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Oxadiazoles as bioisosteric transformations of carboxylic functionalities. II*

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Summary — In order to improve the in vivo efficacy of a series of known benzodiazepine receptor (BZR) ligands, 1-(2-phenyl-4-quinolinyl)-4-piperidinecarboxamides, a series of analogs has been prepared in which the amide group of these ligands has been replaced by a 1,2,4-oxadiazole moiety or converted to other carboxylic isosters such as esters or nitriles. An increase in the in vivo efficacy was observed for some of the compounds prepared in this investigation compared to the parent carboxamide derivatives.

2-aryl-4-aminoquinoline / 2-aryl-4-oxyquinoline / benzodiazepine receptor / 1,2,4-oxadiazole

Introduction

2-Aryl-4-piperidinoquinoline derivatives of general formula I (fig 1) have been reported [2] to displace ^{3}H-diazepam from the benzodiazepine receptor (BZR) in a nanomolar concentration. Other research groups have successfully replaced ester groups in known BZR ligands with oxadiazole moieties and thereby obtained compounds with generally higher in vivo efficacies [3–5]. In a continuation of our investigations of agonists on the BZR published earlier [1] we now wish to report the results of replacing the carboxamide group in compounds of general formula I (R = $CONH_2$) with an oxadiazole moiety (I, R = 1,2,4-oxadiazol-3-yl or 1,2,4-oxadiazol-5-yl). Other modifications of the carboxamide group in compounds of general formula I (R = $CONH_2$) into acid derivatives such as carboxylic esters and carbonitriles (I, R = CO_2R', CN) have also been investigated. Further, the influence of the substitution pattern (R^1 and R^2) on binding to the BZR in compounds of general formula I (R = $CONH_2$ or 1,2,4-oxadiazol-5-yl) has been investigated.

Considering the piperidine moiety as a spatial linker between the carboxylic-derived groups and the quinoline moiety, we have tried to modify this linker by preparing compounds of general formula II (fig 1) in which the nitrogen bound directly on the quinoline nucleus in the 4-position has been exchanged by oxygen. Oxygen was chosen instead of nitrogen for two reasons; firstly, oxygen substitution is known to be allowed in this position [6] in other analogous BZR ligands of the quinoline type; secondly, if a nitrogen was retained, a secondary amine instead of a tertiary amine would have been formed which may have led to quite different binding properties of this part of the molecule. Two linker units, 1,3-propylene and 1,3-phenylene, were found to fulfil a steric requirement for the spatial linker A. This was found by comparison of known receptor active structures of general formula I with structures of general formula II in which A represented various alkylene and phenylene moieties [7]. Compounds of the general formula II, with A represented by a 1,3-propylene or 1,3-phenylene moiety, have been prepared together with other 2-aryl-4-alkoxyquinolines.

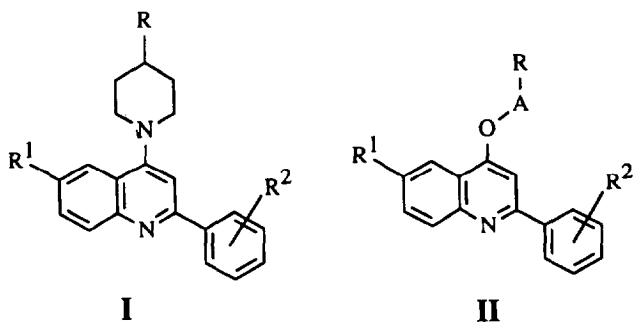


Fig 1.

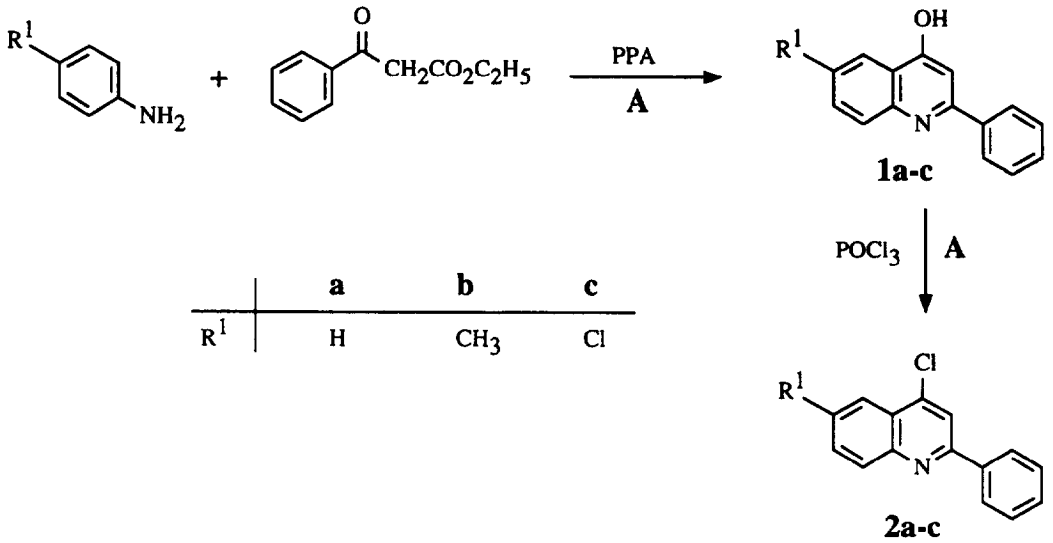
*For Part I see [1]

Chemistry

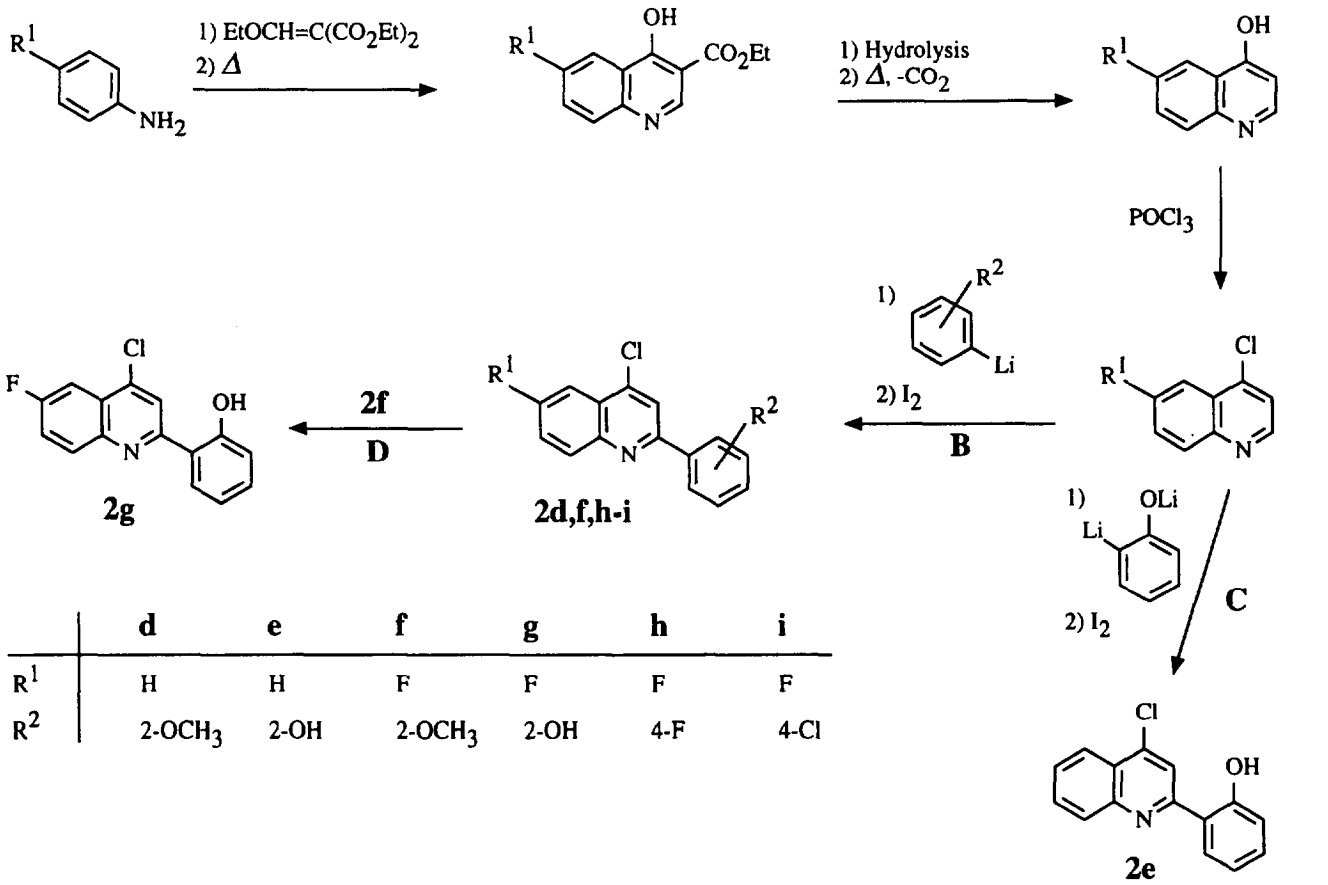
The starting 2-arylquinolines **1a–c** and **2a–i** were prepared essentially by known methods [2, 8, 9] herein denoted method A (scheme 1) and methods B, C and D (scheme 2) as shown in table I.

