. The residue was purified by column chromatography on neutral aluminum oxide eluting with methylene chloride/methanol (95/5 followed by 90/10). The purified product was triturated with petroleum ether, the solid product was collected by filtration and dried under vacuum to give 2-(N-methyl-N-(pyridazin-4-yl)amino)ethanol (275mg, 91%).

^{1}H NMR Spectrum: ($CDCl_3$) 3.06(s, 3H); 3.57(t, 2H); 3.89(t, 2H); 6.52(dd, 1H); 8.48(d, 1H); 8.54 (d, 1H)

MS - ESI: 153 $[MH]^+$

n) 4-(2,3-Dimethylindol-5-ylamino)-7-hydroxy-6-methoxyquinazoline (68 mg, 0.2 mmol) was reacted with 2-(2-morpholinoethoxy)ethanol (50 mg) to give **4-(2,3-dimethylindol-5-ylamino)-6-methoxy-7-(2-(2-morpholinoethoxy)ethoxy)quinazoline.**

^{1}H NMR Spectrum: ($DMSOd_6$) 2.18 (s, 3H), 2.35 (s, 3H), 2.35-2.45 (m, 4H), 2.45-2.5 (m, 2H), 3.5-3.55 (m, 4H), 3.65 (t, 2H), 3.8-3.85 (m, 2H), 3.95 (s, 1H), 4.25 (m, 2H), 7.15 (s, 1H), 7.22 (d, 1H), 7.3 (dd, 1H), 7.55 (s, 1H), 7.85 (s, 1H), 8.3 (s, 1H), 9.4 (s, 1H), 10.62 (s, 1H)

The starting material was prepared as follows :

2-(2-Chloroethoxy)ethanol (1.25g, 10mmol) was added to a mixture of morpholine (2.58g, 30mmol) and potassium carbonate (5.5g, 40mmol) in acetonitrile (50ml). The mixture was heated at reflux for 6 hours and then stirred for 18 hours at ambient temperature. The insolubles were removed by filtration and the volatiles were removed from the filtrate by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol (95/5 followed by 90/10 and then 80/20) to give 2-(2-morpholinoethoxy)ethanol (600mg, 34%).

^{1}H NMR Spectrum: ($CDCl_3$) 2.5(br s, 4H); 2.59(t, 2H); 3.6-3.85(m, 10H)

MS - (EI): 175 $[M.]^+$

o) 4-(2,3-Dimethylindol-5-ylamino)-7-hydroxy-6-methoxyquinazoline (68 mg, 0.2 mmol) was reacted with 3-(2-hydroxyethyl)pyridine (35 mg) to give **4-(2,3-dimethylindol-5-ylamino)-6-methoxy-7-(2-(3-pyridyl)ethoxy)quinazoline**.

^{1}H NMR Spectrum: ($DMSOd_6$) 2.15 (s, 3H), 2.32 (s, 3H), 3.15 (t, 2H), 3.95 (s, 3H), 4.4 (t, 2H), 7.2 (s, 1H), 7.22 (d, 1H), 7.3 (dd, 1H), 7.35 (dd, 1H), 7.55 (s, 1H), 7.8 (d, 1H), 7.85 (s, 1H), 8.32 (s, 1H), 8.45 (dd, 1H), 8.6 (s, 1H), 9.4 (s, 1H), 10.68 (s, 1H)

p) 4-(2,3-Dimethylindol-5-ylamino)-7-hydroxy-6-methoxyquinazoline (68 mg, 0.2 mmol) was reacted with 1-(3-hydroxypropyl)pyrrolidin-2-one (41 mg) to give **4-(2,3-dimethylindol-5-ylamino)-6-methoxy-7-(3-(2-oxopyrrolidin-1-yl)propoxy)quinazoline**.

^{1}H NMR Spectrum: ($DMSOd_6$) 1.9-2.05 (m, 4H), 2.12 (s, 3H), 2.15-2.3 (m, 2H), 2.6 (s, 3H), 3.3-3.45 (m, 4H), 4.0 (s, 3H), 4.15 (t, 2H), 7.15 (s, 1H), 7.82 (s, 1H), 8.0 (dd, 1H), 8.17 (d, 1H), 8.3 (s, 1H), 8.45 (s, 1H), 9.6 (s, 1H), 10.95 (s, 1H)

Example 146

Using an analogous procedure to that described for Example 121, 4-chloro-6-methoxy-7-(3-pyrrolidinopropoxy)quinazoline (150 mg, 0.47 mmol), (prepared as described for the starting material in Example 9), was reacted with 6-hydroxy-2-methylindole (83 mg, 0.56 mol), (Eur. J. Med. Chem. 1975, 10, 187), to give **6-methoxy-4-(2-methylindol-6-yloxy)-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline** (170 mg, 85 %).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.65-1.8 (m, 4H), 1.95-2.05 (m, 2H), 2.42 (s, 3H), 2.5 (br s, 1H), 2.6 (t, 2H), 4.0 (s, 3H), 4.27 (t, 2H), 6.2 (s, 1H), 6.85 (dd, 1H), 7.2 (s, 1H), 7.4 (s, 1H), 7.45 (d, 1H), 7.6 (s, 1H), 8.5 (s, 1H)

MS-ESI : 433 $[MH]^+$

Elemental analysis	Found	C 68.3	H 6.4	N 12.8
$C_{25}H_{28}N_4O_3$ 0.4 H_2O	Requires	C 68.3	H 6.6	N 12.7%

Example 147

Using an analogous procedure to that described in Example 123, 6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(piperidin-4-yl)ethoxy)quinazoline (120 mg, 0.28 mmol) was used to give **7-(2-(1-(2-methoxyethyl)piperidin-4-yl)ethoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline** (55 mg, 40 %).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.15-1.3 (m, 2H), 1.4-1.55 (m, 1H), 1.65-1.8 (m, 4H), 1.95 (t, 2H), 2.4 (s, 3H), 2.42 (t, 2H), 2.85 (d, 2H), 3.25 (s, 3H), 3.42 (t, 2H), 4.0 (s, 3H), 4.22 (t, 2H), 6.15 (s, 1H), 6.85 (dd, 1H), 7.25 (s, 1H), 7.3 (d, 1H), 7.38 (s, 1H), 7.59 (s, 1H), 8.5 (s, 1H).

MS-ESI : 491 $[MH]^+$

Elemental analysis	Found	C 65.3	H 7.1 N 10.9
$C_{28}H_{34}N_4O_4$ 1.3 H_2O	Requires	C 65.4	H 7.2 N 10.9%

Example 148

Using an analogous procedure to that described in Example 120 OR 121 PER PP, 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (160 mg, 0.48 mmol), (prepared as described for the starting material in Example 1), was reacted with 1,2-dimethyl-5-hydroxyindole (92 mg, 0.57 mol), (Tetrahedron 1994, 50, 13433), to give **4-(1,2-dimethylindol-5-yloxy)-6-methoxy-7-(3-morpholinopropoxy)quinazoline** (163 mg, 74 %).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.95-2.1 (m, 2H), 2.4 (br s, 4H), 2.45 (s, 3H), 2.5 (t, 2H), 3.65 (t, 4H), 3.75 (s, 3H), 4.0 (s,3H), 4.25 (t, 2H), 6.25 (s, 1H), 6.95 (dd, 1H), 7.3 (s, 1H), 7.38 (s, 1H), 7.45 (d, 1H), 7.6 (s, 1H), 8.5 (s, 1H)

MS-ESI : 463 $[MH]^+$

Elemental analysis	Found	C 67.2	H 6.5 N 12.1
$C_{26}H_{30}N_4O_4$	Requires	C 67.5	H 6.5 N 12.1%

Example 149

Using an analogous procedure to that described in Example 124, 7-hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (2.3 g, 7.16 mmol), (prepared as described in Example 49), was reacted with (N-methyl-N-*tert*-butoxycarbonyl)ethanolamine (1.51 g, 8.6 mmol) to give **6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(N-methyl-N-*tert*-butoxycarbonylamino)ethoxy)quinazoline** (1.93 g, 56 %).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.4 (s, 9H), 2.4 (s, 3H), 2.90 (s, 3H), 3.65 (t, 2H), 4.0 (s, 3H), 4.35 (t, 2H), 6.15 (s, 1H), 6.8 (dd, 1H), 7.28 (s, 1H), 7.35 (d, 1H), 7.42 (s, 1H), 7.6 (s, 1H), 8.5 (s, 1H) ;

MS-ESI : 479 $[MH]^+$

Elemental analysis	Found	C 65.0	H 6.4 N 11.7
$C_{26}H_{30}N_4O_5S$	Requires	C 65.3	H 6.3 N 11.7%

Example 150

A solution of 6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(N-methyl-N-*tert*-butoxycarbonylamino)ethoxy)quinazoline (550 mg, 1.15 mmol), (prepared as described in Example 149), in methylene chloride (10 ml) containing TFA (12 ml) was stirred for 3 hours at ambient temperature. After removal of the volatiles under vacuum, the residue was partitioned between methylene chloride and sodium hydrogen carbonate. The pH of the aqueous layer was adjusted to 11 with 2N sodium hydroxide. The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and evaporated. The residue was triturated with ether, filtered and dried under vacuum to give **6-methoxy-4-(2-methylindol-5-yloxy)-7-(2-(N-methylamino)ethoxy)quinazoline** (356 mg, 82 %).

^{1}H NMR Spectrum: ($DMSOd_6$) 2.4 (s, 3H), 2.5 (s, 3H), 2.9 (t, 2H), 4.0 (s, 3H), 4.25 (t, 2H), 6.25 (s, 1H), 6.9 (dd, 1H), 7.25 (s, 1H), 7.3 (d, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 8.5 (s, 1H), 11.0 (s, 1H)

MS-ESI : 379 [MH]+

Elemental analysis	Found	C 64.6	H 5.8	N 14.2
$C_{21}H_{22}N_4O_3$ 0.7 H_2O	Requires	C 64.5	H 6.0	N 14.3%

Example 151

A mixture of 6-methoxy-4-(2-methylindol-5-yloxy)-7-(piperidin-4-ylmethoxy)quinazoline (419 mg, 1 mmol), (prepared as described in Example 70), in DMF (6 ml) containing chloroacetonitrile (114 mg, 1.5 mmol), potassium carbonate (346 mg, 2.5 mmol) and potassium iodide (50 mg, 0.3 mmol) was stirred at ambient temperature overnight. The mixture was poured into water and the precipitate was filtered, washed with water and dried under vacuum. The residue was purified by column chromatography, eluting with methylene chloride, followed by methylene chloride/methanol (98/2 and 95/5). After removal of the solvent under vacuum, the residue was triturated with ether, filtered, washed with ether and dried under vacuum to give **7-((1-cyanomethyl)piperidin-4-ylmethoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline** (304 mg, 66 %).

^{1}H NMR Spectrum: ($DMSOd_6$, CF_3COOD) 1.6-1.8 (m, 2H), 2.05-2.2 (d, 2H), 2.2-2.3 (m, 1H), 2.45 (s, 3H), 3.2 (t, 2H), 3.65 (d, 2H), 4.1 (s, 3H), 4.22 (d, 2H), 4.6 (s, 2H), 6.2 (s, 0.5H, partially exchanged), 6.9 (dd, 1H), 7.35 (s, 1H), 7.4 (d, 1H), 7.55 (s, 1H), 7.8 (s, 1H), 9.1 (s,

1H)

MS-ESI : 458 $[MH]^+$

Elemental analysis	Found	C 67.6	H 6.1	N 15.2
$C_{26}H_{27}N_5O_3$ 0.2 H_2O	Requires	C 67.7	H 6.0	N 15.2%

Example 152

A mixture of 4-chloro-6-methoxy-7-(3-(N-methyl-N-methylsulphonylamino)propoxy)quinazoline (360 mg, 1.00 mmol), potassium carbonate (215 mg, 1.56 mmol) and 5-hydroxyindole (147 mg, 1.10 mmol) in DMF (8.0 ml) was stirred at 100 °C for 5 hours and allowed to cool to ambient temperature. The solvent was removed by evaporation and the residue purified by silica column chromatography eluting with methanol (2.5 to 5%) in dichloromethane. The resulting solid was recrystallised from ethyl acetate, filtered and washed with diethyl ether to give **4-(indol-5-yloxy)-6-methoxy-7-(3-(N-methyl-N-methylsulphonylamino)propoxy)quinazoline** (77mg, 17%).

^{1}H NMR Spectrum: ($DMSOd_6$) 2.07 (m, 2H), 2.78 (s, 3H), 2.87 (s, 3H), 3.25 (t, 2H), 3.97 (s, 3H), 4.23 (t, 2H), 6.43 (br s, 1H), 6.96 (dd, 1H), 7.32 (s, 1H), 7.41 (m, 3H), 7.59 (d, 1H), 8.48 (s, 1H) and 11.17 (s, 1H)

MS (ESI) : 457 $(MH)^+$

Elemental analysis	Found	C 57.5	H 5.3	N 12.0	
$C_{22}H_{24}N_4O_5S$	Requires	C 57.9	H 5.3	N 12.3%	

The starting material was prepared as follows:

Using an analogous procedure to that described for the synthesis of the starting material in Example 5, 4-(4-bromo-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline was made in a similar way to 4-(4-chloro-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline using 4-bromo-2-fluorophenol instead of 4-chloro-2-fluorophenol.

