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Synthesis and Pharmacology of New Enantiopure *2S*-4-Arylkainoids

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Abstract—Seven Δ^3-4-arylkainoids possessing various 4-position aromatic and heteroaromatic groups were synthesized and their apparent affinities were measured in order to explore the influences of 4-position electron density and stereochemistry on receptor affinity and specificity. Kainoids **1a**–**f** were shown to be selective agonists at the NMDA receptor and the electron rich furanyl and thienyl analogues exhibited the highest affinities. Naphthylkainoid **1g** proved to be a nonselective antagonist at the iGluRs.

Introduction

Glutamic acid mediates synaptic transmission in the mammalian central nervous system at two classes of receptors: the ionotropic glutamate receptors (iGluRs) and the metabotropic glutamate receptors (mGluRs).[1,2] Glutamate receptor ligands that act as selective agonists (Fig. 1) have been used to define three subtypes of ionotropic receptors: kainate, AMPA and NMDA.[3–5]

Five kainate receptors have also been identified: KA, KA1, GluR5, GluR6, and GluR7.[6] Biological evaluation of natural and synthetic ligands has shown that kainoid neuroexcitatory activity is contingent on the combination of a glutamate-like structure, the nature of the *C*-4 substituent and the ring stereochemistry.[5,7,8] For example, *trans*-carboxy-3-pyrrolidineacetic acid possesses the Glu core structure characteristic of kainic acid and exhibits agonist activity at kainate and NMDA receptor subtypes.[9] π-Electron density at the *C*-4 position is essential for excitatory activity as demonstrated by the complete loss of neurotoxicity upon reduction of the isopropenyl double bond of kainic acid.[10] In addition, the naturally occuring kainoids, domoic acid, and acromelic acids A and B exhibit potent neuroexcitatory activity.[5] Furthermore, the higher depolarizing activity exhibited by 4-*o*-methoxy- and 4-*o*-hydroxyphenyl kainoids relative to kainic acid has led to the suggestion that "the excitatory activities of the kainoids depend on the height of HOMO (highest occupied molecular orbital) energies of the π-systems existing in the substituents at C4".[11] Finally, the natural kainic acid ring stereochemistry manifests maximal activity and inversion of the 4-position results in a more dramatic reduction of activity than inversion of the 3-position stereochemistry.[11]

In this report, seven novel Δ^3-4-arylkainoids[12] **1a**–**g** were synthesized and their apparent affinities were measured in order to explore further the influences of the 4-position electron density and stereochemistry on receptor affinity and specificity. The synthesis and examination of Δ^3-4-arylkainoids possessing electron rich heteroaromatic 4-position substituents has provided additional evidence to suggest that increased electron density at the π-system augments receptor affinity. The influence of the Δ^3-unsaturation on receptor specificity has also illustrated the importance of structure on receptor selectivity.[13,14]

Results and Discussion

Enantiopure (2*S*)-Δ^3-4-arylkainoids **1a**–**g** were synthesized by Pd(0)-catalyzed cross-couplings of different arylboronic acids[15–17] to (2*S*)-benzyl-3-methoxycarbonylmethyl-Δ^3-4-triflyloxy-*N*-(PhF)prolinate (**2**) that was conveniently prepared by a five step sequence in 64%

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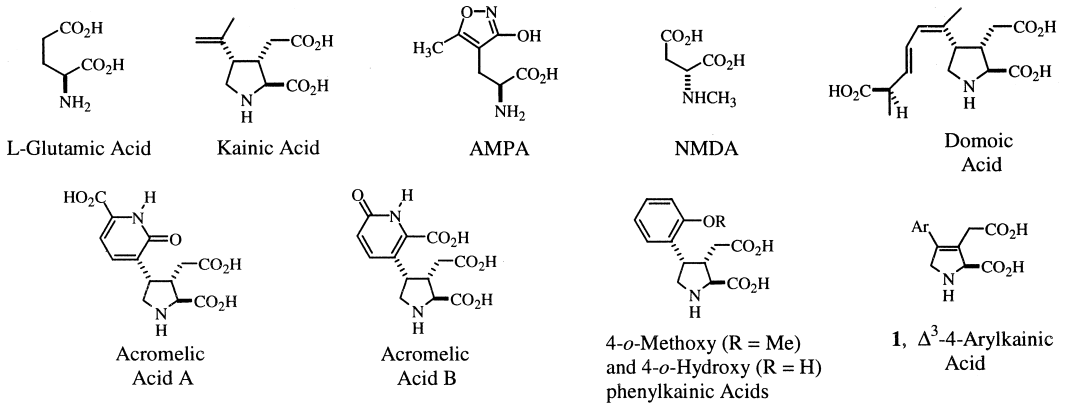


