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NONPEPTIDE GLYCOPROTEIN IIB/IIIA INHIBITORS. 12. POTENT AND ORALLY ACTIVE CENTRALLY CONSTRAINED THIENO[2,3-c]PYRIDONES

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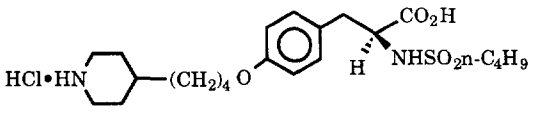
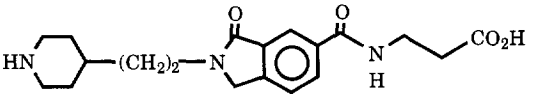
Abstract: A series of potent, orally active thieno[2,3-c]pyridone GPIIb/IIIa inhibitors featuring β-alanine C-2 sulfonamide substitution is described. Copyright © 1996 Elsevier Science Ltd

The final common pathway in the aggregation of platelets involves the binding of fibrinogen to its platelet receptor glycoprotein IIb/IIIa (GP IIb/IIIa).[1] This key protein interaction, and consequently platelet aggregation, can be inhibited by a wide variety of peptides and nonpeptides that mimic the Arg-Gly-Asp segments that are harbored in the α-chains of fibrinogen.[2]

Recently, our laboratories identified the nonpeptide platelet aggregation inhibitor tirofiban hydrochloride (AGGRASTAT™, MK-383)[3,4] that features an α-sulfonamido moiety as a unique potency enhancing feature. Since the sulfonamido group had no analogous correlate from SAR established by earlier peptide and nonpeptide RGD mimics, we[3] were led to postulate an "exosite" interaction[5] for this key functionality. Following intravenous administration, MK-383 in both the preclinical[6,7] and clinical[8] settings has proven to be a safe agent with potential for the modulation of acute coronary ischemic disease. Importantly, the pharmacokinetic and pharmacodynamic lifetimes of MK-383 are brief, ensuring a rapid return of platelet function after dosing.



AGGRASTAT™ (MK-383)



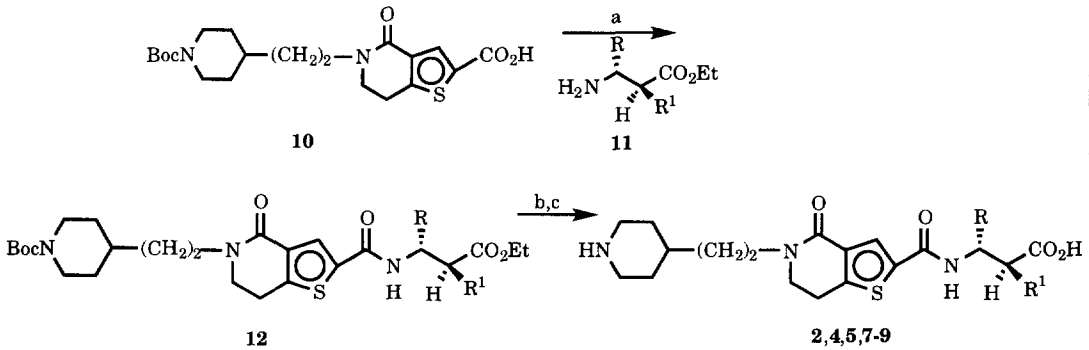
1 (L-709,780)

In pursuit of orally active GP IIb/IIIa inhibitors, we have identified the "centrally constrained" isoindolinone nucleus of **1**[9,10,11] as a key structural unit that maintains potency for inhibition of platelet aggregation and selectivity for GP IIb/IIIa. Based on the SAR in this class, we[12] and others[13] have postulated a 'cup-shaped' conformation for the most potent examples. We have extended these studies to the thieno[2,3-c]pyridone series and now report new in vitro inhibition of platelet aggregation and oral activity data that highlight the opportunities in this structural class.

