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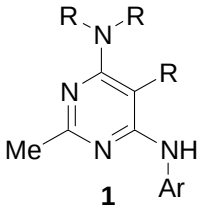
SYNTHESIS OF PYRROLOPYRIMIDINE CRF-R1 ANTAGONISTS CONTAINING A TRICYCLIC CORE *VIA* AN INTRAMOLECULAR HECK REACTION

Brian Dyck* and James R. McCarthy[†]

Department of Medicinal Chemistry, Neurocrine Biosciences, Inc., 10555 Science Center Drive, San Diego, CA 92121, USA

Abstract – A synthetic route to pharmaceutically important tricyclic pyrrolopyrimidines was developed. The method employs a palladium-mediated Heck cyclization as the critical step in the construction of the final six membered ring.

The corticotropin-releasing factor (CRF) peptide/receptor system plays an important role in regulating mammalian stress response, in addition to its participation in other significant biological pathways.[1] The attenuation of signaling through the CRF receptor 1 (CRF-R1) has been postulated to be the next frontier in the treatment of anxiety and depression and, consequently, is an actively pursued target by many drug companies. Among the many reported potent antagonists of the CRF-R1 receptor are pyrimidines (**1**)[2] and pyrrolopyrimidines (**2**).[3,4] We believed that introducing an additional ring to afford compounds of general structure (**3**) would result in an increase in basicity of the pyrimidine nitrogen atoms. It was postulated that this modification would provide the ligand with a more suitable pharmacokinetic profile and, therefore, we pursued the synthesis of this structural class of CRF-R1 ligands.



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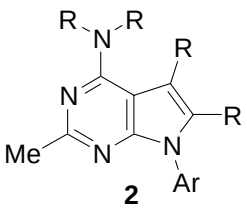

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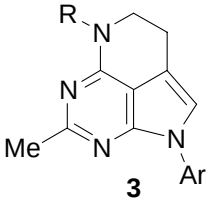

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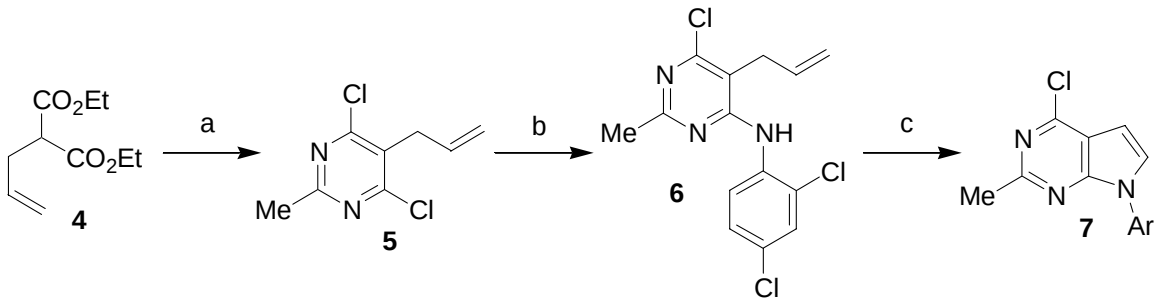
The synthesis of the bicyclic pyrrolopyrimidine core is described in Scheme 1. Heating a mixture of diethyl allylmalonate (**4**), acetamidine hydrochloride and sodium methoxide in refluxing methanol afforded

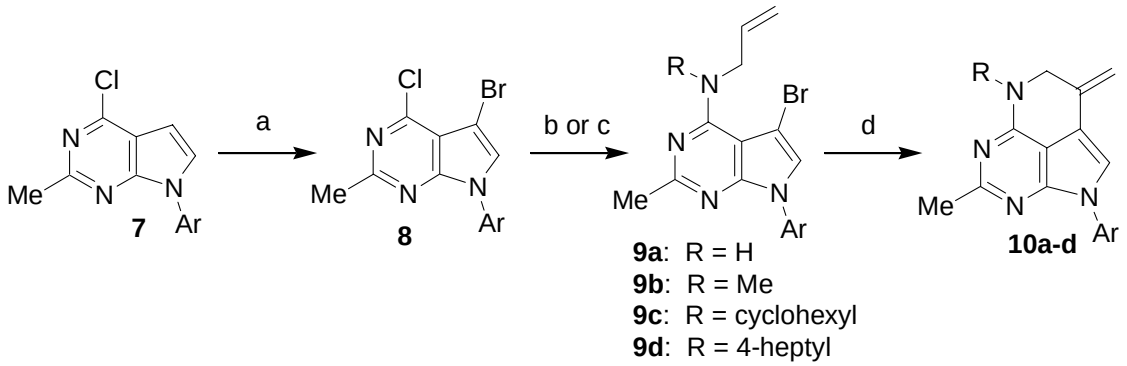
[†] Current address: Lilly Corporate Center, Eli Lilly and Company, Indianapolis, Indiana, USA 46285.

