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1,2,4-Triazolo[3,4-*a*]pyridine as a Novel, Constrained Template for Fibrinogen Receptor (GPIIb/IIIa) Antagonists

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Abstract—Conformationally constrained analogues of the GPIIb/IIIa antagonist elarofiban (RWJ-53308) have been synthesized and biologically evaluated. The 1,2,4-triazolo[3,4-*a*]pyridine scaffold provided potent antagonists with favorable pharmacodynamic and pharmacokinetic attributes in dogs. Compounds **12a** and **13a** exhibited enhancements in oral bioavailability, $t_{1/2}$, and ex vivo duration of action (inhibition of ADP-induced platelet aggregation) relative to elarofiban.

Myocardial infarction and unstable angina are associated with the activation and aggregation of platelets. The final pathway in platelet aggregation induced by diverse agents, such as collagen, ADP, and thrombin, involves binding of the adhesive protein fibrinogen to the integrin GPIIb/IIIa.[1] Prevention of resulting platelet crosslinking, and thrombus formation, by GPIIb/IIIa antagonists has therapeutic significance at least in the acute-care setting, as demonstrated by the intravenous drugs abciximab (monoclonal antibody),[2] eptifibatide (cyclic peptide),[3] and tirofiban (nonpeptide).[4] As a sequel, several research groups have pursued orally efficacious fibrinogen receptor antagonists for chronic antithrombotic therapy, although this field has been clouded recently by serious issues that have emanated from certain advanced human clinical trials.[5–7]

Studies in our laboratories have focused on nipecotic acid-based, orally active GPIIb/IIIa antagonists. Previously, we disclosed promising results on the potent, selective agent elarofiban (RWJ-53308; Table 1), which was under clinical development.[8a] Despite its zwitterionic character, elarofiban exhibited an adequate pharmacokinetic (PK) profile in dogs (16% oral bioavailability, $t_{1/2}=2$ h) along with strong pharmacodynamic (PD) effects (5-h duration for inhibition of ex vivo ADP-induced platelet aggregation) at a dose level of 1 mg/kg, po. In an effort to improve the PK and PD characteristics of elarofiban, we have explored a wide range of analogues. Among these, we examined a bicyclic 1,2,4-triazolo[3,4-*a*]pyridine scaffold, which serves to replace the nipecotic acid central unit of elarofiban with a conformationally constrained tertiary amide.[9] Fortunately, this scaffold was found to impart worthwhile PK/PD characteristics. We report herein the synthesis and biological properties of selected compounds from our novel triazolopyridine series.

Compounds **9**–**17** in Table 1 were prepared according to the chemistry in Scheme 1.[10] Reaction of hydrazide **1**[11] with imino ether **2** generated the corresponding amidrazone intermediate, which was cyclized thermally to give **3**. Ethyl ester **3** was saponified with LiOH to the corresponding carboxylic acid and then coupled by HBTU[12] activation with the appropriate amino ester followed by sequential saponification and deprotection to provide the target compounds **4**. The hydrogen α to the carboxamide in **4** is stereochemically labile. Enantiomerically enriched β-amino esters were prepared as reported.[8] The methyl group α to the carboxamide in target **11a** was installed by treating 3-carboethoxy-2-pyridone with sodium *t*-butoxide/MeI in THF at 0 °C, and then proceeding to the key α-methyl analogue of **3**, as indicated above.[11]

Compounds **9b** and **12b** were prepared according to the chemistry in Scheme 2.[10] Reaction of **5** with hydrazine, followed by the coupling of carboxylic acid **6**, produced

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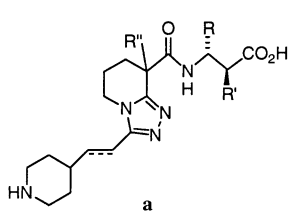
an amidrazone intermediate, which was cyclized thermally under acidic conditions to yield **7**. Saponification of the ethyl ester with aqueous NaOH, amide bond formation with BOP-Cl,[13] saponification, and deprotection provided target compounds **8**.

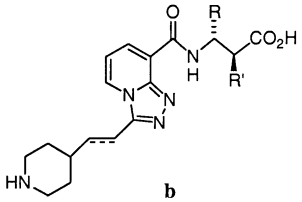
In our previous SAR studies,[8] elarofiban and RWJ-53419 exhibited nearly comparable in vitro activity (Table 1). Therefore, we prepared two sets of triazolopyridine target compounds: one with R = 3-pyridyl and R′ = H and one with R = H and R′ = NHCbz (both sets with *S* configuration). In the elarofiban series, we also found that the carbon α to the carboxamide prefers the *R* stereochemistry.[8] However, we tested the triazolopyridine series as a mixture of diastereomers because the hydrogen α to the carboxamide was stereochemically labile. The triazolopyridines were examined in vitro for activity in fibrinogen binding and platelet aggregation (Table 1).[14] Compounds **9**–**11** contain a single-bond link to the 4-position of the pendant piperidine to assess the conformational effect of triazole fusion to the six-membered-ring scaffold present in the elarofiban series. Compound **9a** establishes the effectiveness of the tetrahydro-triazolopyridine scaffold in so far as the in vitro activity of **9a** compares quite favorably to elarofiban.[15] By comparison, **9b** showed significantly decreased activity in receptor binding and gel-filtered platelet aggregation. Compound **10a** exhibited nearly comparable in vitro activity to nipecotic acid derivative RWJ-53419, and it retained good ex vivo duration against ADP-induced platelet aggregation.[15] Methylation α to the carboxamide, as in **11a** (two diastereomers in ca. 1:1 ratio), caused a significant decrease in potency.

