Synthetic Access to 2-Amido-5-aryl-8-methoxy-triazolopyridine and 2-Amido-5-morpholino-8-methoxy-triazolopyridine Derivatives as Potential Inhibitors of the Adenosine Receptor Subtypes

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Abstract: Two versatile and complementary synthetic strategies towards 2-amido-5-aryl-8-methoxy-triazolopyridine derivatives and 2-amido-5-morpholino-8-methoxy-triazolopyridine derivatives in five steps are presented. The key step in each synthetic route can be constituted as the formation of the respective triazolopyridine derivative precursors in 78% and 57% yield, respectively, through an intermediately formed 4H-[1,2,4]oxadiazol-5-one. The final Suzuki coupling/amidation allowed the straightforward access to the desired triazolopyridine derivatives which have not been described previously. Notably, these triazolopyridine-scaffold bears three vectors of diversity which offer maximum flexibility in design and combinatorial synthesis of molecules with a potentially useful inhibitory activity towards adenosine receptor subtypes.

Key words: triazolopyridine derivatives, 4H-[1,2,4]oxadiazol-5-one, Suzuki coupling, combinatorial chemistry

In the course of a medicinal chemistry project the Adenosine 2a (A2a) receptor was considered as a potential modulating site towards the treatment of neurodegenerative diseases.1 A2a receptor antagonists inhibit the motor depressant effects of dopamine antagonists, such as haloperidol, which makes them of particular interest for treatment of neurodegenerative disorders, such as Parkinson’s disease.2 It was previously established that triazolopyridine derivatives can act as potent and selective (versus Adenosine A1) antagonists based on a small heterocyclic molecule scaffold.3 In order to further investigate the potential of triazolopyridine derivatives with different substitution pattern to those previously described 8-methoxy-[1,2,4]triazolo[1,5-a]pyridine derivatives 1 were considered as potentially interesting. Structurally related compounds have been identified as potential herbicidal agents.4 However, to the best of our knowledge, synthetic access to 5-aryl-8-methoxy-[1,2,4]triazolo[1,5-a]pyridines 1 and 5-amino-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine derivatives 2 have not been described. To allow for maximum synergies from the synthetic point of view our unified synthetic approach towards both types of triazolopyridines ought to go through a pivotal aromatic iodo-triazolopyridine 3 intermediate to be transformed into the respective aryl/amino derivatives through palladium-catalysed reaction sequences. Therefore, 2-amino-3-methoxy pyridine 4 was reacted with ethoxycarbonyl isothiocyanate to yield almost quantitatively the thiourea derivative 5 which was subjected to a cyclisation procedure employing hydroxylamine and DMAP in a protic solvent to afford 8-methoxy-triazolopyridine 6 in 78% yield (Scheme 1).

Although this type of procedure was previously described the reaction mechanism remained ambiguous. We postu-
late a mechanism starting with the substitution of the thio moeity in thiourea 5 with hydroxylamine which consecu-
tively forms the 4H-[1,2,4]oxadiazol-5-one 7 upon loss of
ethanol. Subsequent loss of CO₂ from 7 and simultaneous
ammonolysis can be regarded as the driving force for the
formation of the desired triazolopyridine 6. Regioselect-
tive iodination with KIO₃ in sulfuric acid⁷ yielded iodo-
triazolopyridine 3 in 49% yield. It is noteworthy that this
low molecular weight building block carries 2 ‘handles’
(i.e. aromatic iodide and amino functionality) for orthog-
onal derivatisation. Considering the early introduction of
a methoxy group onto the scaffold these type of triazol-
opyridines constitute a versatile class of heterocyclic
compounds with three orthogonal vectors of diversity.
The aromatic iodide 3 conveniently underwent Suzuki
coupling reactions with a total of 34 boronic acids or es-
ters. Reaction conditions employing Pd(dpdpf)Cl₂.CH₂Cl₂
in dioxane with sodium carbonate as base at elevated tem-
peratures furnished 5-aryl-8-methoxy-triazolopyridine
derivative 8 in yields up to 83% (Table 1).