In method A (scheme 1) the 2-phenyl-4-hydroxyquinolines **1a–c** were prepared by condensation of the appropriate substituted aniline with ethyl benzoylacetate in the presence of polyphosphoric acid [9]. The 4-hydroxyquinolines **1a–c** were then heated with phosphorous oxychloride to afford the 2-aryl-4-chloroquinolines **2–c** [8]. The 4-chloroquinolines leading to compounds **2d–i** were prepared from the appropriate substituted aniline and ethoxymethylenemalonic acid diethyl ester in three steps as previously described [2] (scheme 2). In method B the 4-chloroquinolines were allowed to react with the appropriate substituted aryllithio derivative at room temperature to give the corresponding 1,2-dihydro-2-aryl-4-chloroquinolines as intermediates. These dihydro intermediates were oxidized in situ with iodine to give the 2-aryl-4-chloroquinolines **2d,f,h,i** in 30–64% yield. Compounds of general formula **2** with an unprotected hydroxy group (R^2 = OH) could be obtained by either method C or D (scheme 2). In method C compound **2e** (R^1 = H; R^2 = 2-OH) was obtained in a similar way to method B, by reacting the dilithio compound derived from 2-bromophenol with 4-chloroquinoline followed by iodine oxidation. In method D the hydroxy derivative **2g** (R^1 = F; R^2 = OH) was obtained in 81% yield by *O*-demethylation of **2f** (R^1 = F; R^2 = OCH_3) with BBr_3 at low temperature.

The 2-aryl-4-chloroquinolines **2a–i** described above were converted into the 4-amino derivatives of general formulae **3–7** by methods E-K as outlined in scheme 3. The piperazine derivatives **3a** (R^4 = CONHEt) and **3b** (R^4 = $CSNHCH_3$) were prepared by method E in which **2a** was allowed to react with piperazine in 2-ethoxyethanol to give N-(2-phenyl-4-quinolinyl)piperazine. This crude piperazine derivative was allowed to react with ethyl isocyanate or methyl isothiocyanate in THF to give **3a** and **3b** with yields of 81 and 21% respectively. In method F the 2-aryl-4-chloroquinolines **2a–i** were allowed to react with 4-piperidinecarboxamide in an appropriate alcohol. This afforded the amide derivatives **4a–i** in 11–85% yields. The ethyl ester derivatives **4j** and **4k** were prepared in 60–86% yield by heating the respective 2-aryl-4-chloroquinolines **2a** and **2g** with an excess of ethyl 4-piperidinecarboxylate (method G). In method H the 1,2,4-oxadiazole derivatives **5a–i** were prepared in 14–82% yield by heating the amide derivatives **4a–i** with *N,N*-dimethylacetamide dimethyl acetal and hydroxylamine successively. The nitrile derivatives **6a** and **6b** were prepared by the two different methods I and J. In method I the amide derivative **4a** (R^1 = H; R^2 = H) was dehydrated by heating with phosphorous oxychloride to give the nitrile **6a** (R^1 = H; R^2 = H) in 57% yield. In method J the nitrile **6b** (R^1 = F; R^2 = OH) was prepared in 37% yield by heating the 2-aryl-4-chloroquinoline **2g** (R^1 = F; R^2 = OH) with an excess of 4-piperidinecarbonitrile [10]. In method K the nitrile **6a** (R^1 = H; R^2 = H) was reacted with hydroxylamine affording the intermediate amidoxime derivative which was then heated with acetic anhydride to give **7** in 27% yield.



Scheme 1.



	d	e	f	g	h	i
R^1	H	H	F	F	F	F
R^2	2-OCH_3	2-OH	2-OCH_3	2-OH	4-F	4-Cl

Scheme 2.

Alkylation of the 2-aryl-4-hydroxyquinolines **1a–c** with various alkyl or aralkylhalides in acetone in the presence of K_2CO_3 afforded the corresponding O-alkylated derivatives **8a–e** (scheme 4, method L) in 32–69% yield. In the methylation of **1a** the *N*-alkylated product **9a** was produced in an amount which allowed it to be isolated by column chromatography. Structural assignment of **8a** and **9a** to the *O*- and *N*-alkylated products respectively were based on IR and ^{13}C NMR measurements. For compound **9a** the band observed in the IR spectrum at 1673 cm^{-1} and a low field chemical shift in the ^{13}C NMR spectrum at 177.6 ppm were assigned to the carbonyl group. Further, compounds **8a** and **9a** have been prepared previously by other methods, and the structural assignments in this paper were in agreement with those already described [11–14].

Reaction of 2-aryl-4-chloroquinoline **2a** and the sodium salt of ethyl 3-hydroxybenzoate in DMF afforded the ethyl ester derivative **10** in 62% yield (scheme 4, method M). The amide derivative **11** was then prepared from **10** in 63% yield via the acid chloride (method N).

