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CRF Ligands Via Suzuki and Negishi Couplings of 3-Pyridyl Boronic Acids or Halides with 2-Benzyloxy-4-chloro-3-nitropyridine

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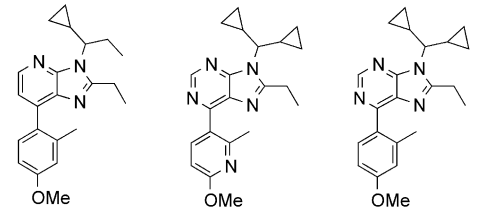
Abstract—A series of imidazo[4,5-*b*]pyridines with a 7-(3-pyridyl) substituent is described as high affinity CRF receptor ligands. Individual analogues were synthesized from key intermediates obtained via palladium-catalyzed coupling of 3-pyridyl zinc or boronic acid organometallic intermediates with 2-benzyloxy-4-chloro-3-nitropyridine **12**.

In a previous communication we described a 7-phenyl-imidazo[4,5-*b*]pyridine series as potent CRF receptor ligands.[1] Several of these compounds had high affinity ($K_i \leq 1$ nM) for the rat CRF receptor, as well as good pharmacokinetic parameters. In general, these compounds were rather lipophilic with limited water solubility, and introduction of a pyridine ring in the place of the phenyl substituent was pursued to improve these properties.

A 3-pyridyl ring can be accommodated in that position without loss of affinity, as has been demonstrated in the corresponding purine series, where the phenyl and 3-pyridyl analogues were equipotent (Fig. 1, compounds **II** and **III**).[2]

In order to synthesize and evaluate these analogues of **I** we needed to develop a synthesis for the new pyridyl key 4-(3-pyridyl)pyridine intermediates **1** which is described in Scheme 1. Because of the reactivity of 2-halo pyridines toward nucleophilic substitution we decided to introduce (2-methyl-6-methoxy) and (2-trifluoromethyl-6-methoxy)-3-pyridyl substituents as phenyl replacements.

3-Bromo-6-methoxy-2-methylpyridine **9** was coupled with **12** under Negishi coupling conditions[3] to give **1b**.



I $K_i = 0.5$ **II** $K_i = 1.8$ **III** $K_i = 1.9$

Figure 1. Activity of an imidazo[4,5-*b*]pyridine (in nM) compared to purines with and without a 3-pyridyl.

In the case of 3-iodo-6-methoxy-2-trifluoro-methyl-pyridine **10**,[4] attempts to effect Li–I exchange, followed by $ZnCl_2$, were unsuccessful under standard conditions (*n*BuLi, *s*BuLi, and *t*BuLi), presumably because of the instability of the lithiated species that was generated. Similar attempts with the corresponding bromide were also unsuccessful. However, treatment of the iodide **10** with commercial Rieke Zn®, followed by $Pd(PPh_3)_4$ catalyzed coupling to **12** afforded **1c** in good yield.[5] Negishi or Rieke Zn® conditions were not successful in coupling the 5-bromo- or 5-iodo-2-methoxy-4-methyl pyridine with **12**.[6] 5-Bromo-2-methoxy-4-methyl pyridine **8** was converted to the corresponding 5-boronic acid **11** by treatment with *n*BuLi, followed by isopropyl borate,[7] then acidic aqueous workup. Compound **11** was coupled with **12**, under Suzuki coupling conditions[8] to give **1a**.

