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Bioorganic & Medicinal Chemistry Letters 13 (2003) 3375–3379

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Synthesis and SAR of 8-Arylquinolines as Potent Corticotropin-Releasing Factor$_1$ (CRF$_1$) Receptor Antagonists

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Received 6 March 2003; accepted 23 March 2003

Abstract—A series of 4-substituted 8-aryl-2-methylquinolines **4** was designed and synthesized as highly potent antagonists for the human CRF$_1$ receptor. This series of compounds displayed parallel SAR to other bicyclic systems such as pyrazolo[1,5-*a*]pyrimidines, with several compounds possessing low nanomolar binding affinity. In addition to the high potency, the basicity of this 4-aminoquinoline core may offer CRF$_1$ antagonists with lower lipophilicity.

Corticotrophin-releasing factor (CRF) is the key regulator of an organism's response to stress and as such, mediates the endocrine, autonomic, behavioral and immune response to stressful stimuli.[1] The binding of the released hypothalamic CRF to the CRF$_1$ receptors in the pituitary is responsible for the increased release of ACTH and other pro-opiomelanocortin derived peptides in response to the stressful stimuli in the periphery.[2] On the other hand, prolonged activation of the brain CRF receptors by the released hypothalamic CRF is thought to be related to the psychological effects of stress leading to anxiety and depression. Therefore, blockade of central CRF$_1$ receptor activation has been proposed as a novel approach for the treatment of these psychiatric disorders.[3]

The recent discovery of non-peptide antagonists of the CRF receptors has opened a new era for the study of this neurotransmitter. Several small molecules have been reported to have good CRF$_1$ receptor antagonistic activity.[4] For example, anilinopyrimidine (such as NBI 27914),[5] pyrrolo[1,2-*d*]pyrimidine (CP-154,526),[6] imidazolo[3,4-*d*]pyrimidine (**1**),[7] pyrazolo[1,5-*a*]pyrimidine (**2**, NBI 30545) show good binding affinity as well as in vivo activity.[8] A recent human clinical trial with NBI 30775 (**3**) on a group of severely depressed patients revealed very encouraging results in an open label clinical.[9] Since the pyrazolo[1,5-*a*]pyrimidine core is not very basic (an estimated pK_a value is less than 6),[10] we successfully incorporated a basic 4-methyl-6-dimethylamino-3-pyridyl group in **3** to make the compound with suitable water-solubility (the pK_a value of **3** is 7.1, and water solubility is >10 mg/mL at pH 4) as a drug candidate (Fig. 1). The clinical trial was discontinued due to unexpected liver toxicity.[11]

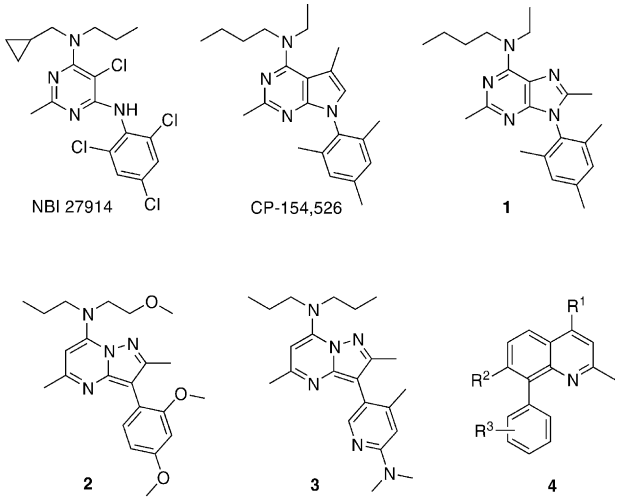

Figure 1.