Results and discussion

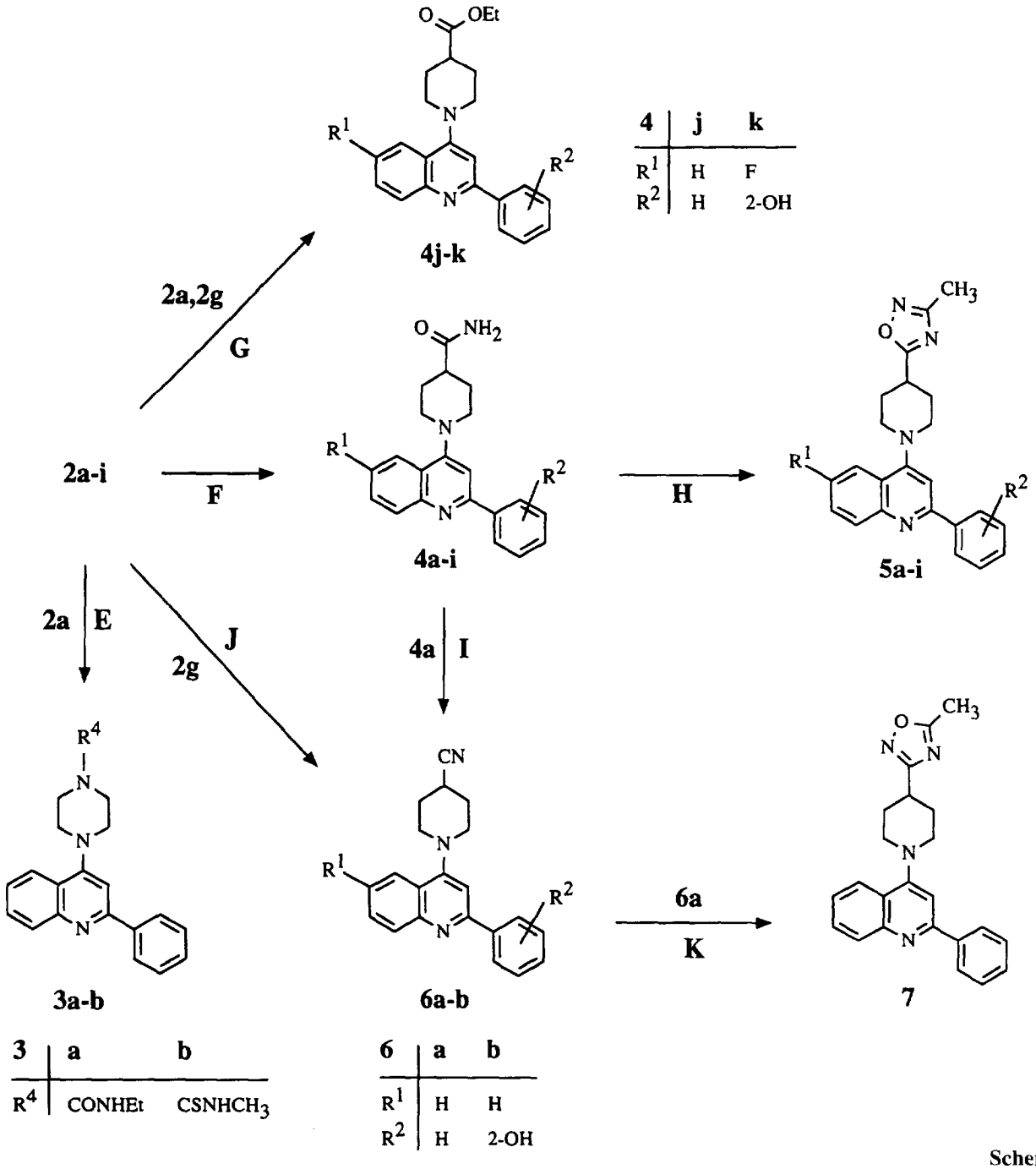
In vitro study

The compounds **1** and **3–11** were tested for their affinity to the benzdiazepine receptor (BZR) using ^3H-flunitrazepam as radioligand; the test results are shown in table I. As can be seen from these results, the affinity to the BZR of compounds **4a–i** is generally lowered when the amide group is changed to a 1,2,4-oxadiazol-5-yl moiety as in compounds **5a–i**, a 1,2,4-oxadiazol-3-yl moiety as in compound **7**, an ethyl ester as in compounds **4j** and **4k** or a carbonitrile as in compounds **6a** and **6b**.

Table I. Chemical and biological data of 2-arylquinolines **1–11**.