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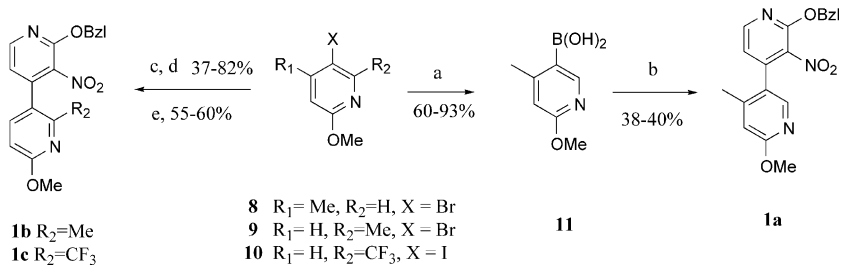
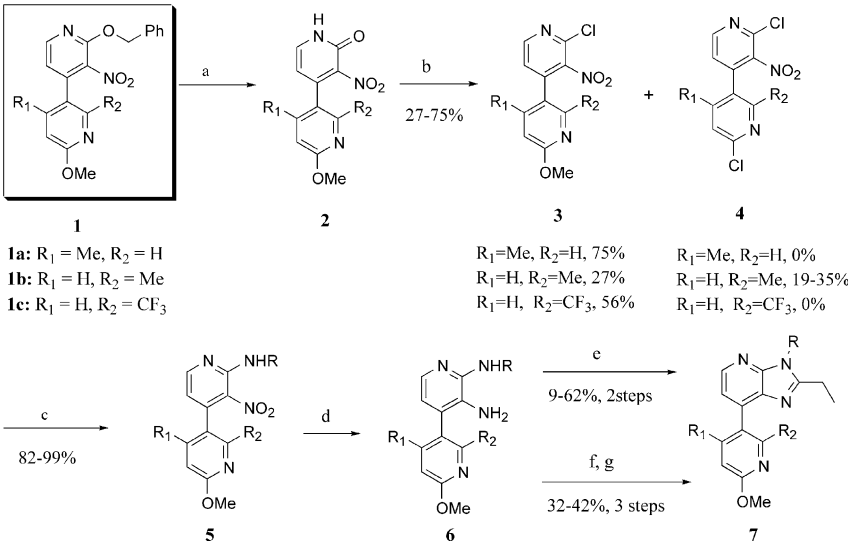


Scheme 1. (a) $B(OiPr)_3$, *n*BuLi, −90 °C; HCl; (b) 2-BzlO-4-Cl-3-NO_2-pyridine (**12**), $Pd(PPh_3)_2Cl_2$, $Ba(OH)_2{\cdot}8H_2O$, DME/water, reflux 18 h; (c) *n*BuLi, THF, −78 °C; $ZnCl_2$; (d) **12**, reflux; (e) Rieke Zn®, THF, **12**, 25 °C; $Pd(PPh_3)_4$, reflux.

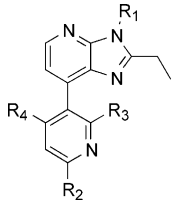


Scheme 2. (a) TFA, 25 °C, 2 h; (b) $POCl_3$, reflux, 4 h; (c) RNH_2, MeCN, 80 °C sealed vial, 48 h; (d) $Na_2S_2O_4$, NH_4OH, dioxane/water, 25 °C, 18 h; (e) $EtCO_2H$, reflux, 48 h; (f) $EtCO_2H$, $EtC(OEt)_3$, reflux, 18 h; (g) $EtCO_2H$, toluene, reflux, 18 h.

The general synthetic route for the synthesis of the target analogues is described in Scheme 2. The key intermediates 2-benzyloxy-3-nitro-4-(3-pyridyl)pyridines **1** were deprotected in TFA to give the pyridones **2**, which were converted to the corresponding chloropyridines **3** in refluxing $POCl_3$. In one case, the formation of dichloropyridine **4** was observed as a contaminant due to cleavage of the methyl ether and subsequent conversion of the pyridone to the chloropyridine. Intermediates **3** were reacted with the appropriate primary branched amines to give compounds **5**, which were reduced with $Na_2S_2O_4$ and cyclized to the imidazo[4,5-*b*]pyridines **7**.