Compounds **12**–**17**, which contain a carbon–carbon double-bond linkage to the piperidine 4-position, were

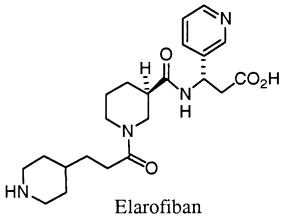
Table 1. Biological data for triazolopyridine derivatives



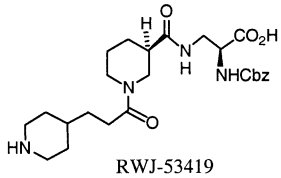
a



b



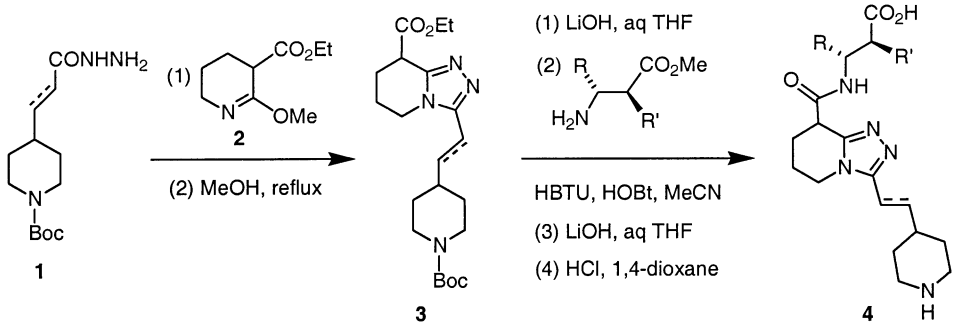
Elarofiban



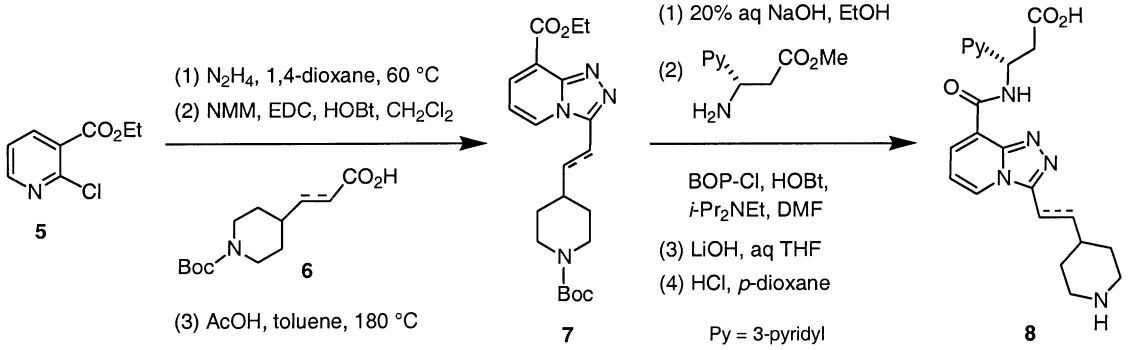
RWJ-53419

Compd[a]	R	R′	R″	Variable C–C bond	Fg binding[b] IC_{50} (nM)	GFP aggr[c] IC_{50} (μM)	Oral duration[d] at 1 mg/kg (h)
9a	3-Pyridyl	H	H	Single	0.53 ± 0.13	0.016 ± 0.001	3
9b	3-Pyridyl	H	—[e]	Single	4.2 ± 1.3	0.37 ± 0.24	NT
10a	H	NHCbz	H	Single	0.48 ± 0.01	0.068 ± 0.002	4
11a	H	NHCbz	Me	Single	18.3 ± 0.20	2.7 ± 0.6	< 0.5
12a	3-Pyridyl	H	H	Double	0.21 ± 0.08	0.061 ± 0.009	> 6.0
12b	3-Pyridyl	H	—[e]	Double	440 ± 220	Inactive @ 50	NT
13a	H	NHCbz	H	Double	0.32 ± 0.08	0.041 ± 0.002	> 6.0
14a	3-Quinolinyl	H	H	Double	0.44 ± 0.14	0.057 ± 0.01	4.5
15a	H	$NHSO_2Bn$	H	Double	0.51 ± 0.01	0.043 ± 0.017	< 0.5
16a	H	$NHCOCH_2$-3-Py	H	Double	1.36 ± 0.03	0.12 ± 0.01	NT
17a	H	$NHCO_2$-*i*-Bu	H	Double	0.60 ± 0.20	0.60 ± 0.10	NT
Elarofiban					0.36 ± 0.27	0.060 ± 0.01	5.0
RWJ-53419[e]					0.17 ± 0.03	0.027 ± 0.02	3.0