the intermediate dihydrohydroxypyrimidone, which was heated in phosphorus oxychloride to provide the known dichloropyrimidine (**5**) as a colorless oil.[5] The symmetry of **5** renders the chlorine atoms chemically equivalent, so treatment with the sodium salt of 2,4-dichloroaniline in DMF gave the unique isomer (**6)**. Dichlorophenyl was chosen as a representative substituent because it was assumed to be inert to subsequent manipulations and this group is present in some of the most potent examples of **1** and **2**. Having installed the 2,4-dichlorophenylamino group, the unconjugated vinyl group was subjected to oxidative cleavage with osmium tetroxide and sodium periodate. The resulting aldehyde spontaneously cyclized to a hemiaminal, which was treated with acid to effect dehydration and generate pyrrolopyrimidine (**7**).



Scheme 1. (a) (i) acetamidine hydrochloride, NaOMe, MeOH, reflux; (ii) $POCl_3$, reflux (30%, 2 steps);[5] (b) 2,4-dichloroaniline, NaH, DMF (37%); (c) (i) OsO_4, $NaIO_4$, acetone, H_2O; (ii) 37% HCl, DCM (53%, 2 steps).

With the central aromatic bicyclic core in place, it remained to construct the final saturated ring. It was anticipated that this could be accomplished *via* a palladium-mediated cyclization of the aryl bromide onto the olefin of key intermediate (**9**), which was prepared from pyrrolopyrimidine (**7**).[6] The chlorine atom of **7** was readily displaced with nucleophilic amines under acidic catalysis to afford compound (**8**), but the reaction failed with hindered secondary amines. However, when **7** was first brominated, the resulting nucleophilic displacement proceeded much more readily, indicating that although the chlorine-substituted carbon atom is necessarily more hindered due to the presence of the proximal bromine atom in **8**, the decreased electron density on this carbon atom results in a net increase in substitution rate. Unfortunately, even for the activated ring system of **8**, very hindered amines provided only modest yields of the products. For example, allylcyclohexylamine afforded only 17% of **9c**. Therefore, in the case of the 4-heptylamine analog, it was found that more satisfactory yields could be obtained by displacing with 4-heptylamine, and subsequently allylating the secondary nitrogen atom under basic conditions to afford **9d**.



Scheme 2. (a) Br_2, dioxane (100%); (b) allylalkylamine, TsOH, reflux (**9a**, 100%; **9b**, 60%; **9c**, 17%); (c) (i) 4-heptylamine, TsOH, 90°C (70%); (ii) NaH, allyl iodide, DMF (**9d**, 58%); (d) $Pd(TPP)_4$, KOAc, DMF, 85°C (**10a**, 0%; **10b**, 43%; **10c**, 52%; **10d**, 86%).

The *N*-alkylated cyclization substrates readily underwent the intramolecular Heck reaction under standard conditions. Heating compounds (**9b-d**) with tetrakis(triphenylphosphine)palladium(0) in degassed DMF at 85°C afforded good yields of the cyclized products. Under these conditions, **9a** failed to react, suggesting that the free NH group interferes with the reaction. An alternative explanation is based on the observation that the cyclization reaction proceeds in higher yield in proportion to the size of the substituent on the allylated nitrogen atom. This could be a consequence of larger groups forcing the olefin closer to the reacting carbon-bromine bond. If this is the case, then the absence of any steric-induced rate acceleration by the NH group could be the cause of the lack of product formation. It is also important to note that a one hour reaction time is optimal for the substrates that do undergo the reaction, otherwise equilibration of the exocyclic methylene to its endocyclic isomer begins to occur.

Pyrimidines (**10b**) and (**10c**) were inactive against *h*CRF-R1 (inhibition < 50% at 10 μM).[7] However, by incorporating a 4-heptyl substituent on the nitrogen of the piperidine ring, a substantial improvement in activity was achieved. Compound (**10d**) possesses a K_i of 7.8 nM, clearly demonstrating that this series of tricyclic-based antagonists is comparably potent to its monocylic (**1**) and bicyclic (**2**) counterparts.

In summary, we have accomplished the synthesis of analogs of pyrimidines (**1**) and pyrrolopyrimidines (**2**) containing a tricyclic core. This was accomplished in 7 steps from the known 5-allyl-4,6-dichloro-2-methylpyrimidine (**5**). These compounds prove to be interesting variations on the pyrimidine core of known CRF-R1 ligands with potent binding affinity and altered pharmacokinetic parameters. Additional biological properties of these molecules will be reported in due course.