A mixture of 4-(4-bromo-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline (9.64g, 26.4 mmol) and triphenylphosphine (20.9g, 79.8 mmol) in dichloromethane (240ml) was stirred under nitrogen, at ambient temperature for 30 minutes. 3-(N-*tert*Butoxycarbonyl)-propanolamine (6.26g, 35.8 mmol) was added followed by diethyl azodicarboxylate (12.4ml, 13.7g, 78.7 mmol). The reaction mixture was stirred for 2 hours. The solvent was then removed by evaporation and the residue taken up in acetonitrile (250ml). The solution was

concentrated to half the original volume and cooled. The resulting crystalline solid was filtered, washed with ether and dried to give 4-(4-bromo-2-fluorophenoxy)-7-(3-(N-*tert*butoxycarbonylamino)propoxy)-6-methoxyquinazoline (10.0g, 73%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.37 (s, 9H), 1.94 (t, 2H), 3.13 (q, 2H), 3.97 (s, 3H), 4.21 (t, 2H), 6.89 (br s, 1H), 7.38 (s, 1H), 7.43 - 7.53 (m, 2H), 7.57 (s, 1H), 7.78 (dd, 1H) and 8.55 (s, 1H)

MS (ESI) : 522 $(MH)^+$

Elemental analysis	Found	C 52.1 H 4.7 N 7.9
$C_{23}H_{25}N_3BrFO_5$	Requires	C 52.3 H 4.9 N 8.0%

4-(4-Bromo-2-fluorophenoxy)-7-(3-(N-*tert*butoxycarbonylamino)propoxy)-6-methoxyquinazoline (5.46g, 10.5mmol) was taken up in trifluoroacetic acid (75ml) and heated at 85°C for 1.5 hours. The solution was allowed to cool and the excess trifluoroacetic acid removed by evaporation. The residue was then treated with aqueous ammonia (0.88) solution, extracted with dichloromethane (3x150ml) and filtered through phase separating paper. The solvent was removed by evaporation to give 7-(3-aminopropoxy)-4-(4-bromo-2-fluorophenoxy)-6-methoxyquinazoline (4.42g, 100%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.87 (m, 2H), 2.73 (t, 2H), 3.98 (s, 3H), 4.26 (t, 2H), 7.40 (s, 1H), 7.50 (m, 2H), 7.55 (s, 1H), 7.78 (dd, 1H) and 8.55 (s, 1H)

MS (ESI) : 422 $(MH)^+$

A solution of 7-(3-aminopropoxy)-4-(4-bromo-2-fluorophenoxy)-6-methoxyquinazoline (2.71g, 6.4mmol) and triethylamine (1.1ml, 0.80g, 7.9mmol) in dichloromethane (15ml) was treated with a solution of methanesulphonyl chloride (0.53ml, 0.79g, 6.9mmol) in dichloromethane (10ml) and stirred at ambient temperature, under nitrogen for 18 hours. The dichloromethane was then removed by evaporation and THF (4ml) added. The resulting solution was treated with saturated aqueous sodium hydrogen carbonate solution (to pH 8), stirred vigorously for 30 minutes and the precipitate filtered, washed with water and dried to give 4-(4-bromo-2-fluorophenoxy)-6-methoxy-7-(3-(N-methylsulphonylamino)propoxy)quinazoline (2.98g, 93%).

^{1}H NMR Spectrum: ($DMSOd_6$) 2.01 (m, 2H), 2.90 (s, 3H), 3.15 (t, 2H), 3.96 (s, 3H), 4.25 (t, 2H), 7.06 (s, 1H), 7.40 (s, 1H), 7.49 (m, 2H), 7.56 (s, 1H), 7.78 (dd, 1H) and 8.54 (s, 1H)

MS (ESI) : 500/502 $(MH)^+$

4-(4-Bromo-2-fluorophenoxy)-6-methoxy-7-(3-(N-

methylsulphonylamino)propoxy)quinazoline (1.0g, 2mmol) was taken up in DMF (10ml), treated with sodium hydride (60% dispersion in mineral oil, 0.11g, 2.7mmol) and stirred, under nitrogen for 30 minutes. Methyl iodide (0.16ml, 2.6mmol) was added and the mixture stirred for 18 hours. The solvent was removed by evaporation and the residue taken up in water and extracted with dichloromethane (3x 30ml). The organic solution was then washed with water, brine, dried ($MgSO_4$) and evaporated to dryness. The crude product was purified by silica column chromatography eluting with methanol (2.5 to 5 %) in dichloromethane to give 4-(4-bromo-2-fluorophenoxy)-6-methoxy-7-(3-(N-methyl N-methylsulphonylamino) propoxy)quinazoline (0.86g, 83%).

^{1}H NMR Spectrum: ($DMSOd_6$) 2.06 (m, 2H), 2.78 (s, 3H), 2.87 (s, 3H), 3.24 (t, 2H), 3.97 (s, 3H), 4.23 (t, 2H), 7.39 (s, 1H), 7.48 (m, 2H), 7.55 (s, 1H), 7.78 (dd, 1H) and 8.54 (s, 1H)

MS (ESI) : 514/516 $(MH)^+$

4-(4-Bromo-2-fluorophenoxy)-6-methoxy-7-(3-(N-methyl N-methylsulphonylamino) propoxy)quinazoline (4.70g, 9.1mmol) was dissolved in 2N aqueous hydrochloric acid solution (85ml) and heated at reflux for 1 hour. After cooling, the solution was carefully poured into saturated aqueous sodium hydrogen carbonate solution (to pH8) and stirred vigorously for 30 minutes. The resulting precipitate was filtered and dried. The filter cake was then taken up as a suspension in acetone, filtered, washed with diethyl ether and dried to give 6-methoxy-7-(3-(N-methyl-N-methylsulphonylamino)propoxy)quinazolin-4-one (3.23g, 88%).

^{1}H NMR Spectrum: ($DMSOd_6$) 2.02 (m, 2H), 2.77 (s, 3H), 2.86 (s, 3H), 3.22 (t, 2H), 3.86 (s, 3H), 4.13 (t, 2H), 7.09 (s, 1H), 7.42 (s, 1H), 7.95 (s, 1H) and 12.02 (s, 1H)

MS (ESI) : 342 $(MH)^+$

6-Methoxy-7-(3-(N-methyl-N-methylsulphonylamino)propoxy)quinazolin-4-one (2.24g, 6.6mmol) was taken up in thionyl chloride (25ml) and treated with DMF (5 drops). The resulting solution was then heated at reflux for 1 hour followed by cooling to ambient temperature. The excess thionyl chloride was removed by evaporation followed by azeotroping with toluene (3x). The residue was basified with saturated aqueous sodium hydrogen carbonate solution (to pH8) and extracted twice with ethyl acetate. The organic solution was washed with water, brine, dried ($MgSO_4$) and evaporated to dryness to give 4-chloro-6-methoxy-7-(3-(N-methyl-N-methylsulphonylamino)propoxy)quinazoline (1.90g, 80%).

^{1}H NMR Spectrum: ($DMSOd_6$) 2.08 (m, 2H), 2.78 (s, 3H), 2.88 (s, 3H), 3.24 (t, 2H), 3.98 (s, 3H), 4.26 (t, 2H), 7.37 (s, 1H), 7.42 (s, 1H) and 8.86 (s, 1H)

MS (ESI) : 360$(MH)^+$

Example 153

A mixture of 4-chloro-6-methoxy-7-(3-(N-methyl-N-methylsulphonylamino)propoxy)quinazoline (360 mg, 1.00 mmol), (prepared as described for the starting material in Example 152), potassium carbonate (215 mg, 1.56 mmol) and 5-hydroxy-2-methylindole (162 mg, 1.10 mmol) in DMF (8.0 ml) was stirred at 100 °C for 5 hours and allowed to cool to ambient temperature. The solvent was removed by evaporation and the residue was purified by silica column chromatography eluting with methanol (2.5 to 5%) in dichloromethane . The resulting solid was recrystallised from ethyl acetate, filtered and washed with diethyl ether to give **6-methoxy-4-(2-methylindol-5-yloxy)-7-(3-(N-methyl-N-methylsulphonylamino)propoxy)quinazoline** (166mg, 35%).

^{1}H NMR Spectrum: ($DMSOd_6$) 2.06 (m, 2H), 2.38 (s, 3H), 2.79 (s, 3H), 2.89 (s, 3H), 3.24 (t, 2H), 3.96 (s, 3H), 4.21 (t, 2H), 6.11 (br s, 1H), 6.87 (dd, 1H), 7.23 (d, 1H), 7.30 (d, 1H), 7.35 (s, 1H), 7.57 (s, 1H), 8.46 (s, 1H) and 10.98 (s, 1H)

MS (ESI) : 471 $(MH)^+$

Elemental analysis	Found	C 58.3	H 5.6	N 11.7	
$C_{23}H_{26}N_4O_5S$	Requires	C 58.7	H 5.6	N 11.9%	

Example 154

A mixture of 4-chloro-6-methoxy-7-(3-(N-methyl-N-methylsulphonylamino)propoxy)quinazoline (150 mg, 0.42 mmol), (prepared as described for the starting material in Example 152), potassium carbonate (90 mg, 0.63 mmol) and 7-hydroxyquinoline (67 mg, 0.46 mmol) in DMF (5.0 ml) was stirred at 100 °C for 2 hours and allowed to cool to ambient temperature. The solvent was removed by evaporation and the residue taken up in 2N. aqueous sodium hydroxide solution. The precipitate was filtered off, dried, taken up in dichloromethane and the solution filtered through phase separating paper. The filtrate was then evaporated to dryness. The resulting solid was recrystallised from acetonitrile, filtered and washed with diethyl ether to give **6-methoxy-7-(3-(N-methyl-N-methylsulphonylamino)propoxy)-4-(quinolin-7-yloxy)quinazoline** (122mg, 63%).

^{1}H NMR Spectrum: ($DMSOd_6$) 2.09 (m, 2H), 2.79 (s, 3H), 2.90 (s, 3H), 3.26 (t, 2H), 3.99 (s, 3H), 4.26 (t, 2H), 7.39 (s, 1H), 7.54 (dd, 1H), 7.56 (dd, 1H), 7.60 (s, 1H), 7.91 (d, 1H), 8.09 (d, 1H), 8.44 (d, 1H), 8.55 (s, 1H) and 8.93 (dd, 1H)

MS (ESI) : 469 $(MH)^+$

Elemental analysis	Found	C 58.6	H 5.1	N 11.9	
$C_{23}H_{24}N_4O_5S$	Requires	C 59.0	H 5.2	N 12.0%	

Example 155

A mixture of 4-chloro-6-methoxy-7-(3-(N-methyl-N-methylsulphonylamino)propoxy)quinazoline (150 mg, 0.42 mmol), (prepared as described for the starting material in Example 152), potassium carbonate (90 mg, 0.63 mmol) and 7-hydroxy-4-methylquinoline (71 mg, 0.46 mmol), (Chem. Berich. 1967, 100, 2077), in DMF (5.0 ml) was stirred at 100 °C for 2 hours and allowed to cool to ambient temperature. The DMF solvent was removed by evaporation and the residue was taken up in 2N aqueous sodium hydroxide solution. The precipitate was filtered off, dried, taken up in dichloromethane and then filtered through phase separating paper. The solution was then evaporated to dryness. The resulting solid was recrystallised from acetonitrile, filtered and washed with diethyl ether to give **6-methoxy-7-(3-(N-methyl-N-methylsulphonylamino)propoxy)-4-(4-methylquinolin-7-yloxy)quinazoline** (84mg, 42%).

^{1}H NMR Spectrum: ($DMSOd_6$) 2.09 (m, 2H), 2.71 (s, 3H), 2.79 (s, 3H), 2.89 (s, 3H), 3.25 (t, 2H), 3.98 (s, 3H), 4.25 (t, 2H), 7.37 (s, 1H), 7.38 (d, 1H), 7.61 (dd, 1H), 7.63 (s, 1H), 7.89 (d, 1H), 8.20 (d, 1H), 8.54 (s, 1H) and 8.76 (d, 1H)

MS (ESI) : 483 $(MH)^+$

Elemental analysis	Found	C 59.1	H 5.3	N 11.5	
$C_{24}H_{26}N_4O_5S$	Requires	C 59.1	H 5.0	N 12.0%	

Example 156

A mixture of (*R*,*S*)-4-chloro-6-methoxy-7-((1-methylpiperidin-3-yl)methoxy)quinazoline (90 mg, 0.28 mmol), (prepared as described for the starting material in Example 7), potassium carbonate (60 mg, 0.44 mmol) and 7-hydroxy-4-trifluoromethylquinoline (65 mg, 0.31 mmol), (prepared as in Ukr. Khim. Zh. (Russ. Ed) Vol. 59, No. 4, pp. 408-411, 1993), in DMF (2 ml) was stirred at 100 °C for 6 hours and then

allowed to cool to ambient temperature. The DMF solvent was removed by evaporation, the residue was taken up in methanol/dichloromethane (1/1) and pre-absorbed onto silica. The crude mixture was purified by silica column chromatography eluting with dichloromethane/methanol/0.880 aqueous ammonia (95/5/1) and the product recrystallised from acetonitrile to give **(*R*,*S*)-6-methoxy-7-((1-methylpiperidin-3-yl)methoxy)-4-(4-trifluoromethylquinolin-7-yloxy)quinazoline** (58mg, 42%).