[a]For compounds of series **a**, the carbon atom bearing R″ has the *R* and *S* configuration; thus, there are two diastereomers. However, this stereogenic center is labile due to proton exchange when R″ = H (series **a** compounds except for **11a**), causing the diastereomers to readily interconvert.
[b]Inhibition of biotinylated fibrinogen binding to immobilized GPIIb/IIIa ($N = 2$).
[c]Inhibition of thrombin-induced human gel-filtered platelet aggregation ($N = 2$).
[d]Oral duration for maintaining at least 50% inhibition of platelet aggregation induced by adenosine diphosphate (ADP) (ex vivo assay). NT = not tested.
[e]Does not apply to chemical series **b**.



Scheme 1. Synthesis of **4**.



Scheme 2. Synthesis of **8**.

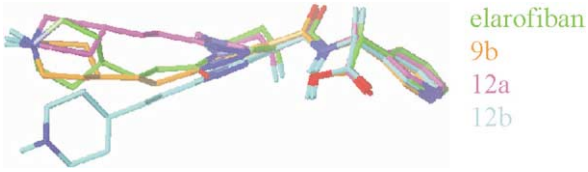


Figure 1. Energy-minimized structures for elarofiban (green), **9b** (orange), **12a** (magenta), and **12b** (light blue); N and O atoms are blue and red, respectively.

synthesized to provide π conjugation with the triazole ring system. With respect to receptor binding and inhibition of platelet aggregation, **12a** and **13a** compared favorably to **9a** and **10a** (Table 1). The structural integrity of **12a** and **13a** was maintained (>98%) over a 90-min time course in a standard liver microsomal metabolism assay,[17] and this metabolic stability was reflected in an excellent duration of action of >6 h (1 mg/kg, po) for inhibition of ex vivo ADP-induced platelet aggregation. The oral bioavailability in dogs for NHCbz analogue **12a** was 31%, with a $t_{1/2}$ of 3.85 h, and for 3-pyridyl analogue **13a** was 23%, with a $t_{1/2}$ of 6.25 h.

The 3-quinolinyl and benzylsulfonamide analogues, **14a** and **15a**, exhibited receptor binding and inhibition of platelet aggregation comparable to **12a** and **13a**. Although **14a** inhibited ex vivo platelet aggregation over a 4.5-h time course, **15a** had a very short duration of <0.5 h. The 3-pyridylmethyl and isobutyl carbamates, **16a** and **17a**, exhibited weaker in vitro activity. Interestingly, **12b** showed a dramatic reduction in receptor binding and inhibition of platelet aggregation.

To gain a further understanding of the structural issues connected with the lack of activity for **12b**, we computed energy-minimized conformations for elarofiban, **9b**, **12a**, and **12b** (Fig. 1).[18] An examination of the overlapping models of these molecules reveals a possible explanation for the loss of activity for **12b**. A comparison of **9b** and **12b** indicates that the single-bond linkage to the piperidine 4-position in **9b** provides an extra degree of freedom that allows for nearly complete overlap with elarofiban. However, it appears that **12b** is not capable of achieving good overlap with elarofiban because of its constraining double-bond linkage to the piperidine 4-position (Fig. 1).

In conclusion, the 1,2,4-triazolo[3,4-*a*]pyridine scaffold was successfully employed as a tertiary amide mimetic in the nipecotic acid series of GPIIb/IIIa antagonists. Although there was a preference in the nipecotic acid series for the *R* stereochemistry at the carbon α to the carboxamide, that center is stereochemically labile in the triazolopyridine series; nevertheless, excellent in vitro and in vivo activity was retained. When this stereocenter was removed, as in **9b**, good activity in receptor binding and gel-filtered platelet aggregation was still observed. Compounds **12a** and **13a** exhibited enhancements in oral bioavailability, $t_{1/2}$, and duration of action (as measured by ex vivo inhibition of ADP-induced platelet aggregation) relative to elarofiban. The triazolopyridine-based GPIIb/IIIa antagonists represent a new chemical series, related to the nipecotamide series, with improved pharmacokinetic and pharmacodynamic properties.[19]

Acknowledgements

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12. 2-(1*H*-Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate.
13. Bis(2-oxo-3-oxazolidinyl)phosphinic chloride.
14. Use of both in vitro assays correlated the antiplatelet activity better with in vivo efficacy.
15. The glycolamide ester[16] prodrug derivatives of **9a** and **10a** showed no benefit over the corresponding carboxylic acids.
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18. The conformations were determined with Sybyl Version 6.7 (Tripos Inc., 1699 South Hanley Road, St. Louis, MO 63144, USA) by using MOPAC (AM1 force field) and are within 2.00 kcal/mol of the next lowest energy conformation, for each case.
19. Nonstandard abbreviations not defined earlier: HOBt, 1-hydroxybenzotriazole; NMM, *N*-methylmorpholine; EDC, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.