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doi:10.1016/S0960-894X(03)00684-X

In our continuing search for novel heterocyclic templates with desirable physicochemical properties, 4-substituted 8-aryl-2-methylquinolines of the general structure **4** were designed. In addition to having a topographical similarity to known CRF_1 receptor antagonists such as CP-154,526, **1** and **3**,[12] this bicyclic nucleus should be relatively basic since the reported pK_a value of 4-aminoquinoline is 9.08,[13] which matches with the ACD calculated value (9.00). With this kind of pK_a value, this class of compounds should be charged in a great proportion under physiological conditions (pH ~7.4). In this paper, we present the synthesis and structure–activity relationship study around this nucleus as a potent class of CRF_1 receptor antagonists.

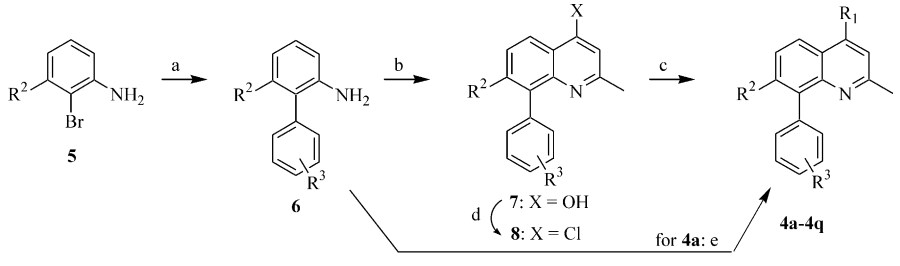
The synthesis of the 4-substituted 8-aryl-2-methylquinolines **4a–4q** is outlined in Scheme 1. Palladium catalyzed cross coupling reaction of 2-bromo- or 2-iodoaniline with 2,4-dichlorophenylboronic acids under Suzuki coupling conditions gave 2-(2,4-dichlorophenyl)aniline in 87% yield,[14] which was condensed with ethyl acetoacetate in benzene under azeotropic conditions to give an enamine intermediate, which was subsequently cyclized upon heating in phenyl ether to give the 4-hydroxyquinoline **7** (42% in two steps).[15] Reaction of **7** with $POCl_3$ at reflux afforded the corresponding 4-chloroquinoline **8** in quantitative yield. Compound **8** was converted to 4-methoxyquinoline **4b** with sodium methoxide (1.2 equiv) in DMF at room temperature. The corresponding methylsulfide **4c** was obtained in a similar manner. The 4-aminoquinolines **4d–4q** were synthesized in very good yields (65–90%) by reacting **8** with various mono- or di-alkylamines promoted by toluenesulfonic acid at an elevated temperature.[16] Compound **4a** was made from cyclization of **6** with 2,5-pentadione in heated phenyl ether in 30% yield.[17]

The quinolines **4r–4v** with various aromatic groups at the 8-position were synthesized according to the route described in Scheme 2. Thus, 2-iodoaniline was cyclized to the 4-hydroxyquinoline **9**, in 65% yield, with ethyl acetoacetate as described above. Compound **9** was reacted with $POCl_3$, followed by dipropylamine in the presence of TsOH to afford the aminoquinoline **11** (77% yield, two steps). Compound **11** was then subjected to a Suzuki coupling reaction with various arylboronic acids to yield the desired products **4r–4v** in 25–80% yields.

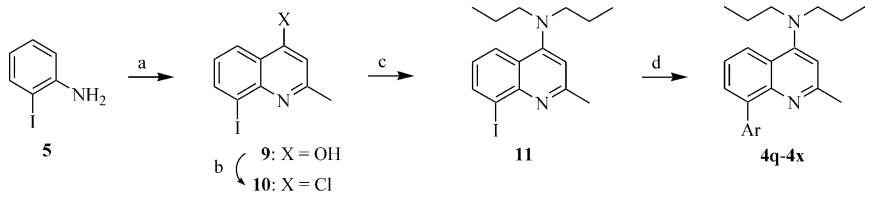
Compound **4w** was synthesized from 2-(2,4-dimethoxyphenyl)-4,4-dimethyl-2-oxazoline. Reaction of **12** with 4-chlorophenylmagnesium chloride gave the biphenyl **13** in good yield with a literature protocol.[18] The oxazole ring was then hydrolyzed to the acid **14**, followed by a Curtis rearrangement with $(PhO)_2PON_3$ in tertiary butanol to afford the urethane **15**, which was deprotected in trifluoroacetic acid to give the aniline **16** (45% yield in three steps). Compound **16** was then converted to the target quinoline **4w** using a similar procedure to that described earlier (Scheme 3).