Chemistry

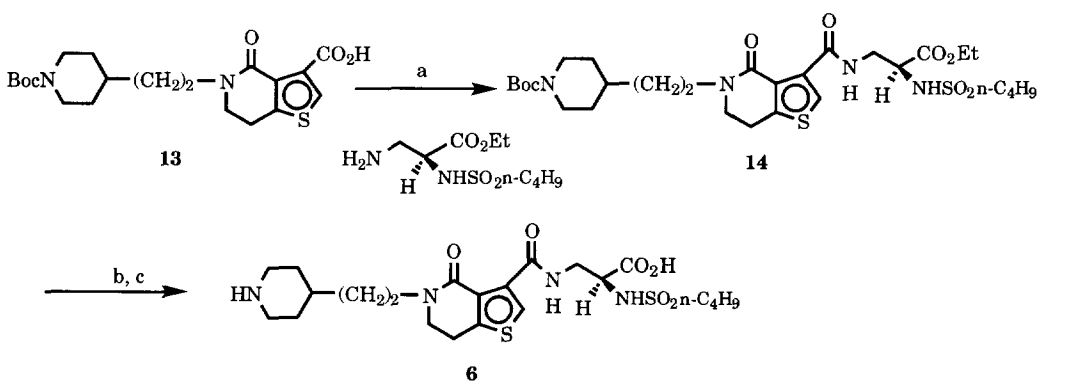
Thieno[2,3-c]pyridone analogs **2**, **4**, **5**, **7**, **8**, and **9** were prepared from **10**[14] and the appropriate β-alanine **11**[10] under standard EDC coupling conditions (Scheme 1). Positional isomer **6** was prepared from **13**[14] in a similar fashion (Scheme 2). Analog **3** was prepared by treatment of the lithio derivative of **15**[14] with δ-valerolactone to provide **16**, which was oxidized and deprotected (Scheme 3).

Scheme 1



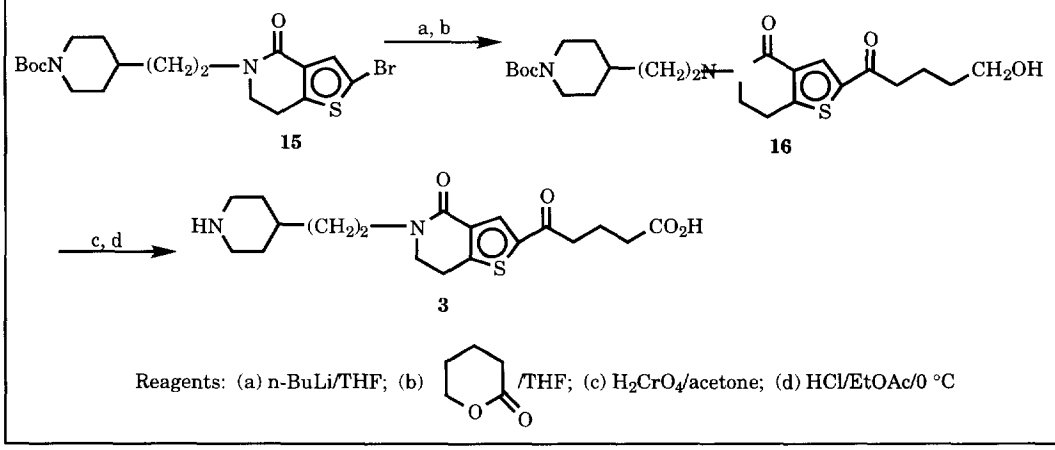
Reagents: (a) EDC/HOBT/NMM/DMF; (b) LiOH/MeOH/THF/H_2O; (c) HCl/EtOAc/0 °C.

Scheme 2



Reagents: (a) EDC/HOBT/NMM/DMF; (b) LiOH/MeOH/THF/H_2O; (c) HCl/EtOAc/0 °C

Scheme 3



Results and Discussion

Replacement of isoindolinone by thieno[2,3-c]pyridone allowed maintenance of the requisite bicyclic constraint while providing the opportunity to alter substitution sites and physical properties in a direct fashion. Compared to the parent isoindolinone L-709,780(**1**),[9] the unsubstituted thieno[2,3-c]pyridone **2** was 6-fold less potent, reflecting a less than optimum, but adequate orientation of the C-terminal β-alanine unit (Table 1). Replacement of the amide nitrogen of **2** with methylene afforded **3**, which harbored another 2-fold loss in potency.

