New Orally Active Non-Peptide Fibrinogen Receptor (GpIIb-IIIa) Antagonists: Identification of Ethyl 3-[*N*-[4-[4-[Amino[(ethoxycarbonyl)imino]methyl]phenyl]-1,3-thiazol-2-yl]-*N*-[1-[(ethoxycarbonyl)methyl]piperid-4-yl]amino]propionate (SR 121787) as a Potent and Long-Acting Antithrombotic Agent

Alain Badorc, Marie-Françoise Bordes, Paul de Cointet, Pierre Savi, André Bernat, Alain Lalé, Maurice Petitou, Jean-Pierre Maffrand, and Jean-Marc Herbert*

Haemobiology Research Department, Sanofi Recherche, Toulouse, France

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The platelet fibrinogen receptor GpIIb-IIIa is curently considered a target of choice for drugs used in the prevention and treatment of thrombosis. Ethyl 3-[*N*-[4-[4-[amino[(ethoxycarbonyl)-imino]methyl]phenyl]-1,3-thiazol-2-yl]-*N*-[1-[(ethoxycarbonyl)methyl]piperid-4-yl]amino]propionate (**6**, SR 121787) is a new antiaggregating agent which generates *in vivo* the corresponding diacid **19d** (SR 121566), a non-peptide GpIIb-IIIa antagonist. *In vitro*, **19d** inhibited ADP-induced aggregation of human and baboon platelets (IC_{50} = 46 ± 11 and 54 ± 6 nM, respectively), and on human platelets, **19d** antagonized the binding of ^{125}I-labeled fibrinogen (IC_{50} = 19.2 ± 6.2 nM). *Ex vivo*, 8 h after an iv administration of **19d** (100 μg/kg, iv) to baboons, ADP-induced aggregation was strongly inhibited (more than 90%). At 8 h, the ED_{50} value was 24 ± 3.3 μg/kg), and even 24 h after the administration of a single dose of 100 μg/kg of **19d**, platelet aggregation was still significantly inhibited (50 ± 6% inhibition, $P < 0.05$). In the same species, the oral administration of 500 μg/kg of **6** produced a nearly complete inhibition of aggregation for up to 8 h (ED_{50} at 8 h was 193 ± 20 μg/kg). After an oral dose of 2 mg/kg of **6**, an antiaggregating effect was still observed at 24 h (44 ± 12% inhibition, $P < 0.05$). **6** was well tolerated in animals, showing that, on the basis of these studies, it is a suitable candidate for development as an orally active antithrombotic agent.

Introduction

Platelets and fibrinogen play major roles in the development of arterial thromboembolic diseases. The binding of the tripeptide Arg-Gly-Asp (RGD) sequence of fibrinogen to its platelet receptor, the activated glycoprotein IIb-IIIa complex (GpIIb-IIIa, also named $\alpha_{IIb}\beta_3$), has been shown to be essential in the process leading to thrombus growth[1−4] and is therefore considered an attractive target for the development of novel antithrombotic drugs.[5]

Platelet GpIIb-IIIa antagonists described to date fall into three classes: specific monoclonal antibodies which bind to GpIIb-IIIa, shown to be clinically effective,[6] peptides containing the recognition sequence RGD,[7,8] and, more recently, several series of non-peptide antagonists which mimic the RGD sequence. Some representatives of this latter category display oral activity in animals (Figure 1, compounds **1**,[9] **2**,[10] **3**,[11] **4**[12]), and a number of them are currently undergoing clinical evaluation.[13−15]

Herein, we describe the synthesis, the structure−activity relationships, and the *in vitro* and *in vivo* activities of a novel series of fibrinogen antagonists.[16] From this study, the [(phenyl-1,3-thiazol-2-yl)amino]-piperidine diacid **19d** was the most potent compound. The carbamoyl ethyl ester prodrug **6** (Figure 1) was found to be orally active in baboons where it inhibited ADP-induced platelet aggregation *ex vivo* at doses lower than any other known GpIIb-IIIa antagonists. Moreover, this compound did not show any undesirable side effects such as bleeding complications, which is a common feature of this class of compounds.

