Synthesis of Azolylalkylquinolines with Cytotoxic Activity

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The syntheses of various azolylalkylquinoline derivatives in which the nature of the linkage between the quinoline and azolylalkyl moieties of the molecule were altered are described. The compounds were tested for cytotoxic activity towards cancer cells and compound **27** was found to exhibit moderate *in vivo* activity in a murine sarcoma model.

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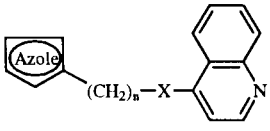
Our work involving the synthesis of azolylalkylquinoline derivatives with cytotoxic activity towards various cancer cell lines has been previously reported [1,2]. Compounds of the general formulae **1** and **2** were demonstrated to exhibit impressive *in vitro* cytotoxic activity which was, in several cases, superior to Adriamycin.



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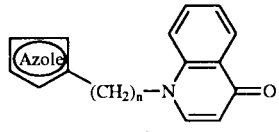


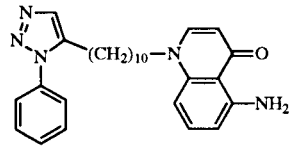
2

Azole: 3-methylisoxazol-5-yl, 1-phenylpyrazol-5-yl
1-methylpyrazol-5-yl, 1-phenyl-1,2,3-triazol-5-yl, *etc.*

X = O, NH, S, SO_2
n = 5-12

Structure-activity relationships showed that in both the quinoline **1** and quinolone **2** classes, for optimal cytotoxic activity, the 1-methylpyrazol-5-yl and 1-phenyl-1,2,3-triazol-5-yl moieties were the most effective azoles. In addition, an alkyl chain of 7 to 10 carbon atoms was necessary for notable cytotoxicity. In the case of the quinoline class, both the oxygen and nitrogen linked derivatives were found to be effective while reduced cytotoxicity was observed for sulfur and sulfonyl linked compounds. Unfortunately, the compounds were ineffective *in vivo* and exhibited signs of acute general toxicity at higher doses. Further chemical modification of the quinolone class of compounds led to **3** which was the most effective compound, *in vitro*, that had been synthesized to date [3]. In addition, **3** exhibited slight activity in an *in vivo* murine sarcoma model.

This result encouraged us to carry out further chemical modifications in attempting to improve the *in vivo* efficacy of these classes of compounds. Our efforts involved reducing the lipophilic nature of the compounds by synthesizing phenolic and phenoxy acetic acid derivatives and altering the nature of the link between the azolylalkyl and quinolyl portions of the molecule. Herein we describe these chemical modifications and their effect on cytotoxic activity.



3

Chemistry.

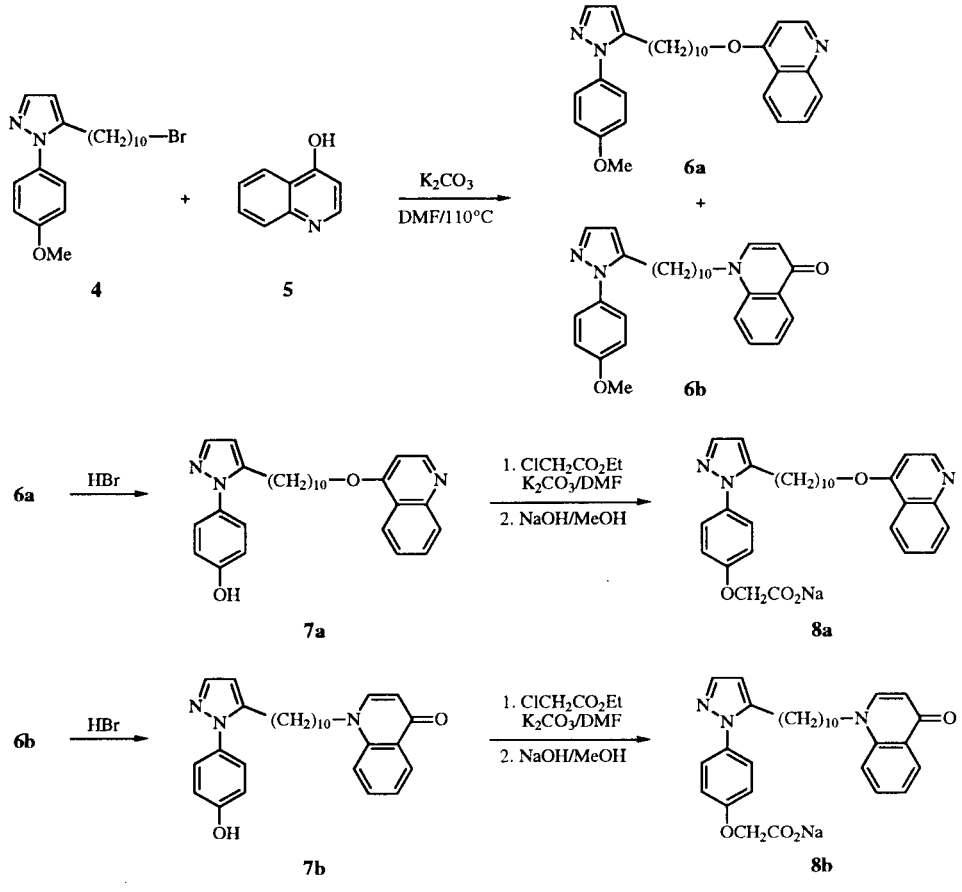
Scheme 1 depicts the synthesis of the 1-(4-hydroxyphenyl)pyrazol-5-yl **7a,b** and 1-(phenoxyacetic acid sodium salt)pyrazol-5-yl **8a,b** derivatives. The synthesis of the azolylalkyl bromide **4** and its reaction with 4-hydroxyquinoline **5** in DMF in the presence of potassium carbonate has been described previously [1]. Tautomerism of **5** leads to both the 4-azolylalkyloxyquinoline **6a** and 1-azolylalkyl-4(1*H*)-quinolone **6b** in comparable yields. Demethylation of **6a** and **6b** with hydrobromic acid resulted in the corresponding phenolic derivatives **7a,b**. Treatment with ethyl chloroacetate in DMF in the presence of potassium carbonate gave ethyl phenoxy acetate intermediates which were treated, after partial purification, with sodium hydroxide in methanol to give the phenoxyacetic acid salts **8a,b**.