A key goal in the thieno[2,3-c]pyridone series was to establish sites of substitution that were associated with potency enhancement. This was particularly crucial at the C-terminal β-alanine unit, since in peptide[15] and some nonpeptide compounds[16,17] 3-substituents were favored, while in other nonpeptide inhibitors 2-substituted analogs[3,4,18] were optimum. The 3(R)-methyl analog of **2** was chosen for study, since earlier work[17] had established a 5-to 10-fold potency enhancement for this substituent in an analogous structural series. However, when **4** was found to be similar in potency to **2**, our attention was focused on 2-substituted analogs (Table 2). Gratifyingly, the 2(S)-n-butylsulfonylamino analog **5** proved to be at least 15-fold more potent than the parent **2**. The position of side-chain substitution on the thiophene was of crucial importance, as the 3-thienyl analog **6** was more than 4000-fold less potent than **5**.

Empirically, we find that inhibitor molecules that are linear peptides or unconstrained nonpeptides exhibit greater potency enhancements when substitution is at the 3-position, compared to the 2-position of the C-terminal β-alanine. Conversely, those molecules that we have classified as "centrally constrained", or those others that have significant conformational restraint at the N-terminus[17] require C-2 β-alanine substitution for optimum potency enhancement.

A variety of C-2 substituted analogs of **5** were studied. For example, the phenylsulfonyl(**7**) and 3-pyridyl(**8**) variants were prepared and found to be of similar potency to **5**. However, the benzylurea derivative **9** was modestly less potent than the alkyl- or arylsulfonyl compounds mentioned, in analogy to earlier results in the isoindolinone series.[10,11]

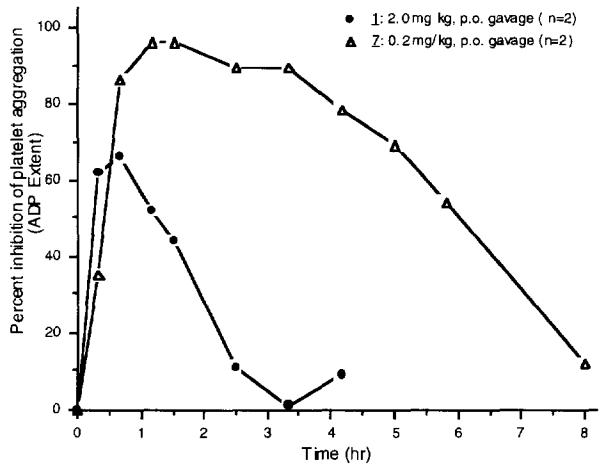


Figure 1. Inhibition of the extent of exvivo platelet aggregation in response to ADP (10 μM ADP + 1 μM epinephrine) after oral administration of **1** or **7** in conscious mongrel dogs.

The oral activity of **7**[19] was studied in the mongrel dog. Intravenous bolus administration of 10 μg/kg of **7** resulted in 100% inhibition of ex vivo ADP-mediated platelet aggregation[20] with platelet activity returning to baseline levels after 3 h. Oral administration of 0.2 mg/kg **7** (Figure 1) resulted in 80-100% inhibition from 1-4 h post dose, with platelet function gradually recovering during the 4-8 h post dose time period. Thus, the oral profile of **7** at 0.2mg/kg in the dog represents a dramatic improvement over that found with **1** at 2 mg/kg.[11]