Chemistry

The novel platelet aggregation inhibitors can be prepared following the general synthetic sequence outlined in Scheme 1, which is based on the well-known Hantzsch's reaction for thiazole preparation.[17] Commercially available 4-amino-1-benzylpiperidine **7** and *tert*-butyl isothiocyanate reacted together to give the *tert*-butylated thiourea, which gave **8** (hydrobromide) after hydrobromic acid treatment. Treatment of **8** with the commercially available α-bromoketone **9** in refluxing methanol gave the aminothiazole **10**. *N*-Debenzylation of the piperidine ring was carried out using the chloroformate method[18] and 1-chloroethyl chloroformate[19] to give **11**. Several benzonitriles **12** were prepared by *N*-alkylation of the piperidine with α-halogenoacetic acid ester in warm DMF in the presence of potassium carbonate, or by Michaël reaction with α,β-unsatured esters in warm methanol. The benzonitriles **12** were then converted into the benzamidines **13** using Pinner's reaction[20] with the appropriate alcohol and then ammonia treatment. For *in vitro* testing, the amidino ester **13** was cleaved to the active amidino acid **14** by acid hydrolysis.

After optimization of the carboxyalkyl borne by the piperidine, several compounds were prepared in which the amino group adjacent to the thiazole ring was alkylated (Scheme 2). Then, **10** was alkylated to **15** using the appropriate halogenoalkyl or halogenoalkyl carboxylic ester in warm DMF under phase-transfer-catalyzed (PTC) conditions with tetrabutylammonium bromide (TBAB) as a catalyst. The carboxyethyl group

* Address correspondence to: J. M. Herbert, Haemobiology Research Department, Sanofi Recherche, 195 Route d'Espagne, 31036 Toulouse, France. Tel: (33) 05 61 16 23 61. Fax: (33) 05 61 16 22 86. E-mail: jean-marc.herbert@tls1.elfsanofi.fr.

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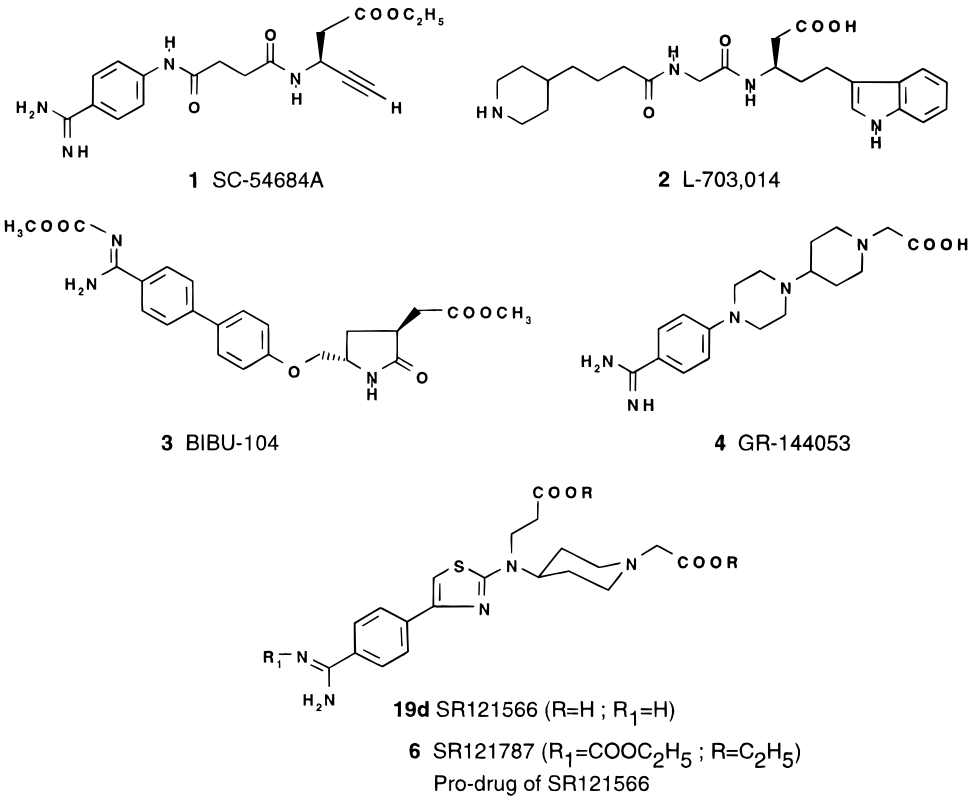


Figure 1. Orally active GpIIb-IIIa antagonists.

was introduced on the amino group of **10** by Michaël addition[21] of ethyl acrylate in warm DMF using TBAB catalysis. *N*-Deprotection of the piperidine as above gave **16**. The carboxymethyl group was introduced, and the resultant nitriles **17** were converted to the amidines **18** as described for **13** and then hydrolyzed to the acids **19**. The prodrug **6** was prepared (Scheme 3) by carbamoylation of the amidino group of the amidino diester **18d**.

