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Imidazo[4,5-*b*]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-*b*]pyridine core is described. Individual analogues were synthesized and tested in a rat CRF receptor binding assay. The best compounds were further tested in the dog N-in-1 pharmacokinetic model to assess plasma levels at 1 mg/kg (po) and in the rat situational anxiety model to assess anxiolytic efficacy at 3 mg/kg (po). The structure–activity relationships for good receptor binding affinity are described herein.

Corticotropin releasing factor (CRF) is a 41-amino acid peptide, first isolated, sequenced and characterized by Vale and coworkers at the Salk Institute.[1] It is synthesized in small nuclei of the hypothalamus and acts on 7-transmembrane receptors on the anterior pituitary by inducing the production of adenylyl cyclase. It is the major physiologic regulator of the basal and stress-induced release of ACTH from the pituitary, which stimulates the release of glucocorticoids, such as cortisol, from the adrenal cortex. CRF also mediates behavior by binding to receptors in the frontal cortex and consequently may play a role in major neuropsychiatric disorders, such as anxiety related disorders (panic disorders), post-traumatic stress disorder and depression.[2]

Two CRF receptors have been identified: CRF_1 and CRF_2, the former mainly expressed in the rat brain and the later in the rat periphery. Recent experiments on CRF_1 knock-out mice implicated the involvement of CRF_1 receptors in the stress response.[3]

A potent and selective CRF_1 antagonist will clarify the role of CRF antagonism as an effective therapy for the treatment of depression and/or anxiety.

In the past we described SV030, which possessed a purine core, as a high affinity selective CRF_1 receptor antagonist with good pharmacokinetic parameters.[4] Extending our work aimed toward the discovery and development of novel CRF receptor antagonists we became interested in exploring the corresponding imidazo[4,5-*b*]pyridines **I** as a new series with potentially improved biological and physical properties over the purine based series (Fig. 1).

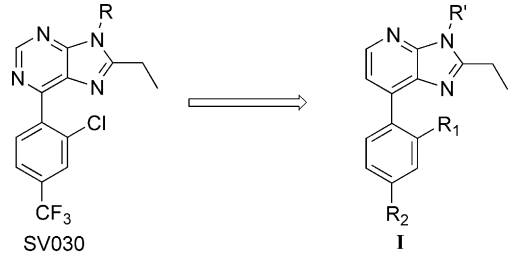

Figure 1. Purine and imidazo[4,5-*b*]pyridine cores.

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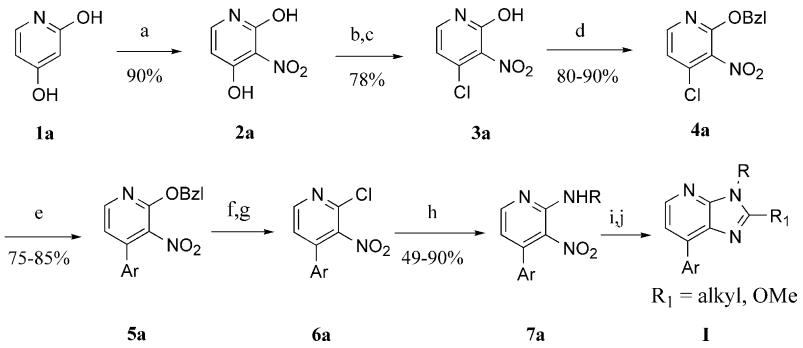


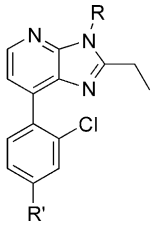
Scheme 1. (a) HNO_3, Δ; (b) cycloheptyl amine, MeOH, Δ; (c) $POCl_3$, 25 °C: (d) Ag_2CO_3, BzlBr, C_6H_6 60 °C, 5 h; (e) $ArB(OH)_2$, $Pd(PPh_3)_2Cl_2$, $Ba(OH)_2$, DME/water, Δ, 5–16 h; (f) CF_3CO_2H, 25 °C, 16 h; (g) $POCl_3$, reflux, 6 h; (h) RNH_2, 2–3 equiv, MeCN, reflux, 16–36 h; (i) $Na_2S_2O_4$, dioxane/water/NH_4OH; (j) R_1CO_2H or R_1CO_2H/ $R_1C(OEt)_3$, Δ, or $EtCO_2H/C(OMe)_4$, 48 h.