^{1}H NMR Spectrum: ($DMSOd_6$ 100°C) 1.24 (m, 1H), 1.59 (m, 1H), 1.70 (m, 1H), 1.83 (m, 1H), 2.05 (m, 2H), 2.17 (m, 1H), 2.24 (s, 3H), 2.64 (dt, 1H), 2.84 (dd, 1H), 4.05 (s, 3H), 4.18 (d, 2H), 7.43 (s, 1H), 7.69 (s, 1H), 7.87 (dd, 1H), 7.96 (d, 1H), 8.18 (s, 1H), 8.25 (dd, 1H), 8.59 (s, 1H) and 9.16 (d, 1H)

MS (ESI) : 499 $(MH)^+$

Elemental analysis	Found	C 62.2 H 5.1 N 11.0
$C_{26}H_{25}N_4F_3O_3$	Requires	C 62.6 H 5.1 N 11.2%

Example 157

A mixture of (*R*,*S*)-4-chloro-6-methoxy-7-((1-methylpiperidin-3-yl)methoxy)quinazoline (150 mg, 0.46 mmol), (prepared as described for the starting material in Example 7), potassium carbonate (106 mg, 0.77 mmol) and 3-fluoro-7-hydroxyquinoline (119 mg, 0.73 mmol) in DMF (5 ml) was stirred at 100 °C for 2 hours and then allowed to cool to ambient temperature. The solvent was removed by evaporation and the residue treated with 1.0 N aqueous sodium hydroxide solution (30 ml) then allowed to stir for 30 minutes. The crude solid was collected by filtration and washed with water. The resultant solid was dissolved in dichloromethane and filtered through phase separating paper. The solvent was removed by evaporation and the solid residue was recrystallised from acetonitrile to give **(*R*,*S*)-4-(3-fluoroquinolin-7-yloxy)-6-methoxy-7-((1-methylpiperidin-3-yl)methoxy)quinazoline** (83mg, 40%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.11 (m, 1H), 1.50 (m, 1H), 1.64 (m, 1H), 1.84 (m, 3H), 2.10 (m, 1H), 2.15 (s, 3H), 2.62 (d, 1H), 2.83 (d, 1H), 4.00 (s, 3H), 4.08 (d, 2H), 7.38 (s, 1H), 7.62 (s, 1H), 7.68 (dd, 1H), 7.97 (d, 1H), 8.10 (d, 1H), 8.34 (dd, 1H), 8.54 (s, 1H) and 8.97 (d, 1H)

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

Elemental analysis	Found	C 66.2 H 5.6 N 12.3
$C_{25}H_{25}N_4FO_3$ 0.2 H_2O	Requires	C 66.4 H 5.7 N 12.4%

The starting material, 3-fluoro-7-hydroxyquinoline was prepared as follows:

3-Fluoro-7-methoxyquinol-2(1*H*)-one (300mg, 1.55mmol), (prepared as in Tetrahedron, Vol. 52, No. 9, pp. 3223-3228, 1996), was dissolved in thionyl chloride (3ml), treated with DMF (1 drop) and heated at reflux for 1 hour. The excess thionyl chloride was removed by evaporation and the residue azeotroped with toluene (3x). The residue was basified to pH8 with saturated aqueous sodium hydrogen carbonate solution and extracted with ethyl acetate (3 x 20ml). The organic solution was washed with water and brine then dried ($MgSO_4$) and evaporated to dryness to give 2-chloro-3-fluoro-7-methoxyquinoline (320mg, 97%).

^{1}H NMR Spectrum: ($CDCl_3$) 3.95 (s, 3H), 7.25 (dd, 1H), 7.37 (d, 1H), 7.67 (d, 1H) and 7.78 (d, 1H)

MS (ESI) : 212 $(MH)^+$

A mixture of 2-chloro-3-fluoro-7-methoxyquinoline (310mg, 1.47mmol), triethylamine (310mg, 0.4ml, 3.07mmol) and 10% palladium on activated charcoal (50mg) in dry ethanol (5ml) was stirred under hydrogen gas at ambient temperature for 24 hours. The mixture was then filtered through celite. The celite was washed with methanol and the solvent was removed by evaporation from the combined filtrates. The crude material was purified by chromatography on silica, eluting with 10% ethyl acetate in isohexane to give 3-fluoro-7-methoxyquinoline (130mg, 54%).

^{1}H NMR Spectrum: ($CDCl_3$) 3.96 (s, 3H), 7.24 (dd, 1H), 7.44 (d, 1H), 7.66 (d, 1H) and 7.73 (dd, 1H) and 8.76 (d, 1H)

MS (ESI) : 178 $(MH)^+$

3-Fluoro-7-methoxyquinoline (130mg, 0.74mmol) was taken up in dichloromethane (2ml) under nitrogen and treated with boron tribromide (4ml of a 1.0M solution of in dichloromethane). The reaction mixture was stirred for 24 hours at ambient temperature followed by quenching the reaction by the slow addition of excess methanol. The solution was stirred for a further 2 hours and evaporated to dryness to give 3-fluoro-7-hydroxyquinoline which was used without further purification.

MS (ESI) : 164 $(MH)^+$

Example 158

A mixture of (*R*,*S*)-4-chloro-6-methoxy-7-((1-methylpiperidin-3-yl)methoxy)quinazoline (240 mg, 0.75 mmol), (prepared as described for the starting material in Example 7), potassium carbonate (160 mg, 1.16 mmol) and 3-fluoro-7-hydroxy-2-methylquinoline (150 mg, 0.85 mmol) in DMF (6 ml) was stirred at 100 °C for 5 hours and then allowed to cool to ambient temperature. The solvent was removed by evaporation, then the residue was treated with water and 1.0 N aqueous sodium hydroxide solution (30 ml) then allowed to stir for 30 minutes. The crude solid was collected by filtration and washed with water. The resulting solid was dissolved in dichloromethane and filtered through phase separating paper. The solvent was removed by evaporation to give a solid residue which was recrystallised from acetonitrile to give **4-(3-fluoro-2-methylquinolin-7-yloxy)-6-methoxy-7-((1-methylpiperidin-3-yl)methoxy)quinazoline** (71mg, 21%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.11 (m, 1H), 1.68 (m, 5H), 2.10 (m, 1H), 2.20 (s, 3H), 2.64 (m, 4H), 2.87 (d, 1H), 3.98 (s, 3H), 4.09 (d, 2H), 7.37 (s, 1H), 7.57 (dd, 1H), 7.60 (s, 1H), 7.86 (d, 1H), 8.02 (d, 1H), 8.20 (d, 1H) and 8.53 (s, 1H)

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

Elemental analysis	Found	C 66.4	H 6.1	N 11.8
$C_{26}H_{27}N_4FO_3$ 0.4 H_2O	Requires	C 66.5	H 6.0	N 11.9%

The starting material was prepared as follows:

2-Chloro-3-fluoro-7-methoxyquinoline (210mg, 1mmol), (prepared as described for the starting material in Example 157), in anhydrous THF (1ml) was added to a mixture of copper(I)bromide (570mg, 4.0mmol) and methylmagnesium bromide (3.0M solution in diethyl ether, 2.7ml, 8mmol) in anhydrous THF (20ml) at -78°C. The mixture was stirred for 1 hour at -78°C, allowed to warm to ambient temperature and then stirred for a further 18 hours. Saturated aqueous ammonium chloride solution and 5N aqueous sodium hydroxide solution (pH 12) were added and the product extracted with ethyl acetate (3x). The organic solution was washed with water, brine, dried ($MgSO_4$) and evaporated to dryness to yield 3-fluoro-7-methoxy-2-methylquinoline (0.17g, 91%).

^{1}H NMR Spectrum: ($CDCl_3$) 2.70 (d, 3H), 3.94 (s, 3H), 7.17 (dd, 1H), 7.37 (d, 1H) and 7.61 (m, 2H)

MS (ESI) : 192 $(MH)^+$

3-Fluoro-7-methoxy-2-methylquinoline (0.16g, 0.85mmol) was taken up in

dichloromethane (4ml) under nitrogen and treated with boron tribromide solution (4ml of a 1.0M solution in dichloromethane, 4.0mmol). The reaction was stirred for 24 hours at ambient temperature followed by the slow addition of excess methanol. The solution was stirred for a further 2 hours and then evaporated to dryness to give 3-fluoro-7-hydroxy-2-methylquinoline which was used without further purification.

MS (ESI) : 178 $(MH)^+$

Example 159

A mixture of 4-chloro-6-methoxy-7-(3-piperidinopropoxy)quinazoline (400mg, 1.19mmol), (prepared as described for the starting material in Example 67), potassium carbonate (255 mg, 1.84 mmol) and 7-hydroxyquinoline (180mg, 1.32 mmol) in DMF (10 ml) was stirred at 100 °C for 4 hours and then allowed to cool to ambient temperature. The resulting mixture was treated with 1.0 N aqueous sodium hydroxide solution (30 ml) and allowed to stir for 1 hour. The crude solid was collected by filtration and washed with water. The resulting solid was dissolved in dichloromethane and filtered through phase separating paper. The solvent was removed by evaporation to give a solid residue which was recrystallised from acetonitrile to give **6-methoxy-7-(3-piperidinopropoxy)-4-(quinolin-7-yloxy)quinazoline** (0.27 g, 52%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.37 (m, 2H), 1.51 (m, 4H), 1.95 (m, 2H), 2.32 (m, 4H), 2.42 (t, 2H), 3.98 (s, 3H), 4.23 (t, 2H), 7.38 (s, 1H), 7.56 (m, 2H), 7.62 (s, 1H), 7.91 (d, 1H), 8.09 (d, 1H), 8.44 (d, 1H), 8.54 (s, 1H) and 8.91 (dd, 1H)

MS (ESI) : 445 $(MH)^+$

Elemental analysis	Found	C 70.9	H 6.3	N 12.7	
$C_{26}H_{28}N_4O_3$	Requires	C 70.3	H 6.3	N 12.6%	

Example 160

A mixture of 4-chloro-6-methoxy-7-(3-(N-methyl-N-methylsulphonylamino)propoxy)quinazoline (360 mg, 1.00 mmol), (prepared as described for the starting material in Example 152), potassium carbonate (215 mg, 1.56 mmol) and 2,3-dimethyl-5-hydroxyindole (177 mg, 1.10 mmol), (Arch. Pharm. 1972, 305, 159), in DMF (8.0 ml) was stirred at 100 °C for 5 hours and allowed to cool to ambient temperature. The solvent was removed by evaporation and the residue purified by silica column chromatography

eluting with methanol (2.5%) in dichloromethane. The resulting solid was recrystallised from *tert*butyl methyl ether/acetonitrile, filtered and washed with diethyl ether to give **4-(2,3-dimethylindol-5-yloxy)-6-methoxy-7-(3-(N-methyl-N-methylsulphonylamino)propoxy)quinazoline** (201mg, 42%).

^{1}H NMR Spectrum: ($DMSOd_6$) 2.07 (m, 2H), 2.12 (s, 3H), 2.31 (s, 3H), 2.79 (s, 3H), 2.89 (s, 3H), 3.25 (t, 2H), 3.97 (s, 3H), 4.23 (t, 2H), 6.86 (dd, 1H), 7.20 (d, 1H), 7.25 (d, 1H), 7.35 (s, 1H), 7.58 (s, 1H), 8.46 (s, 1H) and 11.17 (s, 1H)

MS (ESI) : 485 $(MH)^+$

Elemental analysis	Found	C 59.5	H 5.8	N 11.4	
$C_{24}H_{28}N_4O_5S$	Requires	C 59.5	H 5.8	N 11.6%	

Example 161

A mixture of 7-hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (322 mg, 1.00 mmol), (prepared as described in Example 49), potassium carbonate (414 mg, 3.00 mmol) and epibromohydrin (274 mg, 2.00 mmol) in DMF (7.0 ml) was stirred at 60 °C for 2 hours and allowed to cool to ambient temperature. The solvent was removed by evaporation and the residue taken up in dichloromethane (10ml). An aliquot (5ml) of this solution was treated with morpholine (48ul, 0.6 mmol) and stirred for 24 hours at ambient temperature. The solvent was removed by evaporation, treated with water and stirred vigorously for 30 minutes. The precipitate was filtered, washed with water and dried. The resultant solid was stirred as a suspension in acetone, filtered, washed with diethyl ether and dried to give **7-(2-hydroxy-3-morpholinopropoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline** (127mg, 27%).

^{1}H NMR Spectrum: ($DMSOd_6$) 2.38 (s, 3H), 2.45 (m, 6H), 3.57 (t, 4H), 3.95 (s, 3H), 4.03 - 4.14 (m, 2H), 4.23 (m, 1H), 4.95 (s, 1H), 6.12 (s, 1H), 6.86 (dd, 1H), 7.23 (d, 1H), 7.29 (d, 1H), 7.37 (s, 1H), 7.57 (s, 1H), 8.47 (s, 1H) and 10.98 (s, 1H)

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

Elemental analysis	Found	C 62.7	H 5.9	N 11.5	
$C_{25}H_{28}N_4O_5 0.7H_2O$	Requires	C 62.9	H 6.2	N 11.7%	

Example 162

A mixture of 7-(2,3-epoxypropoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (100mg, 0.27 mmol) and piperidine (79ul, 0.8mmol) in DMF (4ml) was heated at 70°C for 24

hours. The solvent was removed by evaporation and the residue was recrystallised from acetonitrile. The solid was filtered, washed with diethyl ether and dried to give **7-(2-hydroxy-3-piperidinopropoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline** (80mg, 65%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.35 (m, 2H), 1.51 (m, 4H), 2.39 (m, 9H), 3.96 (s, 3H), 4.08 (m, 2H), 4.21 (dd, 1H), 4.86 (br s, 1H), 6.11 (s, 1H), 6.87 (dd, 1H), 7.23 (d, 1H), 7.29 (d, 1H), 7.37 (s, 1H), 7.56 (s, 1H), 8.45 (s, 1H) and 10.98 (s, 1H)

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

Elemental analysis	Found	C 66.2	H 6.4	N 11.9	
$C_{26}H_{30}N_4O_4 0.4H_2O$	Requires	C 66.5	H 6.6	N 11.9%	

The starting material was prepared as follows:

A mixture of 7-hydroxy-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (1.89 g, 5.90 mmol), (prepared as described in Example 49), potassium carbonate (2.43 g, 17.6 mmol) and epibromohydrin (1.61 g, 11.7 mmol) in DMF (40 ml) was stirred at 60 °C for 2 hours and allowed to cool to ambient temperature. The insoluble inorganic material was removed by filtration and the solvent was removed by evaporation. The residue was triturated with diethyl ether, filtered, washed with further diethyl ether and dried to give 7-(2,3-epoxypropoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline (1.97g, 89%).