Results and Discussion

Our strategy in structure design was based on classical methods to obtain non-peptide GpIIb-IIIa antagonists with oral activity, i.e. a benzamidino or a guanidino group and a carboxylic acid were placed at a certain distance from each other on a rigid template. Modeling studies showed that (1,3-thiazol-2-yl)-4-aminopiperidino constituted such an optimal template to connect the benzamidine and the carboxylic acid group.

The compounds were evaluated in an aggregation assay to assess their ability to inhibit ADP-induced aggregation of human platelets.

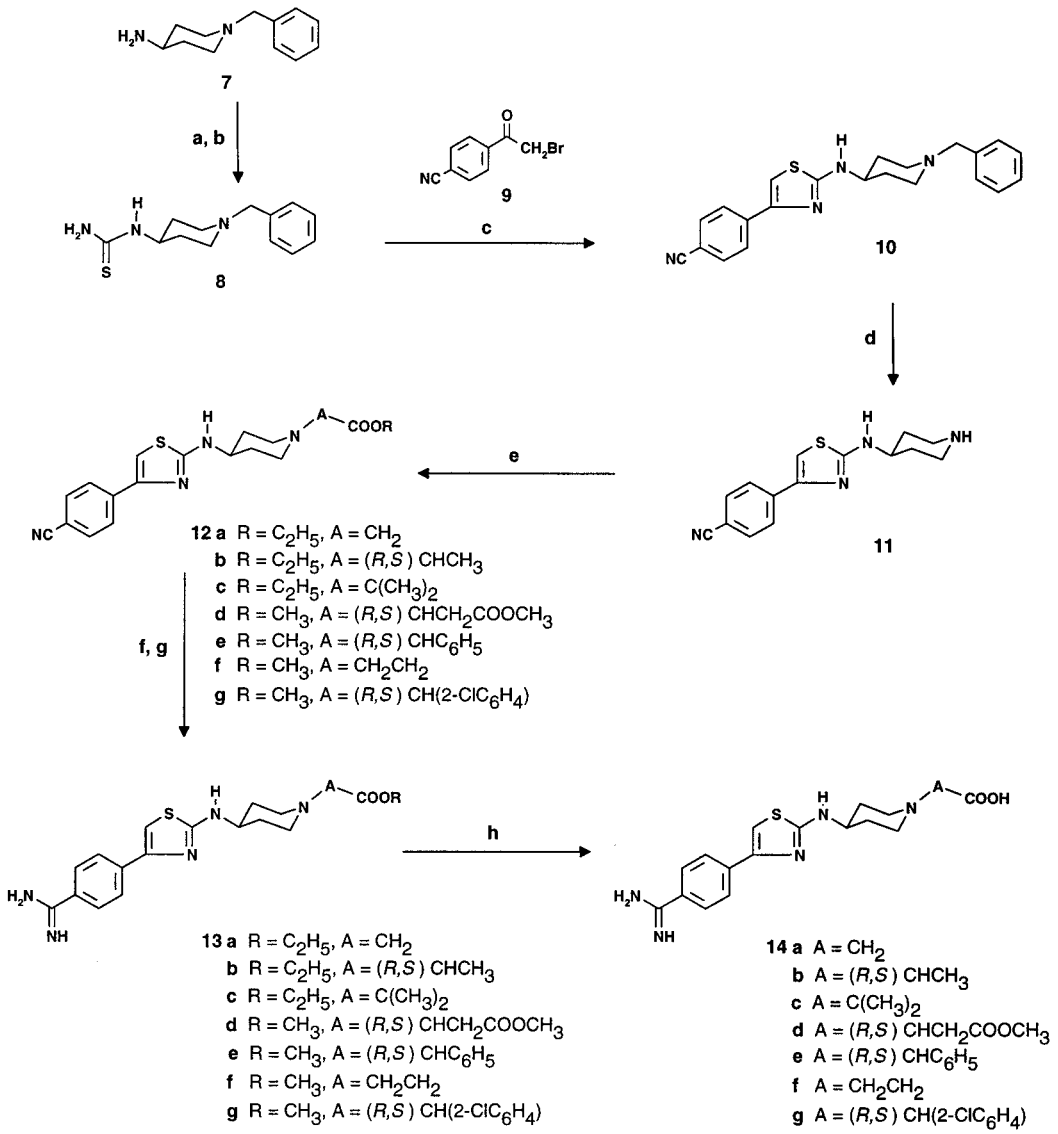
We first optimized (Table 1) the *N*-carboxyalkyl chain on the piperidine ring (compounds **14 a**−**g**). The difference in activity between **14a** (IC_{50} = 42 nM) and **14f** (IC_{50} = 1800 nM) demonstrated the importance of the distance between the amidino group and the carboxylic acid function. Substitution at the α-position to the carboxylic acid group did not increase the activity, and only monosubstitution was tolerated [**14b**,**d**,**e** with regard to **14c** (IC_{50} > 10 μM)].

