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FIRST SYNTHESIS OF PIPERAZINE-DERIVED [1,2,4]TRIAZOLO[1,5-*a*]PYRAZINE AS AN ADENOSINE A_{2A} RECEPTOR ANTAGONIST

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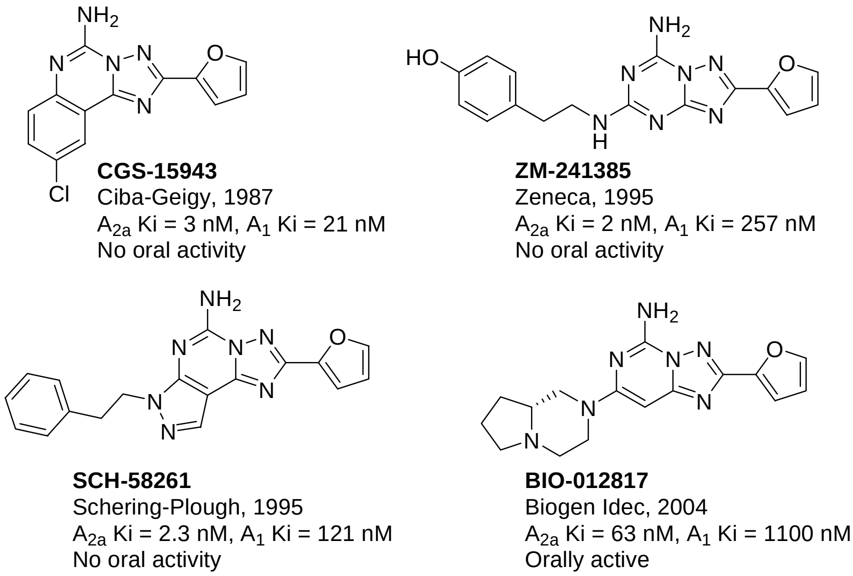
Abstract – Synthesis of piperazine-derived 2-furan-2-yl-[1,2,4]triazolo[1,5-*a*] pyrazines was achieved using methyl 3-amino-2-pyrazinecarboxylate. Introduction of the piperazine to the pyrazine template was achieved through a pteridin-4-one intermediate (**7**). Cyclization of the [1,2,4]triazolo[1,5-*a*]pyrazine 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 A_{2a} receptor binding affinity and selectivity over the A_1 receptor.

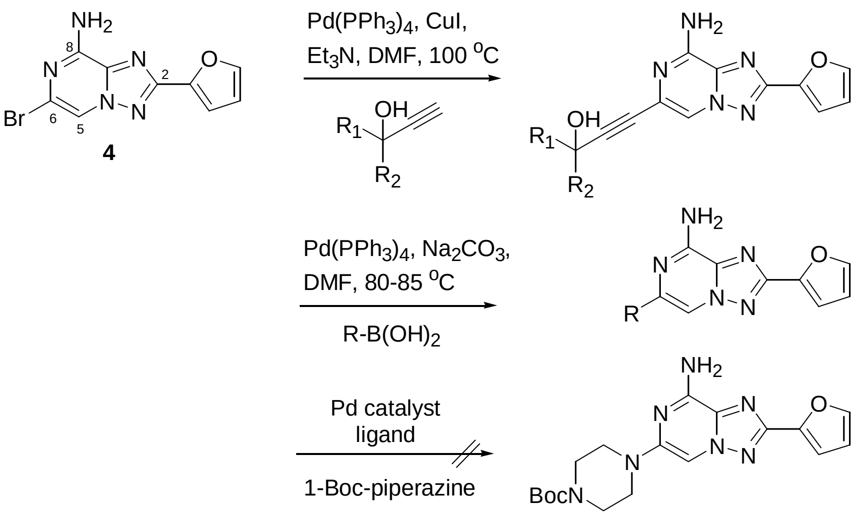
In recent years, significant effort has been directed at the development of adenosine A_{2a} receptor antagonists because of their potential for the treatment for Parkinson's disease.[1] As represented by compounds in Figure 1, a variety of bicyclic or tricyclic heterocyclic templates have been discovered as potent A_{2a} antagonists.[2-7] Effort in our lab to develop adenosine A_{2a} antagonist has led to the recent disclosure of several diamine-derived triazolotriazine and triazolopyrimidine series as highly potent and selective A_{2a} 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.[8-10]