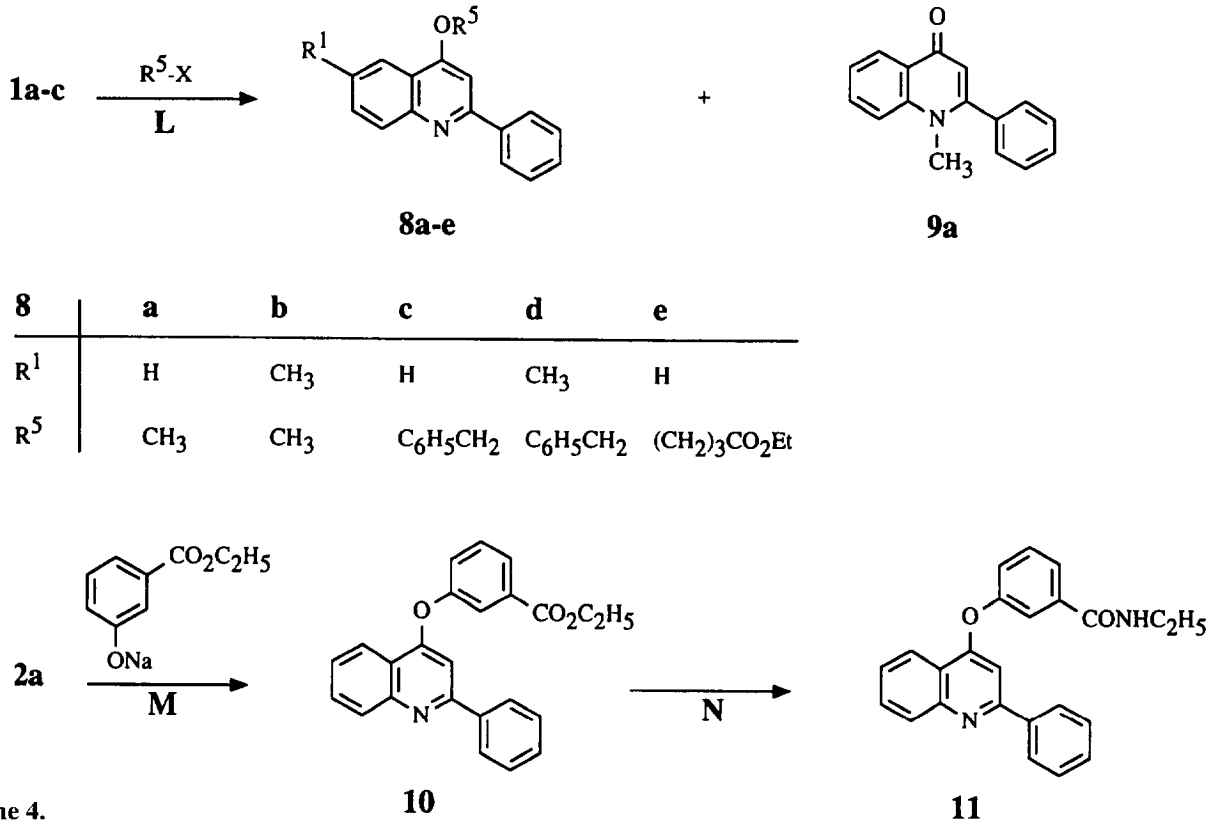
No	*R^1*	*R^2*	*R^3*	*R^4*	*R^5*	*Method*	*Mp (°C)*	*Formula or lit mp (°C)*	*In vitro ^{3}H-FNM IC_{50} (nM)*[o]	*In vivo ^{3}H-FNM ED_{50} (mg/kg)*[p]	*Relative in vivo efficacy*[q]
1a	H	H	–	–	–	A	250–252[a]	254 [9]	6390 ± 286	ND	–
1b	CH_3	H	–	–	–	A	298–300[b]	296–297 [9]	587 ± 34	>100	>0.2
1c	Cl	H	–	–	–	A	> 300[b]	351–352 [9]	430 ± 18	>100	>0.2
2d	H	2-OCH_3	–	–	–	B	92–94[a]	$C_{16}H_{12}ClNO$	ND	ND	–
2e	H	2-OH	–	–	–	C	145–148[j]	$C_{15}H_{10}ClNO\frac{1}{2}H_2O$	ND	ND	–
2f	F	2-OCH_3	–	–	–	B	151–152[c]	$C_{16}H_{11}ClFNO$	ND	ND	–
2g	F	2-OH	–	–	–	D	126–130[a]	$C_{15}H_9ClFNO$	ND	ND	–
2h	F	4-F	–	–	–	B	121–124[a]	130–133 [2]	ND	ND	–
2i	F	4-Cl	–	–	–	B	171–174[c]	169–172 [2]	ND	ND	–
3a	H	H	–	CONHEt	–	E	180–182[d]	$C_{22}H_{24}N_4O$	85 ± 18	62 ± 3.5	0.6–1.0
3b	H	H	–	$CSNHCH_3$	–	E	gum[m]	$C_{21}H_{22}N_4S\frac{1}{2}H_2O$	50.4 ± 1.1	35 ± 2.5	0.6–0.8
4a	H	H	NH_2	–	–	F	200–201[a]	$C_{21}H_{21}N_3O$	11.3 ± 0.5	>100	>8.8
4b	CH_3	H	NH_2	–	–	F	232–235[a]	245–247 [2]	104 ± 4	ND	–
4c	Cl	H	NH_2	–	–	F	245–246[a]	253–255 [2]	20.6 ± 3.0	ND	–
4d	H	2-OCH_3	NH_2	–	–	F	227–228[e]	$C_{22}H_{23}N_3O_2$	1062 ± 21	ND	–
4e	H	2-OH	NH_2	–	–	F	237–239[e]	$C_{21}H_{21}N_3O_2\frac{1}{2}H_2O$	19.4 ± 0.9	31 ± 9	1.1–2.2
4f	F	2-OCH_3	NH_2	–	–	F	227–229[e]	$C_{22}H_{22}FN_3O_2\frac{1}{4}H_2O$	50.7 ± 1.5	63 ± 4	1.1–1.4
4g	F	2-OH	NH_2	–	–	F	257–258[f]	$C_{21}H_{20}FN_3O_2\frac{1}{4}H_2O$	7.1 ± 0.7	>100	>14.1
4h	F	4-F	NH_2	–	–	F	234–235[e]	244–246 [2]	8.7 ± 0.9	6.4 ± 0.3	0.6–0.9
4i	F	4-Cl	NH_2	–	–	F	249–250[c]	259–261 [2]	36.0 ± 0.8	ND	–
4j	H	H	OEt	–	–	G	85–86[a]	$C_{23}H_{24}N_2O_2\frac{1}{2}H_2O$	181 ± 19	ND	–
4k	F	2-OH	OEt	–	–	G	140–142[a]	$C_{23}H_{2420}FN_2O_3$	138 ± 11	ND	–
5a	H	H	–	–	–	H	125–127[h]	$C_{23}H_{22}N_4O$	63.4 ± 6.9	28 ± 6.5	0.3–0.6
5b	CH_3	H	–	–	–	H	141–143[m]	$C_{24}H_{24}N_4O\frac{1}{4}C_4H_8O_2$	250 ± 10	ND	–
5c	Cl	H	–	–	–	H	123–125[m]	$C_{23}H_{21}ClN_4O$	81.9 ± 3.3	>100	>1.2
5d	H	2-OCH_3	–	–	–	H	127–129[c]	$C_{24}H_{24}N_4O_2$	1721 ± 221	ND	–
5e	H	2-OH	–	–	–	H	177–178[m]	$C_{23}H_{22}N_4O_2\frac{1}{4}C_4H_8O_2$	31.5 ± 3.8	>100	>3.2
5f	F	2-OCH_3	–	–	–	H	125–127[m]	$C_{24}H_{23}FN_4O_2\frac{1}{4}H_2O$	192 ± 0	ND	–
5g	F	2-OH	–	–	–	H	18 1–183[a]	$C_{23}H_{21}FN_4O_2$	35.9 ± 0.7	>100	>2.8
5h	F	4-F	–	–	–	H	147–149[m]	$C_{23}H_{20}F_2N_4O\frac{1}{4}C_4H_8O_2$	29.2 ± 4.7	>100	>3.4
5i	F	4-Cl	–	–	–	H	174–176[i]	$C_{23}H_{20}ClFN_4O$	219 ± 19	ND	–
6a	H	H	–	–	–	I	140–142[j]	$C_{21}H_{19}N_3$	68.2 ± 4.3	29 ± 3	0.4–0.5
6b	F	2-OH	–	–	–	J	220–221[i]	$C_{21}H_{18}FN_3O$	50.3 ± 5.4	>30	>0.6
7	H	H	–	–	–	K	149–150[k]	$C_{23}H_{22}N_4O$	68.4 ± 1.4	ND	–
8a	H	H	–	–	CH_3	L	64–66[n]	66 [12]	466 ± 111	>100	>0.2
8b	CH_3	H	–	–	CH_3	L	134–136[j]	$C_{17}H_{15}NO$	4450 ± 179	ND	–
8c	H	H	–	–	$C_6H_5CH_2$	L	106–109[j]	92–94 [14]	2291 ± 365	ND	–
8d	CH_3	H	–	–	$C_6H_5CH_2$	L	140–142[j]	$C_{23}H_{19}NO$	23500 ± 1970	ND	–
8e	H	H	–	–	$(CH_2)_3CO_2Et$	L	74–76[j]	$C_{21}H_{21}NO_3$	645 ± 53	ND	–
9a	H	H	–	–	–	L	142[n]	142–145 [11]	27800 ± 4500	ND	–
10	–	–	–	–	–	M	122–124[l]	$C_{24}H_{19}NO_3$	38300 ± 3100	ND	–
11	–	–	–	–	–	N	146–149[d]	$C_{24}H_{20}N_2O_2$	499 ± 44	ND	–

Crystallized from [a]ethanol; [b]water; [c]ethyl acetate; [d]diethyl ether; [e]pyridine/water; [f]chloroform/ethanol; [g]2-ethoxyethanol/water; [h]cyclohexane/diethyl ether; [i]2-propanol; [j]cyclohexane; [k]diisopropyl ether/ethyl acetate; [l]diethyl ether/ligroin; isolated by column chromatography on silica gel using as eluent [m]ethyl acetate/*n*-heptane (1:1); [n]ethylacetate/petrolether (1:9); [o]mean ± SEM (n = 2–4); [p]mean ± SEM (n = 2–6); [q]defined as ED_{50} (mg/kg)/IC_{50} (nM). ND = not determined. ^{3}H-FNM is ^{3}H-flunitrazepam.



Scheme 3.