Binding affinities of various analogues synthesized are listed in Table 1. Data on Table 1 indicate that several analogues possess high affinity. Generally analogues with the 2′-trifluoromethyl group (**7a**–**7e**) are more potent than the corresponding analogues with a 2′-methyl group (**7i**–**7m**). *O*-Demethylation led to diminished affinity (**7f** and **7q**) which was not recovered with introduction of a large substituent (**7g**). The affinity could be increased by reduction of the ester functionality to the corresponding alcohol (**7h**). Generally affinity of the 2′-methyl analogues (**7i**–**7m**) seemed to be more sensitive to the alkyl substitution (R_1) than the 2′-trifluoromethyl analogues and the 1-cyclopropylpropyl chain was optimal (**7i**). On the 6′-position the methoxy substituent was optimal, since replacing it with chloro- or *N*,*N*-dimethyamino led to compounds of lower affinity (**7n** and **7p**, respectively).

Table 1. Biological data of 3′-pyridyl analogues[b]



Compd	R_1[a]	R_2	R_3	R_4	K_i (nM)
7a	–CH(Me)Pr	OMe	CF_3	H	0.6
7b	–CH(Me)Et	OMe	CF_3	H	0.7
7c	–CH(cPr)Et	OMe	CF_3	H	0.7
7d	–CH(cBu)Me	OMe	CF_3	H	0.8
7e	–CH(C_2H_4OMe)Et	OMe	CF_3	H	1.6
7f[9]	–CH(Me)Pr	OH	CF_3	H	602
7g[10]	–CH(Me)Pr	OCH_2CO_2Et	CF_3	H	1045
7h	–CH(Me)Pr	OC_2H_4OH	CF_3	H	10.1
7i	–CH(cPr)Et	OMe	Me	H	0.7
7j	–CH(Me)Pr	OMe	Me	H	1.1
7k	–CH(cPr)Me	OMe	Me	H	2.0
7l	–CH(cBu)Me	OMe	Me	H	2.1
7m	–CH(Me)Et	OMe	Me	H	9.2
7n	–CH(cPr)Et	Cl	Me	H	3.3
7o	–CH(Me)Pr	Cl	Me	H	6.6
7p	–CH(cPr)Et	NMe_2	Me	H	7.5
7q	–CH(Me)Pr	OH	Me	H	>10,000
7r	–CH(Me)Pr	OMe	H	Me	17.1
	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.

Finally the 4′-methyl analogue (**7r**) had significantly lower affinity than the corresponding 2′-methyl analogue (**7j**).

In summary, a series of 7-(3-pyridyl)imidazo[4,5-*b*]pyridines was explored and individual compounds were identified with high affinity for the rat CRF receptor. Physical and biological data will be described in subsequent publications.

Acknowledgements

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References and Notes

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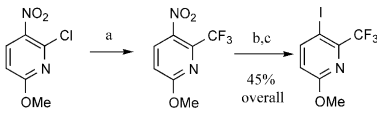
3. To 5-bromo-2-methoxy-6-methylpyridine (6.0 g, 29.7 mmol) in 100 mL dry THF (−78 °C) was added *n*-BuLi (1.6M/hexanes, 20.4 mL, 32.7 mmol) dropwise, via addition funnel. The reaction was stirred 30 min and then $ZnCl_2$ (0.5 M/THF, 59.4 mL, 29.7 mmol) was added dropwise, via addition funnel. The reaction was warmed to 0 °C, and tetrakis(triphenylphosphine)palladium(0) (172 mg, 0.149 mmol) and 2-beznyloxy-4-chloro-3-nitropyridine (3.93 g, 14.85 mmol) were added. The reaction was then heated at reflux for 5 h, after which time it was concentrated in vacuo. The crude product was partitioned between ethyl acetate and 1 M EDTA disodium (aq). The ethyl acetate was washed with brine, dried and concentrated. The residue was chromatographed on silica gel using ethyl acetate/hexane (1:4) as eluent. 4.28 g, 12.1 mmol, 82% yield.
4. The 3-iodo-6-methoxy-2-trifluoromethylpyridine was synthesized by the following scheme.



(a) $ClCF_2CO_2Me$, CuI, KF, DMF 130 °C; (b) $Na_2S_2O_4$, NH_4OH, dioxane/water, 25 °C, 48 h; (c) $NaNO_2$, HCl; KI, water/cyclohexane.