The synthesis of the azolylalkyloxy ethenylquinoline derivatives **11,12** is depicted in Scheme 2. In the presence of sodium *tert*-butoxide in DMSO, 4-acetylquinoline **10** underwent *O*-alkylation of the corresponding enolate by azolylalkyl bromides **9** to form **11** and **12** in moderate yields. The structures of these compounds were verified by the lack of a carbonyl absorption in their respective IR spectra and by carbon-proton heteronuclear correlation nmr experiments. No product of *C*-alkylation was isolated.

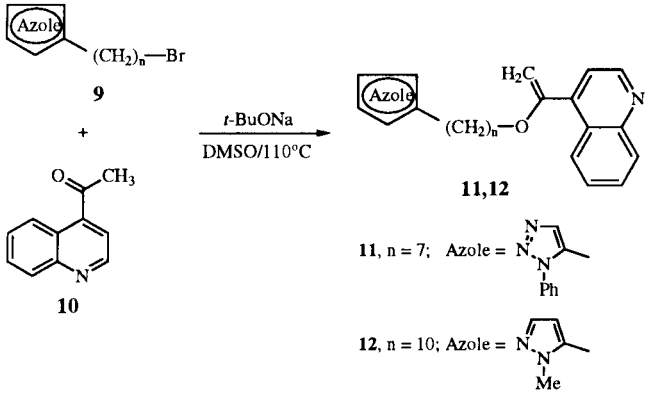
Scheme 3 depicts the synthesis of the piperazine-linked derivative **17**. An excess of piperazine **14** was heated with 4-chloroquinoline **13** in the absence of solvent to give 4-(piperazin-1-yl)quinoline **15**. Alkylation with azolylalkyl bromide **16** in DMF resulted in **17** in 40% yield.

The synthesis of *N*-azolylalkyl-4-quinolinecarboxamides **20-22** is depicted in Scheme 4. Azolylalkylamines **18** [3] were treated with 4-quinolinecarboxylic acid **19** in DMF in the presence of 1,1'-carbonyldiimidazole (CDI) to give **20-22** in 40% to 60% yields.