Changing the substituents R^1 and R^2 on the 2-phenylquinoline moiety in both the amide series **4a–l** and the oxadiazole series **5a–i**, did not improve the affinity for the BZR compared to the unsubstituted (R^1 = R^2 = H) examples, **4a** and **5a** respectively. Interestingly, introduction of a 2-OCH_3 substituent is generally not well tolerated as seen in compounds **4d**, **4f**, **5d** and **5f**, but demethylation of these compounds produced compounds **4e**, **4g**, **5e**, and **5g** with up to 60 times better binding affinity for the BZR.



8	a	b	c	d	e
R^1	H	CH_3	H	CH_3	H
R^5	CH_3	CH_3	$C_6H_5CH_2$	$C_6H_5CH_2$	$(CH_2)_3CO_2Et$

Scheme 4.

As previously mentioned, it should be possible spatially to replace the piperidine moiety by either a 1,3-propylene or 1,3-phenylene moiety. Compounds with these structural features, **8e** and **11**, actually show a reasonable affinity for the BZR compared to their corresponding piperidine analogs **4j** and **4a**. The affinities of compounds **8e** and **11** are, however, still considered too weak for further optimization.

Animal study

Compounds with the highest in vitro affinity on the BZR found in this study were selected for in vivo testing. The selected compounds were tested for their in vivo affinity on the BZR in NMRI mice using ^{3}H-flunitrazepam as radioligand (table I). Further, the relative in vivo efficacy defined as the ratio ED_{50} (mg/kg)/IC_{50} (nM) was calculated and is presented in table I. This relative in vivo activity can be considered as a relative measurement of bioavailability of the compounds tested. As can be seen from table I all the compounds tested for in vivo binding to the BZR were moderately active or inactive except for compound **4h** which showed a resonable in vivo affinity. From the relative in vivo efficacy (table I) it is evident that the bioavailability of the compounds tested is more dependent on substitution on the 2-phenylquinoline moiety than on substitution on the piperidine moiety. Actually, the aim of this investigation was to improve the bioavailability of compounds **4a–4i** by replacing the amide group on the piperidine ring with a 1,2,4-oxadiazolyl moiety. Therefore, in conclusion, it seems that the opposite has been obtained as generally a lower bioavailability is observed for compounds having an 1,2,4-oxadiazolyl moiety. However, replacing the amide group on the piperidine ring with a nitrile group as in compound **6a**, or replacing the piperidinecarboxamide with a piperazinecarboxamide as in compounds **3a** and **3b**, seems beneficial to the bioavailability.

Experimental protocols

Chemistry

Melting points are uncorrected. ^{1}H NMR spectra were run on a Bruker WM 400 MHz apparatus and chemical shifts (δ) are in parts per million relative to tetramethylsilane. Column chromatography was performed using Merck silica gel 9385. Microanalyses were performed at Novo-Nordisk A/S, 2880

Bagsvaerd, supervised by R Amsler. All the new compounds gave C, H, N analyses within ±0.4% unless otherwise stated. Compounds **1a–c**, **2a–c**, **2h–i**, **4a–c** and **4h–j** were prepared according to published methods [2, 8, 9].

Method B

4-Chloro-6-fluoro-2-(2-methoxyphenyl)quinoline ***2f***. To a stirred mixture of *n*-butyl lithium (80 mL, 2.5 M in hexane) and dry diethyl ether (150 mL) cooled in an ice-bath, a solution of 2-bromoanisol (35 g, 0.20 mol) in diethyl ether (75 mL) was added dropwise. When addition was complete the reaction mixture was stirred at room temperature for 1 h. A solution of 4-chloro-6-fluoroquinoline [2] (18.2 g, 0.10 mol) in dry diethyl ether (100 mL) was added at room temperature within 15 min. The mixture was stirred at room temperature for 1 h and then cooled in an ice-bath. Water (15 mL) and iodine (15.2 g, 0.12 mol) were added and stirring was continued for another 10 min. A 4 N aqueous sodium hydroxide solution (25 mL) was added and the mixture was stirred at room temperature for 30 min. The yellow pricipitate was isolated by filtration and dried in air to give a first crop of crude **2f**. From the filtrate the organic phase was separated, washed with water, dried (Na_2SO_4) and the solvent evaporated in vacuo to give a second crop of crude **2f**. The two crops were combined and recrystallized from ethyl acetate to give 9.8 g (34%) of **2f**; mp 151–152 °C; ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 3H); 7.06 (d, 1H); 7.16 (t, 1H); 7.48 (dt, 1H); 7.55 (m, 1H); 7.88 (m, 2H); 8.09 (s, 1H); 8.21 (dd, 1H). Anal $C_{16}H_{11}ClFNO$ (C, H, N).

Compounds **2d** and **2h–i** were prepared by a procedure similar to that described above in 30–64% yield (table I).

Method C

4-Chloro-2-(2-hydroxyphenyl)quinoline ***2e***. To a stirred mixture of *n*-butyl lithium (50 mL, 2.5 M in hexane) and dry diethyl ether (50 mL) a solution of 2-bromophenol (10.8 g, 62.5 mmol) in diethyl ether (25 mL) was added dropwise at such a rate that reflux was maintained. When addition was complete the reaction mixture was stirred at room temperature for 0.5 h. A solution of 4-chloroquinoline [2] (10.2 g, 62.5 mmol) in dry THF (50 mL) was added at room temperature within 15 min and the mixture was stirred at room temperature for 1.5 h. Water (12 mL), iodine (12.7 g, 0.1 mol) and a 4 N aqueous sodium hydroxide solution (25 mL) were added and the mixture was stirred at room temperature for 30 min. The phases were separated and the organic phase was washed with water then a 2 N sodium hydroxide solution, and dried (Na_2SO_4). The solvent was evaporated in vacuo to give a solid which was stirred with ethanol (30 mL), filtered and dried. The crude product was recrystallized from cyclohexane to give 2.4 g (15%) of **2e**; mp 145–148 °C; ^{1}H NMR (DMSO-d_6) δ 6.95–7.05 (m, 2H); 7.42 (t, 1H); 7.80 (t, 1H); 7.95 (t, 1H); 8.17 (d, 1H); 8.22–8.25 (m, 2H); 8.12 (s, 1H); 14.15 (s, 1H). Anal $C_{15}H_{10}ClNO\cdot\frac{1}{2}H_2O$ (C, H, N).

Method D

4-Chloro-6-fluoro-2-(2-hydroxyphenyl)quinoline ***2g***. A stirred solution of **2f** (7.5 g, 26 mmol) in dry toluene (150 mL) was cooled to –78 °C and BBr_3 (15 mL) was added. The temperature was kept at –78 °C for 15 min and then the cooling bath was removed. The reaction mixture was stirred for 2.5 h at room temperature and then poured into iced water (500 mL). After adjusting the pH of the solution to 6 with a 4 N aqueous sodium hydroxide solution it was extracted with ethyl acetate (3 x 300 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated in vacuo to give a solid which was recrystallized from ethanol. This afforded 5.8 g (81%) of **2g**; mp 126–130 °C; ^{1}H NMR (DMSO-d_6) δ 6.93–6.98 (m, 2H); 7.36 (t, 1H); 7.75 (dt, 1H); 7.83 (dd, 1H); 8.12 (d, 1H); 8.17 (dd, 1H); 8.52 (s, 1H); 13.74 (br, s, 1H). Anal $C_{15}H_9ClFNO$ (C, H, N).

