FIRST SYNTHESIS OF PIPERAZINE-DERIVED [1,2,4]TRIAZOLO[1,5-a]PYRAZINE AS AN ADENOSINE A2A RECEPTOR ANTAGONIST


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Abstract – Synthesis of piperazine-derived 2-furan-2-yl-[1,2,4]triazolo[1,5-a]pyrazines was achieved using methyl 3-amino-2-pyrazinecarboxylate. Introduction of the piperazine to the pyrazine template was achieved through a pteridin-4-one intermediate (7). Cyclization of the [1,2,4]triazolo[1,5-a]pyrazine ring was accomplished by amination of pyrazine (8) followed by condensation with 2-furaldehyde. Curtius rearrangement installed the amine to afford template (11). As one example of derivatizing 11, 6N-(4-(2,4,6-trifluorobenzyl)piperazin-1-yl)-2-(furan-2-yl)-[1,2,4]triazolo-[1,5-a]pyrazin-8-amine (12) showed moderate adenosine A2a receptor binding affinity and selectivity over the A1 receptor.

In recent years, significant effort has been directed at the development of adenosine A2a receptor antagonists because of their potential for the treatment for Parkinson’s disease.1 As represented by compounds in Figure 1, a variety of bicyclic or tricyclic heterocyclic templates have been discovered as potent A2a antagonists.2-7 Effort in our lab to develop adenosine A2a antagonist has led to the recent disclosure of several diamine-derived triazolotriazine and triazolopyrimidine series as highly potent and selective A2a antagonists, some of them showed good oral efficacy in rodent models of Parkinson’s disease.8-10 The diamines along with their capping groups in these antagonists were shown to be instrumental to the favorable in vitro/in vivo activities observed.8-10 In hope to achieve improved potency, selectivity and oral efficacy, we have recently developed a novel [1,2,4]triazolo[1,5-a]pyrazine template (4) (Scheme 1). However, introduction of diamine through Pd-catalyzed amination, to the 6-position of this
template, was found to be very difficult. We report here the first synthesis of a piperazine
derived-triazolopyrazine as an adenosine $A_{2a}$ antagonist.\textsuperscript{8-10}

**Figure 1**

![Chemical structures of CGS-15943, ZM-241385, SCH-58261, and BIO-012817](images)

The initial attempts to the synthesis of piperazine-derived [1,2,4]triazolo[1,5-$\alpha$]pyrazine were directed at
amination of bromide (4) using Buchwald/Hartwig conditions for the ease of preparing bromide (4),\textsuperscript{11} as
well as for our previous success on Sonogashira\textsuperscript{11} and Suzuki\textsuperscript{12} couplings with this bromide under standard
Pd-catalyzed conditions (Scheme 1). However, we encountered significant difficulties with Pd-catalyzed
amination of triazolopyrazinyl bromide (4). Intensive screening of a variety of ligands, catalyst-ligand-base
combinations, and solvents\textsuperscript{13-20} was unsuccessful, mostly resulting in decomposition or recovery of the
uncoupled starting materials. (Some examples\textsuperscript{24} are shown in Table 1, Entries 1-9). Converting the bromide
to chloride, iodide or triflate did not solve the problem. Protection of the 8-amine as an imide did not
improve the coupling reaction, either.

**Scheme 1**

![Chemical structures and reactions](images)
Although the results were discouraging, it is not surprising since the current scope of transition metal-catalyzed amination of heteroaromatic halides with alkyl amines is still limited, especially for aryl halides containing functional groups with acidic protons, such as hydroxyl, amide, or enolizable keto groups. The problem that we encountered likely arose from the presence of an acidic proton at the 5-position, in addition to the 8-amine. Proton signals from both positions disappeared in NMR spectrum when using methanol-d₄ as solvent. Eventually, we decided to synthesize piperazinyltriazolopyrazines from scratch by introducing piperazinyltriazolopyrazines before cyclizing the furanyltriazole.

We envisioned a retrosynthetic strategy (Scheme 2) whereby the amino group at the 8-position of 12 may arise from the carboxylate of the pyrazine intermediate (9). The furanyltriazolo ring in 9 would be installed by amination of the pyrazine (8) followed by condensation with 2-furaldehyde. Intermediate (8) would be available via piperazinyltriazolopyrazines from scratch by introducing piperazinyltriazolopyrazines before cyclizing the furanyltriazole.

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With 8 in hand, we then pursued incorporation of the furanyltriazole. Since our previous report\textsuperscript{11} on the synthesis the furanyltriazole moiety in compound (4), we have improved the procedure by using acid-catalyzed condensation of the aminopyrazine with 2-furonitrile, followed by oxidation/cyclization using lead tetraacetate.\textsuperscript{12} Unfortunately, we were not able to convert 8 to 9 using 2-furonitrile and AlCl\textsubscript{3}, or milder Lewis acids such as TiCl\textsubscript{4} and Et\textsubscript{2}AlCl. Base-catalyzed conditions using potassium tert-butoxide were also unsuccessful. Therefore, we turned our attention to the amination-condensation-cyclization method using O-mesitylsulfonylhydroxylamine and 2-furaldehyde. Treatment of pyrazine (8) with aminating agent O-mesitylsulfonylhydroxylamine\textsuperscript{22} gave a pyrazinium salt, which was condensed with 2-furaldehyde in 1,4-dioxane at 100 °C, and oxidized by air to give 9 with combined yield of 19% for the two steps after chromatography on silica. Hydrolysis of 9 using 1N KOH in methanol gave the acid intermediate in 67% yield, which was then rearranged under Curtius conditions using DPPA in refluxing tert-butanol to afford 10 (54%) and 11 (15%). The Boc protecting groups were removed using 10% TFA/CH\textsubscript{2}Cl\textsubscript{2}. As one example of derivatizing this piperazinyl-triazolopyrazine template, compound (12) was synthesized by reductive alkylation with 2,4,6-trifluorobenzaldehyde using NaBH(OAc)\textsubscript{3}. Compound (12) was tested in competition binding assays\textsuperscript{23} against the adenosine A\textsubscript{2a} and A\textsubscript{1} receptors and showed moderate binding potency and selectivity (A\textsubscript{2a} Ki = 260 nM, A\textsubscript{1} Ki = 8490 nM).