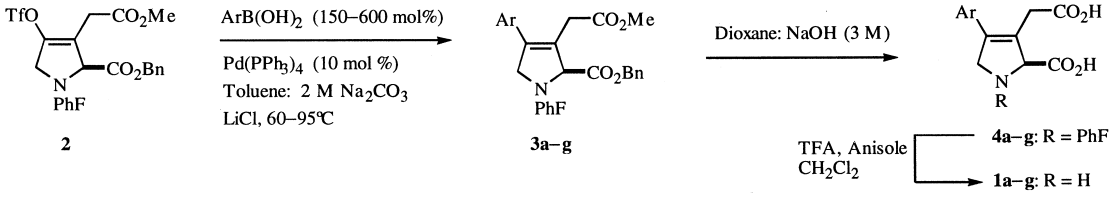
Figure 1. Representative neuroexcitatory amino acids.

overall yield from (2*S*,4*R*)-hydroxyproline as an inexpensive chiral educt (Scheme 1, Table 1, PhF = 9-(9-phenylfluorenyl)).[12,18] (2*S*)-Benzyl-3-methoxycarbonylmethyl-Δ^3-4-aryl-*N*-(PhF)prolinates **3a**–**g** were obtained in 72–99% yields by heating **2** and the respective boronate with 10 mol% of $Pd(PPh_3)_4$ and LiCl (300 mol%) in a two phase system of toluene and 2 M Na_2CO_3, followed by purification by silica gel chromatography. Deprotection of **3** was accomplished in two steps. First, (2*S*)-Δ^3-4-aryl-*N*-(PhF)kainoids **4a**–**g** were isolated in 71–99% yields from ester hydrolysis on heating **3** in a 1:1 solution of 3 M NaOH: dioxane and subsequent chromatography. Finally, (2*S*)-Δ^3-4-arylkainoids **1a**–**g**[19] were isolated in 71–99% yields as solids after PhF group solvolysis on stirring a dilute solution of **4** in a mixture of TFA and anisole in CH_2Cl_2 at rt, followed by removal of the hydrocarbon impurities by trituration with hexane. Arylkainoids **1** are presumed to be of >99% enantiomeric purity based on an analysis involving conversion of (2*S*)-Δ^3-4-phenylkainic acid **1a** into (*S*)- and (*R*)-*N*-α-methylbenzylurea dimethyl esters and observation of the diastereomeric methyl ester singlets by 300 MHz ^{1}H NMR spectroscopy in C_6D_6 during incremental additions of the opposite isomer which demonstrated a >99% de.[12]

Compounds **1a**–**g** were tested on the rat cortical wedge preparation by a method modified from Simmons and Harrison.[20] Δ^3-4-Arylkainoids **1a**–**f** exhibited weak agonist activity at the NMDA receptor subtype. The introduction of the electron-rich thienyl and furanyl heteroaromatic 4-position substituents in **1c**–**f** resulted in a significant increase in the excitatory effect in comparison with aromatic analogues **1a** and **1b**. The 2-furanyl and 2-thienyl analogues were respectively more potent that their 3-substituted counterparts. On the other hand, the increased size of the 4-position substituent led to antagonistic activity, as **1g** proved to be a nonselective antagonist at ionotropic glutamate receptors.

Conclusion

Enantiopure Δ^3-4-arylkainoids **1a**–**g** were synthesized in 28% to 42% overall yields from (2*S*, 4*R*)-hydroxyproline.



Scheme 1. Synthesis of (2*S*)-Δ^3-4-Arylkainoids **1a**–**g**.

Table 1. Synthesis yields and affinity of Δ^3-4-arylkainoids **1a**–**g**[19]

				Ar =						
	R^1	R^2	R^3	A	b	c	d	e	f	g
% Yield **3**	PhF	Me	Bn	92	82	80	93	99	72	99
4	PhF	H	H	99	88	87	81	78	88	71
1	H	H	H	82	76	78	99	72	95	71
Apparent K_D (μM)[a]				560	380	20	45	70	85	250

[a]NMDA receptor.

The presence of the Δ^3-double bond altered the receptor selectivity such that **1a**–**f** bound to the NMDA receptor subtype. Increased receptor affinity was observed in the 4-thienyl and furanyl analogues relative to their phenyl and methoxyphenyl counterparts indicating that greater electron density at the 4-position substituent increases receptor affinity. The combination of the Δ^3-unsaturation and naphthyl 4-position substituent led to a non-selective antagonist. Because similar relative affinities may be obtained at the kainate receptor on saturation of the Δ^3-double bond, we are now examining hydrogenation conditions to afford new arylkainoids.

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