Method E

N-Ethyl-4-(2-phenyl-4-quinolinyl)-1-piperazinecarboxamide ***3a***. To a solution of 4-chloro-2-phenylquinoline **2a** [8] (2.3 g, 9.6 mmol) in 2-ethoxyethanol (40 mL) was added piperazine (2.5 g, 29.0 mmol) and the mixture was heated at reflux temperature for 18 h. The reaction mixture was cooled and filtered to remove insoluble material. The solvent was evaporated in vacuo leaving a residue which was dissolved in hot pyridine (25 mL) and subsequently diluted with water (500 mL). On standing a precipitate formed which was isolated by filtration, washed with water and dried in air. The solid was stirred with diethyl ether and filtered to give 1.3 g of crude *N*-(2-phenyl-4-quinolinyl)piperazine.

Ethyl isocyanate (0.43 mL) was added to a solution of crude *N*-(2-phenyl-4-quinolinyl)piperazine (0.80 g, 2.8 mmol) in dry THF (25 mL) and the mixture was stirred for 18 h at room temperature. The solvent was evaporated in vacuo to give a residue that was trituated with diethyl ether. The solid was isolated by filtration and dried in air to give 0.80 g (81%) of **3a**; mp 180–182 °C; ^{1}H NMR ($CDCl_3$) δ 1.20 (t, 3H); 3.30–3.38 (m, 6H); 3.70 (m, 4H); 3.54 (br, t, 1H); 7.31 (s, 1H); 7.46–7.56 (m, 4H); 7.70 (t, 1H); 8.03 (d, 1H); 8.10 (d, 2H); 8.18 (d, 1H). Anal $C_{22}H_{24}N_4O$ (C, H, N).

By using methyl isothiocyanate instead of ethyl isocyanate, compound **3b** was prepared by a procedure similar to that described above, in 21% yield (table I).

Method F

1-(2-Phenyl-4-quinolinyl)-4-piperidinecarboxamide ***4a***. A mixture of 4-chloro-2-phenylquinoline **2a** [8] (9.8 g, 41 mmol), 4-piperidinecarboxamide (10.5 g, 82 mmol) and ethanol (50 mL) was heated at reflux temperature for 78 h. The mixture was cooled and the solvent was evaporated in vacuo to give an oil which was treated with a mixture of water (100 mL) and ethanol (20 mL). The solid formed was isolated by filtration and recrystallized from ethanol to give 5.3 g (39%) of **4a**; mp 200–201 °C; ^{1}H NMR (DMSO-d_6) δ 1.96 (m, 4H); 2.36–2.44 (m, 1H); 2.91–2.98 (m, 2H); 3.67–3.71 (m, 2H); 6.93 (br, s, 1H); 7.46 (br, s, 1H); 7.53–7.62 (m, 5H); 7.76 (t, 1H); 8.04–8.08 (m, 2H); 8.30 (d, 2H). IR (KBr) υ 3394 (NH), 1664 (C=O) cm^{-1}. Anal $C_{21}H_{21}N_3O$ (C, H, N).

Compounds **4b–c** and **4i** were prepared by a procedure similar to that described above in 11–85% yield (table I).

1-(2-(2-Hydroxyphenyl)-6-fluoro-4-quinolinyl)-4-piperidinecarboxamide ***4g***. A mixture of **2g** (2.0 g, 7.3 mmol) and 4-piperidinecarboxamide (2.3 g, 18.3 mmol) in 2-ethoxyethanol (30 mL) was heated at reflux temperature for 8 h. The hot reaction mixture was poured into ethanol (150 mL) and allowed to cool to room temperature. The solid was isolated by filtration, washed with ethanol and dried in air. Recrystallization from a 1:1 mixture of chloroform/ethanol (400 mL) afforded 1.0 g (36%) of **4g**; mp 263–265 °C; ^{1}H NMR (DMSO-d_6) δ 1.93–1.94 (m, 4H); 2.35–2.43 (m, 1H); 2.94–3.01 (m, 2H); 3.63–3.66 (m, 2H); 6.88 (br, s, 1H); 6.92–6.96 (m, 2H); 7.34 (t, 1H); 7.38 (br, s, 1H); 7.56–7.68 (m, 3H); 8.04–8.06 (m, 1H); 8.17 (d, 1H); 14.86 (s, 1H). Anal $C_{21}H_{20}FN_3O_2\cdot\frac{1}{4}H_2O$ (C, H, N).

Compounds **4d–e** were prepared by a procedure similar to that described above (table I).

*1-(6-Fluoro-2-(2-methoxyphenyl)-4-quinolinyl)-4-piperidinecarboxamide **4f**.* A mixture of **2f** (1.44 g, 5.0 mmol), 4-piperidinecarboxamide (1.60 g, 12.5 mmol) and phenol (3.0 g) was heated on an oil bath at 180 °C for 3 h. Water was added (75 mL) and the mixture was stirred vigorously for 30 min. A mixture of 4 N aqueous sodium hydroxide solution (3 mL), ethyl acetate (25 mL) and isopropyl ether (25 mL) was then added and the mixture was stirred for another 15 min. The solid was isolated by filtration, washed with water and recrystallized from a 1:10 mixture of pyridine/water to give 1.0 g (41%) of **4f**; mp 227–229 °C; ^{1}H NMR ($CDCl_3$) δ 2.08–2.14 (m, 4H); 2.42 (m, 1H); 2.87 (m, 2H); 3.62–3.66 (m, 2H); 3.85 (s, 3H); 5.50 (br, s, 1H); 5.58 (br, s, 1H); 7.01 (d, 1H); 7.10 (t, 1H); 7.34 (s, 1H); 7.38–7.43 (m, 2H); 7.59 (d, 1H); 7.75 (d, 1H); 8.10 (dd, 1H). Anal $C_{22}H_{22}FN_3O_2 \cdot \frac{1}{4}H_2O$ (C, H, N).

Compound **4h** was prepared by a procedure similar to that described above in 51% yield (table I).

Method G

*1-(6-Fluoro-2-(2-hydroxyphenyl)-4-quinolinyl)-4-piperidinecarboxylic acid ethyl ester **4k**.* A mixture of **2g** (1.37 g, 5.0 mmol) and 4-piperidinecarboxylic acid ethyl ester (2.36 g, 15.0 mmol) was heated with stirring on an oil-bath at 150 °C for 1.5 h. The reaction mixture was allowed to cool to 100 °C and water (75 mL) was added. An oil separated immediately which crystallized on cooling. The solid was isolated by filtration and recrystallized from ethanol (60 mL) to give 1.7 g (86%) of **4k**; mp 140–142 °C; ^{1}H NMR ($CDCl_3$) δ 1.32 (t, 3H); 2.06–2.20 (m, 4H); 2.56–2.62 (m, 1H); 2.94–3.01 (m, 2H); 3.60–3.62 (m, 2H); 4.21 (q, 2H); 6.92 (t, 1H); 7.05 (d, 1H); 7.31–7.44 (m, 3H); 7.56 (dd, 1H); 7.85 (dd, 1H); 7.94 (dd, 1H); 15.18 (br, s, 1H). Anal $C_{23}H_{23}FN_2O_3$ (C, H, N).

Compound **4j** was prepared by a procedure similar to that described above in 60% yield (table I).