^{1}H NMR Spectrum: ($DMSOd_6$) 2.38 (s, 3H), 2.76 (m, 1H), 2.90 (t, 1H), 3.43 (m,1H), 3.97 (s, 3H), 4.04 (m, 1H), 4.57 (dd, 1H), 6.11 (s, 1H), 6.86 (dd, 1H), 7.27 (m, 2H), 7.38 (s, 1H), 7.59 (s, 1H), 8.46 (s, 1H) and 10.92 (s, 1H)

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

Example 163

A mixture of 7-(2,3-epoxypropoxy)-6-methoxy-4-(2-methylindol-5-yloxy) quinazoline (100mg, 0.27 mmol), (prepared as described for the starting material in Example 162), and pyrrolidine (67ul, 0.8mmol) in DMF (4ml) was heated at 70°C for 24 hours. The solvent was removed by evaporation and the residue purified by silica column chromatography eluting with dichloromethane/methanol/0.880 aqueous ammonia (100/8/1). The relevant fractions were evaporated to dryness then the residue treated with a little dichloromethane and dried under high vacuum to give **7-(2-hydroxy-3-pyrrolidin-1-ylpropoxy)-6-methoxy-4-(2-**

methylindol-5-yloxy)quinazoline (44mg, 37%) as a white foam.

^{1}H NMR Spectrum: ($DMSOd_6$) 1.69 (br s, 4H), 2.38 (s, 3H), 2.50 (m, 6H), 3.97 (s, 3H), 4.07 (m, 2H), 4.21 (dd, 1H), 4.96 (br s, 1H), 6.11 (s, 1H), 6.86 (dd, 1H), 7.23 (d, 1H), 7.29 (d, 1H), 7.35 (s, 1H), 7.56 (s, 1H), 8.46 (s, 1H) and 10.98 (s, 1H)

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

Elemental analysis	Found	C 65.5	H 6.3	N 11.8	
$C_{25}H_{28}N_4O_4 0.4H_2O$	Requires	C 65.9	H 6.4	N 12.3%	

Example 164

A mixture of 7-(2,3-epoxypropoxy)-6-methoxy-4-(2-methylindol-5-yloxy) quinazoline (100mg, 0.27 mmol), (prepared as described for the starting material in Example 162), and diethylamine (100ul, 0.8mmol) in DMF (4ml) was heated at 70°C for 24 hours. The solvent was removed by evaporation and the residue was purified by silica column chromatography eluting with dichloromethane/methanol/0.880 aqueous ammonia (100/8/1). The relevant fractions were evaporated to dryness then the residue treated with a little dichloromethane and dried under high vacuum to give **7-(3-(N,N-diethylamino)-2-hydroxypropoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline** (55mg, 46%) as a white foam.

^{1}H NMR Spectrum: ($DMSOd_6$) 0.96 (t, 6H), 2.38 (s, 3H), 2.52 (m, 6H), 3.96 (s, 3H), 3.97 (m, 1H), 4.09 (m, 1H), 4.23 (dd, 1H), 4.84 (br s, 1H), 6.12 (s, 1H), 6.88 (dd, 1H), 7.24 (d, 1H), 7.29 (d, 1H), 7.36 (s, 1H), 7.56 (s, 1H), 8.45 (s, 1H) and 10.98 (s, 1H)

MS (ESI) : 452 $(MH)^+$

Elemental analysis	Found	C 66.2	H 6.7	N 12.4	
$C_{25}H_{30}N_4O_4$	Requires	C 66.6	H 6.7	N 12.4%	

Example 165

A mixture of 7-(2,3-epoxypropoxy)-6-methoxy-4-(2-methylindol-5-yloxy) quinazoline (100mg, 0.27 mmol), (prepared as described for the starting material in Example 162), and N-methylpiperazine (200ul, 1.8mmol) in DMF (4ml) was heated at 70°C for 24 hours. The solvent was removed by evaporation and the residue was recrystallised from acetonitrile. The solid was filtered, washed with diethyl ether and dried to give **7-(2-hydroxy-3-(4-methylpiperazin-1-yl)propoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline** (41mg, 32%).

^{1}H NMR Spectrum: ($DMSOd_6$) : 2.11 (s, 3H), 2.29 (m, 4H), 2.40 (s, 3H), 2.47 (m, 6H), 3.96 (s, 3H), 4.07 (m, 2H), 4.20 (dd, 1H), 4.89 (d, 1H), 6.11 (s, 1H), 6.87 (dd, 1H), 7.23 (d, 1H), 7.29 (d, 1H), 7.35 (s, 1H), 7.58 (s, 1H), 8.46 (s, 1H) and 10.98 (s, 1H)

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

Elemental analysis	Found	C 64.4	H 6.5	N 14.4	
$C_{26}H_{31}N_5O_4 0.3H_2O$	Requires	C 64.7	H 6.6	N 14.5%	

Example 166

A mixture of 7-(2,3-epoxypropoxy)-6-methoxy-4-(2-methylindol-5-yloxy) quinazoline (100mg, 0.27 mmol), (prepared as described for the starting material in Example 162), and isopropylamine (100ul, 0.8mmol) in DMF (4ml) was heated at 70°C for 24 hours. The solvent was removed by evaporation and the residue was purified by silica column chromatography eluting with dichloromethane/methanol/0.880 aqueous ammonia (100/8/1) to give **7-(2-hydroxy-3-(isopropylamino)propoxy)-6-methoxy-4-(2-methylindol-5-yloxy)quinazoline** (18mg, 16%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.00 (d, 6H), 2.40 (s, 3H), 2.56 - 2.78 (m, 3H), 3.97 (m, 4H), 4.07 - 4.28 (m, 2H), 5.04 (m, 1H), 6.12 (s, 1H), 6.88 (dd, 1H), 7.22 - 7.33 (m, 2H), 7.38 (s, 1H), 7.58 (s, 1H), 8.48 (s, 1H) and 10.98 (s, 1H)

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

Example 167

A mixture of 4-chloro-6-methoxy-7-(3-piperidinopropoxy)quinazoline (168 mg, 0.5 mmol), (prepared as described for the starting material in Example 67), potassium carbonate (276 mg, 2.0 mmol) and 5-hydroxy-6-trifluoromethylindole (110 mg, 0.55 mmol) and DMA (4.0 ml) were stirred at 95°C for 1.5 hours and allowed to cool to ambient temperature. The reaction mixture was filtered and the filtrate evaporated under vacuum. The residue was purified by silica column chromatography eluting with dichloromethane/methanol/0.880 aqueous ammonia (89/10/1) to give a partially purified oil. This oil was further purified by high performance column chromatography on octadecylsilane reverse phase silica eluting with acetonitrile/water/trifluoroacetic acid (60/39.8/0.2) to give an oil which was dissolved in dichloromethane and washed with saturated aqueous sodium hydrogen carbonate solution. The dichloromethane layer was evaporated to give **6-methoxy-7-(3-piperidinopropoxy)-4-**

(6-trifluoromethylindol-5-yloxy)quinazoline (62 mg, 25%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.45 (m, 2H), 1.60 (m, 4H), 2.13 (m, 2H), 2.44 (m, 4H), 2.56 (m, 2H), 4.04 (s, 3H), 4.27 (t, 2H), 6.63 (br s , 1H), 7.33 (s, 1H), 7.40 (t, 1H), 7.61 (s, 1H), 7.67 (s, 1H), 7.75 (s, 1H) and 8.60 (m, 2H)

MS (ESI) : 501 $(MH)^+$

Elemental analysis	Found	C 62.0 H 5.6 N 10.6
$C_{26}H_{27}F_3N_4O_3$ 0.35 H_2O,	Requires	C 61.6 H 5.5 N 11.0%

The starting material was prepared as follows:

Sodium hydride (1.8g, of a 60% dispersion in oil, 45 mmol) was added in portions to a stirred solution of benzyl alcohol (10.8g, 100 mmol) in DMA (100ml) with vigorous stirring under an atmosphere of nitrogen at ambient temperature. After warming to 45°C for 30 minutes the mixture was cooled to ambient temperature and added dropwise to a stirred solution of 2-chloro-5-nitro-trifluoromethylbenzene (11.3g, 50 mmol) in DMA (30ml), keeping the temperature below 10°C. The mixture was stirred at 25°C for 1 hour, then acidified with acetic acid and evaporated to give a yellow solid. The residue was dissolved in dichloromethane, washed with water then dried ($MgSO_4$), and evaporated. The residue was suspended in a mixture of hexane (70 ml) and diethyl ether (10 ml) and the resulting solid filtered off to give 2-benzyloxy-5-nitro-trifluoromethylbenzene (6.6g, 49%).

^{1}H NMR Spectrum: ($CDCl_3$) 5.33 (s, 2H), 7.13 (d, 1H), 7.31-7.43 (m, 5H), 8.35 (dd, 1H), 8.52 (d, 1H)

Potassium *tert*-butoxide (3.94g, 35.4mmol) was dissolved in anhydrous DMF (15ml) and a mixture of 2-benzyloxy-5-nitro-trifluoromethylbenzene (3.5g, 16.1 mmol) and 4-chlorophenylacetonitrile (2.96g, 17.7 mmol) in DMF (20 ml) was added over 30 minutes keeping the temperature at -15°C. The mixture was stirred at -10°C for 1 hour, then poured into 1M hydrochloric acid (150ml) and the product extracted with dichloromethane (2x100ml). The organic extracts were dried ($MgSO_4$) and purified by silica column chromatography eluting with dichloromethane/hexane (1/1) to give 5-benzyloxy-2-nitro-4-(trifluoromethyl)phenylacetonitrile (5.2g, 77%).

^{1}H NMR Spectrum: ($CDCl_3$) 4.30 (s, 2H), 5.38 (s, 2H), 7.25 (s, 1H), 7.33-7.50 (m, 5H) and 8.51 (s, 1H)

MS (ESI) : 335 $(M-H)^-$

5-Benzyloxy-2-nitro-4-(trifluoromethyl)phenylacetonitrile (2.22g, 6.6mmol) was dissolved in ethanol (45 ml), water (5ml) and acetic acid (0.32 ml) then hydrogenated with 10% palladium on carbon at 1 atmosphere pressure for 2 hours. The catalyst was filtered off and filtrate evaporated to give 5-hydroxy-6-trifluoromethylindole (1.12g, 84%).

^{1}H NMR Spectrum: ($CDCl_3$) 4.48 (s, 1H), 6.48 (m, 1H), 7.14 (s, 1H), 7.32 (t, 1H), 7.57 (s, 1H) and 8.20 (br s, 1H)

MS (ESI) : 200 $(M-H)^-$

Example 168

A mixture of 4-chloro-6-methoxy-7-(3-piperidinopropoxy)quinazoline (200mg, 0.6 mmol), (prepared as described for the starting material in Example 67), potassium carbonate (248 mg, 1.8 mmol) and 5-hydroxy-6-methoxyindole (127 mg, 0.78 mmol) in DMA (4.0 ml) was stirred at 95°C for 2.5 hours. The reaction mixture was allowed to cool to ambient temperature, filtered and the filtrate evaporated under vacuum. The residue was purified by silica column chromatography eluting with dichloromethane /methanol/0.880 aqueous ammonia (89/10/1) and the resulting oil triturated with diethyl ether to give **4-(6-methoxyindol-5-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline** (106 mg, 38%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.38 (m, 2H), 1.47 (m, 4H), 1.95 (m, 2H), 2.32 (m, 4H), 2.40 (m, 2H), 3.66 (3H, s), 3.97 (s, 3H), 4.28 (t, 2H), 6.35 (br s, 1H), 7.06 (s, 1H), 7.24 (t, 1H), 7.34 (s, 1H), 7.36 (s, 1H), 7.55 (s, 1H) and 8.41 (s, 1H)

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

Elemental analysis	Found	C 65.2 H 6.8 N 11.2
$C_{26}H_{30}N_4O_4$ 1.0 H_2O, 0.3 diethyl ether	Requires	C 64.9 H 7.0 N 11.1%

The 5-hydroxy-6-methoxyindole starting material was made as follows:

5-Benzyloxy-6-methoxyindole (253mg, 1.0mmol) was hydrogenated at 1 atmosphere pressure in methanol (10 ml) with 10% palladium on carbon (50 mg) for 2 hours at 25°C. The catalyst was filtered off and the filtrate evaporated to give 5-hydroxy-6-methoxylindole (141mg, 87%).

