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Derivatives of tetrahydroisoquinoline: Synthesis and initial evaluation of novel non-peptide antagonists of the $\alpha_{IIb}\beta_3$-integrin

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ABSTRACT

The novel RGDF mimetics were synthesized with the use of 4-(1,2,3,4-tetrahydroisoquinoline-7-yl)amino-4-oxobutyric or 5-(1,2,3,4-tetrahydroisoquinoline-7-yl)amino-5-oxopentanoic acids as a surrogate of Arg-Gly motif. The synthesized compounds have demonstrated a high potency to inhibit platelet aggregation in vitro and to block FITC-Fg binding to $\alpha_{IIb}\beta_3$ on washed human platelets.

Key events of thrombotic disorders, which result in various cardiovascular diseases including unstable angina, myocardial infarction, and arterial re-occlusion following coronary angioplasty procedures, are the activation and aggregation of platelets.[1] The clinical trials of monoclonal antibody c7E3 (ReoPro®),[2] the peptide Integrilin®,[3] and the non-peptides Tirofiban (Aggrastat®)[4] and Lamifiban[5] have demonstrated the utility of fibrinogen receptor (glycoprotein IIb/IIIa, $\alpha_{3IIb}\beta_3$) antagonists for the treatment of thrombotic disorders. Furthermore, RGD mimetic prodrugs Xemilofiban, Orbofiban[6] and Sibrafiban[7] succeeded in treatment of unstable angina events (Fig. 1). Fragments with the residues of *p*-benzamidine, piperidine, *p*-benzguanidine, etc., and β-alanines with different substituents in β-position are successfully applied as bioisosteres of arginine and Asp-Phe moieties, correspondingly, for the design of non-peptide fibrinogen receptor antagonists mimicking RGDF sequence.[8,9]

Previous reports from our laboratories described the discovery of the novel series of RGDF mimetics as non-peptide fibrinogen receptor antagonists.[10,11] These compounds represent derivatives of isoindoline **1**[10]or tetrahydroisoquinoline **2** (Fig. 2).[11] As an extension of this work, the synthesis of new tetrahydroisoquino-

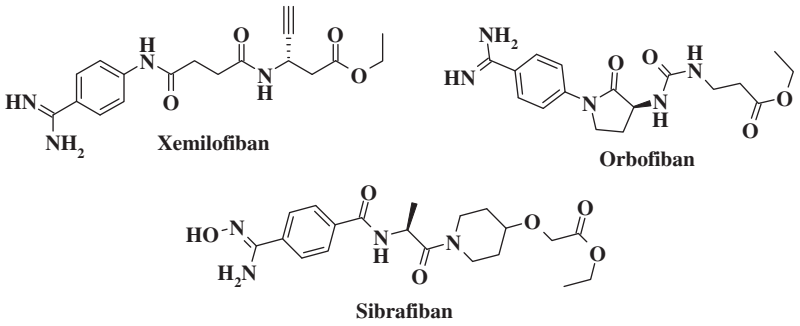

Figure 1. Structures of Xemilofiban, Orbofiban, and Sibrafiban.

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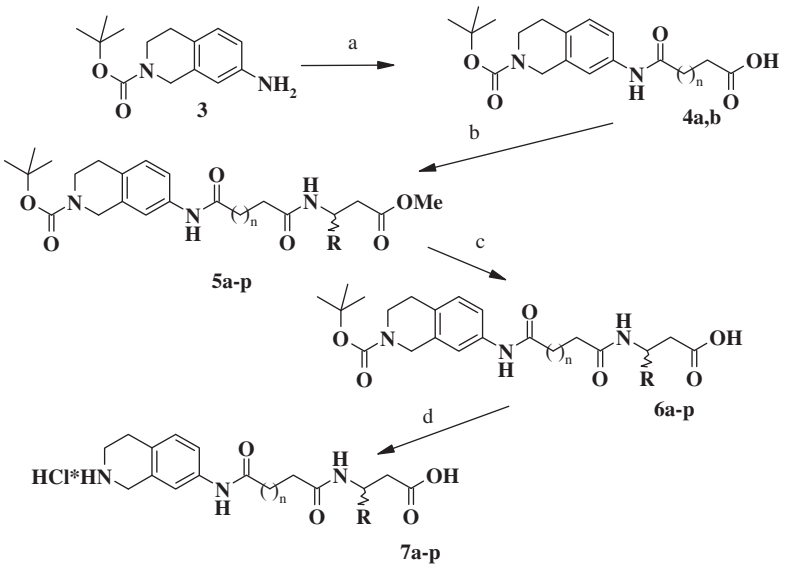


