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DESIGN AND SYNTHESIS OF AMIDINO-TYROSINE DERIVATIVES AS NON-PEPTIDE FIBRINOGEN RECEPTOR ANTAGONISTS

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Abstract: The design, synthesis and antiaggregation activity of amidino-tyrosine derivatives based on Arg-Gly-Asp (RGD) tripeptide sequence as non-peptide fibrinogen receptor antagonists is described. Optimization of the spacer and the substituent at the C-terminal is reported. © 1999 Elsevier Science Ltd. All rights reserved.

Uncontrolled platelet aggregation and platelet adhesion to the subendothelium of damaged blood vessels cause life-threatening diseases such as myocardial infarction, transient ischemic attack, and unstable angina. Regardless of the activating signal, the binding of plasma protein fibrinogen to the glycoprotein (GPIIb/IIIa) on the surface of activated platelets[1] would be the main reason. This binding is mediated in part by Arg-Gly-Asp (RGD) sequence present in fibrinogen[2], therefore, compounds that are characteristic of this tripeptide have the possibility of inhibiting platelet aggregation. Many groups have reported the potent compounds synthesized by mimicking the RGD sequence that possess vectors of the pharmaphore: a basic functional group that mimics the side chain of arginine residue and an acidic group that represents the aspartyl side chain of C-terminal amino acid, which are linked by various spacers.[3]

We now report the synthesis and pharmacology of a series of the designed compounds based on RGD sequence. We selected amidino group as basic terminal and tyrosine fragment as acidic terminal since both of them are very popular and proved to be important in some non-peptide receptor antagonists reported.[4,5] We also noticed the spacer that linked the two terminals in proper spatial positions were quite critical for variations of molecules. We selected polar aminocarbonylmethylene as the spacer mimicking the polar linker of RGD. For further optimization of the structure in polarity and in length on the compound activity, we also synthesized a series of compounds that possess oxyalkylene as the spacer.

The synthesis of the target compounds **5a-d** was achieved in 10 steps beginning with L-tyrosine and 4-nitrobenzoic acid. The L-tyrosine was converted to N-substituted-L-tyrosine methyl ester **1** with satisfied yield upon esterification at the carboxylate[6] and selected acylation at the nitrogen atom.[7] 4-Nitrobenzoic acid reacted

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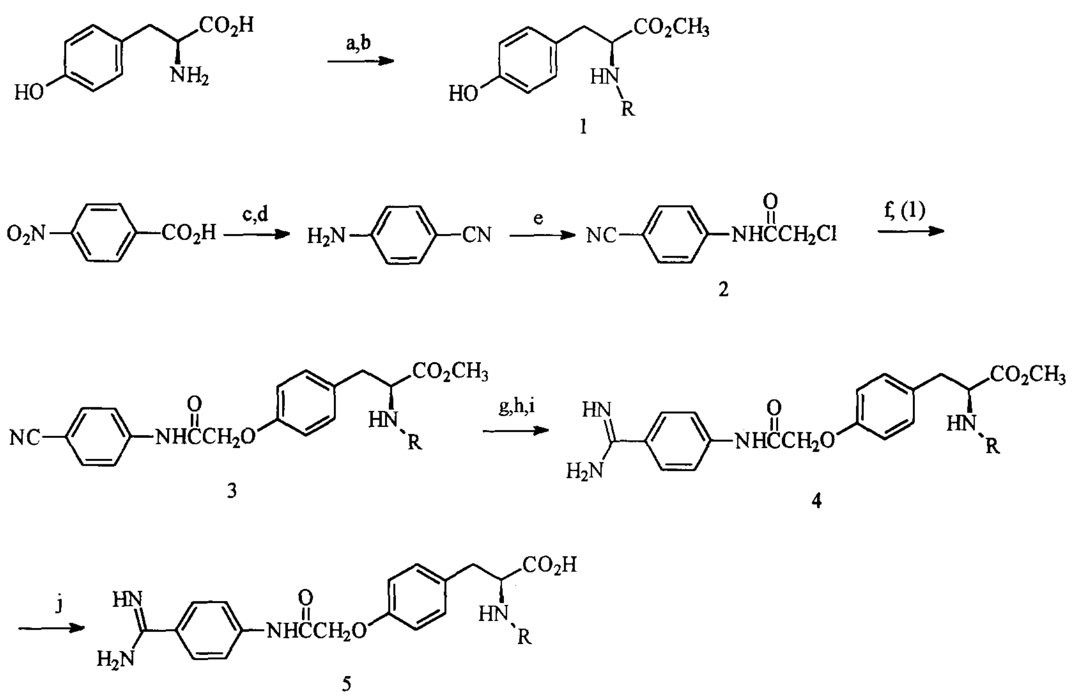
with p-toluenesulfonamide to give 4-nitrobenzonitrile,[8] followed by reduction upon iron power to afford 4-aminobenzonitrile. By acylation of 4-aminobenzonitride with chloroacetyl chloride in pyridine, the key intermediate N-(4-cyanophenyl)chloroacetamide **2** was prepared in reasonable yield. Coupling compound **2** with N-substituted –L-tyrosine methyl ester **1** led to nitrile **3**. The nitrile group in **3** was converted to the amidino group in **4** following the known three-step standard procedures:[4] The nitrile **3** in pyridine/TEA solution saturated with H_2S changed to thioamide, which reacted with iodomethane in acetone led to thioiminomethyl ester, and finally transformed to amidino compounds **4** upon ammonification with ammonium acetate in methanol. Conversion of compounds **4** to free acid **5a-d** was carried out by optimized method of selective hydration of methyl ester with lithium hydroxide in THF/aqueous solution (Scheme 1).