^{1}H NMR Spectrum: ($CDCl_3$) 3.92 (s, 3H), 5.40 (s, 1H), 6.42 (br s, 1H), 6.87 (s, 1H), 7.07 (m, 1H), 7.13 (s, 1H), 7.93 (br s, 1H)

MS (ESI) : 162 $(M-H)^-$

Example 169

A mixture of 4-chloro-6-methoxy-7-(3-piperidinopropoxy)quinazoline (200mg, 0.595 mmol), (prepared as described for the starting material in Example 67), potassium carbonate (411 mg, 2.98 mmol) and 4-hydroxyindole (103 mg, 0.774 mmol) in DMA (2.0 ml) was stirred at 85 °C for 3 hours and allowed to cool to ambient temperature. The reaction mixture was filtered and the filtrate evaporated to give a solid residue. The residue was purified by silica column chromatography, with gradient elution using dichloromethane with 0%, 2%, 4%, 10% methanolic ammonia to give **4-(indol-4-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline** (131 mg, 51 %).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.39 (m, 2H), 1.50 (m, 4H), 1.98 (t, 2H), 2.35 (m, 4H), 2.40 (t, 2H), 3.98 (s, 3H), 4.25 (t, 2H), 6.10 (t, 1H), 6.90 (d, 1H), 7.15 (t, 1H), 7.30 (t, 1H), 7.35 (d, 1H), 7.38 (s, 1H), 7.62 (s, 1H), 8.45 (s, 1H) and 11.29 (s, 1H)

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

m.p. 80 - 82 °C

Example 170

A mixture of 4-chloro-6-methoxy-7-(3-piperidinopropoxy)quinazoline (200mg, 0.595 mmol), (prepared as described for the starting material in Example 67), potassium carbonate (411 mg, 2.98 mmol) and 3-hydroxycarbazole (142 mg, 0.774 mmol) in DMA (2.0 ml) was stirred at 85 °C for 3 hours then allowed to cool to ambient temperature. The reaction mixture was filtered and the filtrate evaporated to give a solid residue. The residue was purified by silica column chromatography with gradient elution using dichloromethane with 0%, 2%, 4%, 10% methanolic ammonia to give **4-(9*H*-carbazol-3-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline** (212 mg, 74 %).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.39 (m, 2H), 1.50 (m, 4H), 2.35 (m, 4H), 2.40 (t, 2H), 3.98 (s, 3H), 4.25 (t, 2H), 7.05 (dd, 1H), 7.15 (t, 1H), 7.35 (t, 1H), 7.38 (s, 1H), 7.40 (s, 1H), 7.50 (d, 1H), 7.60 (s, 1H), 8.10 (d, 1H), 8.15 (d, 1H), 8.55 (s, 1H) and 11.33 (s, 1H)

MS (ESI) : 483 $(MH)^+$

Example 171

A mixture of 4-chloro-6-methoxy-7-(3-piperidinopropoxy)quinazoline (84 mg, 0.24 mmol), (prepared as described for the starting material in Example 67), potassium carbonate (162 mg, 1.18 mmol) and ethyl 7-chloro-5-hydroxyindole-2-carboxylate (62 mg, 0.26 mmol) in DMA (2.0 ml) was stirred at 100 °C for 2 hours and allowed to cool to ambient temperature. The reaction mixture was filtered and the filtrate evaporated. The residue was purified by silica column chromatography using gradient elution dichloromethane with 2.5%, 5%, 10% methanol, then dichloromethane with 2% ammonia) to give **4-(7-chloro-2-(ethoxycarbonyl)indol-5-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline** (78 mg, 63 %).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.30 (t, 3H), 1.40 (m, 2H), 1.50 (m, 4H), 1.98 (t, 2H), 2.35 (m, 4H), 2.40 (t, 2H), 3.98 (s, 3H), 4.25 (t, 2H), 4.30 (q, 2H), 7.15 (m, 1H), 7.18 (s, 1H), 7.60 (s, 1H), 8.40 (s, 1H) and 12.60 (s, 1H)

MS (ESI) : 539 $(MH)^+$

Elemental analysis	Found	C 61.2 H 5.9 N 10.3
$C_{28}H_{31}ClN_4O_5$ 0.5 H_2O	Requires	C 61.4 H 5.9 N 10.2%

The starting material was prepared as follows:

2-Chloro-4-methoxyaniline (2.719g, 14 mmol) was added to 8.0M aqueous hydrochloric acid (15 ml) and the suspension cooled to -5 °C. Sodium nitrite (1.063g, 15.4 mmol) was added as a solution in water (3 ml). After addition the pH was brought to pH 4-5 by addition of sodium acetate. In a separate flask, ethyl-α-ethyl acetoacetate (2.18 ml, 15.4 mmol) in ethanol (15 ml) at -5 °C was treated with potassium hydroxide (864 mg, 15.4 mmol) in water (3 ml) followed by ice (4 g). The diazonium salt prepared initially was then added rapidly to the second solution and stirred at -5 °C for 4 hours then allowed to warm to ambient temperature overnight. The mixture was extracted with ethyl acetate (3 x 100 ml) and the organic solutions dried ($MgSO_4$), filtered and solvent removed *in vacuo* to give an orange oil. This oil was dissolved in ethanol (35 ml) and the flask fitted with a reflux condenser. Concentrated sulphuric acid (35 ml) was then added dropwise, this caused the reaction to reflux with no external heating. The solution was stirred for 1 hour then the solvent removed by evaporation. The residue was taken up in water then extracted with ethyl acetate (3 x 100 ml). The organic solution was washed with brine, dried ($MgSO_4$), filtered and evaporated to give a brown oil. The crude oil was purified by silica column chromatography, eluting with

dichloromethane to give ethyl 7-chloro-5-methoxyindole-2-carboxylate (125 mg, 4%).
^{1}H NMR Spectrum: ($CDCl_3$) 1.40 (t, 3H), 3.98 (s, 3H), 4.40 (q, 2H), 6.60 (d, 1H), 7.05 (d, 1H), 7.15 (s, 1H) and 9.10 (s, 1H)
MS (ESI) : 254 $(MH)^+$

To a solution of ethyl 7-chloro-5-methoxyindole-2-carboxylate (82 mg, 0.323 mmol) in dichloromethane (5 ml) at -78 °C was added boron tribromide (1.07 ml of a 1.0M solution in DCM, 1.07 mmol) and the reaction stirred at -78 °C for 30 minutes then allowed to warm to ambient temperature overnight. Water was carefully added and the pH adjusted to pH 6-7 by addition of 2M sodium hydroxide. The mixture was extracted with ethyl acetate (2 x 50 ml), and the organic solution washed with brine, dried ($MgSO_4$), filtered and evaporated to give ethyl 7-chloro-5-hydroxyindole-2-carboxylate (55 mg, 71%) as an orange solid.
^{1}H NMR Spectrum: ($DMSOd_6$) 1.38 (t, 3H), 4.35 (q, 2H), 6.60 (d, 1H), 6.95 (d, 1H), 7.10 (d, 1H), 9.80 (s, 1H) and 11.80 (s, 1H)
MS (ESI) : 238 $(MH)^-$

Example 172

A mixture of 7-benzyloxy-4-chloro-6-methoxyquinazoline (1.5 g, 4.99 mmol), (prepared as described for the starting material in Example 1), potassium carbonate (2.07 g, 15 mmol) and 2,3-dimethyl-5-hydroxyindole (1.21 g, 7.5 mmol), (Arch. Pharm. 1972, 305, 159), in DMF (75 ml) was stirred at 100 °C for 2 hours and allowed to cool to ambient temperature. The reaction mixture was filtered and the filtrate evaporated. The solid residue was purified by silica column chromatography, eluting with 2.5% methanol in dichoromethane to give **7-benzyloxy-4-(2,3-dimethylindol-5-yloxy)-6-methoxyquinazoline** (976 mg, 46 %).
^{1}H NMR Spectrum: ($CDCl_3$) 2.10 (s, 3H), 2.30 (s, 3H), 3.98 (s, 3H), 5.30 (s, 2H), 6.85 (dd, 1H), 7.20 (d, 1H), 7.25 (d, 1H), 7.40 (m, 6H), 7.60 (s, 1H), 8.40 (s, 1H) and 10.74 (s, 1H)
MS (ESI) : 426 $(MH)^+$

Example 173

A mixture of 7-benzyloxy-4-(2,3-dimethylindol-5-yloxy)-6-methoxyquinazoline (912 mg, 2.14 mmol), (prepared as described in Example 172), di-*tert*-butyl dicarbonate (1.871 g, 8.56 mmol) and 4-dimethylaminopyridine (70 mg, 5 mol%) in acetonitrile (40 ml) was stirred at ambient temperature overnight. The solvent was then evaporated and the residue dissolved

in ethyl acetate. The organic solution was washed with 2N hydrochloric acid twice and then with brine. The organic layer was then dried ($MgSO_4$), filtered and evaporated to give **7-benzyloxy-4-(1-*tert*-butoxycarbonyl-2,3-dimethylindol-5-yloxy)-6-methoxyquinazoline** (1.108 g, 99%) as a yellow solid.

^{1}H NMR Spectrum: ($CDCl_3$) 1.70 (s, 9H), 2.08 (s, 3H), 2.50 (s, 3H), 4.10 (s, 3H), 5.35 (s, 2H), 7.15 (dd, 1H), 7.38 (m, 6H), 7.60 (s, 1H), 8.20 (d, 1H) and 8.60 (s, 1H)

MS (ESI) : 526 $(MH)^+$

Example 174

A mixture of 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (225 mg, 0.67 mmol), (prepared as described for the starting material in Example 1), potassium carbonate (106 mg, 0.77 mmol) and 2-hydroxyquinoline (111 mg, 0.76 mmol) in DMF (7.5 ml) was stirred at 100 °C for 5 hours and allowed to cool to ambient temperature. The reaction mixture was treated with 1.0 N aqueous sodium hydroxide solution (40 ml) and allowed to stir at ambient temperature for a few minutes. The reaction mixture was extracted 3 times with ethyl acetate and the extracts washed with water and brine. The organic extracts were dried over magnesium sulphate, filtered and the solvent removed by evaporation. The residue was purified by silica column chromatography eluting with dichloromethane/methanol (95/5) to give a solid which was triturated with ether, filtered and dried to give **6-methoxy-7-(3-morpholinopropoxy)-4-(quinolin-2-yloxy)-quinazoline** (33 mg, 11%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.98 (m, 2H), 2.38 (m, 4H), 2.48 (t, 2H), 3.58 (m, 4H), 3.98 (s, 3H), 4.26 (t, 2H), 7.41 (s, 1H), 7.52 (d, 1H), 7.58 (s, 1H), 7.64 (t, 1H), 7.78 (m, 1H), 7.88 (d, 1H), 8.06 (d, 1H), 8.56 (d, 1H) and 8.57 (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 12.4%

Example 175

A mixture of 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (225 mg, 0.67 mmol), (prepared as described for the starting material in Example 1), potassium carbonate (106 mg, 0.77 mmol) and 5-hydroxyquinoline (111 mg, 0.77 mmol) in DMF (7.5 ml) was stirred at 100 °C for 5 hours and allowed to cool to ambient temperature. The reaction

mixture was treated with 1.0 N aqueous sodium hydroxide solution (40 ml) and allowed to stir at ambient temperature for a few minutes. The resulting precipitate was filtered off, washed with water and air dried for a short while. The damp solid was dissolved in dichloromethane, filtered through phase separating paper and the filtrate evaporated under vacuum. The residue was triturated with ether, filtered and dried to give **6-methoxy-7-(3-morpholinopropoxy)-4-(quinolin-5-yloxy)-quinazoline** (178 mg, 59%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.98 (m, 2H), 2.39 (m, 4H), 2.48 (t, 2H), 3.59 (t, 4H), 4.01 (s, 3H), 4.28 (t, 2H), 7.42, (s, 1H), 7.50 (m, 1H), 7.59 (d, 1H), 7.74 (s, 1H), 7.87 (t, 1H), 8.02 (d, 1H), 8.20 (m, 1H), 8.44 (s, 1H) and 8.96 (m, 1H)

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

Elemental analysis	Found	C 66.2	H 5.7	N 12.4
$C_{25}H_{26}N_4O_4$ 0.4 H_2O	Requires	C 66.2	H 6.0	N 12.4%

Example 176

A mixture of 4-chloro-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline (200 mg, 0.57 mmol), potassium carbonate (106 mg, 0.77 mmol) and 7-hydroxyquinoline (111 mg, 0.76 mmol) in DMF (7 ml) was stirred at 100 °C for 5 hours and allowed to cool to ambient temperature. The reaction mixture was treated with 1.0 N aqueous sodium hydroxide solution (40 ml) and allowed to stir at ambient temperature for a few minutes. The reaction mixture was extracted 4 times with ethyl acetate and the organic extracts washed with water and brine. The organic extracts were dried over magnesium sulphate, filtered and the solvent removed by evaporation. The residue was triturated with ether/isohexane, filtered and dried to give **6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)-4-(quinolin-7-yloxy)quinazoline** (102 mg, 39%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.96 (m, 2H), 2.15 (s, 3H), 2.35 (m, 8H), 2.46 (t, 2H), 3.99 (s, 3H), 4.24 (t, 2H), 7.39 (s, 1H), 7.56 (m, 1H), 7.61 (m, 1H), 7.62 (s, 1H), 7.92 (d, 1H), 8.10 (d, 1H), 8.44 (d, 1H), 8.54 (s, 1H) and 8.92 (m, 1H)

MS (ESI) : 460 $(MH)^+$

Elemental analysis	Found	C	67.2	H	6.2	N	15.0
$C_{26}H_{29}N_5O_3$ 0.3 H_2O	Requires	C	67.2	H	6.4	N	15.1%

The starting material was prepared as follows:

A solution of 1-(3-hydroxypropyl)-4-methylpiperazine (2.4 g, 15 mmol), (prepared as described for the starting material in Example 133), in dichloromethane (60 ml) was treated with triethylamine (4.6 ml, 33 mmol) and p-toluenesulphonyl chloride (3.2 g, 17mmol) and stirred at ambient temperature for 2 hours. The solution was washed with saturated aqueous sodium hydrogen carbonate solution followed by water and filtered through phase separating paper. The filtrate was evaporated under vacuum to give 3-(4-methyl-piperazin-1-yl)propyl-4-toluene sulphonate as an oil which crystallised on standing (3.7 g, 78 %).

MS (ESI) : 313 $(MH)^+$

A mixture of 2-amino-4-benzyloxy-5-methoxybenzamide (J. Med. Chem. 1977, vol 20, 146-149, 10g, 0.04mol) and Gold's reagent (7.4g, 0.05mol) in dioxane (100ml) was stirred and heated at reflux for 24 hours. Sodium acetate (3.02g, 0.037mol) and acetic acid (1.65ml, 0.029mol) were added to the reaction mixture and it was heated for a further 3 hours. The mixture was evaporated, water was added to the residue, the solid was filtered off, washed

with water and dried. Recrystallisation from acetic acid gave 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (8.7g, 84%).