Method H

*5-(1-(6-Fluoro-2-(2-hydroxyphenyl)-4-quinolinyl)-4-piperidinyl)-3-methyl-1,2,4-oxadiazole **5g**.* A mixture of **4g** (0.60 g, 1.6 mmol) and 85% dimethyl acetamide dimethylacetal (3.0 g, 19.1 mmol) was heated at reflux temperature for 1 h and then evaporated to an oil in vacuo. Dioxane (5 mL), hydroxylamine hydrochloride (0.20 g, 2.9 mmol), acetic acid (5 mL) and a 2 N aqueous sodium hydroxide solution (2.2 mL) was added and the mixture was stirred at room temperature for 2 h. Then the reaction mixture was heated at reflux temperature for 30 min, cooled to room temperature and poured into iced water (150 mL). After the pH of the aqueous solution had been adjusted to 7–8 using a 4 N aqueous sodium hydroxide solution, it was extracted with ethyl acetate (2 x 75 mL). The combined organic phase was dried (Na_2SO_4) and the solvent evaporated in vacuo. The residue was recrystallized from ethanol to give 0.34 g (52%) of **5g**; mp 181–183 °C; ^{1}H NMR (DMSO-d_6) δ 2.10–2.30 (m, 4H); 2.38 (s, 3H); 3.14–3.20 (m, 2H); 3.32–3.37 (m, 1H); 3.63–3.67 (m, 2H); 6.94–6.96 (m, 2H); 7.36 (t, 1H); 7.65–7.68 (m, 3H); 8.04–8.08 (m, 1H); 8.20 (d, 1H); 14.83 (s, 1H). Anal $C_{23}H_{21}FN_4O_2$ (C, H, N).

Compounds **5a–f** and **5h–i** were prepared by a procedure similar to that described above in 14–82% yield (table I).

Method I

*1-(2-Phenyl-4-quinolinyl)-4-piperidinecarbonitrile **6a**.* A mixture of **4a** (7.0 g, 21.0 mmol) and phosphorous oxychloride (50 mL) was heated on an oil bath at 90 °C for 5.5 h. The reaction mixture was cooled and excess phosphorous oxychloride was evaporated in vacuo. The solid residue was scraped onto crushed ice (40 g) and the mixture was stirred for 20 min. The resulting acidic suspension was neutralized with a 4 N aqueous sodium hydroxide solution and then stirred for 5 min. The solid was isolated by filtration, washed with water and dried in air. The solid was then stirred with a 1 N aqeous hydrochloric acid solution for 1.5 h. The mixture was neutralized with a 4 N aqueous sodium hydroxide solution and the solid isolated by filtration. The solid was dissolved into dichloromethane (150 mL) and washed with a 10% aqueous sodium bicarbonate solution, brine and dried (Na_2SO_4). The solvent was evaporated in vacuo to give a residue which was recrystallized from cyclohexane. This afforded 3.8 g (57%) of **6a**; mp 140–142 °C; ^{1}H NMR (DMSO-d_6) δ 2.04–2.20 (m, 4H); 3.20–3.45 (m, 5H); 7.50–7.58 (m, 5H); 7.74 (t, 1H); 8.03 (t, 2H); 8.28 (d, 2H). IR (KBr) υ 2231 (CN) cm^{-1}. Anal $C_{21}H_{19}N_3$ (C, H, N).

Method J

*1-(6-Fluoro-2-(2-hydroxyphenyl)-4-quinolinyl)-4-piperidinecarbonitrile **6b**.* A mixture of 4-piperidinecarbonitrile [10] (1.2 g, 11.0 mmol) and **2g** (1.0 g, 3.7 mmol) was heated with stirring on an oil bath at 150 °C for 1 h. The reaction mixture was allowed to cool to 100 °C and ethanol (50 mL) was added. The precipitate was collected and recrystallized from isopropanol to give 0.35 g (37%) of **6b**; mp 220–221 °C; ^{1}H NMR ($CDCl_3$) δ 2.24 (m, 4H); 3.00 (m, 1H); 3.25 (m, 2H); 3.48 (m, 2H); 6.95 (t, 1H); 7.06 (d, 1H); 7.36 (t, 1H); 7.44–7.54 (m, 3H); 7.85 (d, 1H); 7.98 (dd, 1H). IR (KBr) υ 2241 (CN) cm^{-1}. Anal $C_{21}H_{18}FN_3O$ (C, H, N).

Method K

*5-Methyl-3-(1-(2-phenyl-4-quinolinyl)-4-piperidinyl)-1,2,4-oxadiazole **7**.* A mixture of **6a** (1.25 g, 4.0 mmol), hydroxylamine hydrochloride (0.40 g, 6.0 mmol), potassium carbonate (1.10 g, 8.0 mmol) and ethanol (20 mL) was heated at reflux temperature for 60 h. The solvent was evaporated in vacuo to give a solid residue containing crude 1-(2-phenyl-4-quinolinyl)-4-piperidinecarboxamide oxime.

The crude amidoxime obtained above (1.4 g) was dissolved into glacial acetic acid (10 mL) and a solution of acetic anhydride (0.45 g, 4.4 mmol) in glacial acetic acid (5 mL) was added. The reaction mixture was heated at reflux temperature for 10 min. Acetic anhydride (1 g) was added and heating was continued for another 50 min at reflux temperature. The cooled reaction mixture was poured into iced water (25 mL) and extracted with ethyl acetate (3 x 25 mL). The combined organic phase was dried (Na_2SO_4) and the solvent was evaporated in vacuo to give an oil which was submitted to column chromatography using ethyl acetate as eluent. Collecting the proper fractions afforded 0.4 g (27% calculated from **6a**) of **7** as an oil which crystallized on standing. Recrystallization from diisopropyl ether/ethyl acetate afforded an analytically-pure sample of **7**; mp 149–150 °C; ^{1}H NMR ($CDCl_3$) δ 2.22–2.28 (m, 4H); 2.62 (s, 3H); 3.02–3.12 (m, 3H); 3.73–3.76 (m, 2H); 7.32 (s, 1H); 7.42–7.52 (m, 4H); 7.64–7.68 (m, 1H); 8.01 (dd, 1H); 8.07–8.12 (m, 4H). Anal $C_{23}H_{22}N_{24}O$ (C, H, N).

Method L

*4-Methoxy-2-phenylquinoline **8a** and 1-methyl-2-phenylquinolin-4(1H)-one **9a**.* A mixture of **1a** (2.2 g, 10.0 mmol), dry potassium carbonate (1.0 g, 7.2 mmol) and methyl iodide (8 mL)

in dry acetone (200 mL) was heated at reflux temperature for 9 h, where additional portions of methyl iodide (2 x 8 mL) were added after 3 and 6 h of reaction. The reaction mixture was filtered and the solvent evaporated in vacuo leaving an oil which was purified by chromatography using a 1:9 mixture of ethyl acetate/petrol ether as eluent. This afforded 1.1 g (47%) of **8a** and 0.32 g (14%) of **9a**. Compound **8a**: mp 64–66 °C; lit [12] mp 66 °C; ^{1}H NMR ($CDCl_3$) δ 4.13 (s, 3H); 7.19 (s, 1H); 7.44–7.55 (m, 4H); 7.68–7.73 (m, 1H); 8.10–8.13 (m, 3H); 8.20 (dd, 1H); ^{13}C NMR (DMSO-d_6) δ 56.1; 98.2; 119.9; 121.3; 125.5; 127.3; 128.6; 128.9; 129.4; 130.0; 139.3; 148.5; 157.6; 162.4. Compound **9a**: mp 142 °C, lit [11] mp 142–145 °C; ^{1}H NMR (DMSO-d_6) δ 3.59 (s, 3H); 6.01 (s, 1H); 7.44–7.49 (m, 1H); 7.58 (s, 5H); 7.82–7.83 (m, 2H); 8.25 (d, 1H); ^{13}C NMR (DMSO-d_6) δ 37.3; 111.2; 117.2; 123.4; 125.3; 126.3; 128.5; 128.6; 129.4; 132.2; 135.7; 141.7; 154.6; 175.6; IR (KBr) υ 1673 (C=O) cm^{-1}.