Figure 1



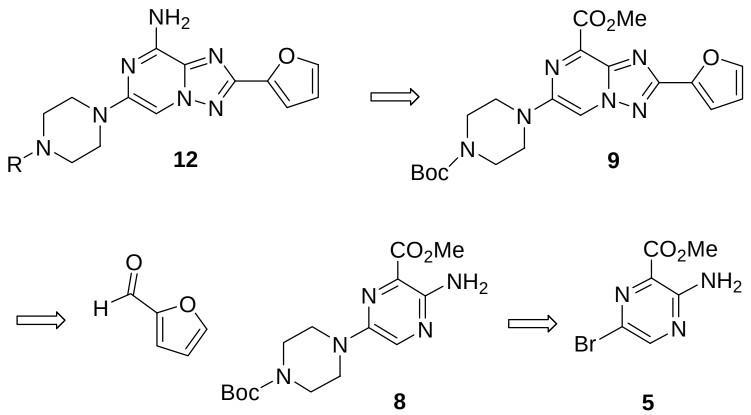
The initial attempts to the synthesis of piperazine-derived [1,2,4]triazolo[1,5-*a*]pyrazine were directed at amination of bromide (**4**) using Buchwald/Hartwig conditions for the ease of preparing bromide (**4**),[11] as well as for our previous success on Sonogashira[11] and Suzuki[12] couplings with 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[13-20] was unsuccessful, mostly resulting in decomposition or recovery of the uncoupled starting materials. (Some examples[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



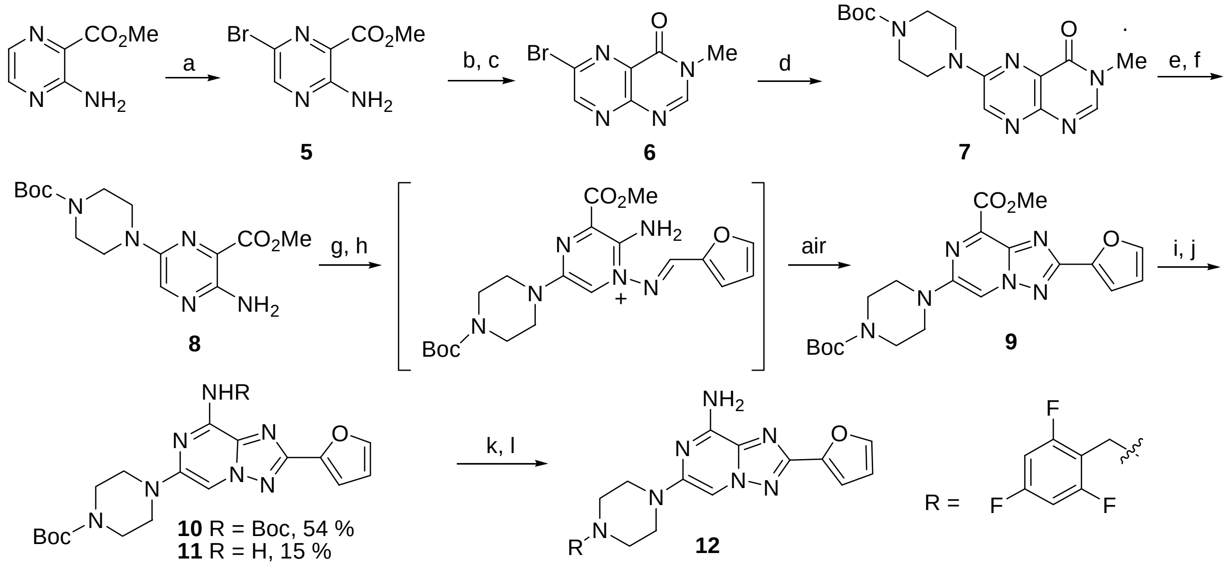
Although the results were discouraging, it is not surprising since the current scope of transition metal-catalyzed amination of heteroaromatic halides with alkyl amines is still limited, especially for aryl halides containing functional groups with acidic protons, such as hydroxyl, amide, or enolizable keto groups.[19,20] The problem that we encountered likely arose from the presence of an acidic proton at the 5-position, in addition to the 8-amine.[25] Proton signals from both positions disappeared in NMR spectrum when using methanol-d_4 as solvent. Eventually, we decided to synthesize piperazinyltriazolopyrazines from scratch by introducing piperazine before cyclizing the furanyltriazole.

Scheme 2



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* piperazinylation of bromide (**5**). As shown in Scheme 3, the synthesis of **12** commenced with bromination of commercial methyl 3-amino-2-pyrazinecarboxylate to afford a corresponding bromide (**5**) in 94% yield. However, attempts at nucleophilic displacement of the bromide in **5** to obtain **8** using Boc-piperazine were unsuccessful. At the time we explored the chemistry, there were no successful examples in the literature on the Pd-catalyzed amination of pyrazines, especially those bearing a free amino group. Based on the previous difficulties with amination of triazolopyrazinyl bromide (**4**), we decided to take an alternative route by cyclizing bromide (**5**) into its pteridin-4-one analogue (**6**), a chloride version of which was reported to undergo facile nucleophilic aromatic substitution.[21] Therefore, 6-bromo-3-methyl-3*H*-pteridin-4-one (**6**) was synthesized in two steps (90% and 89% yield, respectively) by converting **5** to its methyl amide analogue followed by condensing with triethyl orthoformate in acetic anhydride at reflux. Bromide (**6**) was then easily displaced by Boc-piperazine to give **7** in 92% yield. Hydrolysis followed by methylation of the free carboxylate using trimethylsilyldiazomethane gave the key intermediate (**8**) in reasonable yield.

