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Synthesis and Structure–Activity Relationships of Aroylpyrrole Alkylamide Bradykinin (B_2) Antagonists

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Abstract—The synthesis and structure–activity relationships of a novel series of aroylpyrrole alkylamides as potent selective bradykinin B_2 receptor antagonists are described. Several members of this series display nanomolar affinity at the B_2 receptor and show activity in an animal model of antinociception.

Bradykinin is an endogenous nonapeptide that plays an important role in a variety of inflammatory diseases and pain states.[1] Bradykinin (BK) and the decapeptide kallidin are released from plasma and tissue protein kininogens by the proteolytic action of kallikreins. These peptides cause pain by stimulating nociceptors (C and Aδ fibers) through their action upon distinct G-protein coupled receptors subtypes, B_1 and B_2.[2] Bradykinin is among the most potent of known algesic substances and therefore small-molecule bradykinin receptor antagonists may be useful in the treatment of various pain states.[3]

A variety of B_2 antagonists has been reported but most have been peptides and peptide mimetics.[4,5] However, more recently, several novel classes of non-peptide bradykinin B_2 receptor antagonists have been disclosed; among them, a series of potent antagonists exemplified by Fujisawa FR173657 (Fig. 1).[6–8] Studies by Fujisawa indicate that 2,6-disubstitution of the central phenyl ring, along with the *N*-methylacetamide were necessary for binding to the human BK_2 receptor. The role of the unsaturated amide group was presumably electrostatic, possibly contributing to interaction with the BK_2 receptor as a hydrogen bond donor.[9]

We attempted to design and synthesize novel bradykinin antagonists in which pyrrolyl ring systems could serve as replacements for amide linkages found in the Fujisawa series. Such a strategy could lead to compounds with improved solubility, metabolic stability and in vivo properties. As reported herein, we have synthesized a series of aroylpyrrole alkylamides (e.g., Fig. 2) that possess nanomolar binding affinity for the human B_2 receptor, and display activity in an in vivo model of antinociception.

Our general synthetic approach was centered upon the propensity of the pyrrole ring system to undergo facile

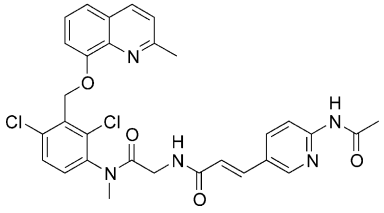
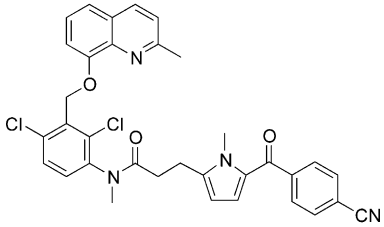


Figure 1. Structure of FR 173657.



B_2 K_i = 4 nM

Figure 2. Aroylpyrrole alkylamide B_2 antagonist.

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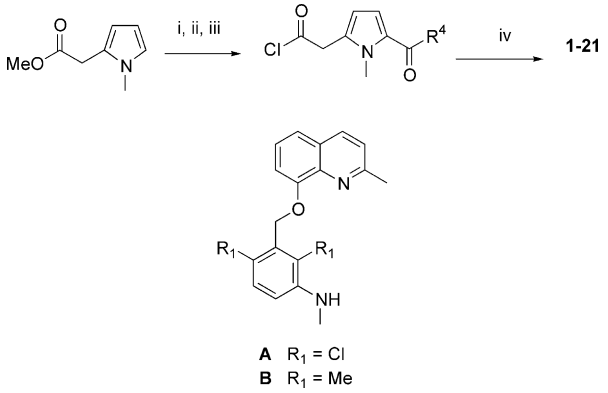
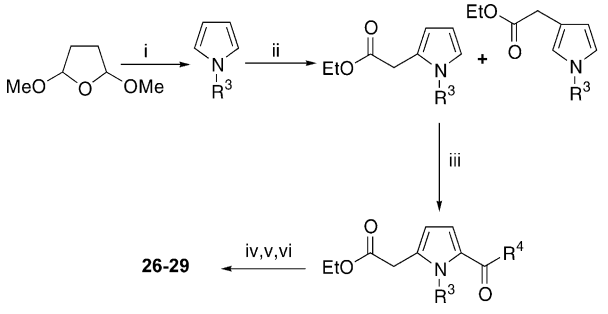
and often predictable acylation. The route to 2,5-disubstituted pyrrolyl congeners (entries 1–21) is shown below. Thermal acylation of *N*-methyl-pyrrole-2-methylacetate with various acyl chlorides[10] followed by saponification yielded the corresponding carboxylic acids. Reaction with oxalyl chloride at low temperature afforded acyl chlorides that were immediately reacted with the anilino intermediates to construct the target compounds. The anilino intermediates were prepared by modification of known procedures (Scheme 1).[11]

