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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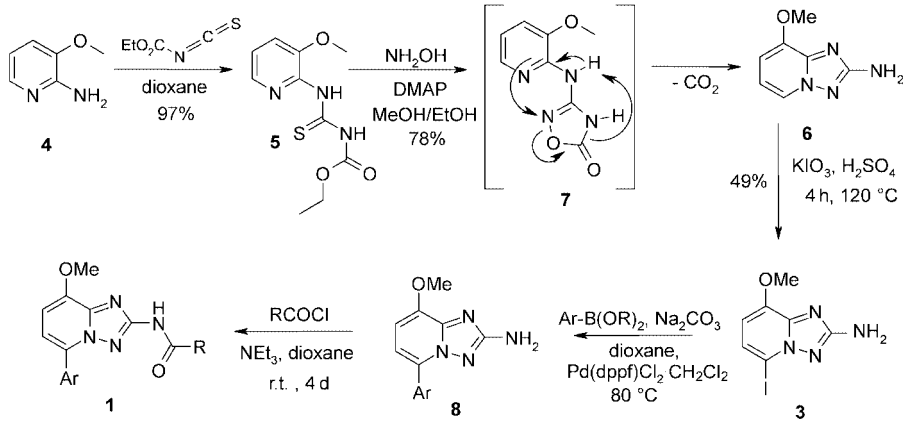
Abstract: Two versatile and complementary synthetic strategies towards 2-amido-5-aryl-8-methoxy-triazolopyridine derivatives and 2-amido-5-morpholino-8-methoxy-triazolopyridine derivatives in five steps are presented. The key step in each synthetic route can be constituted as the formation of the respective triazolopyridine derivative precursors in 78% and 57% yield, respectively, through an intermediately formed 4*H*-[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, 4*H*-[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 deseases.[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 herbicidial 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**[5] 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-



Scheme 1 Synthetic sequence for preparation of 2-amido-5-aryl-8-methoxy-triazolopyridines **1**

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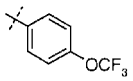
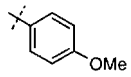
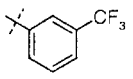
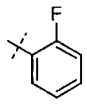
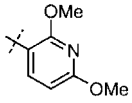
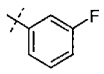
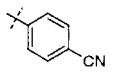
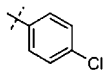
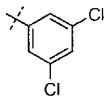
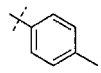
late a mechanism starting with the substitution of the thio moiety in thiourea **5** with hydroxylamine which consecutively forms the 4*H*-[1,2,4]oxadiazol-5-one **7** upon loss of ethanol. Subsequent loss of CO_2 from **7** and simultaneous aromatisation can be regarded as the driving force for the formation of the desired triazolopyridine **6**. Regioselective iodination with KIO_3 in sulfuric acid[6] yielded iodotriazolopyridine **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 orthogonal derivatisation. Considering the early introduction of a methoxy group onto the scaffold these type of triazolopyridines 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 esters. Reaction conditions employing $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ in dioxane with sodium carbonate as base at elevated temperatures 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 triazolopyrididnes **1**. However, the yield of the final products **1** are mainly influenced by the reactivity of the starting materials (**8**/acid chlorides) which are dependent on their respective steric and electronic properties.

Following the initial concept of a unified synthetic sequence approach taking advantage of the common intermediate iodo-triazolopyridine **3** proved to be unsuccessful. Unfortunately, none of the various palladium-catalysed amination reactions tried, described in analogy by Buchwald[7] and Hartwig,[8] with **3** and morpholine as a model amine (and desired replacement for an aryl moiety) yielded a detectable amount of triazolopyridine **9**, which led to the design of a new synthetic route.

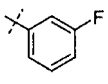
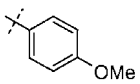
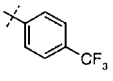
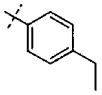
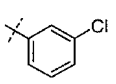
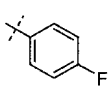
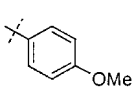
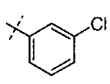
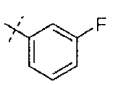
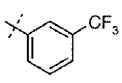
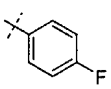
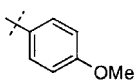
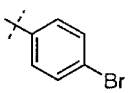
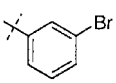
Table 1 Representative Selection of 5-Aryl-8-methoxy-triazolopyridine Derivatives **8**