The phenyl derivative (**14e**) was as potent as the parent compound **14a**. In contrast the 2-chlorophenyl analog (**14g**) was 100 times less potent thant **14a** (IC_{50} = 6000 versus 42 nM) at inhibiting ADP-induced platelet aggregation. Presumably, the presence of the chlorine at position 2 of the phenyl forced the carboxymethyl group to adopt a less favorable conformation. Compounds **14d** and **14e** contain a chiral center. Since this substitution did not enhance the anti GpIIb-IIIa activity, the achiral **14a** (SR 121012) was selected for further refinement of future structure−activity relationships.

After optimization of the carboxyalkyl chain on the piperidine, several derivatives were prepared, in which the amino group adjacent to the thiazole ring was alkylated. The compounds were evaluated, first in a platelet aggregation assay *in vitro* to assess the ability to inhibit ADP-induced human and baboon platelets (Table 2) and secondly *ex vivo*, to test the antiaggregating effect on baboon after iv administration (Figure 2). The *N*-methyl (**19a**) and the *N*-benzyl (**19b**) derivatives were prepared and compared to the unsubstituted analog **14a**. IC_{50} for **19a** and **19b** increased to 160 and 230 nM, respectively, showing that alkylation of the α-amino group of the thiazole resulted in a negative effect *in vitro*. A series of *N*-carboxyalkyl derivatives of **14a** were prepared to enhance the *in vitro* potency (Table 2). Compound **19c**, with a carboxymethyl group, was approximately 4 times less active than **14a**, and the potency of the equivalent **19d**, with a carboxyethyl group, was comparable to that of **14a**. However **19e**, with a carboxypropyl group, showed little activity. *In vitro*, compounds **14a** and **19d** antagonized the binding of labeled [^{125}I]fibrinogen on stimulated human platelets, with respective IC_{50} values of 17.8 ± 4.3 and 19.5 ± 6.2 nM.

The profile of the selected achiral inhibitors described herein (**14a**, **19c**, and **19d**) was assessed in the baboon by measuring *ex vivo* the inhibition of ADP-induced platelet aggregation as a function of time (Figure 2). When these compounds were injected iv (100 μg/kg, iv), they showed good activity 5 min after injection but, 4 h after the administration of **14a**, the level of inhibition

Scheme 1[a]



[a] Reagents: (a) tBuNCS, CH_2Cl_2; (b) 33% HBr in AcOH; (c) CH_3OH, reflux; (d) $ClCOOCHClCH_3$, $ClCH_2CH_2Cl$; then CH_3OH; (e) X-A-COOR, DMF, K_2CO_3; or $H_2C{=}CHCOOCH_3$, DMF (**12f**); or (*E*)-$H_3COOCCH{=}CHCOOCH_3$, DMF (**12d**); (f) HCl/ROH; (g) NH_3/ROH; (h) 6 N HCl, reflux.