Compounds containing *N*-alkylated pyrroles (entries 26–29) were obtained by condensation of alkyl amines with dimethoxytetrahydrofuran and then elaboration via a carbenoid reaction with ethyl diazoacetate in the presence of copper bronze.[12] This chemistry produced 2,5-disubstituted *N*-alkyl pyrrole esters along with minor amounts of isomeric 3,5 *N*-alkyl pyrrole esters which were separable by flash chromatography. As previously described, saponification, acid chloride formation followed by coupling to the aniline gave final products (Scheme 2).

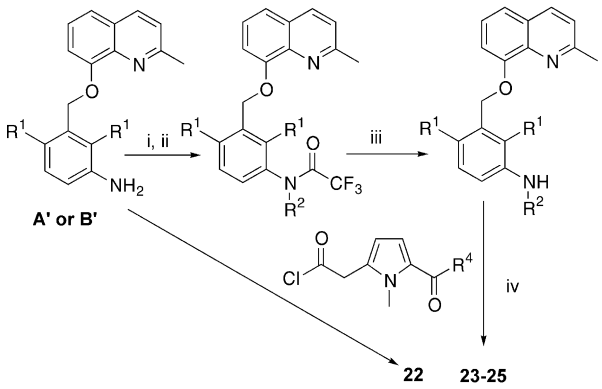
Substitution on the aniline nitrogen center was achieved by trifluoroacetylation followed by alkylation using sodium hydride and an alkyl halide. Trifluoroacetamide cleavage was accomplished by reaction with sodium borohydride in methanol to yield the *N*-alkyl aniline. The *N*-alkyl anilines were then elaborated to the final targets (entries 23–25) (Scheme 3).



Scheme 1. (i) R^4COCl, toluene, heat; (ii) LiOH, THF/H_2O; (iii) $(COCl)_2$, cat DMF, DCM, 0 °C; (iv) A (R_1 = Cl) or B (R_1 = Me), cat DMAP, DCM.



Scheme 2. (i) R^3NH_2, HOAc, heat; (ii) $N_2{=}CHCO_2Et$, Cu(bronze), heat; (iii) R^4COCl, toluene, heat; (iv) LiOH, THF/H_2O; (v) $(COCl)_2$, cat DMF, DCM, 0 °C; (vi) A or B, cat DMAP, DCM.



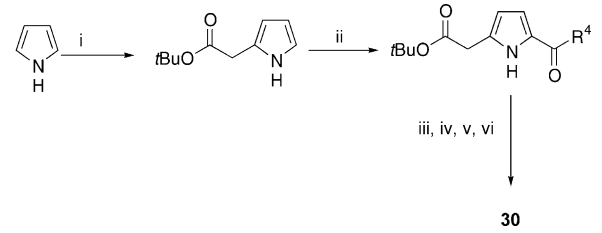
Scheme 3. (i) TFAA, $CHCl_3$; (ii) NaH, R^2X, DMF; (iii) $NaBH_4$, MeOH; (iv) cat DMAP, DCM.

Compounds lacking an alkyl substituent on the pyrrole nitrogen center were prepared by generating a pyrrolyl Grignard reagent followed by acylation with an appropriate Vilsmeier–Haack reagent to yield the *t*-butyl ester.[13] The ester was taken on in the usual fashion to give the target compound (entry 30) (Scheme 4).

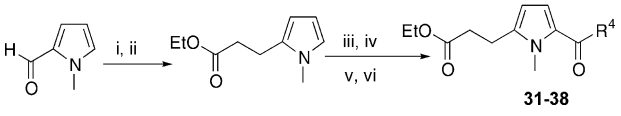
Wittig homologation of the *N*-methyl pyrrole carboxaldehyde produced the unsaturated propionate. Hydrogenation and standard methods afforded 2,5-disubstituted (pyrrolyl)propionic acids that were coupled to the anilino intermediates to give the pyrrole propionamide homologues (Table 2, entries 31–38) (Scheme 5).