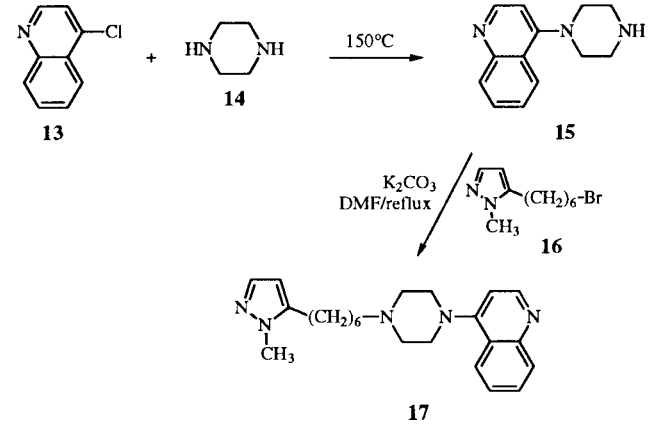
Scheme 1



Scheme 2



Scheme 3

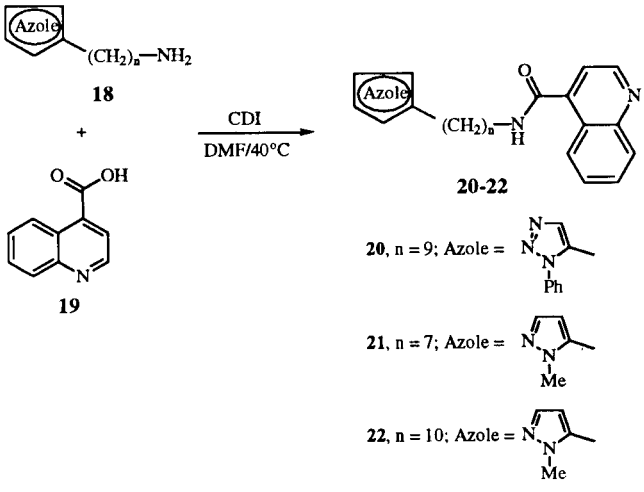


Scheme 5 depicts the synthesis of *N*-(4-quinolyl)azolylalkanamides **26,27**. Azolylalkylbromides **9** were converted to the corresponding nitriles **23a,b** by heating in DMSO with sodium cyanide [4]. Carboxylic acids **24a,b** were obtained by treating **23a,b** with aqueous sodium hydroxide/hydrogen peroxide. Amides **26** and **27** were obtained by heating **24a,b** with 4-aminoquinoline **25** in DMF in the presence of CDI.

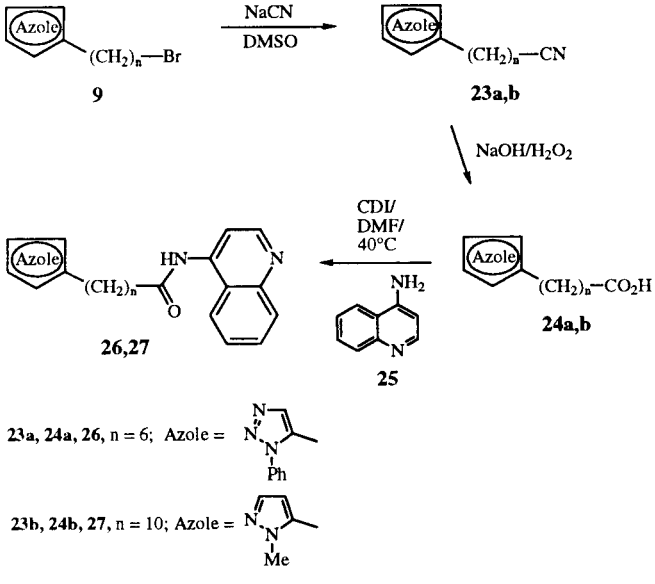
Results and Discussion.

The results of *in vitro* screening of selected compounds against cancer cell lines are summarized in Table 1. One possible explanation for the lack of *in vivo* efficacy observed for previously synthesized compounds related to their high lipophilicity. The water-soluble compounds **8a,b** were designed to explore the possibility that reducing the

Scheme 4



Scheme 5



lipophilicity of the molecule may increase cytotoxic activity. Unfortunately, both compounds exhibited only weak cytotoxicity *in vitro*. Interestingly, the phenolic intermediates **7a,b** both showed *in vitro* activity comparable to Adriamycin. Clearly, further study of the effects of substitution on the phenyl portion of the molecule is necessary.

In investigating the effect on cytotoxicity of changing the nature of the link between the azolylalkyl and quinolyl moieties of the molecule, several approaches were carried out. The azolylalkyloxy ethenylquinoline derivatives **11,12** were only weakly to moderately cytotoxic. In attempting to add more hydrophilic character to the molecule, piperazine was employed as a linkage resulting in **17**. Again this modification led only to moderate cytotoxicity. In general, the quinolinecarboxamide derivatives **20-22** were only weakly cytotoxic. Note the difference in

Table 1

In vitro Cytotoxicity of Selected Compounds

No.	TD50 (μg/ml) [a,b] KB [c]	L1210 [d]
7a	0.016	0.018
7b	0.008	0 009
8a	6.51	–
8b	8.15	–
11	0.591	–
12	2.00	–
17	0.875	–
20	2.10	–
21	3.56	–
22	0.714	–
26	0.048	0.225
27	0.014	0.023
Adriamycin	0.016	0.015

[a] TD_{50} = dose at which there was a 50% reduction in cell viability compared to cell controls. [b] Tests were carried out in duplicate and variability of results between duplicate runs was no more than one dilution. [c] Human nasopharyngeal carcinoma. [d] Murine lymphocytic leukemia.