Product	Ar	Yield [%][a] (purity)[b] MH^+ (found)	Product	Ar	Yield [%][a] (purity)[b] MH^+ (found)
8a		29 (100) 241.3	**8g**		28 (100) 324.3
8b		33 (100) 270.3	**8h**		31 (100) 308.3
8c		41 (100) 258.3	**8i**		38 (79 301.3
8d		11 (100) 258.3	**8j**		16 (95) 265.3
8e		27 (97) 274.7	**8k**		59 (100) 309.2
8f		14 (100) 254.3	**8l**		83 (100) 246.1

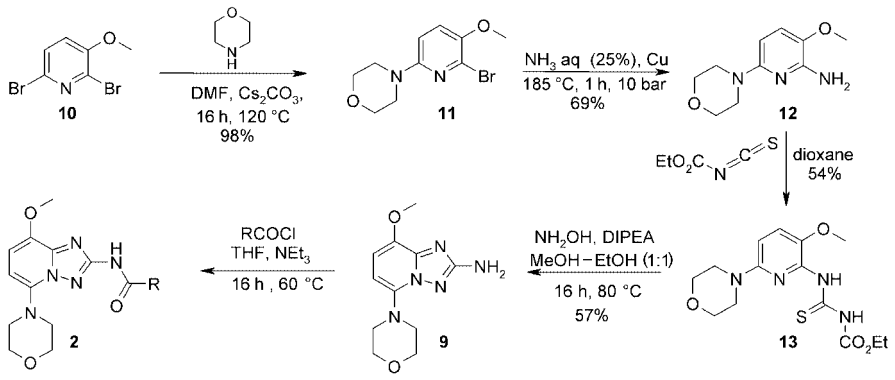
[a] Isolated yields
[b] Purity was determined by analytical HPLC-MS at 230 nm.

2,6-Dibromo-3-methoxy pyridine (**10**)[9] can be reacted regioselectively with morpholine in DMF to afford in almost quantitative yield the morpholino derivative **11**. Under more forcing conditions the bromo-derivative **11** can be transformed into amine **12** by reaction with aqueous 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**

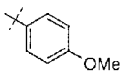
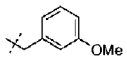
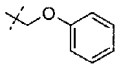
Product	Ar	R	Yield [%][a] MH^+ (found)	Product	Ar	R	Yield [%][a] MH^+ (found)	Product	Ar	R	Yield [%][a] MH^+ (found)
1a			48 379.3	**1e**			21 363.1	**1i**			10 381.3
1b			43 433.3	**1f**			19 345.3	**1j**			10 379.3
1c			61 397.2	**1g**			18 409.3	**1k**			21 369.2
1d			53 431.4	**1h**			63 455.3	**1l**			12 431.3

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



Scheme 2 Synthetic sequence for preparation of 2-amido-5-morpholino-8-methoxy-triazolopyridines **2**

Table 3 Representative Triazolopyridine Derivatives **2**

Product	R	Yield (%)[a] MH^+ (found)	Product	R	Yield (%)[a] MH^+ (found)	Product	R	Yield (%)[a] MH^+ (found)	Product	R	Yield (%)[a] MH^+ (found)
2a		23 388.2	**2c**		25 384.3	**2e**		25 398.4	**2g**		20 384.3
2b		23 388.2	**2d**		36 368.3	**2f**		25 374.4	**2h**		33 346.4

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

cess to 2-amino-5-morpholino-8-methoxy-triazolopyridine **9** in 57% yield. The final amidation with 22 acid chlorides concluded this novel 5-step synthetic sequence for the preparation of the desired triazolopyrididnes **2** with yields up to 36% (Scheme 2).[10] Representative examples are shown in Table 3.

In conclusion, we have designed and developed two versatile and complementary 5-step synthetic strategies for the preparation of 2-amido-5-aryl-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 4*H*-[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 recordered on a Bruker AC250 MHz spectromer 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*′-ethyldiisopropylamine (32.2 mL, 188.2 mmol) in a mixture of CH_3OH–EtOH (130 mL, 1:1) was added *N*-(3-methoxy-2-pyridinyl)-*N*′-carboethoxy-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 H_2O (100 mL). The resulting precipitate was washed with CH_3OH–Et_2O (25 mL, 4:1) and then with Et_2O (25 mL). After drying under high vacuum **6** (8 g, 48.7 mmol, 78%) of was collected as off-white cystals.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 8.13 (dd, J_1 = 6.6 Hz, J_2 = 1 Hz, 1 H, H-5), 6.89 (dd, J_1 = 7.1 Hz, J_2 = 1 Hz, 1 H, H-7), 6.77 (dd, J_1 = 7.1 Hz, J_2 = 6.6 Hz, 1 H, H-5), 5.88 (br s, 2 H, NH_2), 3.90 (s, 3 H, OCH_3).