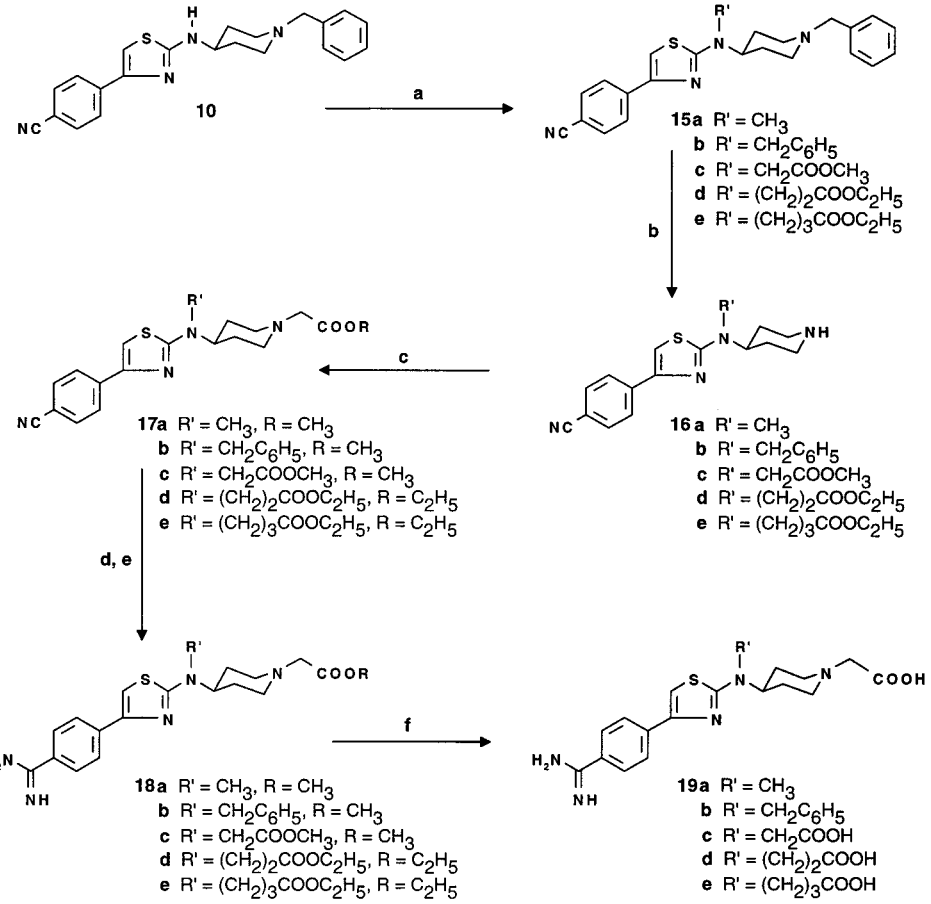
returned to baseline. **19c**, a derivative with a carboxymethyl group on the α-aminothiazole, showed 50% inhibition of platelet aggregation 6 h after the iv administration of 100 μg/kg and the inhibitory effect returned to baseline at 24 h. The most potent inhibitor was **19d.** When **19d** was administered to baboons by iv route at 100 μg/kg, the inhibition of ADP-stimulated platelet aggregation exceeded 90% until 8 h, and then it declined down to 50 ± 6% inhibition ($P < 0.05$) at 24 h. The ED_{50} value measured at 8 h was 24 ± 3.3 μg/kg. This long-lasting inhibition observed with **19d**, compared to the GpIIb-IIIa antagonists **1**,[9] **2**,[10] **3**,[11] and **4**,[12] could be explained by the presence in **19d** of a second carboxylic group which might favor the pharmacokinetic profile. Since compounds with carboxymethyl (**19c**) or carboxypropyl (**19e**) groups exhibited lower activity *ex vivo*, the carboxyethyl group (**19d**) seemed of an optimal length.

The oral activity of the more potent inhibitor (**19d**) described herein was measured in baboons by monitoring the inhibition of *ex vivo* ADP-induced platelet aggregation as a function of time (Figure 3). Compound **19d** at an oral dose of 0.5 mg/kg showed a peak inhibition of aggregation of around 35% at 4 h, falling below 15% inhibition after 8 h. This weak activity might seem to be due to a low absorption of **19d** by the gastrointestinal tract.

We next examined the effect of the ester prodrug **18d** to see if esterification would lead to increased absorption and a prolonged duration of action. Indeed, one would suggest that, by converting the carboxylate function into an ester, the zwiterionic character was canceled and the polarity of the molecule was attenuated.

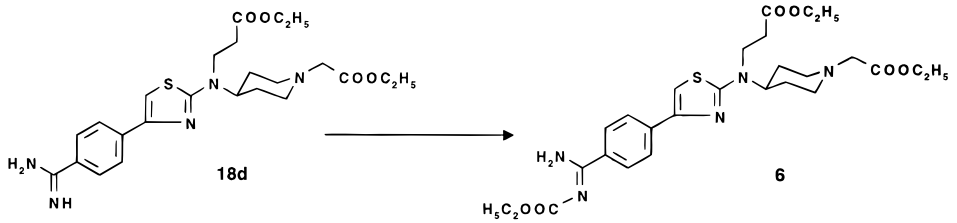
The diester **18d** was assessed in the baboon, but neither the potency nor the duration of action were increased compared to that of **19d**. Although the pharmacokinetics of the compounds can influence this behavior, we cannot exclude that the high basicity of the molecules decreases their ability to cross the intestinal wall. For this reason we then tried to improve the oral bioavailability by decreasing the basicity and, at the same time, by increasing the lipophilicity. The prodrug **6** of the amidino group was thus prepared by carbamoylation of **18d**. No antiaggregating effect was observed when **6** was tested *in vitro* on human platelets. A study was performed in baboons comparing the

Scheme 2[a]



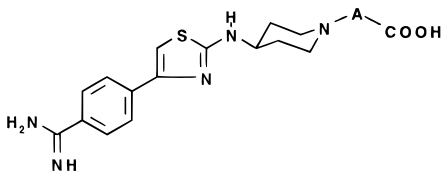
[a] Reagents: (a) R′X, NaH, DMF; or $H_2C{=}CHCOOC_2H_5$, K_2CO_3, TBAB, DMF (**15d**); (b) $ClCOOCHClCH_3$, $ClCH_2CH_2Cl$; then ROH, reflux; (c) XCH_2COOR, K_2CO_3, DMF; (d) HCl/ROH; (e) NH_3/ROH; (f) 6 N HCl, reflux.