In summary, we have demonstrated, for the first time, the synthesis of a piperazine-derived [1,2,4]triazolo[1,5-\alpha]pyrazine, a novel addition to the current collection of heterocyclic templates that are explored as A\textsubscript{2a} antagonists (Figure 1). A preliminary derivative with a hydrophobic capping group...
exhibited encouraging potency and selectivity, suggesting a potentially new avenue to pursue A2a antagonists with good potency, selectivity and oral efficacy. Optimization of the conditions is underway to improve the yield of the key steps, and to conduct more extensive optimization of the capping group.

ACKNOWLEDGEMENTS
We thank Azita Kaffashan for carrying out the high–resolution MS spectrum.

REFERENCES AND NOTES
23. Detailed description for membrane preparation and radioligand binding assay has been reported.8,9
24. All proton and 13C magnetic resonance spectra were determined in the indicated solvent using a 300 MHz Bruker NMR spectrometer with the appropriate internal standard. HRMS spectra were obtained on a MALDI-TOF MS (Voyager-DE STR, Perseptive Biosystems) in the reflector mode with delayed extraction and an accelerating voltage of 20 kV. Preparative HPLC was carried out using a Gilson platform equipped with UV/VIS detector and an automatic fraction collector. The data for target compound (12) is included as an example: white amorphous powder, 1H NMR (300 MHz, CDCl3) δ 2.66 (t, J = 4.5 Hz, 4H), 3.34 (t, J = 4.5 Hz, 4H), 3.73 (s, 2H), 5.61 (s, 2H), 6.54 (dd, J = 1.8, 3.6 Hz, 1H), 6.67 (d, J = 7.8 Hz, 1H), 6.70 (d, J = 7.8 Hz, 1H), 7.07 (d, J = 3.6 Hz, 1H), 7.26 (s, 1H), 7.57 (d, J = 1.8 Hz, 1H); 13C NMR (100 MHz, CDCl3) δ 46.5, 48.4, 51.5, 95.6, 99.8, 100.1, 100.3, 110.2, 111.7, 134.8, 143.8, 146.0, 146.4, 149.0, 155.1; HRMS calculated for C20H18N7OF3 (M+ + H) 429.1525, found 429.1531; Anal. Calcd for C20H18N7OF3: C, 55.94; H, 4.23; N, 22.82. Found: C, 55.60, H, 4.28, N, 23.00.
25. To address the problem of acidic protons in the Pd-catalyzed coupling reaction of compound (4), we chose Buchwald’s conditions using LHMDS as the base, which was proposed to protect the deprotonated species in situ as lithiate/aggregate, to prevent deactivation of the Pd catalyst.20 We were delighted to observe a clean reaction potentially forming the desired product as monitored by LC-MS spectrum. However, the crude product decomposed into baseline material during work-up (Table 1, Entry 9). So far, we haven’t been able to figure out the underlining problem.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Catalyst</th>
<th>Ligand</th>
<th>Base (4 eq.)</th>
<th>Conditions</th>
<th>Results</th>
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<tr>
<td>1</td>
<td>Toluene</td>
<td>Pd3(dba)3</td>
<td>dppp</td>
<td>NaOBu-t</td>
<td>85 °C/4 h</td>
<td>SM/decomp a</td>
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<td>Pd(OAc)2</td>
<td>1 (rac)-trans-1,2-cyclo-</td>
<td>NaOBu-t</td>
<td>95 °C/5 h</td>
<td>decomp b</td>
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<td>CuI</td>
<td>hexanediamine</td>
<td>K3PO4</td>
<td>100 °C/18 h</td>
<td>SM/decomp a</td>
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<td>No.</td>
<td>Solvent</td>
<td>Catalyst</td>
<td>Ligand</td>
<td>Base</td>
<td>Temperature/Time</td>
<td>Product/Decomp</td>
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<tr>
<td>4</td>
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<td>(rac)PPF-OMe</td>
<td>Cs$_2$CO$_3$</td>
<td>100 °C/18 h</td>
<td>SM/decomp$^a$</td>
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<td>Pd$_2$(dba)$_3$</td>
<td>dppf</td>
<td>Cs$_2$CO$_3$</td>
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<td>SM/decomp$^a$</td>
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<tr>
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<td>Pd$_2$(dba)$_3$</td>
<td>2</td>
<td>K$_3$PO$_4$</td>
<td>100 °C/18 h</td>
<td>decomp$^b$</td>
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<tr>
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<td>POPd$_2$</td>
<td>Ref. 18</td>
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<td>SM/decomp$^a$</td>
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<tr>
<td>8</td>
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<td>Pd(OAc)$_2$</td>
<td>3</td>
<td>NaOBu-t</td>
<td>65 °C/18 h</td>
<td>SM/decomp$^a$</td>
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<tr>
<td>9</td>
<td>THF</td>
<td>Pd$_2$(dba)$_3$</td>
<td>2</td>
<td>LHMDS</td>
<td>65 °C/18 h</td>
<td>decomp$^c$</td>
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</table>

a) Starting material partially decomposed. No product observed.  
b) No product formed. Starting material decomposed completely.  
c) Crude product formed as monitored by LC-MS, but decomposed during work-up.