A mixture of 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (2.82g, 0.01mol), thionyl chloride (40ml) and DMF (0.28ml) was stirred and heated at reflux for 1 hour. The mixture was evaporated and azeotroped with toluene to give 7-benzyloxy-4-chloro-6-methoxyquinazoline hydrochloride (3.45g).

4-Chloro-2-fluoro-phenol (264mg, 1.8mmol) was added to a solution of 7-benzyloxy-4-chloro-6-methoxyquinazoline hydrochloride (506mg, 1.5mmol) in pyridine (8ml) and the mixture heated at reflux for 45 minutes. The solvent was removed by evaporation and the residue partitioned between ethyl acetate and water. The organic layer was washed with 0.1M HCl, water and brine, dried ($MgSO_4$) and the solvent removed by evaporation. The solid residue was triturated with petroleum ether and the crude product collected by filtration and purified by flash chromatography eluting with methylene chloride/ether (9/1) to give 7-benzyloxy-4-(4-chloro-2-fluorophenoxy)-6-methoxyquinazoline (474mg, 77%) as a cream solid.

m.p. 179-180°C

^{1}H NMR Spectrum: ($DMSOd_6$) 3.99(s, 3H); 5.36(s, 2H); 7.35-7.5(m, 4H); 7.55-7.65(m, 5H); 7.72(d, 1H); 8.6(s, 1H)

MS - ESI: 411 $[MH]^+$

Elemental analysis: Found C 63.38 H 4.07 N 6.78

$C_{22}H_{16}ClFN_2O_3$ $0.06H_2O$ $0.05CH_2Cl_2$ Requires C 63.64 H 3.93 N 6.73%

A solution of 7-benzyloxy-4-(4-chloro-2-fluorophenoxy)-6-methoxyquinazoline (451mg, 1.1mmol) in TFA (4.5ml) was heated at reflux for 3 hours. The mixture was diluted with toluene and the volatiles removed by evaporation. The residue was triturated with methylene chloride, collected by filtration, washed with ether and dried under vacuum to give 4-(4-chloro-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline (320mg, 90%).

^{1}H NMR Spectrum: ($DMSOd_6$) 4.0(s, 3H); 7.27(s, 1H); 7.43(dd, 1H); 7.56(t, 1H); 7.57(s, 1H); 7.72(dd, 1H); 8.5(s, 1H)

MS - ESI: 321 $[MH]^+$

A mixture of the trifluoroacetic acid salt of 4-(4-chloro-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline (3.2 g, 7.4 mmol), potassium carbonate (6.1 g, 44.2 mmol) and 3-(4-methyl-1-piperazinyl)propyl-4-toluene sulphonate (3.0 g, 9.6 mmol) in DMF (60 ml) was

stirred at 90 °C for 5 hours and allowed to cool to ambient temperature. The reaction mixture was poured into water (700 ml) and extracted 5 times with ethyl acetate. The combined extracts were washed with water, saturated aqueous sodium hydrogen carbonate, water and saturated brine. The ethyl acetate solution was dried over magnesium sulphate, filtered and the solvent removed under vacuum to give a residue which was purified by silica column chromatography, eluting with dichloromethane/methanol/0.880 aqueous ammonia (100/8/1). The relevant fractions were combined and evaporated under vacuum to give a residue which was triturated with ether, filtered and dried to give 4-(4-chloro-2-fluorophenoxy)-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline (1.64 g, 48 %).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.95 (m, 2H), 2.14 (s, 3H), 2.35 (m, 8H), 2.44 (t, 2H), 3.96 (s, 3H), 4.22 (t, 2H), 7.38 (s, 1H), 7.40 (m, 1H), 7.54 (m, 2H), 7.68 (m, 1H) and 8.55 (s, 1H)

MS (ESI) : 461 $(MH)^+$

Elemental analysis	Found	C 59.6	H 5.7	N 12.2
$C_{23}H_{26}ClFN_4O_3$	Requires	C 59.9	H 5.7	N 12.2%

4-(4-Chloro-2-fluorophenoxy)-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline (2.6 g, 5.6 mmol) was treated with 2.0 N aqueous hydrochloric acid (45 ml) and the mixture stirred at 95 °C for 2 hours. The mixture was cooled, basified by the addition of solid sodium hydrogen carbonate and the water removed by azeotroping with toluene. The residue was purified by silica column chromatography eluting with dichloromethane/methanol/0.880 aqueous ammonia (50/8/1) to give 6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)-3,4-dihydroquinazolin-4-one (1.8 g, 96%).

MS (ESI) : 333 $(MH)^+$

6-Methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)-3,4-dihydroquinazolin-4-one (2.15 g, 6.48 mmol) was suspended in thionyl chloride (25 ml) and DMF (0.18 ml) and stirred under reflux for 2 hours. The thionyl chloride was evaporated under vacuum and the residue azeotroped twice with toluene. The residue was taken up in water, basified with saturated with aqueous sodium hydrogen carbonate solution and the aqueous solution extracted 4 times with dichloromethane. The combined extracts were washed with water and brine then filtered through phase separating paper. The filtrate was evaporated under vacuum and the residue purified by silica column chromatography eluting with dichloromethane/methanol/0.880 aqueous ammonia (100/8/1) to give a solid which was triturated with a little acetone, filtered

and dried to give 4-chloro-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline (1.2 g, 53 %). This was used without further purification.

MS (ESI) : 351 $(MH)^+$

Example 177

A mixture of 4-chloro-6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)quinazoline (200 mg, 0.64 mmol), potassium carbonate (102 mg, 0.74 mmol) and 7-hydroxyquinoline (107 mg, 0.74 mmol) in DMSO (5 ml) was stirred at 100 °C for 5 hours and allowed to cool to ambient temperature. The mixture was poured into water, washed with dichloromethane and extracted twice with a 10/1 mixture of dichloromethane/methanol. The extracts were washed with water and brine, dried over magnesium sulphate, filtered and the filtrate evaporated under vacuum. The residue was purified by silica column chromatography, eluting with dichloromethane/methanol/0.880 aqueous ammonia (100/8/1) to give an oil which crystallised on trituration with ether to give **6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)-4-(quinolin-7-yloxy)quinazoline** (148 mg, 55 %).

^1H NMR Spectrum: ($DMSOd_6$) 3.25 (s, 3H), 3.50 (t, 2H), 3.60 (t, 2H), 3.80 (t, 2H), 4.00 (s, 3H), 4.30 (t, 2H), 7.40 (s, 1H), 7.55 (m, 1H), 7.60 (m, 1H), 7.65 (s, 1H), 7.90 (d, 1H), 8.10 (d, 1H), 8.40 (m, 1H), 8.50 (s, 1H) and 8.90 (m, 1H)

MS (ESI) : 422 $(MH)^+$

Elemental analysis	Found	C 65.8	H 5.2	N 10.0
$C_{23}H_{23}N_3O_5$	Requires	C 65.6	H 5.5	N 10.0%

The starting material was prepared as follows:

Diethyl azodicarboxylate (864µl, 5.5mmol) was added dropwise to a mixture of 7-hydroxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (1.2g, 3.9mmol) (prepared as described for the starting material in Example 12), triphenylphosphine (1.44g, 5.5mmol) and 2-(2-methoxyethoxy)ethanol (653µl, 5.5mmol) in methylene chloride (70ml) cooled at 0°C. The mixture was stirred for 1.5 hours at ambient temperature and the solvent was removed by evaporation. The residue was purified by column chromatography eluting with a mixture of ethyl acetate/methylene chloride (50/50 followed by 80/20). The purified solid was suspended in ether, collected by filtration and dried under vacuum to give 6-

methoxy-7-(2-(2-methoxyethoxy)ethoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (1.70g, 100%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.13(s, 9 H); 3.26(s, 3H); 3.5(m, 2H); 3.65(m, 2H); 3.85(m, 2H); 3.91(s, 3H); 4.3(m, 2H); 5.9(s, 2H); 7.2(s, 1H); 7.5(s, 1H); 8.4(s, 1H)

Saturated methanolic ammonia (20ml) was added to a solution of 6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (2.26g, 5.5mmol) in a mixture of ethanol (40ml) and methylene chloride (15ml). The mixture was stirred for 24 hours at ambient temperature, and further methanolic ammonia (20ml) was added. The mixture was stirred for a further 24 hours at ambient temperature and the volatiles were removed by evaporation. The residue was triturated with ether, collected by filtration, dried under vacuum to give 6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)-3,4-dihydroquinazolin-4-one (975mg, 78%).

^{1}H NMR Spectrum: ($DMSOd_6$) 3.25(s, 3H); 3.45(t, 2H); 3.6(t, 2H); 3.8(t, 2H); 3.9(s, 3H); 4.2(t, 2H); 7.15(s, 1H); 7.45(s, 1H); 8.0(s, 1H)

MS - EI: 294 $[M]^+$

A solution of 6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)-3,4-dihydroquinazolin-4-one (930mg, 3.16mmol) in thionyl chloride (15ml) and DMF (150µl) was heated at 60°C for 1.5 hours. The mixture was allowed to cool and the volatiles were removed by evaporation and by azeotroping with toluene. The residue was dissolved in methylene chloride and 5% aqueous sodium hydrogen carbonate solution was added until the aqueous layer was at pH8. The organic layer was separated, washed with brine, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by flash chromatography eluting with ethyl acetate to give 4-chloro-6-methoxy-7-(2-(2-methoxyethoxy)ethoxy)quinazoline (863mg, 87%).

^{1}H NMR Spectrum: ($DMSOd_6$) 3.24(s, 3H); 3.47(m, 2H); 3.62(m, 2H); 3.84(t, 2H); 4.01(s, 3H); 4.25(t, 2H); 7.41(s, 1H); 7.49(s, 1H); 8.88(s, 1H)

Example 178

A mixture of 4-chloro-6-methoxy-7-(3-piperidinopropoxy)quinazoline (168 mg, 0.5 mmol), (prepared as described for the starting material in Example 67), potassium carbonate (207 mg, 1.5 mmol), 3-methyl-5-hydroxyindole (88mg, 0.6 mmol), (Can. J. Chem. 1964, 42, *514*), and DMA (2.0 ml) was purged with nitrogen for 5 minutes at 25°C. This mixture was then stirred at 100°C for 3 hours then allowed to cool to ambient temperature, was filtered and

the filtrate evaporated under vacuum. The residue was purified by silica column chromatography eluting with dichloromethane/methanolic ammonia (7M) (90/10) to give **6-methoxy-4-(3-methylindol-5-yloxy)-7-(3-piperidinopropoxy)quinazoline** (155 mg, 69%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.37 (m, 2H), 1.50 (m, 4H), 1.95 (m, 2H), 2.21 (s, 3H), 2.34 (m, 4H), 2.42 (t, 2H), 3.96 (s, 3H), 4.22 (t, 2H), 6.95 (dd, 1H), 7.16 (s, 1H), 7.35 (m, 3H), 7.58 (s, 1H), 8.48 (s, 1H) and 10.82 (s, 1H)

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

Elemental analysis	Found	C 68.2 H 6.8 N 12.6
$C_{26}H_{30}N_4O_3$ 0.5 H_2O,	Requires	C 68.5 H 6.8 N 12.3%

Example 179

Using an analogous procedure to that described in Example 178, 4-chloro-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline, (prepared as described for the starting material in Example 9), was used to give

6-methoxy-4-(3-methylindol-5-yloxy)-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline (154 mg, 79%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.68 (m, 4H), 1.97 (m, 2H), 2.22 (s, 3H), 2.43 (m, 4H), 2.55 (t, 2H), 3.96 (s, 3H), 4.22 (t, 2H), 6.93 (dd, 1H), 7.16 (s, 1H), 7.35 (m, 3H), 7.58 (s, 1H), 8.48 (s, 1H) and 10.82 (br s, 1H)

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

m.p. 75-77°C

Example 180

Using an analogous procedure to that described in Example 178, 4-chloro-6-methoxy-7-(2-piperidinoethoxy)quinazoline was used to give **6-methoxy-4-(3-methylindol-5-yloxy)-7-(2-piperidinoethoxy)quinazoline** (156mg, 80%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.38 (m, 2H), 1.50 (m, 4H), 2.24 (s, 3H), 2.73 (t, 2H), 3.96 (s, 3H), 4.28 (t, 2H), 6.93 (dd, 1H), 7.16 (s, 1H), 7.32 (d, 1H), 7.37 (m, 2H), 7.58 (s, 1H), 8.47 (s, 1H) and 10.82 (br s, 1H)

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

Elemental analysis	Found	C 67.0 H 6.5 N 13.0
$C_{25}H_{28}N_4O_3$ 0.75 H_2O	Requires	C 67.3 H 6.6 N 12.6%

The starting material was prepared as follows:

1-(2-Chloroethyl)piperidine hydrochloride (0.83g, 4.5mmol) was added to 7-hydroxy-6-methoxy-4-phenoxyquinazoline (1.0g, 3.73mmol), (prepared as described for the starting material in Example 1), and potassium carbonate (2.6g, 18.8mmol) in DMF (30ml), and the mixture heated at 110°C for 2.5 hours and allowed to cool. The insolubles were removed by filtration, and the volatiles were removed from the filtrate by evaporation. The residue was purified by column chromatography eluting with methylene chloride/methanol (9/1) to give 6-methoxy-4-phenoxy-7-(2-piperidinoethoxy)quinazoline (1.2g, 85%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.38(m, 2H); 1.50(m, 4H); 2.4-2.5(m, 4H); 2.75(t, 2H); 3.95(s, 3H); 4.27(t, 2H); 7.30(m, 3H); 7.40(s, 1H); 7.46(m, 2H); 7.54(s, 1H); 8.52(s, 1H)

MS - ESI: 380 $[MH]^+$

A mixture of 6-methoxy-4-phenoxy-7-(2-piperidinoethoxy)quinazoline (1.15g, 3.0mmol) and 2M hydrochloric acid (20ml) was heated at 90°C for 2 hours and allowed to cool. The mixture was neutralised with solid sodium hydrogen carbonate and extracted with methylene chloride. The organic phase was separated, passed through phase separating paper and the volatiles removed by evaporation to give a solid product (230mg). The aqueous phase was adjusted to pH10, the resulting precipitate was collected by filtration, washed with water and dried to give a second crop of product (220mg). The products were combined to give 6-methoxy-7-(2-piperidinoethoxy)-3,4-dihydroquinazolin-4-one (450mg, 50%).