Scheme 3[a]



[a] Reagents: $ClCOOC_2H_5$, Et_3N, DMF, room temperature.

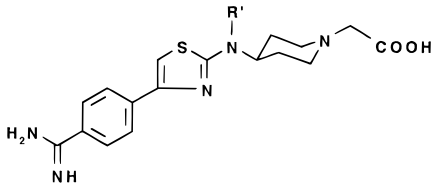
Table 1



compd	A	inhibn of platelet aggreg[a] IC_{50} (nM)	compd	A	inhibn of platelet aggreg[a] IC_{50} (nM)
14a	CH_2	42	**14e**	CHC_6H_5	65
14b	$CHCH_3$	250	**14f**	CH_2CH_2	1800
14c	$C(CH_3)_2$	>10000	**14g**	$CH(2\text{-}ClC_6H_4)$	6000
14d	$CHCH_2COOH$	85			

[a] *In vitro* inhibition of ADP-induced (2.5 μM) human platelet aggregation. See the Experimental Section for details.

Table 2



compd	R′	inhibn of platelet aggreg[a] IC_{50} (nM) human	baboon
14a	H	48	53
19a	CH_3	160	ND[b]
19b	$CH_2C_6H_5$	230	ND
19c	CH_2COOH	170	ND
19d	$(CH_2)_2COOH$	46	54
19e	$(CH_2)_3COOH$	96	ND

[a] *In vitro* inhibition of ADP-induced (2.5 μM) human platelet aggregation. See the Experimental Section for details. [b] Not determined.

antiaggregating activity of the amidino diacid **19d** with that of its prodrug **6** at an oral dose of 0.5 mg/kg during 24 h. The effects on ADP-induced platelet aggregation *ex vivo* are shown Figure 3. Whereas **19d** showed maximum inhibition of 35% at 4 h, the prodrug **6** at the same oral dose produced a nearly complete inhibition of aggregation in baboons for up to 8 h (ED_{50} at 8 h was

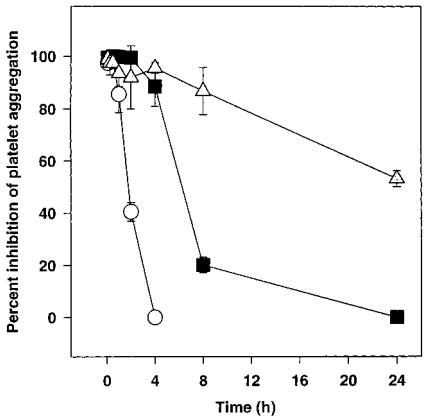


Figure 2. *Ex vivo* effect of drugs on ADP-induced platelet aggregation expressed as percent inhibition over time (h) in conscious baboons. Drugs were administered as follows: 0.1 mg/kg, iv (○) for **14a** ($n = 4$), (■) **19c** ($n = 3$), (▲) **19d** ($n = 4$).

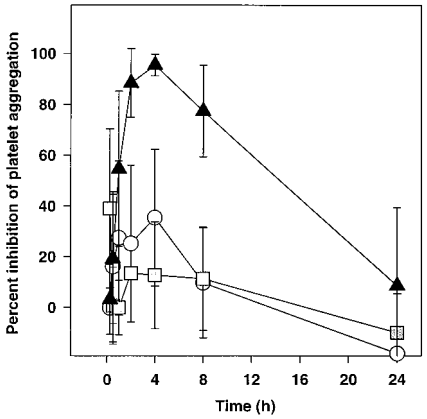


Figure 3. *Ex vivo* effect of drugs on ADP-induced platelet aggregation expressed as percent inhibition over time (h) in conscious baboons. Drugs were administered as follows: 0.5 mg/kg, po (○) for **19d** ($n = 2$), (■) **18d** ($n = 2$), (▲) **6** ($n = 4$).

193 ± 20 μg/kg). After an oral dose of 2 mg/kg of **6**, an antiaggregating effect (44 ±12% inhibition) was still observed 24 h after the administration.