Scheme 1. Reagents: (a) succinic or glutaric anhydride, 90–95%; (b) (i) Et_3N, HBTU or HATU; (ii) β-amino acid methyl ester, Et_3N, 65–70%, two steps; (c) (i) 1 M NaOH, H_2O; (ii) 1 M HCl, H_2O, 60–74%, two steps; (d) HCl (gas)/DCM, 95–98%.

line based $\alpha_{IIb}\beta_3$ antagonists and study of their antiaggregative properties were carried out. With the aim to improve an antiplatelet activity, β-aryl substituted β-alanines were proposed for imitation of Asp-Phe moiety.

We used DCC/SuOH method for the preparation of previously reported RGD mimetics **7a** (n = 1, R = H) and **7b** (n = 1, R = C_6H_5). This method was employed at the stage when acid **4a** (n = 1) was coupled with sodium salts of appropriate β-alanines.[11a] The target

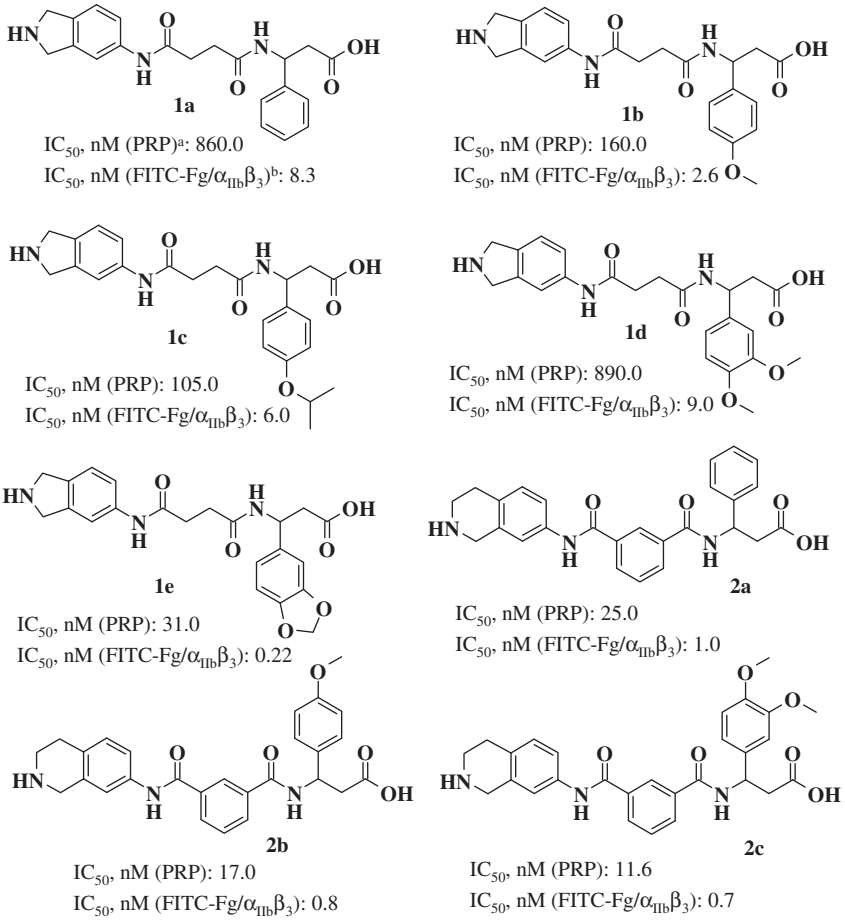
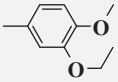
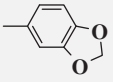
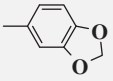


Figure 2. Structures and in vitro activities of $\alpha_{IIb}\beta_3$ antagonists of series **1** and **2**. [a]Concentration required to reduce ADP-induced human platelet aggregation response by 50%. [b]Concentration required to reduce binding of FITC-Fg to $\alpha_{IIb}\beta_3$ on the suspension of washed human platelets by 50%.

