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Synthesis of triazolopyridines as conformationally constrained tertiary amides

Edward C. Lawson, Bruce E. Maryanoff* and William J. Hoekstra*,†

Drug Discovery, The R. W. Johnson Pharmaceutical Research Institute, Spring House, Pennsylvania 19477, USA

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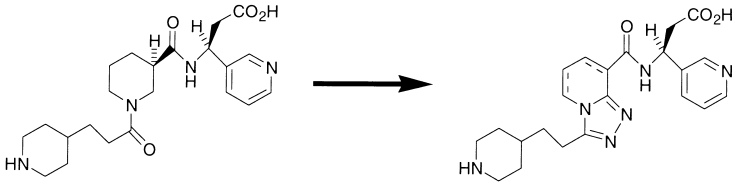
Abstract

Amide derivatives of cyclic amines are common templates for biologically active chemical entities. To constrain the tertiary amide moiety of *N*-acylpiperidine-based GPIIb/IIIa antagonists for further structure–activity study, we have prepared new 1,2,4-triazolo[4,3-*a*]pyridines. The syntheses of two classes of triazolopyridines are reported.

Piperidine-based amides are important templates in biologically active chemical systems.[1–4] Some of their prominent therapeutic applications have been in the areas of kappa-opioid analgesics,[5] antiinflammatory agents,[6] and antithrombotic agents.[7] We identified a novel series of antithrombotic agents based on nipecotic acid as a peptidomimetic scaffold, from which elarofiban[8] (RWJ-53308) was selected for clinical evaluation in humans (Eq. (1)).[9–11] Thus, as a follow-up, we sought to incorporate an element of planar, geometric rigidification into the key tertiary amide group. Possible improvements in the bioactivity and, especially, the pharmacokinetics of these fibrinogen receptor (GPIIb/IIIa) antagonists were envisioned by the use of such ring-fused analogues. In this letter, we report the synthesis of bicyclic triazolopyridines bearing functionality on both rings to accommodate the structure–activity relationship.[8] Besides providing a basis for novel fibrinogen receptor antagonists, our results suggest a general annulation strategy for the preparation of variably functionalized, fused triazole scaffolds suitable for chemical library preparation by high-throughput organic synthesis.



Elarofiban (1)

* Corresponding author. Tel: 215-628-5530; fax: 215-628-4985; e-mail: bmaryano@prius.jnj.com

† Present address: Glaxo Wellcome, Research Triangle Park, NC 27709, USA.

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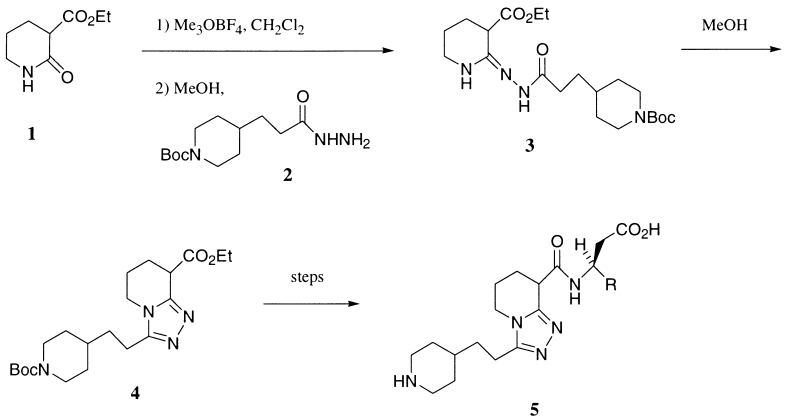
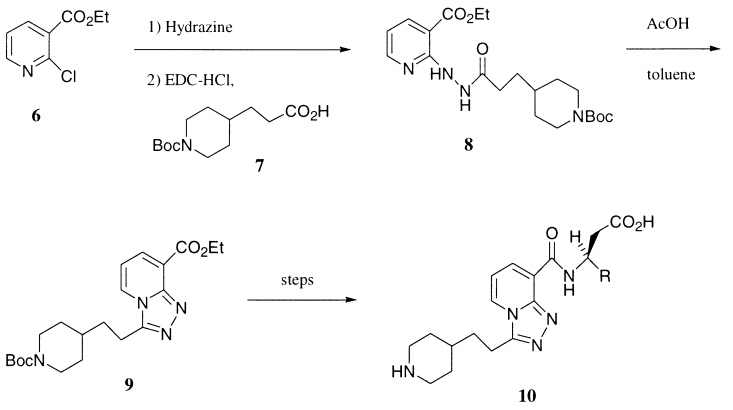
Fusion of a five-membered ring at the N-1/C-2 position of nipecotic acid would elaborate a new bicyclic ring system and thereby remove a potentially metabolically labile tertiary amide (Eq. (1)). A synthetic conversion of 2-pyrrolidinones and acylhydrazides to substituted triazolopyrroles reported by Rigo et al. provided a precedent for our nipecotic acid-type system.[12,13] In Rigo's three-step procedure, 5-carboxy-2-pyrrolidinone was *O*-methylated with dimethyl sulfate, treated with *N*-acetylhydrazide, and warmed to give an amidrazone intermediate, which was heated with chlorotrimethylsilane/triethylamine to afford the bicyclic triazole.