Table 2

In vivo Antitumor Activity of **27** - S180 Model [a]

No.	Dose mg/kg	BWC [b] (g, day 6-1)	Tumor Weight (g, mean ± s.d.)	TWI [c] (%)	Mortality (in 8 days)
Control	–	6.0	2.75 ± 1.52	–	0
27	40	5.0	2.37 ± 0.63	13.8	0
	20	3.3	2.63 ± 0.21	4.4	0
	10	4.4	2.13 ± 0.42	22.5	1/6 (Day 8)
	5	5.2	3.02 ± 0.43	-9.8	0
ADR	5	1.5	1.52 ± 0.37	44.7	0

[a] Murine sarcoma. [b] BWC indicates body weight change; day 6 minus day 1. [c] TWI indicates tumor weight inhibition as calculated from the mean tumor weight against the control group.

TD_{50} values between **21** and **22**. While these compounds differ only in the length of their alkyl chains, **22** with a decyl chain was 5 times more cytotoxic than **21** with only a heptyl chain. This result is consistent with earlier results and reflects the importance of chain length in determining cytotoxicity.

In contrast to the quinolinecarboxamides **20-22,** the oppositely oriented *N*-(4-quinolyl)azolylalkanamides **26, 27** exhibited impressive *in vitro* cytotoxic activity. In particular, **27** had cytotoxicity comparable to Adriamycin and to the previously reported [1,2] nitrogen and oxygen linked analogs.

In an *in vivo* murine sarcoma model (Table 2), **27** was found to be moderately effective (22.5% inhibition) in inhibiting tumor growth when administered at a dose of 10 mg/kg. This result was promising, however signs of acute general toxicity at higher doses were observed. None the less, this result is a further indication that through continued chemical modification, the therapeutic potential of the azolylalkylquinolines can be increased.

EXPERIMENTAL

The *in vitro* and *in vivo* testing protocols used to evaluate cytotoxic activity were as described previously [1].

Melting points were determined on an Electrothermal digital melting point apparatus and are uncorrected. The ^{1}H nmr spectra were acquired on a Bruker AC-E 200 FT nmr spectrometer. Elemental analyses and mass spectra were performed by the Chemistry Department of The University of Alberta, Edmonton, Alberta, Canada. Reproducible analyses of the 4(1*H*)-quinolone compounds **6b, 7b, 8b** could not be obtained and therefore mass and infrared spectra were used to aid in verification. The ir spectra were acquired on a Shimadzu IR-460 spectrophotometer. DMF was distilled over calcium hydride and stored over molecular sieves. Silica gel used was Kieselgel 60, 230-400 mesh, from Merck.

4-[10-[1-(4-Methoxyphenyl)pyrazol-5-yl]decyl]oxyquinoline (**6a**) and 1-[10-[1-(4-Methoxyphenyl)pyrazol-5-yl]decyl]-4(1*H*)-oxoquinoline (**6b**).

To a stirred mixture of 4-hydroxyquinoline **5** (2.4 g, 17 mmoles) and potassium carbonate (2.35 g, 17 mmoles) in 60 ml of DMF was added **4** (6.70 g, 17 mmoles). The mixture was heated at 120° for 3 hours, then cooled and the solids removed by filtration. The DMF was distilled off under reduced pressure and the residual oil dissolved in 100 ml of dichloromethane. This solution was washed consecutively with water, 5% aqueous potassium hydroxide, and water, then dried over sodium sulfate and the solvent evaporated. The residue was purified by elution through a silica gel column using chloroform as eluent to give 2.34 g (30%) of **6a** and 1.77 g (24%) of **6b** as pale yellow oils.

Compound **6a** had ^{1}H nmr (deuteriochloroform): δ 1.26-1.97 (m, 16H), 2.64 (t, J = 7.8 Hz, 2H), 3.80 (s, 3H), 4.20 (t, J = 7.2 Hz, 2H), 6.19 (d, J = 1.2 Hz, 1H), 6.69 (d, J = 5.4 Hz, 1H), 6.93-6.99 (m, 2H), 7.26-7.34 (m, 2H), 7.45-7.57 (m, 2H), 7.65-7.73 (m, 1H), 8.01-8.21 (m, 2H), 8.73 (d, J = 5.4 Hz, 1H).

Anal. Calcd. for $C_{29}H_{35}N_3O_2$: C, 76.11; H, 7.71; N, 9.18. Found: C, 75.90; H, 7.64; N, 8.99.

Compound **6b** had ^{1}H nmr (deuteriochloroform): δ 1.20-1.85 (m, 16H), 2.63 (t, J = 7.8 Hz, 2H), 3.84 (s, 3H), 4.05 (t, J = 7.2 Hz, 2H), 6.15 (d, J = 1.4 Hz, 1H), 6.24 (d, J = 7.9 Hz, 1H), 6.94-6.97 (m, 2H), 7.23-7.69 (m, 7H), 8.47 (d, J = 7.9 Hz, 1H); ir (neat): C=O stretch 1620 cm^{-1}; ms: (FAB) M$^+$ = 458.