Table 1
Biological properties of RGDF mimetics **7** with tetrahydroisoquinoline fragment

Compd	*n*	R	IC_{50}[a], nM (PRP)	IC_{50}[b], nM (FITC-Fg/$\alpha_{IIb}\beta_3$)
7a	1	H	30.0[11a]	1.2[11a]
7b	1	C_6H_5	13.0[11a]	1.0[11a]
7c	1	*p*-C_6H_4–F	8.9	1.0
7d	1	*m*-C_6H_4–F	10000.0	1100.0
7e	1	*o*-C_6H_4–F	570.0	5.0
7f	1	*p*-C_6H_4–Cl	2000.0	65.0
7g	1	*p*-C_6H_4–CH_3	96.0	0.90
7h	1	*p*-C_6H_4–OCH_3	310.0	3.5
7i	1	*p*-C_6H_4-$OCH(CH_3)_2$	87.0	—
7j	1	*m*,*p*-C_6H_3–$(OCH_3)_2$	64.0	0.63
7k	1		510.0	—
7l	1		90.0	0.4
7m	1		5200.0	—
7n	2	*p*-C_6H_4–OCH_3	4200.0	18.0
7o	2	*m*,*p*-C_6H_3–$(OCH_3)_2$	127.0	5.0
7p	2		53.0	0.78
	RGDS		31000.0	13000.0

[a] Concentration required to reduce binding of FITC-Fg to $\alpha_{IIb}\beta_3$ on the suspension of washed human platelets by 50%. The IC_{50} values are expressed as the average of at least two determinations. The average error for the IC_{50} determinations was 15%.
[b] Concentration required to reduce ADP-induced human platelet aggregation response by 50%. The IC_{50} values are expressed as the average of at least two determinations. The average error for the IC_{50} determinations was 15%.

compounds **7** described in this Letter were synthesized from the acids **4** and various β-alanines esters using HBTU or HATU as a coupling reagents (Scheme 1). Esters **5** cleavage followed by deprotection gave the desired products **7**. In our study, we have prepared all mimetics only as racemic mixtures in order to reveal potent compounds and to determinate general characteristics of structure–activity relationship.

Biological activity was assessed in vitro by measuring the ability of compounds to inhibit the binding of fluoresceinisothiocyanate-labeled fibrinogen (FITC-Fg)[12] to $\alpha_{IIb}\beta_3$ (in a suspension of human washed platelets).[13] Functional activity was subsequently determined by measuring the inhibition of ADP induced platelet aggregation in human platelet-rich plasma (PRP) by Born's method.[14] Experimental data (Table 1) evidently show high affinities of the compounds **7** for $\alpha_{IIb}\beta_3$.

Analogue **7c**, which contains a fluorine atom at *para* position of β-phenyl-β-alanine residue, was equipotent with the compound **7b** by affinity and 1.4-fold more active in PRP. Substantial decrease of antiaggregative activity and affinity compared to the lead **7b** was observed for the *meta*-fluorine containing derivative **7d**. For *ortho*-fluorine containing mimetic **7e,** activity in both assays less dramatically decreased related to **7b**. Replacement of the fluorine with chlorine **7f** generally resulted in a diminution of inhibitory properties. Incorporation of a methyl group **7g** negatively impacted antiaggregative activity, while binding affinity was practically unaffected. Introduction of alkoxy substituents to β-phenyl-β-alanine fragment decreased the activity in PRP. It should be mentioned that similar modification for the series **2** afforded more pronounced increase both in antiaggregative activity and affinity.[11b] 3,4-Methylenedioxyphenyl derivative **7l** had the highest affinity among the compounds **7** and quite a good antiaggregative properties, while analogous modification for the derivative **1e** resulted in greater growth of antiaggregative activity and affinity related to the **1a**.[10b] Replacement of succinyl linker with glutaryl one generally had a negative impact on PRP activity and affinity, with the exception of mimetic **7p**, which had IC_{50} values for PRP activity and affinity comparable to the values for **7l**. Decrease of antiaggregative activity relative to the **7b** was observed for analogue **7m** containing the residue of β-(naphthalen-1-yl)-β-alanine.

In summary, we have investigated modification of β-phenyl substituted β-alanines for non-peptide fibrinogen receptor antagonists based on 7-amino-1,2,3,4-tetrahydroisoquinoline. Introduction of fluorine group to *para* position afforded the potent analogue, while incorporation of this into *meta* and *ortho* positions, as well as replacement of fluorine with chlorine atom, resulted in less active compounds. The trend towards lower activity was also seen with methyl and methoxy substituents in *para* position, and at the replacement of succinyl linker by glutaryl one. The use of β-(3,4-methylenedioxyphenyl)-β-alanines leads to the obtaining of fibrinogen receptor antagonists with high affinity and good antiaggregative activity.

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