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TETRAHYDROTHIENOPYRIDINE DERIVATIVES AS NOVEL GPIIB/IIIA ANTAGONISTS

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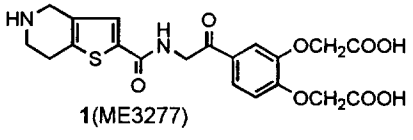
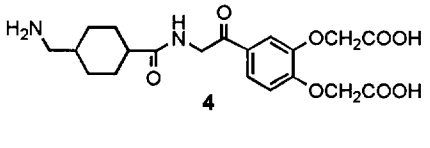
Abstract: The tetrahydrothienopyridine derivatives were derived from aminomethylcyclohexylcarboxylic acid as a lead moiety. Evaluation of the antiplatelet activity and receptor binding assay revealed that compound **1**(ME3277) was a novel and potent non-peptide and non-amidinophenyl GPIIb/IIIa antagonist.

The final obligatory step in platelet aggregation is the binding of fibrinogen to an activated membrane-bound glycoprotein complex, GPIIb/IIIa. [1-4] This receptor, which is a member of the integrin super family of adhesion molecule, is known to recognize the Arg-Gly-Asp(RGD) sequence in fibrinogen. [5-7] Blocking of this binding has been demonstrated to inhibit platelet aggregation, and may provide a possible therapeutic approach for the treatment of thrombotic diseases such as myocardial infarction and stroke. [8, 9]

Recently a number of non-peptide GPIIb/IIIa antagonists have been synthesized and characterized. [10-12] Most of them contain an amidinophenyl group **2** as a basic function to mimic the guanidine group of Arg and a carboxylic acid to substitute for the carboxylate of Asp. Our effort to develop a new GPIIb/IIIa antagonist was focussed on finding a new basic function in place of an amidinophenyl group **2** which is often used as a pharmacophor of thrombin inhibitors and may associate with bleeding complication caused by additional anti-coagulation activity. In this paper, we report the synthesis and antiplatelet activity of a new series of non-peptide and non-amidinophenyl GPIIb/IIIa antagonists, leading to the discovery of compound **1**(ME3277).



1(ME3277)



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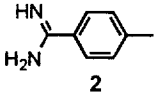

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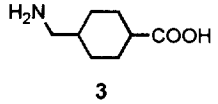


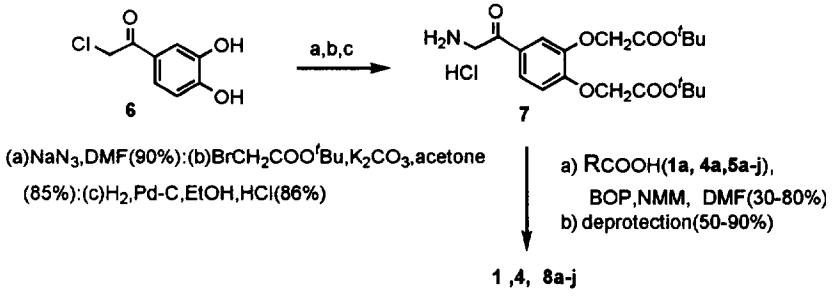
3

The compound **3**, which was designed by the reduction of amidinophenyl group and known as tranexamic acid, was chosen as a starting lead of a basic portion, and was coupled with [4-(aminoacetyl)-o-phenylene]dioxy diacetic acid [10] through an amide bond to give compound **4**. Evaluation of it's inhibitory activity against ADP-mediated human platelet aggregation [13] (IC_{50} =4.3μM) and biotinylated fibrinogen binding to GPIIb/IIIa [14] (IC_{50} = 0.73μM) revealed that **4** could be an appropriate lead compound as a specific GPIIb/IIIa antagonist.

Synthesis:

The compounds **1,4,8a-j** listed in Table 1 and 2 were synthesized by BOP reagent mediated coupling of the corresponding N-protected amino acids **1a,4a,5a-j** with di-*tert*-butyl [[4-(aminoacetyl)-o-phenylene]dioxy]diacetate **7**, which was afforded by substitution of chloroacetylcatechol **6** with sodium azide and successive alkylation and reduction. The resulting coupling products were deprotected to give **1,4,8a-j** (Scheme 1).