The binding affinities for a series of pyrroyl alkyl amides at the B_2 receptor are shown in Table 1.[14] Compounds were also evaluated in a GTPγS assay to determine their functional activity (data not shown).[15]

As anticipated due to structural similarities, a portion of the structure–activity relationships (SARs) of our series paralleled that reported by Fujisawa. For example, the anilino *N*-substituent was found to be crucial for binding affinity (entry 22); alkyl groups larger than methyl (entries 23–25) diminished binding affinity, in support of

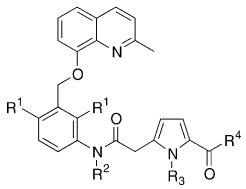


Scheme 4. (i) $BrCH_2CO_2t$-Bu, EtMgBr, THF, −10 °C to rt; (ii) $R^4C(Cl){=}NMe_2^+Cl^-$, DCM; (iii) aq NaOAc; (iv) TFA/DCM; (v) $(COCl)_2$, cat DMF, DCM, 0 °C; (vi) A or B, cat DMAP, DCM.



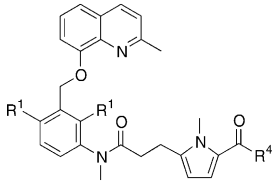
Scheme 5. (i) $Ph_3P{=}CHCO_2Et$, benzene; (ii) H_2, Pd/C, EtOH; (iii) R^4COCl, toluene, heat; (iv) LiOH, THF/H_2O; (v) $(COCl)_2$, cat DMF, DCM, 0 °C; (vi) A or B, cat DMAP, DCM.

Table 1. Binding affinities at the B_2 receptor



Entry	R^1	R^2	R^3	R^4	K_i (nM)
1	Cl	Me	Me	*t*-Butyl	1710
2	Cl	Me	Me	Cyclohexyl	1790
3	Cl	Me	Me	Ph	2290
4	Cl	Me	Me	CH_2Ph	2370
5	Cl	Me	Me	(4-Cl)Ph	752
6	Cl	Me	Me	(4-CF_3)Ph	476
7	Cl	Me	Me	(4-$CONMe_2$)Ph	204
8	Cl	Me	Me	(4-OMe)Ph	92
9	Cl	Me	Me	(4-SO_2Me)Ph	34
10	Cl	Me	Me	(4-SO_2NH_2)Ph	76
11	Cl	Me	Me	(4-NH_2)Ph	300
12	Cl	Me	Me	(2-NHAc)Ph	869
13	Cl	Me	Me	(3-NHAc)Ph	73
14	Cl	Me	Me	(4-NHAc)Ph	57
15	Cl	Me	Me	2-Thienyl	239
16	Cl	Me	Me	(4-CN)Ph	23
17	Me	Me	Me	(4-CN)Ph	69
18	Cl	Me	Me	(6-Cl)3-Pyridyl	121
19	Me	Me	Me	(6-Cl)3-Pyridyl	271
20	Cl	Me	Me	(6-CN)3-Pyridyl	74
21	Me	Me	Me	(6-CN)3-Pyridyl	103
22	Cl	H	Me	(4-CN)Ph	5500
23	Cl	Et	Me	(4-CN)Ph	55
24	Cl	*n*-Pr	Me	(4-CN)Ph	3890
25	Cl	Allyl	Me	(4-CN)Ph	514
26	Cl	Me	Et	(4-CN)Ph	10
27	Cl	Me	*n*-Pr	(4-CN)Ph	27
28	Cl	Me	*n*-Bu	(4-CN)Ph	29
29	Cl	Me	*i*-Amyl	(4-CN)Ph	44
30	Cl	Me	H	(4-CN)Ph	38

Table 2. Binding affinities of pyrrolyl propionamides at the B_2 receptor

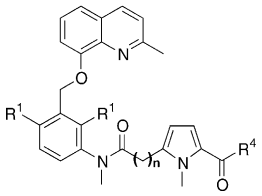


Entry	R^1	R^4	K_i (nM)
31	Me	2-Thienyl	141
32	Me	3-Pyridyl	304
33	Me	(6-Cl)3-Pyridyl	126
34	Me	(4-CN)Ph	19
35	Cl	2-Thienyl	304
36	Cl	3-Pyridyl	15
37	Cl	(6-Cl)3-Pyridyl	38
38	Cl	(4-CN)Ph	4

a steric requirement previously suggested by Fujisawa.[16] Secondly, compounds derived from either the dichlorinated or dimethylated anilines were essentially equipotent (entries 16–17, 18–19, and 20–21).

However, there were exquisite and unique SAR features attributed to the incorporation of pyrrolyl scaffolds. In contrast to the anilino *N*-substituent, replacement of the pyrrolyl *N*-methyl group with other alkyl groups had little effect on the binding affinity and even a group as large as *i*-amyl retained activity. In addition, analogues that lacked substitution on the pyrrole nitrogen center were also potent binders (entry 30).