4-[10-[1-(4-Hydroxyphenyl)pyrazol-5-yl]decyl]oxyquinoline (**7a**).

A mixture of **6a** (2.34 g, 5.1 mmoles) and 48% hydrobromic acid (15 ml) was stirred at 100° for 5 hours. The solution was then cooled in an ice bath and neutralized with 10% aqueous sodium hydroxide and extracted with ethyl acetate. The organic phase was washed with brine, dried over magnesium sulfate and the solvent evaporated. The residue was purified by elution through a silica gel column using chloroform/methanol (9:1 v/v) as eluent to give 1.80 g (79%) of **7a** as a viscous yellow oil; ^{1}H nmr (deuteriochloroform): δ 1.22-1.94 (m, 16H), 2.64 (t, J = 7.9 Hz, 2H), 4.20 (t, J = 6.7 Hz, 2H), 6.18 (d, J = 1.8 Hz, 1H), 6.70 (d, J = 5.3 Hz, 1H), 6.81-6.85 (m, 2H), 7.12-7.16 (m, 2H), 7.45-7.71 (m, 3H), 8.02-8.21 (m, 2H), 8.69 (d, J = 5.3 Hz, 1H), 10.52 (br, 1H).

Anal. Calcd. for $C_{28}H_{33}N_3O_2$: C, 75.81; H, 7.45; N, 9.47. Found: C, 76.12; H, 7.29; N, 9.33.

1-[10-[1-(4-Hydroxyphenyl)pyrazol-5-yl]decyl]-4(1*H*)-oxoquinoline (**7b**).

In a similar manner, **7b** was prepared in 76% yield as a viscous yellow oil; ^{1}H nmr (deuteriochloroform): δ 1.16-1.86 (m, 16H), 2.60 (t, J = 7.9 Hz, 2H), 4.06 (t, J = 7.0 Hz, 2H), 6.13 (d, J = 1.4 Hz, 1H), 6.28 (d, J = 7.8 Hz, 1H), 6.86-6.93 (m, 2H), 7.07-7.13 (m, 2H), 7.34-7.70 (m, 5H), 8.46 (d, J = 7.8 Hz, 1H), 10.31 (br, 1H); ir (neat): C=O stretch 1620 cm^{-1}; ms: (FAB) M$^+$ = 444.

4-[10-[1-(4-Phenoxy acetic acid)pyrazol-5-yl]decyl]oxyquinoline Sodium Salt (**8a**).

Ethyl chloroacetate (0.44 g 3.6 mmoles) potassium carbonate (0.46 g, 3.6 mmoles) and **7a** were heated in DMF (25 ml) at 100° for 3 hours. The mixture was cooled and the solids filtered off. The DMF was distilled off under reduced pressure and the residue dissolved in ethyl acetate, washed with water, dried over magnesium sulfate and the solvent evaporated. The residue was eluted through a silica gel column using chloroform/methanol (9:1 v/v) as eluent to give the ethyl phenoxyacetate intermediate which was heated to reflux in methanol in the presence of sodium hydroxide (1 equivalent) for 4 hours. The methanol was evaporated and the residue washed repeatedly with ether to give 1.07 g (60%) of **8a** as a colourless solid, mp 147-149°; ^{1}H nmr (deuterium oxide): δ 0.69-1.50 (m, 16H), 2.11 (br, 2H), 3.62 (br, 2H), 4.18 (s, 2H), 5.64 (m, 1H), 6.29 (m, 1H), 6.70-6.97 (m, 5H), 7.22-7.42 (m, 2H), 7.55-7.82 (m, 2H), 8.41 (m, 1H).

Anal. Calcd. for $C_{30}H_{34}N_3O_4Na$: C, 68.81; H, 6.55; N, 8.03. Found: C, 68.47; H, 6.22; N, 7.71.

1-[10-[1-(4-Carboxymethoxyphenyl)pyrazol-5-yl]decyl]-1,4-dihydro-4-oxoquinoline Sodium Salt (**8b**).

In a similar manner, **8b** was prepared from **7b** in 39% yield as a colourless solid, mp 157-158°; ^{1}H nmr (deuterium oxide): δ 0.50-1.48 (m, 16H), 2.11 (br, 2H), 4.02 (m, 2H), 4.33 (s, 2H), 5.81 (br, 1H), 6.27 (d, J = 6.0 Hz, 1H), 6.89-7.03 (m, 4H), 7.17-7.43 (m, 4H), 7.78-7.86 (m, 1H), 8.10 (d, J = 6.0 Hz, 1H).

7-(1-Phenyl-1,2,3-triazol-5-yl)heptyl 1-(4-Quinolyl)ethenyl Ether (**11**).