Conclusion

We have discovered a novel series of orally active fibrinogen receptor antagonists with a [(4-phenyl-1,3-thiazol-2-yl)amino]piperidine backbone. *N*-Substitution of the α-aminothiazole by a carboxyethyl group gave **19d**, which exhibited an *in vitro* antiaggregating activity similar to that of **14a** (no *N*-substitution), but improved the *ex vivo* profile after iv administration to baboons. In an attempt to improve oral absorption of this compound, ester prodrugs were prepared to increase the lipophilicity and remove the zwiterionic nature of **19d**, which was orally active with regard to inhibition of *ex vivo* platelet aggregation in baboons. Amidino group carbamoylation of **19d** gave the prodrug **6**, which showed better absorption and was rapidly converted into **19d** *in vivo*. On the basis of these studies, **6** has been selected as a candidate for development as an orally active fibrinogen receptor antagonist.

Experimental Section

***In Vitro* Effects on Human Platelet Fibrinogen Receptor.** The binding of [^{125}I]fibrinogen was performed on gel filtered human platelets, according to the method of Foster.[22] Fresh platelet concentrate was centrifuged (900*g*, 15 min), and the platelet pellet was resuspended (2×10^6 cells/μL) in Tyrode's solution. Platelet suspension was incubated for 30 min with hirudin (10 units/mL), fructose (1.75 mM), $CaCl_2$ (2 mM), and PGI_2 (10 μM) and gel-filtered on Sepharose 2B. Platelets were then diluted in Tyrode's buffer, and samples containing 50×10^6 cells were incubated at 37 °C with ^{125}I-labeled human fibrinogen (2 μg/mL), $CaCl_2$ (2 mM), ADP (20 μM), and epinephrine (20 μM) in the presence of the tested compounds for 15 min. Bound labeled fibrinogen to platelets was evaluated by measuring the radioactivity in a γ counter after centrifugation on dioctyl phthalate/dibutyl phthalate mixture (6/4, v/v). Nonspecific binding was measured in the presence of 1 mM peptide Arg-Gly-Asp-Ser (RGDS).

***In Vitro* Antiaggregating Activity.** Platelet rich plasma (PRP) was obtained by centrifugation (1000*g*, 10 min) of citrated (0.38% final concentration) blood from human volunteers who had not taken any medication for at least 2 weeks. Platelet aggregation was measured on PRP in a ChronoLog after activation by 2.5 μM ADP according to Born.[23] The extent of aggregation was quantified by measuring the maximum height of the curve. Drugs were added 1 min before activation, in a DMSO solution (0.01% final). The antiaggregating activity was expressed as a percent inhibition by comparison with aggregation measured in the presence of the vehicle alone.

***Ex Vivo* Antiaggregating Effect.** Platelet aggregation was measured in PRP from baboons treated by the various compounds administered either intravenously (drugs dissolved in saline, 1 mL/kg) or by oral route (drugs dissolved in 1% ethanol, 5 mL/kg). Blood samples (4.5 mL) were taken from the femoral vein using hirudin as the anticoagulant (100 units/mL), before administration and 5, 15, and 30 min and 1, 2, 4, 8, and 24 h after iv administration or 15 and 30 min and 1, 2, 4, 8 and 24 h after oral administration. PRP was obtained by centrifugation (800*g*, 15 min), and ADP (2.5 μM)-induced platelet aggregation was evaluated as described above. Percent inhibition was calculated by comparison with the aggregation of PRP from each animal withdrawn just prior to the treatment. The dose providing 50% of the effect (ED_{50}) was calculated at 8 h, using the four-parameter logistic model of Ratkovsky and Reedy.[24] This protocol has been approved by the Animal Care and Use Committee of Sanofi Recherche.

Chemistry. ^{1}H-NMR spectra were obtained on a Brucker AC 200 spectrometer; chemical shifts are relative to internal TMS. Melting points were determined on a Mettler FP62 melting point apparatus and are uncorrected. Elemental analyses were performed on a Fisons elemental analyzer. Compound purity was checked by TLC on silica gel 60 F254 (E. Merck). Column chromatographies were performed on Silica gel 70−200 μm (E. Merck). 4-Amino-1-benzylpiperidine **7** (Aldrich) and 4-cyanophenacyl bromide **9** (Lancaster) were used without further purification.