The synthesis started from the commercially available 2,4-dihydroxypyridine **1a** which was nitrated to **2a** under the previously described conditions[5] (Scheme 1). The 4-hydroxy group was selectively converted to the 4-chloro by treatment with cycloheptyl amine to form the salt, which was isolated, dissolved in $POCl_3$ and stirred at 25 °C for 24 h. The reaction mixture was poured into ice/water and the precipitated product was filtered off and dried. Attempts to effect a Suzuki or Stille coupling[6] with arylboronic acids or aryltin reagents on **3a** were unsuccessful, presumably because of the acidity of the OH proton. The pyridine **3a** was therefore converted to the corresponding *O*-benzyl ether **4a** utilizing known conditions[7] in good to excellent yields. Aryl chloride **4a** was treated with a variety of substituted arylboronic acids to give the corresponding coupled products **5a**, which were purified by column chromatography on silica gel. The benzyl group was removed by treatment with CF_3CO_2H at 25 °C[8] and after evaporation of CF_3CO_2H under reduced pressure the crude product was converted to the corresponding 2-chloropyridine **6a**, which was purified by column chromatography on silica gel. The 2-chloro substituent was displaced with a branched primary amine to give **7a**, the 3-nitro group was reduced to the corresponding amine and the 2,3-diamino-4-aryl pyridines were converted to the desired product **I** by heating at reflux in propionic acid for 48 h. In the case of the presence of acid sensitive substituents (1-cyclopropyl alkyl chains) the 2,3-diamino-5-arylpyridine intermediates were heated at reflux in triethylorthopropionate in the presence of a catalytic amount $EtCO_2H$ (20% mol).[9] The 2-methoxy imidazo[4,5-*b*]pyridines **I** (R_1 = OMe) were synthesized by heating at reflux the 2,3-diamino-4-arylpyridine intermediates with tetramethyl orthocarbonate in the presence of a catalytic amount of $EtCO_2H$.

Modifications were made on the side chains, 2-substituents and aryl groups based on previous SAR developed in the purine series. Individual compounds were tested in vitro in the rat receptor binding assay as previously described[10] and the data are summarized in Table 1.

Data on Table 1 indicate that the best R groups for optimal receptor interaction are small lipophilic alkyl groups (**1**–**8**), however polar groups on the alkyl chains,

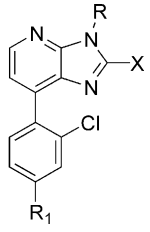
Table 1. Chains on the 1-position of the imidazo[4,5-*b*]pyridine core



Compd	R[a]	R′	K_i (nM)[b]	SD
1	CH(cPr)Me	Cl	0.6	0.3
2(*R*)[c]	CH(cPr)Et	Cl	0.2	—
2′(*S*)[c]	CH(cPr)Et	Cl	0.4	—
3	CH(cBu)Me	Cl	1.0	0.3
4	CH(nPr)Me	Cl	0.5	0.3
5	CHEtMe	Cl	1.3	0.3
6	$CHEt_2$	Cl	1.0	0.2
7	$CH(cPr)C_2H_4OMe$[11]	Cl	1.5	0.7
8	$CH(cBu)C_2H_4OMe$	Cl	2.4	0.9
9	$CH(Et)CH_2OMe$	CF_3	4.7	1.1
10	$CH(Et)C_2H_4OMe$	CF_3	0.7	0.3
	α-Helical CRF(9-41)		7.6	0.8

[a]Racemic mixtures.
[b]Values are means of two or more experiments. Receptor binding affinity for all compounds was determined using rat cortical homogenates. SD, standard deviation.
[c]Single determination.

Table 2. The 2-position group on the imidazopyridine core



Compd	R	X	R_1	K_i[a]	SD
11	$CH(Et)C_2H_4OMe$	OMe	OCF_3	1.9	0.1
12	$CH(Et)C_2H_4OMe$	cPr	CF_3	20.8	5.9
13	CH(nPr)Me	CHF_2	Cl	15.8	2.6
14	$CH(Et)C_2H_4OMe$	CH_2OMe	CF_3	82.7	48

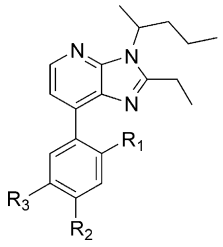
[a]Values are means of two or more experiments. Receptor binding affinity for all compounds was determined using rat cortical homogenates. SD, standard deviation.

such as OMe can be accomodated in high receptor affinity ligands (e.g., **7**–**10**).