Table 3. Antinociceptive evaluation of pyrrolyl alkylamide analogues in the Graded Abdominal Irritant (kaolin) Test



Entry	R^1	*n*	R^4	ED_{50} (μmol/kg, po)
17	Me	1	(4-CN) Ph	61
21	Me	1	(6-CN) 3-Pyr	114
19	Me	1	(6-Cl) 3-Pyr	81
18	Cl	1	(6-Cl) 3-Pyr	69
37	Cl	2	(6-Cl) 3-Pyr	23

Analogues containing simple alkyl or aryl groups at R^4 exhibited weak binding to the B_2 receptor (entries 1–4). Para substitution of the benzoyl terminus appeared to be optimal for binding affinity (entries 12–14). Compounds with lipophilic substituents on the phenyl ring (entries 5 and 6) showed only moderate activity whereas more polar substituents such as methoxy, sulfone, sulfonamide, acetamide or nitrile were quite potent (entries 8–10, 14, and 16, respectively)

Heterocyclic substitution for phenyl was well tolerated. Indeed, replacement of the phenyl (entry 3) with thienyl (entry 15) gave a compound with a 10-fold increase in binding affinity. In addition, one of the most potent analogues contained a nitrile-substituted pyridyl group. This result was not surprising given that one of the most potent phenyl analogues also contained a nitrile substituent. Other pyrrole regioisomers were explored but the 2,4 and the 3,5 isomers exhibited weaker activity than the 2,5 isomers. In addition, removal of the carbonyl group between the pyrrole and the phenyl ring abolished activity (data not shown).

We also synthesized a select number of congeners in which the chain length was increased. Using the SAR extracted from the pyrrolyl acetamide series, we were able to obtain propionamide homologues with excellent affinity for the B_2 receptor (Table 2). These homologues were also shown to be functional antagonists at the B_2 receptor.

Potent compounds were further evaluated in an in vivo model of antinociception (Table 3).[17] Although compounds containing a benzoyl terminus generally exhibited better binding affinities, pyridyl-containing analogues demonstrated more consistent oral activity in vivo. For example, cyano-substituted phenyl propionamide (**38**) had superior binding affinity at the B_2

receptor but showed weak in vivo activity upon oral dosing (23% inhibition at 160 μmol/kg). By contrast, chloro-substituted pyridyl analogue (**37**) was more active upon oral dosing perhaps due to better aqueous solubility. Furthermore, several analogues exhibited good oral potency in this model with the most potent analogue (**37**) having an ED_{50} value of 23 μmol/kg.

In conclusion, we have designed and synthesized a novel series of alkylpyrrolyl amides with selective, nanomolar binding affinity to the bradykinin B_2 receptor. These compounds have also been shown to have oral activity in an in vivo model of antinociception. These results suggest that this novel series of compounds may be useful for the treatment of various pain and inflammatory states, and asthma.