A mixture of 4-acetylquinoline **10** (0.15 g, 0.89 mmole), 7-(1-phenyl-1,2,3-triazol-5-yl)heptyl bromide (0.28 g, 0.89 mmole) and sodium *tert*-butoxide (0.20 g, 2.06 mmoles) were heated to 100° in dry DMSO for 3 hours. The solvent was distilled off under reduced pressure and water added to the residue. The mixture was extracted with chloroform and the organic phase washed with brine, dried over sodium sulfate and the solvent evaporated. The residue was eluted through a silica gel column using chloroform/methanol (19:1 v/v) as eluent to give 0.24 g (66%) of **11** as a pale yellow oil; ^{1}H nmr (deuteriochloroform): δ 1.26-1.82 (m, 10H), 2.65 (t, J = 7.6 Hz, 2H), 3.93 (t, J = 6.4 Hz, 2H), 4.48 (d, J = 2.3 Hz, 1H), 4.56 (d, J = 2.3 Hz, 1H), 7.39-7.74 (m, 9H), 8.05-8.18 (m, 2H), 8.88 (d, J = 4.5 Hz, 1H).

Anal. Calcd. for $C_{26}H_{28}N_4O$: C, 75.70; H, 6.84; N, 13.58. Found: C, 75.36; H, 6.72; N, 13.22.

10-(1-Methylpyrazol-5-yl)decyl 1-(4-Quinolyl)ethenyl Ether (**12**).

In a similar manner, **12** was prepared in 45% yield from **10** and 10-(1-methylpyrazol-5-yl)decyl bromide as a pale yellow oil; ^{1}H nmr (deuteriochloroform): δ 1.26-1.88 (m, 16H), 2.57 (t, J = 7.5 Hz, 2H), 3.76 (s, 3H), 3.97 (t, J = 6.4 Hz, 2H), 4.49

(d, J = 2.3 Hz, 1H), 4.57 (d, J = 2.3 Hz, 1H), 6.00 (d, J = 1.2 Hz, 1H), 7.36-7.43 (m, 2H), 7.49-7.57 (m, 1H), 7.67-7.74 (m, 1H), 8.09-8.22 (m, 2H), 8.89 (d, J = 4.7 Hz, 1H).

Anal. Calcd. for $C_{25}H_{33}N_3O$: C, 76.69; H, 8.49; N, 10.73. Found: C, 76.43; H, 8.28; N, 10.50.

4-(Piperazin-1-yl)quinoline (**15**).

A mixture of 4-chloroquinoline **13** (1.00 g, 6.1 mmoles) and piperazine **14** (2.58 g, 30.0 mmoles) was heated with stirring at 150° for 2 hours. The excess piperazine was removed by Kugelrohr distillation and water added to the residue. The resulting mixture was extracted with chloroform and the organic phase dried over sodium sulfate and the solvent evaporated. Crystallization from chloroform/ether gave 0.91 g (70%) of **15** as a colourless solid, mp 65-68°. ^{1}H nmr (DMSO-d_6): δ 2.97-3.06 (m, 4H), 3.08-3.17 (m, 5H), 6.95 (d, J = 5.4 Hz, 1H), 7.47-7.56 (m, 1H), 7.61-7.71 (m, 1H), 7.90-8.06 (m, 2H), 8.68 (d, J = 5.4 Hz, 1H).

Anal. Calcd. for $C_{13}H_{15}N_3$: C, 73.21; H, 7.09; N, 19.70. Found: C, 73.06; H, 6.99; N, 19.90.

4-[4-[6-(1-Methylpyrazol-5-yl)hexyl]piperazin-1-yl]quinoline (**17**).

A mixture of **15** (0.66 g, 3.1 mmoles), 6-(1-methylpyrazol-5-yl)hexyl bromide **16** (0.78 g, 3.2 mmoles) and potassium carbonate (1.50 g, 10.9 mmoles) was heated to reflux in DMF for 10 hours. After cooling, the solids were filtered off and the DMF removed by vacuum distillation. The residue was eluted through a silica gel column using chloroform/methanol (19:1 v/v) as eluent to give a yellow oil. Crystallization from dichloromethane gave 0.47 g (40%) of **17** as pale yellow prisms, mp 58-60°; ^{1}H nmr (deuteriochloroform): δ 1.36-1.74 (m, 8H), 2.45 (t, J = 7.5 Hz, 2H), 2.56 (t, J = 7.5 Hz, 2H), 2.67-2.79 (m, 4H), 3.21-3.31 (m, 4H), 3.77 (s, 3H), 6.01 (d, J = 1.2 Hz, 1H), 6.82 (d, J = 5.4 Hz, 1H), 7.36 (d, J = 1.2 Hz, 1H), 7.41-7.52 (m, 1H), 7.60-7.70 (m, 1H), 7.98-8.09 (m, 2H), 8.71 (d, J = 5.4 Hz, 1H).