The CRF_1 receptor binding assay was performed with the cloned human CRF_1 receptor expressed in CHO-cells using [^{125}I]o-CRF as the ligand in a manner similar to that previously reported.[19] Tables 1 and 2 summarize the SAR results of the different substituents at the 4- and 8-positions of the arylquinolines **4**.

As seen in Table 1, the intermediate 4-hydroxyquinoline **7a** exhibited no CRF activity (the inactivity could be related to the acidic hydroxy group), whereas the 4-chloroquinoline **8a** had an unexpected high binding affinity (K_i = 5 nM). The small 4-methyl and 4-methoxy analogues **4a** and **4b** had K_i values of 460 and 140 nM, respectively, and the slightly larger *S*-methyl analogue **4c** showed very good binding affinity (K_i = 12 nM). This set of data suggested a lipophilic group is favored at the 4-position of the quinoline **4**, and the highly lipophilic chlorine was able to mimic the larger-sized *S*-methyl

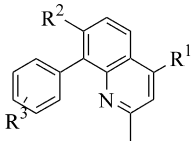


Scheme 1. Reagents and conditions: (a) 2,4-ClPhB(OH)$_2$, Pd(PPh$_3$)$_4$, Na$_2$CO$_3$, benzene, EtOH, H$_2$O; (b) ethyl acetoacetate, TsOH, benzene; then Ph$_2$O, 260 °C; (c) $POCl_3$, reflux; (d) R^{1}H, see text (R^1 = RO, RS or R$_2$N); (e) 2,5-pentadione, Δ.



Scheme 2. Reagents and conditions: (a) ethyl acetoacetate, TsOH, benzene; then Ph$_2$O, 260 °C; (b) $POCl_3$, reflux; (c) Pr$_2$NH, TsOH, 180 °C; (d) ArB(OH)$_2$, Pd(PPh$_3$)$_4$, Na$_2$CO$_3$, benzene, EtOH, H$_2$O.

Table 1. Effects of 4-substituents on the quinolines **4**



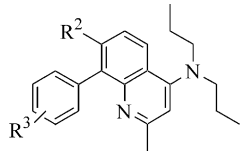
4a-q, 7a, 8a

Compd	R^2	R^3	R^1	K_i (nM)
7a	H	2,4-Cl	OH	>10,000
8a	H	2,4-Cl	Cl	5.0±1.0
4a	H	2,4-Cl	Me	460
4b	H	2,4-Cl	MeO	140
4c	H	2,4-Cl	MeS	16±4
4d	H	2,4-Cl	EtNBu	5.7±1.0
4e	H	2,4-Cl	Pr_2N	0.9±0.3
4f	H	2,4-Cl	$PrNCH_2Pr$-*c*	0.5±0.1
4g	H	2,4-Cl	$(MeOCH_2CH_2)_2N$	5.7±1.0
4h	H	2,4-Cl	PrNBn	3.8±0.5
4i	Me	2,4-Cl	Pr_2N	4.5±0.7
4j	Me	2,4-Cl	$PrNCH_2Pr$-*c*	2.5±0.6
4k	Me	2,4-Cl	$(MeOCH_2CH_2)_2N$	12.1±1.3
4l	H	2,4,6-Me	EtNBu	2.4±0.6
4m	H	2,4,6-Me	Pr_2N	3.0±1.5
4n	H	2,4,6-Me	$PrNCH_2Pr$-*c*	2.2±1.7
4o	H	2,4,6-Me	$(MeOCH_2CH_2)_2N$	6.5±3.3
4p	H	2,4,6-Me	PrNBu-*n*	3.0±0.5
4q	H	2,4,6-Me	PrNBn	3.2±0.7