Scheme 1



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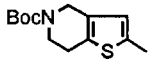
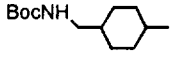
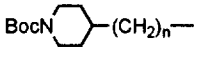
1a		15
4a		-
		
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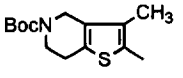
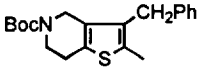
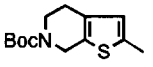
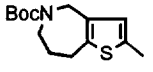
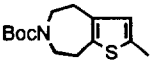
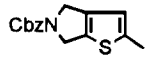
b	n = 1	-
c	n = 2	16
d	n = 3	16

	R	ref.
5e		-
f		-
g		-
h		17
i		17
j		-

N-Protected amino acids **1a,4a,5a-j** were prepared as follows.

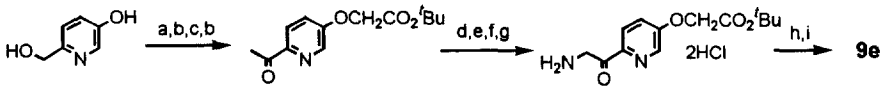
Free amino acids of **1a**, **8b-d** and **8h,i** were obtained by the methods described in the references cited in Scheme 1, and their amino groups were protected with di-*tert*-butyl dicarbonate to give **1a,5b-d** and **5h,i**.

Lithiation of **1a** with 2 equiv. of *n*-BuLi and successive alkylation with methyl iodide or benzyl bromide afforded **5e** and **f**.

Boc-protected 4,5,6,7-tetrahydrothieno[2,3-c]pyridine-2-carboxylic acid **5g** was synthesized by *tert*.-butoxycarbonylation of 4,5,6,7-tetrahydrothieno[2,3-c]pyridine [18] and successive carboxylation with *n*-BuLi- carbon dioxide.

Cbz-protected **5j** was obtained by cyclization of methyl 2,3-bis(chloromethyl)thiophen-5-carboxylate [19] with veratrylamine and successive carbobenzoxylation with carbobenzoxy chloride and saponification of methyl ester.

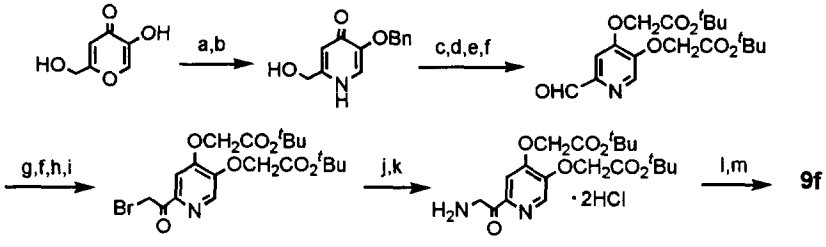
Scheme 2



(a) NaH,$BrCH_2COO^tBu$,DMF(81%); (b) MnO_2,CH_2Cl_2(86%); (c) CH_3MgBr,THF(77%); (d) TMSOTf,NEt_3,$ClCH_2CH_2Cl$; (e) NBS,THF(80%); (f) NaN_3,DMF(71%); (g) H_2,Pd-C,EtOH,HCl(q.y.); (h) **1a**,BOP,NMM,DMF(60%); (i) TFA(73%)

Carboxy terminus of **1** was modified using the corresponding phenolic acetophenone derivatives to give **9a-d**, and phenyl group was converted to pyridine group, as shown in schemes 2 and 3, to give **9e,f**.

Scheme 3

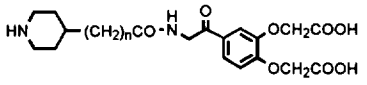


(a) BnCl,K_2CO_3,DMF(75%); (b) NH_4OH,MeOH(82%); (c) $BrCH_2CO_2^tBu$,K_2CO_3,DMF(56%); (d) H_2,Pd-C,MeOH(84%); (e) $BrCH_2CO_2^tBu$,NaH,DMF(71%,); (f) MnO_2,CH_2Cl_2(77%,93%); (g) CH_3MgBr,THF(59%); (h)TMSOTf,NEt_3,$ClCH_2CH_2Cl$; (i) NBS(48%); (j) NaN_3,DMF(88%); (k) H_2,Pd-C,EtOH-$CHCl_3$,HCl(88%); (l) **1a**,BOP,NMM,DMF(47%); (m) TFA(67%)

Result and discussion:

After aminomethylcyclohexyl carboxamide derivative **4** had been proved to be an appropriate lead compound, aminomethylcyclohexyl group was replaced by piperidinyl ethyl group to give **8c**. Then, the distance between the basic terminal and the carboxyl terminal of **8c** was changed by altering the number of methylene unit.