Anal. Calcd. for $C_{23}H_{31}N_5$: C, 73.19; H, 8.28; N, 18.55. Found: C, 73.05; H, 8.30; N, 18.34.

N-[10-(1-Methylpyrazol-5-yl)decyl]-4-quinolinecarboxamide (**22**).

Quinoline-4-carboxylic acid **19** (0.13 g, 0.76 mmoles) was suspended in 2 ml of dry DMF and 1,1'-carbonyldiimidazole (CDI) (0.20 g, 1.20 mmoles) was added and the mixture warmed at 40° until gas evolution ceased. An excess of 10-(1-methylpyrazol-5-yl)decylamine **18** (0.55 g, 2.3 mmoles) was added and the resulting mixture stirred for 10 minutes at 40°. The solution was treated with 0.2 ml of water and the solvent distilled off under reduced pressure. The residue was partitioned between ethyl acetate and 2*N* aqueous sodium carbonate. The organic phase was washed with water followed by brine and then dried over magnesium sulfate and the solvent evaporated. Elution of the residue through a silica gel column using chloroform as eluent gave 0.12 g (41%) of **22** as a colourless solid, mp 76-78°; ^{1}H nmr (deuteriochloroform): δ 1.23-1.78 (m, 16H), 2.53 (t, J = 7.4 Hz, 2H), 3.45 (q, J = 6.9 Hz, 2H), 3.76 (s, 3H), 5.97 (d, J = 1.2 Hz, 1H), 6.96 (br, 1H), 7.23 (d, J = 5.4 Hz, 1H), 7.30 (d, J = 1.2 Hz, 1H), 7.48-7.56 (m, 1H), 7.64-7.73 (m, 1H), 8.01-8.14 (m, 2H), 8.72 (d, J = 5.4 Hz, 1H).

Anal. Calcd. for $C_{24}H_{32}N_4O$: C, 73.43; H, 8.22; N, 14.27. Found: C, 73.10; H, 7.97; N, 14.39.

N-[9-(1-Phenyl-1,2,3-triazol-5-yl)nonyl]-4-quinolinecarboxamide (**20**).

In a similar manner, **20** was obtained in 43% yield as a viscous yellow oil; ^{1}H nmr (deuteriochloroform): δ 1.13-1.67 (m, 14H), 2.63 (t, J = 7.4 Hz, 2H), 3.49 (q, J = 6.8 Hz, 2H), 6.73 (br, 1H), 7.33-7.41 (m, 3H), 7.49-7.60 (m, 5H), 7.68-7.76 (m, 1H), 8.06-8.19 (m, 2H), 8.80 (d, J = 5.4 Hz, 1H).

Anal. Calcd. for $C_{27}H_{31}N_5O$: C, 73.44; H, 7.08; N, 15.87. Found: C, 73.56; H, 6.81; N, 15.63.

N-[7-(1-Methylpyrazol-5-yl)heptyl]-4-quinolinecarboxamide (**21**).

In a similar manner, **21** was obtained in 59% yield as a colourless solid, mp 90-92°; ^{1}H nmr (deuteriochloroform): δ 1.24-1.73 (m, 10H), 2.55 (t, J = 7.5 Hz, 2H), 3.48 (q, J = 6.9 Hz, 2H), 3.69 (s, 3H), 5.98 (d, J = 1.2 Hz, 1H), 6.70 (br, 1H), 7.27-7.36 (m, 2H), 7.51-7.61 (m, 1H), 7.68-7.76 (m, 1H), 8.03-8.19 (m, 2H), 8.77 (d, J = 5.1 Hz, 1H).

Anal. Calcd. for $C_{21}H_{26}N_4O$: C, 71.97; H, 7.48; N, 15.99. Found: C, 71.81; H, 7.28; N, 16.17.

N-(4-Quinolyl)-7-(1-phenyl-1,2,3-triazol-5-yl)heptanamide (**26**).

In a similar manner, **26** was obtained in 41% yield from **24a** and 4-aminoquinoline **25** as a colourless solid, mp 131-133°; ^{1}H nmr (deuteriochloroform): δ 1.26-1.78 (m, 8H), 2.53 (t, J = 7.3 Hz, 2H), 2.65 (t, J = 7.4 Hz, 2H), 7.37-7.57 (m, 7H), 7.66-7.74 (m, 1H), 7.89 (d, J = 8.4 Hz, 1H), 8.11 (d, J = 8.0 Hz, 1H), 8.23-8.33 (m, 2H), 8.83 (d, J = 4.9 Hz, 1H).

Anal. Calcd. for $C_{24}H_{25}N_5O$: C, 72.15; H, 6.31; N, 17.53. Found: C, 72.33; H, 6.48; N, 17.24.