group. The prototypical compound in this series was 8-(2,4-dichlorophenyl)-4-dipropylamino-2-methylquinoline **4e**, which was found to have subnanomolar binding affinity on the CRF_1 receptor ($K_i = 0.9$). Replacement of the 4-chloro-group of quinoline **8a** with *N*-cyclopropanemethyl-*N*-propylamino group also afforded compound with subnanomolar activity (**4f**, $K_i = 0.5$ nM). Replacement of the *N*-cyclopropanemethyl group of compound **4f** with a smaller ethyl resulted in approximately 10-fold loss in binding affinity (**4d**, $K_i = 5.7$ nM). The more polar bis(methoxyethyl)amino analogue **4g** was also 10-fold less active than **4f**.

The 7-methylquinoline derivatives (**4i–4k**), however, were slightly less active than the corresponding des-

Table 2. Effects of 8-aryl substituents on the quinolines **4**

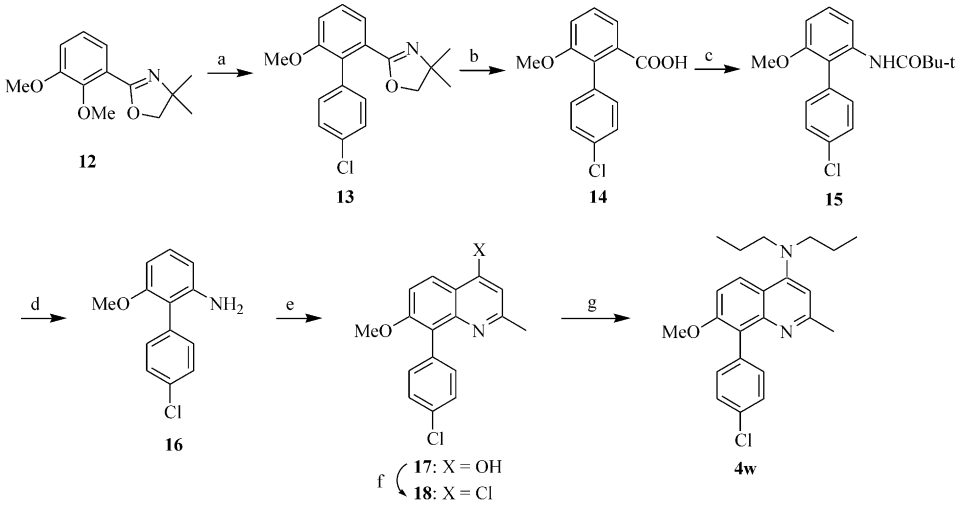


4r-4w

Compd	R^2	R^3	K_i (nM)
4r	H	H	420
4m	H	2,4,6-Me	3.0±1.5
4e	H	2,4-Cl	0.9±0.3
4i	Me	2,4-Cl	4.5±0.7
4s	H	2,4-MeO	14.5±5.1
4t	H	4-MeO	52
4u	H	4-Me	32.5±5.5
4v	H	4-Cl	8.9±0.7
4w	MeO	4-Cl	9.0±3.0

methyl compounds, which was somewhat surprised. We expected the 7-methyl group would help the dichlorophenyl group to take the orthogonal position relative to the quinoline ring.[5b] Additional methyl group at the phenyl ring did not have big effect on the receptor binding, thus, **4l–4q** were also slightly less active than **4d–4h**.

