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Imidazo[4,5-*c*]pyridines as Corticotropin Releasing Factor Receptor Ligands

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Abstract—A series of high affinity CRF receptor ligands with an imidazo[4,5-*c*]pyridine core is described. Individual analogues were synthesized and tested in vitro in rat brain receptors to determine binding affinity. The best compound was further tested in the dog N-in-1 pharmacokinetic model to assess oral bioavailability at 1 mg/kg po.

Corticotropin releasing factor is a 41-amino acid peptide implicated in major neuropsychiatric disorders, such as anxiety related disorders (panic disorders), post-traumatic stress disorder and depression.[1]

As a continuation of our work aimed toward the discovery and development of novel CRF antagonists, we were interested in exploring the corresponding imidazo[4,5-*c*]pyridines **II** as a new series with potentially improved biological and physical properties over the purine core (e.g., SV030)[2] that has been disclosed previously, as well as the imidazo[4,5-*b*]pyridine core described in the previous article (Fig. 1).

Synthesis of various analogues is described in Scheme 1.

The synthesis of various analogues started from intermediate **3a** described in the previous communication. The 4-chloro group was displaced with a primary branched amine to give the corresponding pyridone which was converted to the 4-alkylamino-2-chloro-3-nitropyridines **4a**. Intermediates **4a** were coupled with a wide variety of arylboronic acids in the presence of $Pd(PPh_2)Cl_2$ and $Ba(OH)_2$ to give intermediates **5a** in good to excellent yields.[3] The 3-nitro group was reduced to the corresponding amino group and the resulting diaminopyridines were cyclized to the imidazo[4,5-*c*]pyridine core under the same conditions described in the previous article. The final products were purified by column chromatography on silica gel and were >95% pure by HPLC analysis.

Previous SAR analysis on similar cores, such as the purines and imidazo[4,5-*b*]pyridines, indicated that the ethyl group was optimal at the 2-position, so it was maintained throughout the SAR effort on the series. Modifications were made on the side chains and aryl groups to optimize receptor affinity. Individual compounds were tested in vitro in the rat CRF receptor

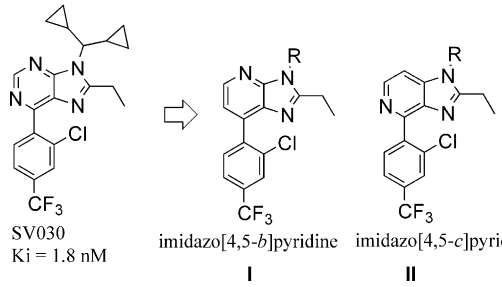

Figure 1. CRF receptor ligands with 5,6-fused ring system.

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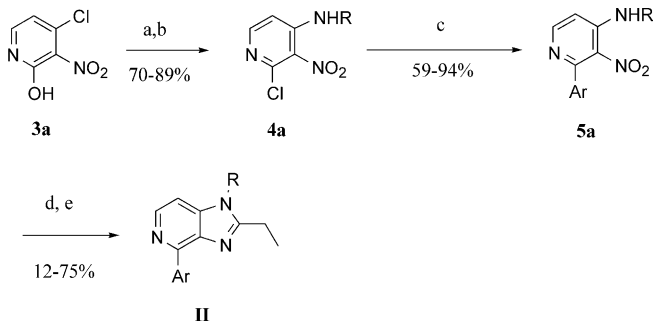


Scheme 1. (a) RNH_2, MeCN, 25 °C; (b) $POCl_3$, 25 °C; (c) $ArB(OH)_2$, $Pd(PPh_3)_2Cl_2$, $Ba(OH)_2$, DME/water, Δ, 5–16 h; (d) $Na_2S_2O_4$, dioxane/water NH_4OH; (e) $EtCO_2H$ or $EtCO_2H/EtC(OEt)_3$, Δ.

assay as previously described. Data for analogues with various alkyl chains and aryl substituents are listed in Table 1.

As a general rule the SAR of the imidazo[4,5-*c*]pyridine series follows closely the previously described for the imidazo[4,5-*b*]pyridine and purine series, with slightly lower affinity. Small lipophilic branched unsymmetric chains are the best substituents for optimal affinity (**1**–**7**). The best phenyl substitution for optimal affinity was the 2-Cl-4-OCF_3 and the best chain was the 2-pentyl (**1**). This was separated to the two enantiomers using chiral HPLC and the *S*-enantiomer (**3**) was synthesized independently from the commercially available (*S*)-2-aminopentane. The data in Table 1 indicate that there is no difference in affinity between the two enantiomers **2** and **3**.