TABLE 1

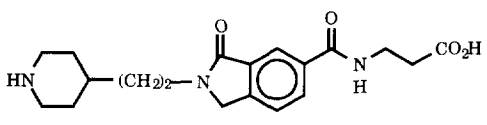
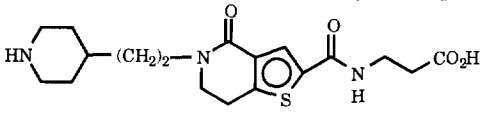
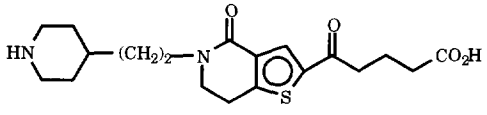
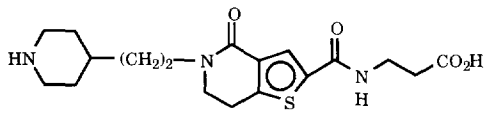
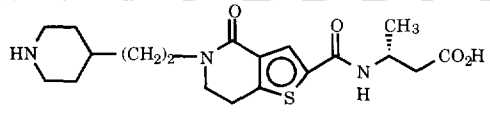
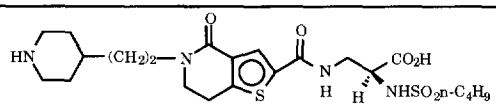
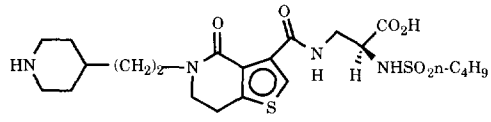
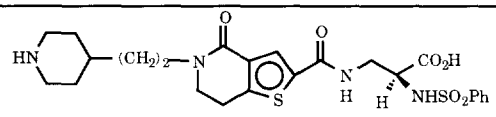
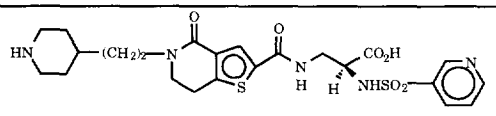
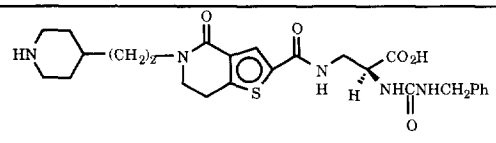
Structure	IC_{50} (nM)[20]
 **1** (L-709,780)	25
 **2**	150
 **3**	260

TABLE 2

Structure	IC_{50} (nM)[20]
 **2**	150
 **4**	220
 **5**	8
 **6**	33,000
 **7**	7
 **8**	13
 **9**	25

Acknowledgements: We thank Dr. Robert L. Smith and Dr. Paul S. Anderson for their support of this work and Ms. Jean Kaysen for preparation of the manuscript.

References and Notes:

1. Fuster, V.; Badimon, L.; Badimon, J.; Chesebro, J. *N. Eng. J. Med.* **1992**, *326*, 310.
2. Hawiger, J.; Kloczewiak, M.; Bednarek, M. A.; Timmons, S. *Biochemistry* **1989**, *28*, 2909.
3. Hartman, G. D.; Egbertson, M. S.; Halczenko, W.; Laswell, W. L.; Duggan, M. E.; Smith, R. L.; Naylor, A. M.; Manno, P. D.; Lynch, R. J.; Zhang, G.; Chang, C. T.-C.; Gould, R. J. *J. Med. Chem.* **1992**, *35*, 4640.
4. Egbertson, M. S.; Chang, C. T.-C.; Duggan, M. E.; Gould, R. J.; Halczenko, W.; Hartman, G. D.; Laswell, W. L.; Lynch, J. J. Jr.; Lynch, R. J.; Manno, P. D.; Naylor, A. M.; Prugh, J. D.; Ramjit, D. M.; Sitko, G. R.; Smith, R. L.; Turchi, L. M.; Zhang, G. *J. Med. Chem.* **1994**, *37*, 2537.
5. Yamada, T.; Kidera, A. *FEBS Lett.* **1996**, *387*, 11.
6. Gould, R. J.; Lynch, J. J. Jr.; Schaffer, L.; Siegl, P. K. S.; Sitko, G. R.; Ramjit, D. R.; Mellott, M. J.; Stabilito, I. I.; Friedman, P. A.; Egbertson, M. S.; Halczenko, W.; Laswell, W. L.; Smith, R. L.; Anderson, P. S.; Hartman, G. D. *Thromb. Hemostas.* **1993**, *69*, 539.
7. Lynch, J. J. Jr.; Cook, J. J.; Sitko, G. R.; Holahan, M. A.; Ramjit, D. R.; Mellot, M. J.; Stranieri, M. T.; Stabilito, I. I.; Zhang, G.; Lynch, R. J.; Manno, P. D.; Chang, C. T.-C.; Egbertson, M. S.; Halczenko, W.; Duggan, M. E.; Laswell, W. L.; Vassallo, L. M.; Shafer, J. A.; Anderson, P. S.; Friedman, P. F.; Hartman, G. D.; Gould, R. J. *J. Pharm. Exp. Ther.* **1995**, *272*, 20.
8. Peerlinck, K.; DeLepeleire, I.; Goldberg, M.; Farrell, D.; Barrett, J.; Hand, E.; Panebianco, D.; Deckonyn, H.; Vermylen, J.; Armont, J. *Circulation* **1993**, *88*, 1512.
9. Egbertson, M. S.; Naylor, A. M.; Hartman, G. D.; Cook, J. J.; Gould, R. J.; Holahan, M. A.; Lynch, J. J. Jr.; Lynch, R. J.; Stanieri, M.; Vassallo, L. M. *Bioorg. Med. Chem. Lett.* **1994**, *15*, 1835.
10. Egbertson, M.S.; Bednar, B.; Bednar, R.A.; Hartman, G.D.; Gould, R. J.; Lynch, R.J.; Vassallo, L.M.; Young, S.D. *Bioorg. Med. Chem Lett.* **1996**, 12, 1415.
11. Egbertson, M. S.; Hartman, G. D.; Gould, R. J.; Bednar, B.; Bednar, R. A.; Cook, J. J.; Gaul, L. S.; Holahan, M. A.; Libby, L. A.; Lynch, J. J., Jr.; Lynch, R. J.; Sitko, G. R.; Stranieri, M. T.; Vassallo, L. M. *Bioorg. Med. Chem. Lett.*, in press.
12. Naylor, A. M.; Egbertson, M. S.; Vassallo, L. M.; Birchenough, L. A.; Zhang, G. A.; Gould, R. J.; Hartman, G. D. *Bioorg. Med. Chem. Lett.* **1994**, *15*, 1941.
13. McDowell, R. S.; Gadek, T. R. *J. Am. Chem. Soc.* **1992**, *24*, 9245.
14. Halczenko, W.; Hartman, G. D. *Synth. Commun.* **1996**, *26*, 1313.
15. Pierschbacher, M. D.; Ruoslahti, E. *J. Biol. Chem.* **1987**, *262*, 17294.
16. Zablocki, J. A.; Miyano, M.; Garland, R. B.; Pirek, D.; Schretzman, L.; Rao, S. N.; Linmark, R. J.; Panzer-Knodle, S. G.; Nicholson, N. S.; Taite, B. B.; Salyers, A. K.; King, L. W.; Campion, J. G.; Feigen, L. P. *J. Med. Chem.* **1993**, *36*, 1811.
17. Duggan, M. E.; Naylor-Olsen, A. M.; Perkins, J. P.; Anderson, P. S.; Chang, C. T.-C.; Cook, J. J.; Gould, R. J.; Ihle, N. C.; Hartman, G. D.; Lynch, J. J.; Lynch, R. J.; Manno, P. D.; Schaffer, L. W.; Smith, R. L. *J. Med. Chem.* **1995**, *38*, 3332.
18. Xue, C. B.; Rafalski, M.; Roderick, J.; Eyermann, C. J.; Mousa, S.; Olson, R. E.; DeGrado, W. F. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 339.
19. No inhibition of HUVEC binding[21] was observed for **7** at 300μM, indicating >3000-fold selectivity for GP IIb/IIIa.
20. Platelet aggregation was measured in a functional assay that monitors the increase in light transmittance that occurs when platelets aggregate. Human gel-filtered platelets were adjusted to a concentration of 2 x 10^8/mL and mixed with 0.1 mg/mL human fibrinogen, 1 mM $CaCl_2$ and the compound of interest. Aggregation was then initiated by addition of the agonist (10 μM adenosine diphosphate (ADP). Inhibition of platelet aggregation was determined by comparison of light transmittance values for the control and subject samples. The IC_{50} was determined as the concentration necessary to inhibit the change in light transmittance by 50%. At least two determinations were made for each compound and the IC_{50} calculated by fitting to a four parameter equation. The average standard error of the IC_{50} determination was ±20%.
21. Albeida, S.M.; Daise, M.; Levine, E.M.; Buck, C.A. *J. Clin. Invest.* **1989**, *83*, 1992.

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