The amidation of 8 with acid chlorides under prolonged
reaction times concluded this 5-step synthetic sequence
giving access to a range of desired triazolopyridines 1
with yields up to 63% (Table 2). This protocol allowed, in
the majority of the performed experiments, straightforward access to triazolopyridines 1. However, the yield
of the final products 1 are mainly influenced by the reactivity
of the starting materials (8/acid chlorides) which are de-
pendent on their respective steric and electronic proper-
ties.

Following the initial concept of a unified synthetic se-
quence approach taking advantage of the common inter-
mediate iodo-triazolopyridine 3 proved to be unsuccessful. Unfortunately, none of the various palladi-
ium-catalysed amination reactions tried, described in anal-
ogy by Buchwald⁷ and Hartwig,⁸ with 3 and morpholine
as a model amine (and desired replacement for an aryl
moeity) yielded a detectable amount of triazolopyridine 9,
which led to the design of a new synthetic route.

Table 1 Representative Selection of 5-Aryl-8-methoxy-triazolopy-
ridine Derivatives 8

<table>
<thead>
<tr>
<th>Prod Ar</th>
<th>Yield [%] a (purity) b MH⁺ (found)</th>
<th>Prod Ar</th>
<th>Yield [%] a (purity) b MH⁺ (found)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8a</td>
<td>29 (100) 241.3</td>
<td>8g</td>
<td>28 (100) 324.3</td>
</tr>
<tr>
<td>8b</td>
<td>33 (100) 270.3</td>
<td>8h</td>
<td>31 (100) 308.3</td>
</tr>
<tr>
<td>8c</td>
<td>41 (100) 258.3</td>
<td>8i</td>
<td>38 (79) 301.3</td>
</tr>
<tr>
<td>8d</td>
<td>11 (100) 258.3</td>
<td>8j</td>
<td>16 (95) 265.3</td>
</tr>
<tr>
<td>8e</td>
<td>27 (97) 274.7</td>
<td>8k</td>
<td>59 (100) 309.2</td>
</tr>
<tr>
<td>8f</td>
<td>14 (100) 254.3</td>
<td>8l</td>
<td>83 (100) 246.1</td>
</tr>
</tbody>
</table>

a Isolated yields
b Purity was determined by analytical HPLC-MS at 230 nm.

2,6-Dibromo-3-methoxy pyridine (10)⁹ can be reacted re-
gioselectively with morpholine in DMF to afford in al-
most quantitative yield the morpholino derivative 11. Under more forcing conditions the bromo-derivative 11
can be transformed into amine 12 by reaction with aque-
ous ammonia in the presence of catalytic amounts of copper at 185 °C and 10 bar pressure in 69% yield. Subsequent reaction with ethoxycarbonyl isothiocyanate yielded precursor 13 in 54% supplied to cyclisation under similar reaction conditions as outlined above to give ac-

Table 2 Selection of 2-Amido-5-aryl-8-methoxy-triazolopyridine Derivatives 1

<table>
<thead>
<tr>
<th>Prod-Ar</th>
<th>R</th>
<th>Yield [%] a MH⁺ (found)</th>
<th>Prod-Ar</th>
<th>R</th>
<th>Yield [%] a MH⁺ (found)</th>
<th>Prod-Ar</th>
<th>R</th>
<th>Yield [%] a MH⁺ (found)</th>
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</thead>
<tbody>
<tr>
<td>1a</td>
<td></td>
<td>48 379.3</td>
<td>1e</td>
<td></td>
<td>21 363.1</td>
<td>1i</td>
<td></td>
<td>10 381.3</td>
</tr>
<tr>
<td>1b</td>
<td></td>
<td>43 433.3</td>
<td>1f</td>
<td></td>
<td>19 345.3</td>
<td>1j</td>
<td></td>
<td>10 379.3</td>
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<tr>
<td>1c</td>
<td></td>
<td>61 397.2</td>
<td>1g</td>
<td></td>
<td>18 409.3</td>
<td>1k</td>
<td></td>
<td>21 369.2</td>
</tr>
<tr>
<td>1d</td>
<td></td>
<td>53 431.4</td>
<td>1h</td>
<td></td>
<td>63 455.3</td>
<td>1l</td>
<td></td>
<td>12 431.3</td>
</tr>
</tbody>
</table>

a Isolated yields; purity was determined by analytical HPLC-MS at 230 nm and greater 95%.