References and Notes

1. (a) Bhoola, K. D.; Figueroa, C. D.; Worthy, K. *Pharmacol. Rev.* **1992**, *44*, 1. (b) Proud, D.; Kaplan, A. P. *Annu. Rev. Immunol.* **1988**, *6*, 49. (c) Dray, A.; Parkins, M. *Trends Neurosci.* **1993**, *16*, 99.
2. (a) Meller, S. T.; Gebhart, G. F. *Neuroscience* **1992**, *48*, 501. (b) Mense, S. *Pain* **1993**, *51*, 241.
3. (a) Hock, F. J.; Wirth, K.; Albus, U.; Linz, W.; Gerhards, H. J.; Wirth, K. J.; Heitsch, H.; Scholkens, B. A. *Can. J. Physiol. Pharmacol.* **1995**, *73*, 797. (b) Greaves, M. W. *Br. J. Dermatol.* **1988**, *119*, 419. (c) Marceau, F.; Lussier, A.; Regoli, D.; Giroud, J. P. *Gen. Pharmacol.* **1983**, *14*, 209. (d) Burch, R. M.; Farmer, S. G.; Steranka, L. R. *Med. Res. Rev.* **1990**, *10*, 237.
4. (a) Hock, F. J.; Wirth, K.; Albus, U.; Linz, W.; Gerhards, H. J.; Wiemer, G.; Henke, S.; Breipohl, G.; Konig, W.; Knolle, J.; Scholkens, B. A. *Br. J. Pharmacol.* **1991**, *102*, 769. (b) Wirth, K.; Hock, F. J.; Albus, U; Linz, W; Alpermann, H.-G.; Henke, S.; Breipohl, G.; Konig, W.; Knolle, J.; Scholkens, B. A. *Br. J. Pharmacol.* **1991**, *102*, 774.
5. Cheronis, J. C.; Whalley, E. T.; Nguyen, K. T.; Eubanks, S. R.; Allen, L. G.; Duggan, M. J.; Lo, S. D.; Bonham, K. A.; Blodgett, J. K. *J. Med. Chem.* **1991**, *35*, 1563.
6. (a) Abe, Y.; Kayakiri, H.; Satoh, S.; Inoue, T.; Sawada, Y.; Imai, K.; Inamura, N.; Asano, M.; Hatori, C.; Katayama, A.; Oku, T.; Tanaka, H. *J. Med. Chem.* **1998**, *41*, 564. (b) Abe, Y.; Kayakiri, H.; Satoh, S.; Inoue, T.; Sawada, Y.; Inamura, N.; Asano, M.; Hatori, C.; Sawai, H.; Oku, T.; Tanaka, H. *J. Med. Chem.* **1998**, *41*, 4053.
7. Hoyer, D.; Awad, M. M. A.; Salvino, J. M.; Seoane, P. R.; Dolle, R. E.; Houck, W. T.; Sawurtz, D. G. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 367.
8. (a) Dziadulewicz, E. K.; Ritchie, T. J.; Hallett, A.; Snell, C. R.; Ko, S. Y.; Wrigglesworth, R.; Hughes, G. A.; Dunstan, A. R.; Bloomfield, G. C.; Drake, G. S.; Brown, M. C.; Lee, W.; Burgess, G. M.; Davis, C.; Yaqoob, M.; Perkins, M. N.; Campbell, E. A.; Davis, A. J.; Rang, H. P. *J. Med. Chem.* **2000**, *43*, 769. (b) Amblard, M.; Daffix, I.; Bedos, P.; Berge, G.; Pruneau, D.; Paquet, J.-L.; Luccarini, J.-M.; Belichard, P.; Dodey, P.; Martinez, J. *J. Med. Chem.* **2000**, *43*, 2386. (c) Heitsch, H.; Wagner, A.; Scholkens, B. A.; Wirth, K. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 327. (d) Dziadulewicz, E. K.; Brown, M. C.; Dunstan, A. R.; Lee, W.; Said, N. B.; Garratt, P. J. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 463.
9. Kayakiri, H.; Abe, Y.; Oku, T. *Drugs Future* **1999**, *24*, 629.
10. Carson, J. R. US Patent 3,998,844, 1976. *Chem. Abst.* **1977**, 584363.
11. Abe, Y.; Kayakiri, H.; Satoh, S.; Inoue, T.; Sawada, Y.; Inamura, N.; Asano, M.; Aramori, I.; Hatori, C.; Sawai, H.; Oku, T.; Tanaka, H. *J. Med. Chem.* **1998**, *41*, 4587.
12. Maryanoff, B. E. *J. Org. Chem.* **1979**, *24*, 4410.
13. Schloemer, G. C. *J. Org. Chem.* **1994**, *59*, 5230.
14. Zhang, S. P.; Codd, E. *Life Sci.* **1998**, *62*, 2303 This series of compounds exhibited no significant binding to the B_1 receptor (data not shown).
15. Zhang, S.-P.; Wamh, H.-Y.; Lovenberg, T.; Codd, E. *Int. Immunopharmacol.* **2001**, 955.
16. Abe, Y.; Kayakiri, H.; Satoh, S.; Inoue, T.; Sawada, Y.; Imai, K.; Inamura, N.; Asano, M.; Hatori, C.; Katayama, A.; Oku, T.; Tanaka, H. *J. Med. Chem.* **1998**, *41*, 564.
17. The Graded Abdominal Irritant Test (GrAIT) is a modification of the methods described by Koster et al. *J. Fed. Proc.* **1959**, *18*, 412. Kaolin (100 mg/kg) was injected intraperitoneally (10 mL/kg) to induce a viscerochemical nociceptive response characterized by phasic contraction of the abdominal musculature. The number of such contractions was counted over the 15-min period immediately following injection of kaolin. The mean number of counts (±SEM) for a group of animals receiving test compound (T) orally, 30 min prior to kaolin, was compared to the mean for animals dosed similarly with vehicle (V, 0.05N HCl). Percent inhibition was calculated for each dose level as $\%I = [1-(T \text{ counts}/V \text{ counts})] \times 100$, from which an oral ED_{50} value was derived.