MS - ESI: 304 $[MH]^+$

A mixture of 6-methoxy-7-(2-piperidinoethoxy)-3,4-dihydroquinazolin-4-one (440mg, 1.45mmol), thionyl chloride (15ml) and DMF (3 drops) was heated at reflux for 3 hours then allowed to cool. The excess thionyl chloride was removed by evaporation and the residue was azeotroped with toluene to give a crude 4-chloro-6-methoxy-7-(2-piperidinoethoxy)quinazoline hydrochloride (640mg).

4-Chloro-6-methoxy-7-(2-piperidinoethoxy)quinazoline hydrochloride was suspended in methylene chloride (10ml) and saturated aqueous sodium hydrogen carbonate solution (5ml) then stirred vigorously for 10 minutes at ambient temperature. The layers were separated and the organic layer dried ($MgSO_4$) then evaporated to give a white solid. This solid was triturated with methanol (2.5ml), the resulting solid filtered off, washed with cold methanol and dried to give 4-chloro-6-methoxy-7-(2-piperidinoethoxy)quinazoline (0.36g).

Example 181

Using an analogous procedure to that described in Example 178, 4-chloro-6-methoxy-7-(3-(N-methyl-N-methylsulphonylamino)propoxy)quinazoline, (prepared as described for the starting material in Example 152), was used to give **6-methoxy-4-(3-methylindol-5-yloxy)-7-(3-(N-methyl-N-methylsulphonylamino)propoxy)quinazoline** (104mg, 49%).

^{1}H NMR Spectrum: ($DMSOd_6$) 2.08 (m, 2H), 2.22 (s, 3H), 2.80 (s, 3H), 2.88 (s, 3H), 3.27 (t, 2H), 3.97 (s, 3H), 4.22 (t, 2H), 6.95 (dd, 1H), 7.17 (s, 1H,), 7.35 (m, 3H), 7.59 (s, 1H), 8.48 (s, 1H) and 10.82 (br s, 1H)

MS (ESI) : 471 $(MH)^+$

Elemental analysis	Found	C 57.0	H 5.6	N 11.4	
$C_{23}H_{26}F_4N_4O_5S$ 0.5 H_2O,	Requires	C 57.5	H 5.7	N 11.7%	

Example 182

A mixture of 4-chloro-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline (218 mg, 0.68 mmol), (prepared as described for the starting material in Example 9), 5-hydroxy-1*H*-pyrrolo[2,3-*b*]pyridine (100 mg, 0.75 mmol) and potassium carbonate (280 mg, 2.0mmol) 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 which was purified by column chromatography, eluting with dichloromethane/methanol/880 ammonia (100/8/1). The relevant fractions were combined and evaporated '*in vacuo*' to give a white solid. This was recolumned using dichloromethane/methanol (4/1) solvent to give a white solid which was triturated with acetone, filtered and dried to give **6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)-4-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)quinazoline** (50 mg, 18%).

m.p. 184.0 - 185.5°C

^{1}H NMR Spectrum: ($DMSOd_6$) 1.70 (m, 4H), 1.99 (m, 2H), 2.46 (m, 4H), 2.58 (t, 2H), 4.00 (s, 3H), 4.26 (t, 2H), 6.48 (t, 1H), 7.36 (s, 1H), 7.55 (t, 1H), 7.60 (s, 1H), 7.92 (d,1H), 8.19 (d, 1H), 8.50 (s,1H) and 11.78 (br s, 1H)

MS (ESI) : 420 $(MH)^+$

Elemental analysis	Found	C 63.9	H 5.9	N 16.1
$C_{23}H_{25}N_5O_3$ 0.7 H_2O	Requires	C 63.9	H 6.2	N 16.2%

The starting material was prepared as follows:-

A suspension of 5-methoxy-1*H*-pyrrolo[2,3-*b*]pyridine (210 mg, 1.42 mmol), (Heterocycles 50, (2), 1065 - 1080, (1999)), in dichloromethane (10 ml) was stirred in an inert atmosphere, a 1.0M solution of boron tribromide in dichloromethane (4.3 ml, 4.3 mmol) added dropwise and the mixture stirred at ambient temperature overnight. The reaction mixture was taken to pH6 by the dropwise addition of 5N aqueous sodium hydroxide and further diluted with water. The aqueous solution was extracted several times with ethyl acetate, the extracts combined, washed with water followed by brine and dried over magnesium sulphate. The ethyl acetate solvent was removed '*in vacuo*' and the residue purified by column chromatography, eluting with dichloromethane/methanol (95/5), to give a white solid. The solid was triturated with ether, filtered and dried to give 5-hydroxy-1*H*-pyrrolo[2,3-*b*]pyridine (108 mg, 57%).

m.p. 206-209°C

^{1}H NMR Spectrum: ($DMSOd_6$) 6.25 (s,1H), 7.27 (s,1H), 7.33 (s, 1H), 7.82 (s, 1H), 9.00 (s,1H) and 11.20 (s, 1H)

MS (ESI) : 135 $(MH)^+$

Example 183

A mixture of 4-chloro-6-methoxy-7-(3-piperidinopropoxy)quinazoline (168 mg, 0.5 mmol), (prepared as described for the starting material in Example 67), potassium carbonate (345 mg, 5.0 mmol), 5-hydroxy-2-indolecarboxylic acid (106mg, 0.6 mmol) and DMA (2.0 ml) was purged with nitrogen for 5 minutes at 25°C. This mixture was then stirred at 100°C for 3 hours, allowed to cool to ambient temperature, filtered and the filtrate evaporated under vacuum. The residue was purified on octadecylsilane reverse phase silica eluting with acetonitrile/water/trifluoroacetic acid (as a gradient from 30/69.8/0.2 to 50/49.8/0.2) and the product further purified by silica column chromatography eluting with dichloromethane/methanolic ammonia (7M) (90/10) to give **4-(2-carboxyindol-5-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline** (85 mg 36%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.43 (m, 2H), 1.56 (m, 4H), 2.04 (m, 2H), 2.59 (m, 6H), 3.97 (s, 3H), 4.24 (t, 2H), 7.01 (s, 1H), 7.11 (dd, 1H), 7.36 (s, 1H), 7.48 (m, 2H), 7.58 (s, 1H), 8.48 (s, 1H) and 11.53 (br s, 1H)

MS (ESI) : 477 $(MH)^+$

Example 184

4-Chloro-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline (0.15 g, 0.45 mmol), (prepared as described for the starting material in Example 50), potassium carbonate (94 mg, 0.68 mmol) and 7-hydroxyquinoline (79 mg, 0.54 mmol) were suspended in anhydrous DMF (1.5 ml) and heated to 90°C overnight. The compound was precipitated upon addition of water. The precipitate was collected by filtration, washed with water and dried under vacuum over phosphorus pentoxide to give **6-methoxy-7-(3-methylsulphonylpropoxy)-4-(quinolin-7-yloxy)quinazoline** (161 mg, 81%).

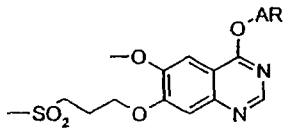
^{1}H NMR Spectrum: ($DMSOd_6$) 2.26 (m, 2H); 3.08 (s, 3H); 3.35 (m, 2H); 4.03 (s, 3H); 4.38 (m, 2H); 7.45 (s, 1H); 7.60 (m, 1H); 7.65 (m, 1H); 7.70 (s, 1H); 7.95 (d, 1H); 8.15 (d, 1H); 8.46 (d, 1H); 8.60 (s, 1H); 8.95 (d, 1H)

MS (ESI) : 440 $[MH]^+$

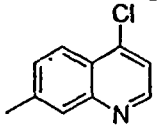
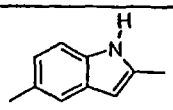
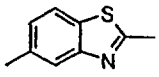
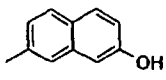
Examples 185-188

Using an analogous procedure to that described in Example 184, 4-chloro-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline (0.15 g, 0.45 mmol), (prepared as described for the starting material in Example 50), was reacted with the appropriate phenols to give the compounds in Table X.

Table X



Example number	weight (mg)	yield %	MS-ESI [MH]+	AR	note

185	199	93	474		a
186	171	85	422		b
187	183	88	460		c
188	83	40	455		d

a) Using 4-chloro-7-hydroxyquinoline (96 mg) gave **4-(4-chloroquinolin-7-yloxy)-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline**.

^{1}H NMR Spectrum: ($DMSOd_6$) 2.24 (m, 2H); 3.04 (s, 3H); 3.35 (m, 2H); 3.99 (s, 3H); 4.32 (m, 2H); 7.42 (s, 1H); 7.64 (s, 1H); 7.80 (d, 2H); 8.04 (d, 1H); 8.29 (d, 1H); 8.55 (s, 1H); 8.87 (d, 1H)

b) Using 5-hydroxy-2-methylindole (80 mg) gave **6-methoxy-4-(2-methylindol-5-yloxy)-7-(3-methylsulphonylpropoxy)quinazoline**.

^{1}H NMR Spectrum: ($DMSOd_6$) 2.24 (m, 2H); 2.40 (s, 3H); 3.05 (s, 3H); 3.35 (m, 2H); 4.0 (s, 3H); 4.32 (m, 2H); 6.13 (s, 1H); 6.88 (d, 1H); 7.25 (d, 1H); 7.32 (d, 1H); 7.39 (s, 1H); 7.60 (s, 1H); 8.50 (s, 1H)

c) Using 5-hydroxy-2-methylbenzothiazole (90 mg) gave **6-methoxy-4-(2-methyl-1,3-benzothiazol-5-yloxy)-7-(3-methylsulphonylpropoxy)quinazoline**.

^{1}H NMR Spectrum: ($DMSOd_6$) 2.24 (m, 2H); 2.28 (s, 3H); 3.05 (s, 3H); 3.35 (m, 2H); 4.0 (s, 3H); 4.32 (m, 2H); 7.36 (d, 1H); 7.41 (s, 1H); 7.65 (s, 1H); 7.87 (d, 1H); 8.11 (d, 1H); 8.53 (s, 1H)

d) Using 2,7-dihydroxynaphtalene (87 mg) gave **4-(7-hydroxy-2-naphthyloxy)-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline**.

^{1}H NMR Spectrum: ($DMSOd_6$) 2.24 (m, 2H); 3.05 (s, 3H); 3.35 (m, 2H); 3.98 (s, 3H); 4.32 (m, 2H); 7.06 (d, 1H); 7.12 (s, 1H); 7.18 (d, 1H); 7.40 (d, 1H); 7.59 (m, 2H); 7.85 (m, 2H); 8.55 (d, 1H); 9.8 (br s, 1H)

Example 189

To a portion of 2-chloro-5-hydroxybenzimidazole (191 mg, 0.75 mmol) in DMF (3 ml) was added sodium hydride (60 mg, 1.5 mmol) under argon at ambient temperature. Ten minutes later 4-chloro-6-methoxy-7-(1-methylpiperidin-4-yl)methoxyquinazoline (200 mg, 0.62 mmol), (prepared as described for the starting material in Example 10), was added and the mixture heated at 100 °C for 2 hours. More 2-chloro-5-hydroxybenzimidazole (30 mg, 0.12 mmol) and sodium hydride (11 mg, 0.28 mmol) were then added as the reaction was found to be incomplete. The heating was continued for an additional 1 hour. Work-up using ethyl acetate and a saturated aqueous solution of ammonium chloride followed by drying of the organic phase ($MgSO_4$) and evaporation of the solvent gave a crude product which was adsorbed on alumina using dichloromethane/methanol and purified by flash chromatography using neutral alumina and dichloromethane/methanol (98:2) as the eluent.
Evaporation of the solvent and trituration in ether gave **4-(2-chloro-1*H*-benzimidazol-6-yloxy)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline** (46 mg, 16%).
^{1}H NMR Spectrum: ($DMSOd_6$ + TFA) 1.60 (m, 2H); 2.05 (d, 2H); 2.15 (m, 1H); 2.80 (s, 3H); 3.05 (m, 2H); 3.55 (m, 2H); 4.05 (s, 3H); 4.15 (d, 2H); 7.20 (dd, 1H); 7.50 (dd, 2H); 7.65 (d, 1H); 7.70 (s, 1H); 8.80 (s, 1H)
MS (ESI) : 454 $[MH]^+$

The starting material was synthesised as follows:

2-Chloro-5-methoxybenzimidazole (0.3 g, 1.64 mmol) was suspended in dichloromethane (20 ml) under argon followed by the addition of boron tribromide (233 ul, 2.46 mmol). The reaction mixture was stirred for 2 hours at ambient temperature. The solvent was evaporated and the resulting powder was added in portions to methanol (30 ml). Silica was added and the solvent was evaporated. The resulting powder was placed on the top of a silica column and the product was eluted off using dichloromethane/methanol (95/5). Evaporation of the solvent and trituration in ether gave 2-chloro-5-hydroxybenzimidazole (440 mg, 99%).