Compound **8b** was prepared by a procedure similar to that described above in 55% yield (table I).

*4-Benzyloxy-6-methyl-2-phenylquinoline **8d***. To a mixture of **1b** [9] (1.2 g, 5.0 mmol) and dry potassium carbonate (0.5 g, 3.6 mmol) in dry acetone (100 mL) was added a solution of benzyl bromide (1.1 g, 6.4 mmol) in dry acetone (20 mL). The reaction mixture was heated at reflux temperature for 22 h, cooled to room temperature and the solvent evaporated in vacuo. The solid residue was dissolved into a mixture of ethyl acetate (50 mL) and iced water (25 mL). The organic phase was separated and washed with water (15 mL) then brine (15 mL) and dried (Na_2SO_4). Evaporation of the solvent in vacuo gave a solid which was recrystallized from cyclohexane to give 1.3 g (81%) of **8d**; mp 140–142 °C; ^{1}H NMR ($CDCl_3$) δ 2.52 (s, 3H); 5.32 (s, 2H); 7.21 (s, 1H); 7.37–7.56 (m, 9H); 8.08–8.09 (m, 4H). Anal $C_{23}H_{19}NO$ (C, H, N).

Compounds **8c** and **8e** were prepared by a procedure similar to that described above in 32–69% yield (table I).

Method M

*3-((2-Phenyl-4-quinolinyl)oxy)benzoic acid ethyl ester **10***. Sodium hydride as 80% oil dispersion (1.25 g, 41.8 mmol) was added slowly to a stirred solution of 3-hydroxybenzoic acid ethyl ester (6.9 g, 41.8 mmol) in dry DMF (50 mL). When addition was complete the mixture was stirred for 30 min at room temperature. A solution of **2a** (5.0 g, 20.9 mmol) in dry DMF (10 mL) was added and the reaction mixture was heated at reflux temperature for 2 h. The mixture was cooled to room temperature, poured into iced water (500 mL) and extracted with ethyl acetate (2 x 200 mL). The organic phase was dried (Na_2SO_4) and the solvent evaporated in vacuo to give a residue which was dissolved into diethyl ether (200 mL). This organic solution was washed with a 2 N aqueous sodium hydroxide solution (25 mL), dried (Na_2SO_4) and concentrated in vacuo to 50 mL. Addition of ligroin (40:60) (100 mL) to the solution resulted in crystallization. The solid was isolated by filtration and dried in air to give 4.75 g (62%) of **10**; mp 122–124 °C; ^{1}H NMR ($CDCl_3$) δ 1.38 (t, 3H); 4.38 (q, 2H); 6.99 (s, 1H); 7.39–7.58 (m, 6H); 7.76 (t, 1H); 7.90–8.00 (m, 4H); 8.17 (d, 1H); 8.31 (dd, 1H). Anal $C_{24}H_{19}NO_3$ (C, H, N).

Method N

*N-Ethyl-3-((2-phenyl-4-quinolinyl)oxy)benzamide **11***. To a solution of **10** (3.0 g, 8.1 mmol) in THF (50 mL) a 12 N sodium hydroxide solution (10 mL) was added and the mixture was heated at reflux temperature for 2 h. The phases were separated and the organic phase was washed with brine (2 x 50 mL). A 4 N aqueous hydrochloric acid solution was added to the organic solution until a pH of 1 was obtained, and the precipitate formed was isolated by filtration, washed with THF and dried in air to give 3.0 g of crude 3-((2-phenyl-4-quinolinyl)oxy)benzoic acid.

A mixture of the above acid (2.5 g, 6.6 mmol) and thionyl chloride (50 mL) was heated at reflux temperature for 1 h. Excess thionyl chloride was removed in vacuo to give a residue which was dissolved into dichloromethane (100 mL). This solution was cooled on an ice-bath and excess ethylamine in dry diethyl ether (1:1) was added. The mixture was stirred at room temperature for 1 h and then poured into iced water (50 mL). The phases were separated and the organic phase was washed with water and dried (K_2CO_3). The solvent was evaporated in vacuo to give 1.55 g (63% calculated from **10**) of **11**; mp 146–149 °C; ^{1}H NMR (DMSO-d_6) δ 1.13 (t, 3H); 3.31 (q, 2H); 7.25 (s, 1H); 7.49–7.58 (m, 4H); 7.66–7.75 (m, 2H); 8.84 (s, 1H); 8.89–8.94 (m, 2H); 8.09 (d, 2H); 8.18 (d, 1H); 8.34 (d, 1H); 8.64 (br, t, 1H). Anal $C_{24}H_{20}N_2O_2$ (C, H, N).

Pharmacology

In vitro inhibition of ^{3}H-flunitrazepam binding

In vitro inhibition of ^{3}H-flunitrazepam (^{3}H-FNM) binding was performed according to general methods [15] using a final concentration of 1 nM of ^{3}H-FNM at 0 °C for 40 min. The concentrations necessary for 50% inhibition (IC_{50}) are shown in table I.

In vivo inhibition of ^{3}H-flunitrazepam binding

Inhibition of specific ^{3}H-FNM binding in the forebrain of living NMRI mice was determined according to the published method [16]. The doses of test compound used were 30 and 100 mg/kg. The doses for 50% inhibition (ED_{50}) are shown in table I.

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References

1 Andersen KE, Jørgensen AS, Braestrup C (1994) *Eur J Med Chem* 29, 393–399
2 Field GF, Zally WJ (1985) USP 4,560,692; *Chem Abstr* 105, 97339q
3 Tully WR, Gardner CR, Gillespie RJ, Westwood R (1991) *J Med Chem* 34, 2060–2067
4 Jensen LH, Watjen F, Honoré T, Hansen JB, Engelstoft M, Schmiechen R (1988) *Adv Biochem Psychopharmacol* 45 (Chloride Channels Their Modulation Transm Drugs), 209–217
5 Watjen F, Baker R, Engelstoft M et al (1989) *J Med Chem* 32, 2282–2291
6 Benavides J, Dubroeucq MC, Le FG, Renault C (1986) EP 205,375A; *Chem Abstr* 107, 175897c
7 SYBYL, Tripos Associates Inc
8 Schock RU, Eichel HJ (1957) USP 2,785,165; *Chem Abstr* 51, 9713i
9 Staskun B, Israelstam SS (1961) *J Org Chem* 26, 3191–3193
10 Gardner TS, Wenis E, Lee J (1957) *J Org Chem* 22, 984–986
11 Coppola GM (1982) *J Heterocyclic Chem* 19, 727–731
12 Finlayson AC, Prager RH (1978) *Aust J Chem* 31, 2751–2755
13 Fournet A, Vagneur B, Richomme P, Bruneton J (1989) *Can J Chem* 67, 2116–2118
14 Kuo SC, Lee HZ, Juang JP et al (1993) *J Med Chem* 36, 1146–1156
15 Braestrup C, Nielsen M, Krogsgaard-Larsen P, Falch E (1979) *Nature* 280, 331–333
16 Braestrup C, Nielsen M (1986) *Recept Biochem Methodol* 5, 167–184