Scheme 3



Reagents and Conditions: a) Br_2, AcOH, H_2O, 94%; b) 40 % aq. $MeNH_2$, rt, 90%; c) triethyl orthoformate, acetic anhydride, reflux, 89%; d) 1-Boc-piperazine, 2-methoxyethanol,100°C, 92%; e) 10 % NaOH, MeOH, rt, formic acid, 67%; f) $TMSCHN_2$, benzene, MeOH, rt, 96%; g) *O*-mesitylsulfonylhydroxylamine, CH_2Cl_2, rt; h) 2-furaldehyde, 1,4-dioxane, 100°C, 19 % for two steps; i) 1 N KOH/MeOH, rt, 68%; j) DPPA, triethylamine, *t*-BuOH, reflux; k) TFA/CH_2Cl_2; l) 2,4,6-trifluorobenzaldehyde, $NaBH(OAc)_3$, AcOH, 56% for two steps.

With **8** in hand, we then pursued incorporation of the furanyltriazole. Since our previous report[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.[12] Unfortunately, we were not able to convert **8** to **9** using 2-furonitrile and $AlCl_3$, or milder Lewis acids such as $TiCl_4$ and Et_2AlCl. Base-catalyzed conditions using potassium *t*-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[22] gave a pyrazinium salt, which was condensed with 2-furaldehyde in 1,4-dioxane at 100 ºC, 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 *t*-butanol to afford **10** (54%) and **11** (15%). The Boc protecting groups were removed using 10% TFA/CH_2Cl_2. As one example of derivatizing this piperazinyl-triazolopyrazine template, compound (**12**) was synthesized by reductive alkylation with 2,4,6-trifluorobenzaldehyde using $NaBH(OAc)_3$. Compound (**12**) was tested in competition binding assays[23] against the adenosine A_{2a} and A_1 receptors and showed moderate binding potency and selectivity (A_{2a} Ki = 260 nM, A_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-*a*]pyrazine, a novel addition to the current collection of heterocyclic templates that are explored as A_{2a} antagonists (Figure 1). A preliminary derivative with a hydrophobic capping group exhibited encouraging potency and selectivity, suggesting a potentially new avenue to pursue A_{2a} 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.

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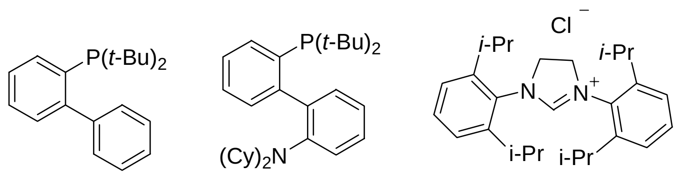
23. Detailed description for membrane preparation and radioligand binding assay has been reported.[8,9]
24. All proton and ^{13}C magnetic resonance spectra were determined in the indicated solvent using a 300 MHz Bruker NMR spectrometer with the appropriate internal standard. HRMS spectra were obtained 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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{20}H_{18}N_7OF_3$ (M^+ + H) 429.1525, found 429.1531; Anal. Calcd for $C_{20}H_{18}N_7OF_3$: C, 55.94; H, 4.23; N, 22.83. 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.
26. Table 1

Entry	Solvent	Catalyst	Ligand	Base (4 eq.)	Conditions	Results
1	Toluene	$Pd_2(dba)_3$	dppp	NaOBu-*t*	85 ^oC/4 h	SM/decomp[a]
2	DMF	Pd $(OAc)_2$	**1**	NaOBu-*t*	95 ^oC /5 h	decomp[b]
3	Dioxane	CuI	(rac)-*trans*-1,2-cyclo-hexanediamine	K_3PO_4	100 ^oC/18 h	SM/decomp[a]

4	Dioxane	Pd $(OAc)_2$	(rac)PPF-OMe	Cs_2CO_3	100 °C/18 h	SM/decomp[a]
5	Dioxane	$Pd_2(dba)_3$	dppf	Cs_2CO_3	100 °C/18 h	SM/decomp[a]
6	Dioxane	$Pd_2(dba)_3$	**2**	K_3PO_4	100 °C/18 h	decomp[b]
7	DMF	$POPd_2$	Ref. 18	KOBu-*t*	100 °C/18 h	SM/decomp[a]
8	THF	Pd $(OAc)_2$	**3**	NaOBu-*t*	65 °C/18 h	SM/decomp[a]
9	THF	$Pd_2(dba)_3$	**2**	LHMDS	65 °C/18 h	decomp[c]

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.



1 **2** **3**