The effect of substitutions on the 8-phenyl ring of the quinolines **4** was also examined (**4r–4x**, Table 2). The non-substituted phenyl analogue **4r** was moderately active ($K_i = 420$ nM). Introduction of a non-polar substituent on the phenyl group generally resulted in more active compounds. Thus, the 2,4,6-trimethylphenyl analogue had an approximately 140-fold increase in binding (**4i**, $K_i = 3$ nM), while the 2,4-dichlorophenyl group exhibited a 460-fold increase (**4e**, $K_i = 0.9$ nM). The relatively polar 2,4-dimethoxyphenyl group had a similar but somewhat reduced effect (**4s**, $K_i = 15$ nM). A *para*-substitution with methyl or methoxy resulted in compounds with good binding affinity (**4u** and **4t**, $K_i = 33$ and 52 nM, respectively). Substitution with a



Scheme 3. Reagents and conditions: (a) 4-ClPhMgBr, Et_2O; (b) MeI then 2 N HCl, reflux; (c) $(PhO)_2PON_3$, Et3N, *t*-BuOH, reflux; (d) TFA; (e) ethyl acetoacetate, TsOH, benzene; then Ph_2O, 260 °C; (f) $POCl_3$, reflux; (g) Pr_2NH, TsOH, 180 °C.

Table 3. Inhibition of CRF-stimulated cAMP production

Compd	K_i (nM)	IC_{50} (nM)
4d	5.7	51
4e	0.9	17
4f	0.5	16
4g	5.7	14
4m	3.0	14

lipophilic chloro group increased the binding affinity to low nanomolar (**4v**, $K_i = 9$ nM). Finally, introduction of a methoxy group at the 7-position of the quinoline core had no effect in binding affinity (**4w**, $K_i = 9$ nM).

Selective compounds from this series were further tested for functional antagonism on the CRF_1 receptor.[20] Thus, in a CRF-stimulated c-AMP production assay, compounds **4e**, **4f**, **4g**, and **4m** inhibited c-AMP accumulation with low nanomolar IC_{50} values (about 15 nM), while compound **4d** was slightly less active ($IC_{50} = 51$ nM) (Table 3). None of these compounds tested alone demonstrated any effects on basal cAMP production, indicating that these compounds are devoid of agonist activity at this receptor subtype. All compounds were examined for activity in a CRF_2-receptor binding assay as previously described[21] and none of the listed compounds showed a does-dependent inhibition of ligand binding and none had a greater than 40% inhibition at a concentration of 10 μM. These data demonstrate these compounds are selective CRF_1 antagonists.

In summary, a series of 8-aryl-2-methylquinolines exemplified by **4e** was designed and synthesized as low nanomolar CRF_1 receptor antagonists. The results of the SAR study suggest that the dipropylamino, or a group with similar size and shape on the 4-amino functionality of the quinoline core structure in conjunction with a *para*-substituent such as chlorine at the 8-phenyl group are required for optimal CRF_1 receptor binding affinity. This series of compounds also demonstrated good antagonistic function in inhibition of CRF-stimulated c-AMP production on the CRF_1 receptor. In addition to the high potency, the basicity of this 4-aminoquinoline core may offer CRF_1 antagonists with lower lipophilicity (a calculated pK_a value for **4w** is 10.7, ACD Software).

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16. Synthesis of 2-methyl-4-(dipropylamino)-8-(2,4-dichlorophenyl)quilonine (**4e**). To a stirring solution of 2-bromoaniline (4.0 g, 23.3 mmol) in 120 mL of toluene was added tetrakis(triphenylphosphine)-palladium(0) (2.7 g, 2.33 mmol, 10% mol) and 2.0 M aqueous sodium carbonate solution (35 mL, 70 mmol). In a separate flask, 2,4-dichlorophenylboronic acid (25.6 mmol) was dissolved in alcohol (35 mL). To the light yellow boronic acid solution was added the 2-bromoaniline mixture. The resulting brown mixture was heated to reflux overnight. The green reaction mixture was cooled, diluted with ethyl acetate and washed with saturated ammonium chloride solution once. The organic layer was dried by sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel to provide the desired 2-(2,4-

dichlorophenyl)aniline in 87% yield. ^{1}H NMR ($CDCl_3$) δ 3.54 (brs, 2H), 6.79 (d, 1H), 6.85 (d, 1H), 7.02 (d, 1H), 7.19–7.35 (m, 3H), 7.53 (d, 1H). GC/MS: $m/z = 237$ (M^+), HR-MS calcd for $C_{12}H_9NCl_2$: 238.0190, Found: 238.0198 (MH^+).