Disubstituted tetrahydrotriazolopyridines[14] were prepared in a similar fashion. A reliable, high-yielding method utilizing existing 3-(4-piperidine)propionic acid and enantiomerically enriched β-amino acid intermediates (R = aryl) was desired to synthesize a number of analogues on a gram scale.[15] To this end, commercially available piperidone **1** was methylated with trimethyloxonium tetrafluoroborate in dichloromethane and treated with Boc-protected acylhydrazide **2** in methanol to give an amidrazone intermediate **3** (Eq. (2)). Rigo's annulation method, which had required basic, chlorotrimethylsilane-mediated conditions at high temperatures, produced a complex mixture of products in our hands when starting with the five-membered ring system, ethyl 2-oxo-3-pyrrolidine carboxylate. By contrast, simply warming the corresponding six-membered ring amidrazone **3** in methanol under neutral conditions for an extended period of time (18–24 h) afforded tetrahydrotriazolopyridine **4** in good yield. The corresponding *N*-benzyloxycarbonyl-protected analogue of **4** was prepared in a similar fashion.



(2)

A triazolopyridine ring system with six-membered ring unsaturation[16] was also prepared to introduce further conformational rigidification of the central scaffold. To address this modification, intermediate ester **9** was prepared in three steps starting with chloronicotinate **6** (Eq. (3)).[17] Initial attempts to add hydrazide **2** directly to **6** (as in Eq. (2)) to provide acylhydrazide **8** proved unsuccessful. Alternatively, compound **6** was treated with hydrazine in warm dioxane followed by water soluble carbodiimide-mediated (EDC) formation of acylhydrazide **8**. Generation of triazolopyridine **9** by cyclization of acylhydrazide **8** utilizing neutral methanol conditions was unsuccessful in this case. Instead, the hydrazide was cyclized under acidic conditions (acetic acid/toluene, reflux) to afford key intermediate **9**.



(3)

In conclusion, we have described concise syntheses of two novel, disubstituted 1,2,4-triazolo[4,3-*a*]pyridines. Given the straightforward, three-step assembly from a key pyridyl–acylhydrazide intermediate, this methodology represents a general approach to new peptidomimetics[18] of tertiary amides. As an application of this chemistry, esters **4** and **9** were carried forward to the biologically interesting antithrombotic compounds **5** and **10**.[19,20]

Acknowledgements

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14. For a patent on 1,2,4-triazolo[4,3-*a*]pyridine-8-acetic acids as angiotensin II receptor antagonists, see: Manning, R. E.; Huang, H. C. US Patent 5,426,105, 1995.
15. Ester **4** was synthesized from **1** as follows: Trimethyloxonium tetrafluoroborate (5.46 g, 36.9 mmol) was added to a solution of ethyl 2-oxo-3-piperidine carboxylate (6.31 g, 36.9 mmol) in CH_2Cl_2 (62 mL) and the reaction was stirred for 18 h. *N*-Boc-3-(4-piperidine)propionic hydrazide (10.0 g, 36.9 mmol) in CH_2Cl_2 (62 mL) was added. The resulting mixture was stirred for 24 h, diluted with CH_2Cl_2 (150 mL), and washed with brine (2×50 mL). The organic layer was dried (Na_2SO_4) and evaporated to give a white solid, which was dissolved in MeOH (365 mL) and heated at reflux for 24 h. The mixture was cooled, concentrated in vacuo, and purified by flash chromatography (CH_2Cl_2:MeOH:NH_4OH, 97:2:1) to give **4** as a white solid (7.79 g, 52% yield, >98% purity). ^{1}H NMR ($CDCl_3$) δ 4.1 (q, 2H), 3.9 (m, 4H), 2.7 (m, 2H), 2.0 (m, 6H), 1.6 (m, 6H), 1.6 (s, 9H), 1.2 (t, 3H), 1.1 (m, 2H); ES/MS *m*/*z* 407.4 (MH^+).
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17. Ester **9** was synthesized from **6** as follows: Ethyl 2-chloronicotinate (2.1 g, 11.3 mmol) and anhydrous hydrazine (0.4 mL, 12.7 mmol) were heated in dioxane (54 mL) at 60°C for 2 h. The mixture was cooled to 23°C and concentrated in vacuo to give ethyl 2-hydrazinenicotinate (2.0 g, 97%). *N*-Boc-3-(4-piperidine)propionic acid (**7**; 2.85 g, 11.1 mmol) was dissolved in CH_2Cl_2 (55 mL), cooled to 0°C, and treated with ethyl 3-dimethylaminopropylcarbodiimide·HCl (2.55 g, 13.3 mmol), *N*-methylmorpholine (1.5 mL, 13.6 mmol), and 1-hydroxybenzotriazole (0.15 g, 1.11 mmol). Ethyl 2-hydrazinenicotinate (2.0 g, 11.0 mmol) was added and the reaction was briefly stirred at 0°C, warmed to 23°C, and stirred for 17 h. The mixture was diluted with CH_2Cl_2 (100 mL) and washed with water (3×50 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give **8** as a white solid (2.24 g, 48%), which was heated with acetic acid (6.0 mL, 105 mmol) in toluene (106 mL) at reflux for 22 h using a Dean–Stark trap containing 4 Å molecular sieves. The mixture was concentrated in vacuo and flash chromatographed (CH_2Cl_2:MeOH, 98:2) to give **9** as a white powder (1.54 g, 77% yield, >98% purity). ^{1}H NMR ($CDCl_3$) δ 8.6 (d, 1H), 8.1 (d, 1H), 7.4 (dd, 1H), 4.6 (m, 2H), 4.4 (q, 2H), 4.1 (q, 2H), 3.5 (m, 1H), 3.2 (t, 2H), 2.7 (m, 2H), 1.8 (m, 4H), 1.6 (s, 9H), 1.3 (t, 3H); ES/MS *m*/*z* 403.4 (MH^+).
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