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Triazolopyridine Derivatives as Potential Inhibitors of the Adenosine Receptor Subtypes

In conclusion, we have designed and developed two versatile and complementary 5-step synthetic strategies for the preparation of 2-amido-5-morpholino-8-methoxy-triazolopyridine derivatives 1 and 2-amido-5-morpholino-8-methoxy-triazolopyridine derivatives 2. The key step in each synthetic route can be constituted as the formation of the triazolopyridine-derivative 6 and 9 in 78% and 57% yield, respectively, through an intermediately formed 4H-1,2,4-oxadiazol-5-one. The final Suzuki coupling/amidation concluded the straightforward access to these previously not described triazolopyridine derivatives 1 and 2. Notably, this triazolopyridine scaffold bears three vectors of diversity which allowed for maximum flexibility in design and combinatorial synthesis of molecules with potential A2a inhibitory activity. Based on these results chemistry efforts towards novel triazolopyridine derivatives with improved biological in vitro activities, and pharmacological profiles are currently undertaken and will be reported fully in due course.

NMR spectra were recorded on a Bruker AC250 MHz spectrometer and a Bruker Avance 500 MHz spectrometer with Bruker BEST-System. Mass spectra were recorded on a API 300 Sciex.

Synthesis of 6
To a solution of hydroxylamine hydrochloride (21.8 g, 313.7 mmol) and N′-ethylisopropylamine (32.2 mL, 188.2 mmol) in a mixture of CH3OH–EtOH (130 mL, 1:1) was added N-(3-methoxy-2-pyridyl)-N′-carboxoethoxy-thiourea (5, 16 g, 62.7 mmol) and stirred for 2 h at r.t. and subsequently for 3 h at 60 °C. The volatiles were removed under reduced pressure and the residue was treated with H2O (100 mL). The resulting precipitate was washed with CH3OH–Et2O (25 mL, 4:1) and then with Et2O (25 mL). After drying under high vacuum (8 g, 48.7 mmol, 78%) of was collected as off-white crystals. The mother liquid was treated with Na2CO3 and extracted with CH2Cl2 (5 × 15 mL) to yield title compound 3 as beige crystals. The mother liquid was treated with Na2CO3 and extracted with CH3Cl (5 × 250 mL). The combined organic layers were dried (MgSO4) and evaporated to dryness to yield an additional amount of title compound 3. The product was recrystallised from EtOH to yield a total of 2.59 g (49%, 8.9 mmol) of 3.

Synthesis of 3
A mixture of 8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-ylamine (6, 3 g, 18.3 mmol), H2O (6 mL) and sulfuric acid (97%, 6 mL) was heated to 100 °C and KIO3 (4.3 g, 20.1 mmol) was added in portions over a period of 1 h. The mixture was heated to 120 °C for 3 h and further H2O (6 mL) and sulfuric acid (97%, 6 mL) was added. After cooling to 0 °C the precipitate was collected and washed with H2O (2 × 15 mL) to yield title compound 3 as beige crystals. The mother liquid was treated with Na2CO3 and extracted with CH4Cl (5 × 250 mL). The combined organic layers were dried (MgSO4) and evaporated to dryness to yield an additional amount of title compound 3. The product was recrystallised from EtOH to yield a total of 2.59 g (49%, 8.9 mmol) of 3.

MS: m/z (%) = 291.0 (100) [M+H+].
Synthesis of 8; General Procedure
A mixture of 3 (50 mg, 0.17 mmol), arylboronic acid (46.2 mg, 0.38 mmol), dichloro[1,1′-bis(diphenylphosphino)-ferrocene]palladium(II) dichloromethane adduct (6.3 mg, 0.008 mmol) and aq Na₂CO₃ solution (2 M, 0.3 mL) in dioxane (1 mL) was heated for 90 min to 80 °C. The mixture was filtered over a short silica pad and eluted with EtOAc (30 mL). The filtrate was then concentrated under reduced pressure and the residue was purified by preparative HPLC on reversed phase eluting with a H₂O–CH₃CN gradient.

Yield: 19%.

Reference