A solution of 2-(2,4-dichlorophenyl)aniline (19.8 mmol), ethyl acetoacetate (2.58 g, 19.8 mmol) and *p*-toluenesulfonic acid monohydrate (20 mg) in 100 mL of benzene was refluxed for 30 min. The reaction mixture was cooled, concentrated and purified by flash chromatography on silica gel to provide a yellow oil. A solution of the above oil (6.68 mmol) in 10 mL diphenylether was heated to reflux for 5 min. The reaction mixture was cooled and the solid was collected by filtration, and rinsed with diethyl ether. The desired 2-methyl-4-hydroxy-8-(2,4-dichlorophenyl)quilonine was obtained as a white solid in 42% yield, mp 282–284 °C. ^{1}H NMR ($CDCl_3$) 2.56 (s, 3H), 6.11 (s, 1H), 7.34–7.44 (m, 4H), 7.58 (d, 1H), 8.38 (d, 1H), 8.82 (brs, 1H). MS (CI): *m*/*z* 304 (MH^+). Anal. calcd for $C_{16}H_{11}NOCl_2$ (304.12) C, 63.18; H, 3.65; N: 4.60, Found: C, 63.34; H, 3.88; N: 4.42.

A mixture of 2-methyl-4-hydroxy-8-(2,4-dichlorophenyl)-quilonine (4.34 mmol) and phosphorous oxychloride (5 mL) was refluxed for 2 h, cooled, poured onto a crack ice, neutralized by 1 N NaOH. The aqueous layer was extracted by ethyl acetate. The organic layer was washed with brine, dried under sodium sulfate, concentrated to give the desired 2-methyl-4-chloro-8-(2,4-dichlorophenyl)quilonine in 94% yield. ^{1}H NMR ($CDCl_3$) δ 2.58 (s, 3H), 7.34 (s, 2H), 7.39 (s, 1H), 7.53 (s, 1H), 7.63–7.65 (m, 2H), 8.26 (dd, 1H). GC/MS: *m*/*z* 321 (M^+), MS (CI): *m*/*z* 322 (MH^+). HR-MS calcd for $C_{16}H_{10}NCl_3$: 321.9957, Found: 321.9970 (MH^+).

A solution of 2-methyl-4-chloro-8-(2,4-dichlorophenyl)-quilonine (0.31 mmol) and *p*-toluenesulfonic acid monohydrate (0.1 g) in 0.4 mL of propylamine in a 5 mL Reacti-Vials was heated at 160 °C for 12 h. The reaction mixture was cooled and then partitioned between ethyl acetate and water. The organic layer was washed with brine, dried under sodium sulfate, concentrated and purified by a preparative TLC plate (hexane/EtOAc, 10:1). The desired 2-methyl-4-(dipropylamino) -8-(2,4-dichlorophenyl)quilonine was isolated as pale yellow oil in 67% yield. ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 6H), 1.56–1.66 (m, 4H), 2.52 (s, 3H), 3.25 (t, 4H), 6.73 (s, 1H), 7.33 (d, 1H),7.36 (d, 1H), 7.43 (d, 1H), 7.49 (d, 1H), 7.52 (s, 1H), 8.11 (d, 1H); GC/MS: *m*/*z* 386 (M^+), MS (ES): *m*/*z* 387 ($M + H^+$). HR-MS calcd for $C_{22}H_{24}N_2Cl_2.MH^+$ 387.1395, Found: 387.1402 (MH^+).

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