N-(4-Quinolyl)-11-(1-methylpyrazol-5-yl)undecanamide (**27**).

In a similar manner, **27** was obtained in 52% yield from **24b** and **25** as a colourless solid, mp 97-99°; ^{1}H nmr (deuteriochloroform): δ 1.27-1.77 (m, 16H), 2.48-2.58 (m, 4H), 3.72 (s, 3H), 6.00 (d, J = 1.2 Hz, 1H), 7.36-7.45 (m, 2H), 7.59-7.67 (m, 1H), 7.93-8.07 (m, 2H), 8.19 (d, J = 5.0 Hz, 1H), 8.79 (d, J = 5.0 Hz, 1H), 9.03 (br, 1H).

Anal. Calcd. for $C_{24}H_{32}N_4O$: C, 73.43; H, 8.22; N, 14.27. Found: C, 73.30; H, 8.06; N, 14.52.

7-(1-Phenyl-1,2,3-triazol-5-yl)heptanenitrile (**23a**).

Dry sodium cyanide (1.00 g, 20.0 mmoles) was added to DMSO (6 ml) in a flask equipped with a reflux condenser, dropping funnel and thermometer. The mixture was heated to 90° and then removed from the heating bath and 6-(1-phenyl-1,2,3-triazol-5-yl)hexyl bromide (5.00 g, 16.0 mmoles) in 5 ml of DMSO was added dropwise at such a rate that the temperature did not exceed 160°. The reaction mixture was stirred for an additional 10 minutes then poured into 30 of ml water and the product extracted with ether. The organic phase was washed five times with water and then dried over magnesium sulfate and the solvent evaporated. Silica gel column chromatography employing hexane/chloroform (1:1 v/v) as eluent gave 4.15 g (98%) of **23a** as a pale yellow oil; ^{1}H nmr (deuteriochloroform): δ 1.20-1.83 (m, 8H), 2.34 (t, J = 7.5 Hz, 2H), 2.61 (t, J = 7.0 Hz, 2H), 7.57 (s, 5H), 7.70 (s, 1H).

Anal. Calcd. for $C_{15}H_{18}N_4$: C, 70.84; H, 7.13; N, 22.03. Found: C, 70.97; H, 6.93; N, 21.78.

11-(1-Methylpyrazol-5-yl)undecanenitrile (**23b**).

In a similar manner, **23b** was obtained in 90% yield as a yellow oil; ^{1}H nmr (deuteriochloroform): δ 1.28-1.86 (m, 16H),

2.37 (t, J = 7.3 Hz, 2H), 2.57 (t, J = 7.2 Hz, 2H), 3.78 (s, 3H), 6.05 (d, J = 1.2 Hz, 1H), 7.40 (d, J = 1.2 Hz, 1H).

Anal. Calcd. for $C_{15}H_{25}N_3$: C, 72.83; H, 10.19; N, 16.97. Found: C, 72.61; H, 10.15; N, 17.11.

7-(1-Phenyl-1,2,3-triazol-5-yl)heptanoic Acid (**24a**).

A mixture of **23a** (4.00 g, 15.7 mmoles), sodium hydroxide (1.00 g, 25.0 mmoles) and 10% aqueous hydrogen peroxide (10 ml) was heated to reflux for 16 hours. The solution was cooled in an ice bath and made acidic with concentrated hydrochloric acid, then extracted with dichloromethane. The organic phase was dried over sodium sulfate and the solvent evaporated. Recrystallization from dichloromethane/ether gave 3.20 g (75%) of **24a** as colourless prisms, mp 102-104°; ^{1}H nmr (deuteriochloroform): δ 1.23-1.86 (m, 8H), 2.35 (t, J = 7.4 Hz, 2H), 2.68 (t, J = 7.4 Hz, 2H), 7.59 (s, 5H), 7.73 (s, 1H), 10.43 (br, 1H).

Anal. Calcd. for $C_{15}H_{19}N_3O_2$: C, 65.91; H, 7.01; N, 15.37. Found: C, 65.82; H, 6.89; N, 15.47.

11-(1-Methylpyrazol-5-yl)undecanoic Acid (**24b**).

In a similar manner, **24b** was obtained in 85% yield as a colourless solid, mp 99-101°; ^{1}H nmr (deuteriochloroform): δ 1.218-1.80 (m, 16H), 2.33 (t, J = 7.3 Hz, 2H), 2.57 (t, J = 7.2 Hz, 2H), 3.76 (s, 3H), 5.99 (d, J = 1.2 Hz, 1H), 7.38 (d, J = 1.2 Hz, 1H), 10.35 (br, 1H).

Anal. Calcd. for $C_{15}H_{26}N_2O_2$: C, 67.63; H, 9.83; N, 10.52. Found: C, 67.27; H, 9.62; N, 10.79.

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