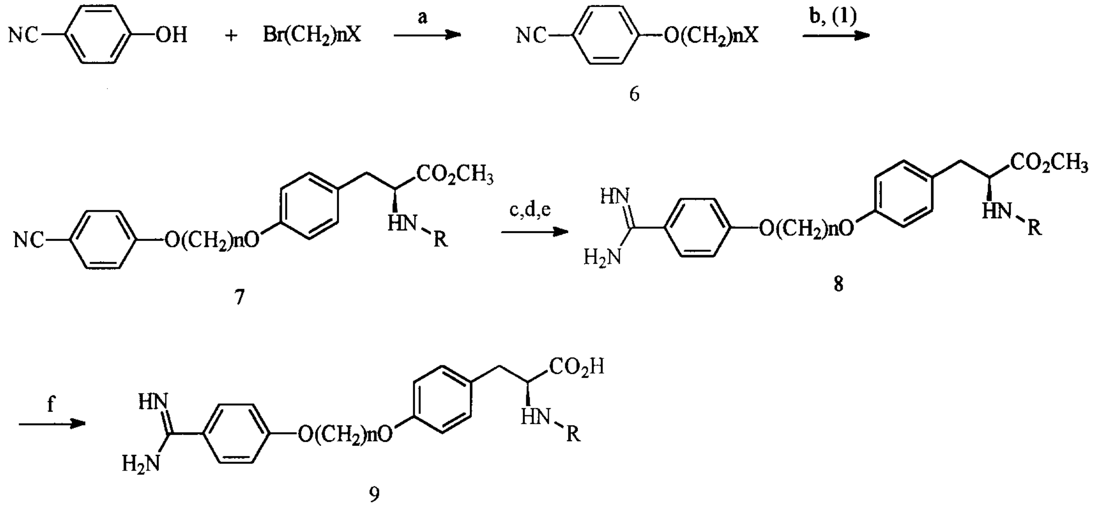
Scheme 1



Reagents: (a) methanol, $SOCl_2$ (95%); (b) acyl chloride, Na_2CO_3, chloroform/water (80-90%); (c) p-Toluenesulfonamide, PCl_5, Py (65%); (d) Fe/HCl, (86%); (e) chloroacetyl chloride, Py (95%); (f) N-Substituted-L-tyrosine methyl ester **1**, Na_2CO_3, acetone (40-70%); (g) H_2S, Py/TEA; (h) CH_3I, methanol; (i) NH_4OAc, methanol (34-78%); (j) LiOH, THF/H_2O (50-85%)

The synthesis of the target compounds **9a-d** was achieved in 6 steps beginning with 4-cyanophenol and N-substituted–L-tyrosine methyl ester **1**. 1,2-Dibromoethane or 1-bromo-3-chloropropane or 1,4-dibromobutane reacted with 4-cyanophenol in sodium hydroxide solution to afford the monosubstituted compounds with one bromo replaced by 4-cyanophenoxyl. Coupling **6** with **1** in DMF led to nitrile intermediate **7**, which was converted to the amidino compounds **8** by the above three-step standard procedures and finally to the target compounds by selective hydration of methyl ester (Scheme 2).

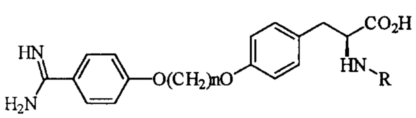
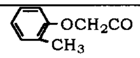
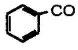
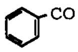
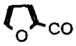
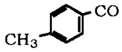
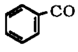
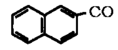
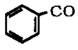
Scheme 2



Reagents: (a) 1,2-dibromoethane or 1-bromo-3-chloropropane or 1,4-dibromobutane, NaOH, H_2O, $Bu_4N^+Br^-$ (50-69%); (b) N-Substituted-L-tyrosine methyl ester **1**, Na_2CO_3, DMF (45-73%); (c) H_2S, Py/TEA; (d) CH_3I, methanol; (e) NH_4OAc, methanol (42-67%); (f) LiOH, THF/H_2O (53-81%)

The inhibitory constants (IC_{50}) upon ADP-induced platelet aggregation of the synthesized compounds **5** and **9** were determined by the known method.[9] The results are presented in Table 1.

Table 1 The Biological Activity of Compounds **5** and **9**

						
compound	R	IC_{50}(mol/L)	compound	n	R	IC_{50}(mol/L)
5a		6.1×10^{-7}	9a	2		7.4×10^{-7}
5b		2.7×10^{-7}	9b	2		7.1×10^{-7}
5c		2.5×10^{-7}	9c	3		$>1\times10^{-6}$
5d		5.1×10^{-7}	9d	4		$>1\times10^{-6}$

As indicated in Table 1, the IC_{50} of most compounds were at the range of 10^{-7}mol/L. In the series of aminomethylene spacer, the compounds being substituted at the C-terminal by benzoyl or p-methylbenzoyl (**5b** and **5c**) were found most potent active, over two-fold potent of the rest of this series and the oxyethylene series. Lengthening the distance between the terminals leads to reduce activity as in the case of benzoyl substituent in the oxypropylene and oxybutylene series (**9a**, **9c** and **9d**). While lower the polarity of the spacer leads to a slight reduce of activity comparing **9a** to **5b**.

In conclusion, we have synthesized and evaluated a new series of amidino-carboxylate derivatives as non-peptide fibrinogen receptor antagonists, in which the spacer was varied in length and polarity by mimicking the RGD tripeptide. It was found that many of these compounds showed inhibitory activity at the range of 10^{-7}mol/L on platelet aggregation.

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