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7. The *h*CRF-R1 binding assay was performed as previously described.[2]
8. Characterization data for key compounds. Compound (**6**): mp 94-95^{o}C; ^{1}H NMR ($CDCl_3$) δ 8.53 (d, *J* = 8.7 Hz, 1 H), 7.40 (d, *J* = 2.4 Hz, 1 H), 7.28 (dd, *J* = 8.9, 2.6 Hz, 1 H), 7.22 (br s, 1 H), 5.97-5.84 (m, 1 H), 5.30-5.23 (m, 2 H), 3.58 (dt, *J* = 6.0, 1.5 Hz, 2 H), 2.58 (s, 3 H); MS (APCI) *m/z* (MH^+) 328. Compound (**7**): mp 150-151^{o}C; ^{1}H NMR ($CDCl_3$) δ 7.62 (t, *J* = 1.2 Hz, 1 H), 7.45-7.44 (m, 2 H), 7.28-7.26 (m, 1 H), 6.73 (d, *J* = 3.6 Hz, 1 H), 2.71 (s, 3 H); MS (APCI) *m/z* (MH^+) 312. Compound (**8**): ^{1}H NMR ($CDCl_3$) δ 7.62 (d, *J* = 2.1 Hz, 1 H), 7.43 (d, *J* = 1.8 Hz, 1 H), 7.42 (s, 1 H), 7.32 (s, 1 H), 2.70 (s, 3 H); MS (APCI) *m/z* (MH^+) 390/392. Compound (**9b**): ^{1}H NMR ($CDCl_3$) δ 7.57 (d, *J* = 2.1 Hz, 1 H), 7.43-7.36 (m, 2 H), 7.10 (s, 1 H), 6.08-5.97 (m, 1 H), 5.34-5.23 (m, 2 H), 4.30 (d, *J* = 6.0 Hz, 2 H), 3.23 (s, 3 H), 2.50 (s, 3 H); MS (APCI) *m/z* (MH^+) 425/427. Compound (**9c**): ^{1}H NMR ($CDCl_3$) δ 7.57 (d, *J* = 2.1 Hz, 1 H), 7.41-7.36 (m, 2 H), 7.11 (s, 1 H), 6.02-5.90 (m, 1 H), 5.26 (dd, J = 17.3, 1.7 Hz, 1 H), 5.04 (dd, J = 10.4, 1.4 Hz, 1 H), 4.28-4.21 (m, 3 H), 2.47 (s, 3 H), 1.95-1.06 (10 H), MS (APCI) *m/z* (MH^+) 493/495. Compound (**9d**): mp 86-88^{o}C; ^{1}H NMR ($CDCl_3$) δ 7.56 (d, *J* = 2.1 Hz, 1

H), 7.42 (d, *J* = 8.4 Hz, 1 H), 7.37 (dd, *J* = 8.7, 2.1 Hz, 1 H), 7.08 (s, 1 H), 6.07 (m, 1 H), 5.24 (dd, *J* = 16.2, 1.8 Hz, 1 H), 5.07 (dd, *J* = 10.2, 1.5 Hz, 1 H), 4.51 (quintet, *J* = 7.1 Hz, 1 H), 4.24 (d, *J* = 5.7 Hz, 2 H), 2.45 (s, 3 H), 1.85-1.72 (m, 2 H), 1.65-1.53 (m, 4 H), 1.38-1.12 (m, 2 H), 0.85 (t, *J* = 7.2 Hz, 6 H); MS (APCI) *m/z* (MH^+) 509/511. Compound (**10b**): ^{1}H NMR ($CDCl_3$) δ 7.57 (d, *J* = 2.1 Hz, 1 H), 7.49 (d, *J* = 8.7 Hz, 1 H), 7.39 (dd, *J* = 8.6, 2.3 Hz, 1 H), 7.01 (s, 1 H), 5.41 (s, 1 H), 5.13 (s, 1 H), 4.20 (s, 2 H), 3.24 (s, 3 H), 2.59 (s, 3 H); MS (APCI) *m/z* (MH^+) 345. Compound (**10c**): ^{1}H NMR ($CDCl_3$) δ 7.57 (d, *J* = 2.1 Hz, 1 H), 7.48 (d, *J* = 8.7 Hz, 1 H), 7.38 (dd, *J* = 8.6, 2.3 Hz, 1 H), 6.99 (s, 1 H), 5.38 (s, 1 H), 5.13 (s, 1 H), 4.72-4.60 (m, 1 H), 4.16 (s, 2 H), 2.57 (s, 3 H), 1.92-1.69 (m, 4 H), 1.68-1.47 (m, 4 H), 1.29-1.20 (m, 2 H); MS (APCI) *m/z* (MH^+) 413. Compound (**10d**): ^{1}H NMR ($CDCl_3$) δ 7.57 (d, *J* = 2.4 Hz, 1 H), 7.49 (d, *J* = 8.4 Hz, 1 H), 7.38 (d, *J* = 8.6 Hz, 1 H), 6.98 (s, 1 H), 5.38 (s, 1 H), 5.12 (s, 1 H), 4.96-4.90 (m, 1 H), 4.03 (s, 2 H), 2.54 (s, 3 H), 1.71-1.46 (m, 4 H), 1.32 (hextet, *J* = 7.5 Hz, 4 H), 0.92 (t, *J* = 7.4 Hz, 6 H); MS (APCI) *m/z* (MH^+) 429.