Table 1.



8a-d

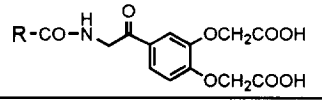
Compd	n	IC_{50} [a]	IC_{50} [b]
8a	0	9.8	>1.0
b	1	10	>0.1
c	2	0.35	0.042
d	3	9.0	>0.1
4	-	4.3	0.73
RGDS		87	0.076

a) Inhibitory activity against ADP(10μM)-mediated platelet aggregation in human platelet rich plasma[13](μM) (n=2)
b) Inhibitory activity against biotinylated fibrinogen binding to GPIIb/IIIa[14](μM) (n=2)

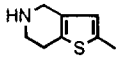
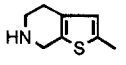
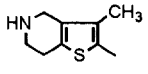
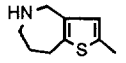
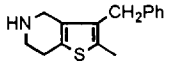
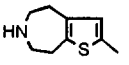
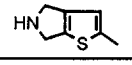
Table 1 shows that **8c**, which possesses a piperidine ring as an amino terminal and two methylene unit, was found to be 10-fold more potent than **4**.

Condensation of piperidine with thiophene ring keeping two methylene distance in **8c** gave **1**, which showed even more potent inhibitory activity than **8c** against both ADP-mediated human platelet aggregation and binding of fibrinogen to GPIIb/IIIa (Table 2).

Table 2



1,8e-j

Compd.	R	IC_{50} [a]	IC_{50} [b]	Compd.	R	IC_{50} [a]	IC_{50} [b]
1		0.16	0.0047	8g		0.23	0.0014
8e		2.5	0.018	h		1.9	0.0087
f		>10	0.062	i		0.15	0.006
	RGDS	87	0.076	j		1.6	>0.1

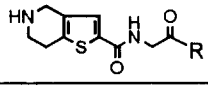
a),b) See the footnotes of Table 1.

Further modification was focused on N-terminus features such as a substituent at β

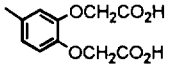
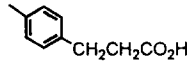
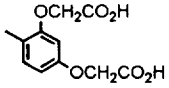
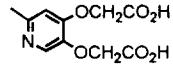
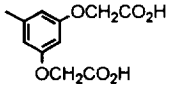
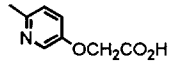
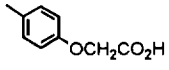
position of thiophene ring, a position of nitrogen and a ring size (Table 2).

Introduction of an alkyl group at the β position of thiophene ring (**8e,f**) resulted in a considerable decrease in potency probably owing to the bulkiness of the substituents. The position of nitrogen and the ring size slightly affected the inhibitory activity against both aggregation and binding (**8g-j**).

Table 3



1,9a-f

Compd.	R	IC_{50} [a]	IC_{50} [b]	Compd.	R	IC_{50} [a]	IC_{50} [b]
1		0.17	0.0056	9d		>10	0.08
9a		1.5	>0.1	e		0.47	0.0098
b		>10	>1.0	f		0.72	0.1
c		1.2	0.031		RGDS	87	0.076

a),b) See the footnotes of Table 1

Structural optimization on the carboxy-terminus of compound **1** revealed that the oxyacetic acid moiety at the para position to ketone function plays an important role in acquring inhibitory activities against both aggregation and binding (Table 3).

We selected **1** as one of the most potent platelet aggregation inhibitors and fibrinogen receptor antagonists, and further evaluated its receptor selectivity as shown in Table 4. Differed from RGDS, **1** didn't affect vitronectin and fibronectin receptors at 100μM and was proved to be specific to GPIIb/IIIa.

Table 4. Receptor selectivity of compoud **1**. [21] IC_{50} (μM) (n=3)

Compounds	GPIIb/IIIa -fibrinogen	GPIIb/IIIa -vWF	vitronectin receptor [20] -vitronectin	fibronectin receptor [20] -fibronectin
1	0.0056	0.028	>100	>100
RGDS	0.076	4.0	1.4	0.51

In summary, we have reported the preparation and evaluation of new tetrahydrothienopyridine derivatives as RGD mimic GPIIb/IIIa antagonists. Structural optimization yielded **1**(ME3277) as a potent and specific GPIIb/IIIa antagonist.

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21. Solid phase binding assay was performed using biotinylated ligand and peroxidase conjugated avidin interaction according to the method described in the reference 14 (n=3).

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