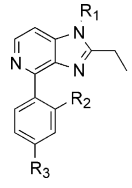
Table 2 lists the physical properties of representative members of the purine, imidazo[4,5-*b*] and imidazo[4,5-*c*]pyridine series that were measured to assess the possibility of salt formulations. The purine core has very low basicity, below the measurement limits. The imidazo[4,5-*b*]pyridine had a modestly higher pK_a value (3.86), while the imidazo[4,5-*c*]pyridine had a pK_a value comparable to pyridine (5.06). These values are substantially different, not influenced dramatically by varying substitution and indicate that the imidazo[4,5-*c*]pyridine core is more likely to give compounds with drug-like properties, such as increased water solubility.

The measured LogP of the imidazo[4,5-*c*]pyridines is also substantially lower to comparable imidazo[4,5-*b*] pyridine.

The analogue **3** was tested in the dog N-in-1 pharmacokinetics model to assess oral bioavailability. The PK parameters are listed below (Table 3).

The data in Table 3 indicate that compound **3** has moderate clearance, a high volume of distribution and a long half life (15 h). Oral dosing at 1 mg/kg in dogs showed a 33% bioavailability.

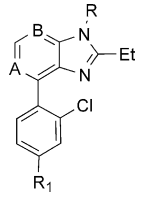
Table 1. Structure–activity relationship of various imidazo[4,5-*c*] pyridine derivatives



Compd	R_1[a]	R_2	R_3	K_i (nM)[b]
1	CH(nPr)Me	Cl	OCF_3	2.8
2 (***R***)	CH(nPr)Me	Cl	OCF_3	1.9
3 (***S***)	CH(nPr)Me	Cl	OCF_3	2.3
4	CH(cPr)Et	Cl	CF_3	2.9
5	CH(nPr)Me	Cl	Cl	3.0
6	CH(nPr)Me	Cl	CF_3	3.5
7	CH(nPr)Me	Me	$OCHF_2$	9.0
8	CH(cPr)Et	CF_3	Cl	4.4
9	$CHEt_2$	Cl	CF_3	5.4
10	CH(nPr)Me	Me	Cl	9.1
11	CH(cPr)Et	Me	Cl	14
12	CHEtMe	Cl	OCF_3	7.8
	a-Helical CRF9-41			7.6

[a]Racemic mixtures unless otherwise indicated.
[b]Values are means of two or more experiments. Receptor binding affinity for all compounds was determined using rat cortical homogenates.

Table 2. Basicity of representative purine, and imidazopyridine analogues



R	A	B	R_1	pK_a	logP
CH(cPr)Me	N	N	Cl	<3.0	4.33
CH(cPr)Et	CH	N	Cl	3.86	5.56
CH(nPr)Me	CH	N	$OCHF_2$	—	5.35
CH(nPr)Me	N	CH	OCF_3	5.09	4.62
CH(cPr)Et	N	CH	Cl	—	4.10

Table 3. Pharmacokinetic parameters in dog ($n=2$) for example **3**[4]

Dose	AUC (nM·h)	Cls (L/h/kg)	Vss (L/kg)	C_{max} (nM)	$t_{1/2}$ (h)
IV (0.2 mg/kg)	341	1.4	19.1	—	15.1
Oral (1 mg/kg)	569	—	—	92.4	9.4

In summary, the imidazo[4,5-*c*]pyridine core represents a new series of CRF receptor ligands with good receptor binding affinity, oral bioavailability, and early measurements suggest lower lipophilicity than the corresponding imidazo[4,5-*b*]pyridine series.

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3. For similar coupling of 2-chloro-3-nitropridines with arylboronic acids see: Mitchell, M. B.; Wallbank, P. J. *Tetrahedron Lett.* **1991**, *32*, 2273. Ali, N. M.; McKillop, A.; Mitchell, M. B.; Wallbank, P. J. *Tetrahedron* **1992**, *48*, 8117.
4. Formulation: iv: 10% (v/v) *N*,*N*-dimethylacetamide, 3% (v/v) ethanol, 65% (v/v) propylene glycol in water; po: 8% (v/v) ethanol, 2% (v/v) *N*,*N*-dimethylacetamide in Labrafil 1944 CS.