Substituents were introduced on the 2-position using procedures described in Scheme 1. Data are listed in Table 2 and indicate that the only good replacement for an ethyl chain is a methoxy group (**11**). Small increases in size to a cyclopropyl or difluoromethyl (**12** and **13**) led to drastic reduction in affinity. Further increases in size to a methoxymethyl group gave a compound with modest affinity (**14**).

After exploring the 2-position, we turned our efforts on the optimization of the substitution on the 7-aryl ring. We wanted to introduce substitution that would maintain receptor affinity, while improving physical properties such as reducing lipohilicity.

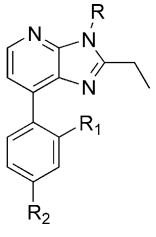
Table 3. The SAR of various aryl groups



Compd	R_1	R_2	R_3	K_i (nM)[a]	SD
15	Cl	CF_3	H	1.1	0.7
16	CF_3	OMe	H	0.7	0.0
17	Me	OMe	H	0.8	0.3
18	CF_3	SMe	H	1.4	0.1
19	Me	OMe	Me	0.6	0.2
20	Cl	F	F	2.4	0.6
21	COMe[12]	Cl	H	95.6	—
22	Cl	COMe[13]	H	1.0	0.2
23	Cl	CH(OH)Me	H	5.1	1.1
24	Cl	$C(OH)Me_2$	H	24.0	0.4
25	Cl	CH(OMe)Me	H	3.5	0.2
26	CF_3	SO_2Me	H	6.8	1.3
27	Cl	C(Me)NOMe	H	2.3	0.1

[a]Values are means of two or more experiments, except **21**. Receptor binding affinity for all compounds was determined using rat cortical homogenates. SD, standard deviation.

Table 4. Dog N-in-1 pharmacokinetic parameters[14] at 1 mg/kg and rat situational anxiety model efficacy for selected compounds



R	R_1	R_2	K_i (nM)	AUC (nM)	C_{max} (nM)	$T_{1/2}$ (h)	Situational anxiety ED_{50}
CH(nPr)Me	CF_3	OMe	0.7	182	62	5.9	3 mpk (po)
CH(nPr)Me	Cl	CF_3	1.1	604	159	4.9	3 mpk (po)
CH(cBu)Me	Cl	OCF_2	0.7	795	185	10	<3 mpk (po)

Data in Table 3 indicate that binding affinity is primarily dependent on the size than polarity of the phenyl substituents. The 2-aryl position has very stringent steric requirements and replacement of the 2′- Cl with an acetyl led to drastic reduction in affinity (**21**). The 4′-aryl position can tolerate a larger number of substituents with various functionalities such as OMe, COMe, SO_2Me, SMe and CH(OH)Me.

The best compounds with respect to binding affinity and physical properties (ClogP) were tested in the dog N-in-1 pharmacokinetics at 1 mg/kg po and in the rat situational anxiety model at 3 mg/kg po to assess anxiolytic efficacy. Data for three compounds are listed in Table 4.

Table 4 shows that two of the compounds showed good plasma levels in the dog N-in-1 study. Plasma concentration was dependent on substitution and the 4-methoxyphenyl group seemed to give the lowest exposure. All of the compounds showed efficacy in the rat situational anxiety model at 3 mpk po.

In conclusion the 4-arylimidazo[4,5-*b*]pyridine series represent a new series of potent CRF receptor ligands. Additionally, certain analogues possessed good oral bioavailability in dog at 1 mg/kg po and showed efficacy in the rat situational anxiety model.

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11. Synthesized from the oxime methyl ether of cyclo-propyl methy lketone by deprotonation with *n*BuLi followed by alkylation with bromomethylmethylether according to the protocol developed by: Shatzmiller, S. *Dolitzki, B-Z. Liebigs Ann. Chem.* **1991**, 189. The alkylated oxime methylether was purified by distillation under reduced pressure and reduced with LiAlH4 in refluxing THF.
12. Synthesized from dichlorophenyl **3** by a Stille coupling with ethoxyvinyl tri-*n*-butyl tin using 2.5% $Pd(PPh_3)_4$ and 2.5% $Pd(PPh_3)_2Cl_2$ in refluxing toluene, followed by acid hydrolysis. Coupling of the 4-Cl was not observed, presumably because of the directing effect of the imidazole N.
13. Synthesized from intermediate **6a** (Ar = 2,4-Cl_2Ph) using the same conditions as ref 12. In this case the coupling of the 4-Cl was selective (~6:1 over 2-Cl) presumably because of the weaker complexing ability of the nitro group.
14. 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.