MS: *m*/*z* (%) = 163.0 (100) [M – H^+].

Synthesis of 3

A mixture of 8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-ylamine (**6**, 3 g, 18.3 mmol), H_2O (6 mL) and sulfuric acid (97%, 6 mL) was heated to 100 °C and KIO_3 (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 H_2O (6 mL) and sulfuric acid (97%, 6 mL) was added. After cooling to 0 °C the precipitate was collected and washed with H_2O (2 × 15 mL) to yield title compound **3** as beige crystals. The mother liquid was treated with Na_2CO_3 and extracted with CH_2Cl_2 (5 × 250 mL). The combined organic layers were dried ($MgSO_4$) 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**.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 7.22 (d, *J* = 8.2 Hz, 1 H, H-7), 6.76 (d, *J* = 8.2 Hz, 1 H, H-6), 6.10 (br s, 2 H, NH_2), 3.89 (s, 3 H, OCH_3).

MS: *m*/*z* (%) = 291.0 (100) [MH^+].

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 Na_2CO_3 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 H_2O–CH_3CN gradient.

8a

Yield: 29%.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 7.82 (dd, J_1 = 8.1 Hz, J_2 = 1 Hz, 2 H, phenyl), 7.48 (m, 3 H, phenyl), 6.81 (dd, J_1 = 8.4 Hz, J_2 = 1 Hz, 2 H, H-6 and H-7), 4.53 (br s, 2 H, NH_2), 4.03 (s, 3 H, OCH_3).

MS: *m*/*z* (%) = 241.3 (100) [MH^+].

Synthesis of 1; General Procedure

A mixture of acid chloride (0.125 mmol), **8** (0.137 mmol) and Et_3N (27 mg) in dioxane (0.5 mL) was shaken at r.t. for 4 d. After addition of formic acid (0.05 mL) the mixture was directly subjected to preparative HPLC on reversed phase eluting with a H_2O–CH_3CN gradient to yield, after evaporation of the product fractions, the title compound.

1f

Yield: 19%.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.95 (m, 4 H, Ph), 7.61 (m, 6 H, Ph), 7.30 (m, 3 H, Ph/NH), 4.05 (s, 3 H, OCH_3).

MS: *m*/*z* (%) = 345.3 (100) [MH^+].

Synthesis of 11

A mixture of **10** (2.64 g, 10 mmol) in DMF (8 mL), morpholine (1.74 mL, 20 mmol) and Cs_2CO_3 (4.87 g, 15 mmol) was heated for 16 h to 120 °C. H_2O (100 mL) was added and the mixture was extracted with Et_2O (3 × 150 mL). The combined organic layers were dried ($MgSO_4$) and evaporated to dryness to yield 2.68 g (98%) of **11**.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 6.95 (d, *J* = 8.1 Hz, 1 H, H-5), 6.90 (d, *J* = 8.1 Hz, 1 H, H-4), 3.82 (m, 7 H, OCH_3/OCH_2), 3.42 (t, *J* = 4.8 Hz, 4 H, NCH_2).

MS: *m*/*z* (%) = 273.0 (100) [MH^+].

Structural identity of **11** was corroborated by NOE expriments.

Synthesis of 9

A solution of hydroxylamine hydrochloride (347.4 mg, 5 mmol) and DIPEA (513 μL, 3 mmol) in MeOH–EtOH (3 mL, 1:1) was treated with *N*-(3-methoxy-6-morpholin-4-yl-2-pyridinyl)-*N*′-carboethoxy-thiourea (**13**, 308 mg, 0.9 mmol) in MeOH–EtOH (2 mL, 1:1) and heated to 80 °C for 16 h. The mixture was evaporated to dryness and purified by flash column chromatography on silica eluting with a mixture of CH_2Cl_2–MeOH (20:1) to yield after evaporation 127.5 mg (57%) of **9**.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8 Hz, 1 H, H-5), 7.07 (d, *J* = 8 Hz, 1 H, H-4), 4.45 (br s, 2 H, NH_2), 3.88 (t, *J* = 4.8 Hz, 4 H, OCH_2), 3.83 (s, 3 H, OCH_3), 3.48 (t, *J* = 4.8 Hz, 4 H, NCH_2).

MS: *m*/*z* (%) = 250.2 (100) [MH^+].

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(10) (a) General procedure for the synthesis of **2** employed similar reaction conditions as for the synthesis of **1**. (b) For a more detailed description of workflow procedures utilised in the preparation of compound arrays please refer to: Nettekoven, M.; Thomas, A. W. *Curr. Med. Chem.* **2002**, *9*, 2179.