Example 190

Using an analogous procedure to that described in Example 189, 4-chloro-6-methoxy-7-(1-methylpiperidin-4-yl)methoxyquinazoline, (prepared as described for the starting material in Example 10), was reacted with 5-hydroxy-2-methylbenzimidazole (200 mg, 0.62 mmol) and after work-up and purification on a 10 g silica ISOLUTE column using successively dichloromethane, dichloromethane/methanol (95/5) and dichloromethane/methanol saturated with ammonia (95/5), gave **6-methoxy-4-(2-methyl-1*H*-benzimidazol-6-yloxy)-7-((1-methylpiperidin-4-yl)methoxy)quinazoline** (68 mg, 25%).

^{1}H NMR Spectrum: ($DMSOd_6$ + TFA) 1.60 (m, 2H); 2.10 (m, 2H); 2.20 (m, 1H); 2.80 (s, 3H); 2.85 (s, 3H); 3.05 (m, 2H); 3.50 (m, 2H); 4.05 (s, 3H); 4.15 (d, 2H); 7.50 (s, 1H); 7.55 (d, 1H); 7.70 (s, 1H); 7.85 (d, 1H); 7.90 (d, 1H); 8.65 (s, 1H)

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

The starting material was prepared as follows:

The free base of 4-methoxy-1,2-phenylenediamine dihydrochloride (10 g) was obtained by shaking it with a mixture of ethyl acetate and a saturated aqueous solution of sodium hydrogen carbonate. The organic phase was then washed with brine, dried ($MgSO_4$) and the solvent evaporated. The obtained dark oil (6.08 g, 50 mmol) was solubilised in toluene (60 ml) and p-toluene sulfonic acid (60 mg) and triethyl orthoacetate (9.15 ml, 50 mmol) were added in turn. The mixture was heated to 110 °C until no more ethanol distilled off. The remaining toluene was removed by rotary evaporation and the residue purified by flash chromatography using dichloromethane/methanol (95/5) as the eluent. The obtained dark oil was triturated in ether and the solid collected by filtration to give 5-methoxy-2-methylbenzimidazole (4.15 g,51%).

^{1}H NMR Spectrum ($DMSOd_6$ + TFA) 2.75 (s, 3H); 3.85 (s, 3H); 7.15 (dd, 1H); 7.25 (s, 1H); 7.70 (d, 1H)

Using an analogous procedure to that described for the synthesis of 2-chloro-5-hydroxybenzimidazole in Example 189, 5-methoxy-2-methylbenzimidazole (4.0 g, 25 mmol) was reacted with boron tribromide (7 ml, 74 mmol) in dichloromethane (150 ml) to give, after work-up and purification by flash chromatography using dichloromethane/methanol (90/10), 5-hydroxy-2-methylbenzimidazole (4.4 g, 76%).

^{1}H NMR Spectrum ($DMSOd_6$) 2.70 (s, 3H); 6.95 (dd, 1H); 7.00 (d, 1H); 7.55 (d, 1H)

Example 191

4-Chloro-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline (200 mg, 0.62 mmol), (prepared as described for the starting material in Example 10), was suspended in DMF (3 ml) under argon. 3-Cyano-7-hydroxyquinoline (116 mg, 0.68 mmol) and potassium carbonate (129 mg, 0.93 mmol) were added and the reaction mixture was heated at 95 °C for 90 minutes. Upon cooling to ambient temperature the mixture was diluted with dichloromethane and poured on the top of an ISOLUTE silica column. Elution was done using successively dichloromethane, dichloromethane/methanol (95/5) and dichloromethane/methanol saturated with ammonia (95/5). Evaporation of the solvent and trituration of the solid in ether gave **4-(3-cyanoquinolin-7-yloxy)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline** (244 mg, 86%).

^{1}H NMR Spectrum: ($DMSOd_6$ + TFA) 1.60 (m, 2H); 2.10 (m, 3H); 2.85 (s, 3H); 3.05 (m, 2H); 3.55 (m, 2H); 4.05 (s, 3H); 4.20 (d, 2H); 7.55 (s, 1H); 7.80 (s, 1H); 7.85 (dd, 1H); 8.15 (s, 1H); 8.3 (d, 1H); 8.85 (s, 1H); 9.20 (s, 1H); 9.25 (s, 1H)

MS (ESI) : 456 $[MH]^+$ 456

The starting material was prepared as follows:

m-Anisidine (50 g, 407 mmol) and diethyl ethoxymethylenemalonate (102 g, 407 mmol) were heated at 60 °C for 20 minutes. Diphenyl ether (270 ml) was then added and the temperature was raised to 240 °C over 30 minutes. The ethanol formed distilled off. Heating was maintained at this temperature for 1 hour then the reaction mixture was allowed to cool to 120 °C at which point the reaction mixture was diluted with heptane and allowed to stand overnight at ambient temperature. The brown solid was collected by filtration and washed with methanol and ether to give ethyl 7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate (45 g, 45%). This reaction was repeated twice.

^{1}H NMR Spectrum: ($DMSOd_6$) 1.25 (t, 3H); 3.85 (s, 3H); 4.20 (q, 2H); 6.95 (d, 1H); 7.00 (s, 1H); 8.05 (d, 1H); 8.50 (s, 1H)

Phosphorus oxychloride (88 ml) was added to ethyl 7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate (58 g, 235 mmol) and the mixture was heated at reflux for 45 minutes under anhydrous conditions. Upon cooling to ambient temperature, phosphorus

oxychloride was evaporated and the solid residue was added in portions to a mixture of ammonia (150 ml) and ice (200g). External cooling as well as further addition of ammonia to maintain the pH around 8 was needed during this hydrolysis step. The aqueous phase was extracted with dichloromethane and the organic phase was washed with water and brine, dried ($MgSO_4$) and concentrated to about 300 ml. Pentane (400 ml) was added and the precipitate formed collected by filtration. Drying under vacuum gave 4-chloro-3-ethoxycarbonyl-7-methoxyquinoline (45.5 g, 73 %).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.40 (t, 3H); 4.00 (s, 3H); 4.45 (q, 2H); 7.45 (dd, 1H); 7.55 (d, 1H); 8.30 (d, 1H); 9.10 (s, 1H)

4-Chloro-3-ethoxycarbonyl-7-methoxyquinoline (43 g, 162 mmol) was dissolved in acetic acid (250 ml), with 10% palladium on charcoal (1.5 g) and hydrogenated at atmospheric pressure during 8 hours. The catalyst was removed by filtration over a pad of celite and the solvent evaporated. The residue was diluted with water and the pH adjusted to 7-8 with a saturated solution of sodium hydrogen carbonate. The solid was collected by filtration, washed with water and dried under vacuum over phosphorus pentoxide to give 3-ethoxycarbonyl-7-methoxyquinoline (33 g, 88%) as a beige powder.

^{1}H NMR Spectrum: ($DMSOd_6$) 1.40 (t, 3H); 3.95 (s, 3H); 4.40 (q, 2H); 7.35 (dd, 1H); 7.50 (d, 1H); 8.15 (d, 1H); 8.90 (d, 1H); 9.25 (d, 1H)

3-Ethoxycarbonyl-7-methoxyquinoline (28 g, 120 mmol) was added to a methanol solution saturated with ammonia. The suspension was stirred at ambient temperature in a glass pressure vessel for 2 weeks. The white solid was collected by filtration, washed with methanol and dried under vacuum to give 3-carbamoyl-7-methoxyquinoline (21g, 86%).

^{1}H NMR Spectrum ($DMSOd_6$) 3.95 (s, 3H); 7.35 (dd, 1H); 7.45 (d, 1H); 7.60 (br s, 1H); 8.00 (d, 1H); 8.20 (br s, 1H); 8.75 (s, 1H); 9.25 (s, 1H)

3-Carbamoyl-7-methoxyquinoline (4 g, 20 mmol) was suspended in anhydrous dichloromethane (60 ml) under argon. Anhydrous dimethyl sulphoxide (2.25 ml, 32 mmol) was added, the mixture was cooled to -78 °C and a solution of oxalyl chloride (2.08 ml, 24 mmol) in dichloromethane (20 ml) was added dropwise over the course of 1 hour. 15 Minutes after the end of the addition, triethylamine (8.3 ml, 60 mmol) was added dropwise and the heterogeneous reaction mixture stirred for an additional 1 hour at -78 °C then left to rise to ambient temperature. The unreacted starting material was removed by filtration and the filtrate was diluted with water and extracted with ethyl acetate. The organic phases were

combined, washed with brine, dried ($MgSO_4$) and the solvent evaporated. The residue was purified by flash chromatography using dichloromethane/methanol (97/3). The obtained solid was triturated with ether and gave, after drying under vacuum, 3-cyano-7-methoxyquinoline (1.47 g, 40%).

^1H NMR Spectrum ($DMSOd_6$) 4.00 (t, 3H); 7.40 (dd, 1H); 7.50 (d, 1H); 8.00 (d, 1H); 8.95 (s, 1H); 9.10 (d, 1H)

3-Cyano-7-methoxyquinoline (380 mg, 2.1 mmol) was suspended in benzene (10 ml), aluminium trichloride (826 mg, 6.2 mmol) was added and the mixture heated at reflux for 30 minutes. More aluminium trichloride (275 mg, 2.1 mmol) was added and the mixture refluxed for a further 2 hours. The solvent was evaporated, the dark green solid was added to ice and extracted with ethyl acetate. The organic phase was washed with brine, dried ($MgSO_4$) and evaporated. The solid was found to contain some aluminium salts which were removed as follows. The solid was dissolved in dichloromethane (200 ml) was stirred vigorously with a saturated sodium hydrogen carbonate solution for 1 hour. The product was collected by filtration of the aqueous phase and dried over phosphorus pentoxide under vacuum to give 3-cyano-7-hydroxyquinoline (238 mg, 68%).

^1H NMR Spectrum ($DMSOd_6$) 7.25 (d, 1H); 7.30(d, 1H); 7.95 (d, 1H); 8.85 (d, 1H); 9.00 (d, 1H)

Example 192

To 6-methoxy-7-(3-morpholinopropoxy)-4-((1-*tert*butoxycarbonyl-1,2,3,4-tetrahydroquinolin-6-yl)oxy)quinazoline (110 mg, 0.2 mmol) in solution in dichloromethane (3 ml) was added TFA (0.3 ml) and the mixture stirred for 1 hour at ambient temperature. The solvents were evaporated and the remaining oil was diluted with dichloromethane and the pH adjusted to 9 with a saturated solution of sodium hydrogen carbonate. The organic phase was washed with, brine, dried ($MgSO_4$), filtered and the solvent evaporated to give **6-methoxy-7-(3-morpholinopropoxy)-4-(1,2,3,4-tetrahydroquinolin-6-yloxy)quinazoline** (84 mg, 93%).

^1H NMR Spectrum: ($CDCl_3$) 1.95 (m, 2H); 2.15 (m, 2H); 2.45 (m, 4H); 2.60 (t, 2H); 2.80 (t, 2H); 3.35 (t, 2H); 3.75 (m, 4H); 3.90 (br s, 1H); 4.05 (s, 3H); 4.30 (t, 2H); 6.55 (d, 1H); 6.85 (m, 2H); 7.30 (s, 1H); 7.55 (s, 1H); 8.65 (s, 1H)

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

Elemental analysis:	Found	C 66.4 H 6.9 N 12.4
$C_{25}H_{30}N_4O_4$;	Requires	C 66.7 H 6.7 N 12.4%

The starting material was prepared as follows:

6-Hydroxyquinoline (1 g, 6.9 mmol) was dissolved in methanol and hydrogenated at 3 atmospheres pressure with platinum(IV) oxide (276 mg) over 24 hours. The catalyst was removed by filtration over a pad of celite and the solvent was evaporated. The solid was washed with ether to give 6-hydroxy-(1,2,3,4)-tetrahydroquinoline (698 mg, 68 %).
^{1}H NMR Spectrum ($DMSOd_6$) 1.75 (m, 2H); 2.60 (m, 2H); 3.05 (m, 2H); 4.90 (br s, 1H); 6.30 (m, 3H); 8.25 (br s, 1H)

6-Hydroxy-(1,2,3,4)-tetrahydroquinoline (250 mg, 1.7 mmol) was suspended in acetone (1 ml) and trichloromethane (1 ml) under argon. *Tert*-Butoxycarbonylanhydride (365 mg, 1.7 mmol) in solution in acetone was added dropwise followed by THF (2ml) to help the solubilisation. 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 resulting gum was purified by flash chromatography using dichloromethane/methanol (97/3) as solvent. Evaporation of the solvent gave 6-hydroxy-4-(1-*tert*butoxycarbonyl-1,2,3,4-tetrahydroquinoline (344 mg, 82%) as a brown foam.
^{1}H NMR Spectrum: ($DMSOd_6$) 1.50 (m, 9H); 1.90 (m, 2H); 2.70 (t, 2H); 3.65 (t, 2H); 4.75 (br s, 1H); 6.55 (d, 1H); 6.65 (dd, 1H); 7.45 (d, 1H)

6-Hydroxy-4-(1-*tert*butoxycarbonyl-1,2,3,4-tetrahydroquinoline (82 mg, 0.32 mmol) was dissolved in anhydrous dimethylformamide under argon, with potassium carbonate (61 mg, 0.44 mmol) and 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (100 mg, 0.3 mmol), (prepared as described for the starting material in Example 1). No reaction occurred after 2 hours at 60 °C. Sodium hydride (12 mg, 0.3 mmol) was added and the reaction mixture was heated at 120 °C for 90 minutes. The cooled mixture was poured into water and ethyl acetate. The organic phase was washed with water, brine, dried ($MgSO_4$), filtered and the solvent evaporated. The residue was purified by flash chromatography using first dichloromethane/methanol (97/3) as solvent. Evaporation of the solvent gave 6-methoxy-7-(3-morpholinopropoxy)-4-((1-*tert*butoxycarbonyl-1,2,3,4-tetrahydroquinolin-6-yl)oxy)quinazoline (115 mg, 71%) as a white solid.