The commercially available 2-chloro-6-methoxy-3-nitropyridine **13** (14.83 g, 78.06 mmol) was heated with CuI (18.74 g, 95.23 mmol), KF (5.51 g, 95.25 mmol) and ClF_2CO_2Me (18.72 mL, 181.48 mmol) in 74 mL DMF at 125–130 °C for 5 h. After cooling it was poured into a 1:9 mixture of NH_4OH/NH_4Cl (300 mL), stirred until homogeneous and extracted with EtOAc (3×250 mL). The organic extracts were washed with brine, dried and stripped in vacuo to give **14**. These reaction conditions have been employed for the conversion of aryl bromides and iodides to CF_3 groups (Su, D.-B.; Duan, J.-X.; Chen, Q.-Y. *Tetrahedron Lett*., **1991**, *32*, 7689). To our knowledge, these conditions have not been previously reported in the literature for the conversion of a 2-Cl–3-NO_2 pyridine to the 2-CF_3–NO_2 pyridine.

The nitro group was reduced with $Na_2S_2O_4$ and the corresponding amine was converted to the iodide **15** under standard conditions in 45% yield after column chromatography.
5. The iodide **13** (2.0 g, 6.6 mmol) was dissolved in dry THF (11 mL) and a suspension of Rieke Zn® in THF (9 mL, 6.86 mmol) was added. The mixture was stirred vigorously for 20 min, allowed to settle for 5 min and the supernatant was transferred into a dry flask containing $Pd(PPh_3)_4$ (202 mg, 0.176 mmol) and **12** (858 mg, 3.36 mmol) and heated to reflux for 24 h. The mixture was filtered through Celite, extracted with EtOAc and the organic solution was dried and stripped in vacuo. The product was purified by silica gel chromatography (15% EtOAc/hexanes eluent), and crystallized from hexanes, 1.15 g, 56% yield. For other zinc-mediated couplings of 3-iodopyridines, see: Sakamoto, T.; Kondo, Y.; Murata, N.; Yamanaka, H. *Tetrahedron Lett*. **1992**, *33*, 5373. Sakamoto, T.; Kondo, Y.; Murata, N.; Yamanaka, H. *Tetrahedron* **1993**, *49*, 7913.
6. Gray, M. A.; Konopski, L.; Langlois, Y. *Synth. Commun.* **1994**, *24*, 1367.
7. To 5-bromo-2-methoxy-4-methylpyridine (3.5 g, 17.3 mmol) and tri-isopropylborate (5.0 mL, 21.7 mmol) in 50 mL dry THF (−100 °C) was added *n*-BuLi (1.6 M/hexanes, 11.9 mL, 19.0 mmol) dropwise. The reaction was stirred at −100 °C for 1.5 h, warmed slowly to room temperature (1 h), and stirred 18 h. To the reaction was then added 1 N HCl and the reaction stirred for 1 h. The pH was adjusted to 9 with NaOH, and the mixture was extracted with ethyl acetate and ether. The pH of the aqueous layer was then adjusted to 7, and again extracted with ethyl acetate. All the extracts when concentrated contained the desired product. 2.7 g, 93% yield.
8. 2-Benzyloxy-4-chloro-3-nitropyridine (198 mg, 0.749 mmol), the pyridyl boronic acid (150 mg, 0.898 mmol), bis(triphenylphosphine)palladium(II) chloride (26 mg, 0.037 mmol), ethylene glycol dimethyl ether (2.5 mL), water (2.5 mL), and barium hydroxide octahydrate (282 mg, 0.898 mmol) were combined, degassed under vacuum, and heated at reflux 18 h. To the cooled reaction was added water, which was extracted with ethyl acetate. The ethyl acetate was washed with brine, dried and concentrated. the residue was chromatographed on silica gel using ethyl acetate/hexane (1:4) as eluent, yielding 105 mg, 40% yield.
9. Synthesized from **7a** by treatment with 48% HBr at 110 °C for 16 h.
10. Synthesized from **7f** by treatment with $Ag_2CO_3/BrCH_2CO_2Et/C_6H_6$. The regiochemistry of the **7g** was established by NOE experiments.