***N*-(1-Benzylpiperid-4-yl)thiourea (8).** To a solution of 4-amino-1-benzylpiperidine **7** (24.93 g, 131 mmol) in CH_2Cl_2 (300 mL) was added dropwise at room temperature *tert*-butyl isothiocyanate (16.7 mL, 131 mmol). After 5 h, water was added and the mixture was allowed to settle. The organic phase was separated, dried (Na_2SO_4), and evaporated. The residue was crystallized from petroleum ether to afford *N*-(1-benzylpiperid-4-yl)-*N*′-*tert*-butylthiourea as a white solid (35.22 g, 88%): mp 137 °C; ^{1}H NMR (DMSO-d_6) δ 1.18−1.36 (m, 2H, CH_2), 1.37 (s, 9H, $C(CH_3)_3$), 1.74−1.88 (m, 2H, CH_2), 1.92−2.08 (m, 2H, CH_2N), 2.58−2.72 (m, 2H, CH_2N), 3.41 (s, 2H, CH_2Ph), 3.92−4.08 (m, 1H, CHN), 6.98 (bs, NH), 7.09 (d, J = 7.7 Hz, NH), 7.17−7.33 (m, 5H, Ph).

The *N*-(1-benzylpiperid-4-yl)-*N*′-*tert*-butylthiourea (17 g, 55.6 mmol) was added to a 33% solution of HBr/AcOH (170 mL). The reaction mixture was stirred for 4 h at room temperature and then poured over diethyl ether. The crystals were filtered and thoroughly washed with diethyl ether to yield **8** (hydrobromide) as a white solid (18.38 g, 100%): mp 120 °C; ^{1}H NMR (DMSO-d_6) δ 1.7−2.03 (m, 4H, $2CH_2$), 3.00−3.40 (m, 4H, $2CH_2N$), 4.00−4.28 (m, 1H, CHN), 4.30 (s, 2H, CH_2Ph), 7.42−7.54 (m, 5H, Ar), 7.91 (NH), 9.67 (NH_2).

4-[2-[*N*-(1-Benzylpiperid-4-yl)amino]-1,3-thiazol-4-yl]-benzonitrile (10). A solution of **8** (18.38 g, 55.6 mmol) and 4-cyanophenacyl bromide **9** (12.46 g, 55.6 mmol) in CH_3OH (200 mL) was heated for 4 h at reflux. After the mixture was cooled to room temperature, diethyl ether (200 mL) was added,

and the precipitate was collected by filtration and washed with diethyl ether to yield **10** (dihydrobromide) as a white solid (25.66 g, 86%): mp 280 °C; ^{1}H NMR (DMSO-d_6) δ 1.62−2.29 (m, 4H, $2CH_2$), 3.02−3.42 (m, 4H, $2CH_2N$), 3.72−3.92 (m, 1H, CHN), 4.26 (s, 2H, CH_2Ph), 7.28 (s, 1H, CHS), 7.40−7.52 (m, 5H, Ar), 7.77 (d, J = 8.5 Hz, 2H, Ar), 7.94 (d, J = 8.5 Hz, 2h, Ar).

4-[2-[*N*-(Piperid-4-yl)amino]-1,3-thiazol-4-yl]benzonitrile (11). To a cold (0 °C) solution of **10** (free base, 18 g, 48 mmol) and 1,8-bis(dimethylamino)naphthalene (6.2 g, 28.8 mmol) in 1,2-dichloroethane (250 mL) placed under argon was added 1-chloroethyl chloroformate (10.4 mL, 96 mmol). The mixture was stirred for 30 min and then heated for 3 h at reflux. The mixture was evaporated to dryness, the residue was taken up in CH_3OH (250 mL), and the solution was heated for 2 h at reflux. After the solution was cooled to room temperature, diethyl ether (250 mL) was added. The precipitate was washed with diethyl ether to afford **11** (dihydrochloride) as a beige solid (14.94 g, 87%): mp 266 °C; ^{1}H NMR (DMSO-d_6) δ 1.68−1.83 (m, 2H, CH_2), 2.09−2.15 (m, 2H, CH_2), 2.98−3.12 (m , 2H, CH_2N), 3.22−3.36 (m, 2H, CH_2N), 3.92−4.08 (m, 1H, CHN), 7.40 (s, 1H, CHS), 7.83 (d, J = 8.5 Hz, 2H, Ar), 8.00 (d, J = 8.5 Hz, 2H, Ar), 9.14 (2NH).

Ethyl [4-[[4-(4-Cyanophenyl)-1,3-thiazol-2-yl]amino]piperidino]acetate (12a). A solution of dihydrochloride **11** (3 g, 8.4 mmol), K_2CO_3 (3.6 g, 26 mmol), and ethyl bromoacetate (1.54 g, 9.23 mmol) in DMF (40 mL) was heated for 2 h at 50 °C. The cooled solution was diluted with ethyl acetate, washed with water, dried (Na_2SO_4), and evaporated. Column chromatography (95:5 CH_2Cl_2/CH_3OH) gave **12a** as a white solid (2.67 g, 86%): mp 153 °C; ^{1}H NMR (DMSO-d_6) δ 1.13−2.02 (t, J = 7.1 Hz, 3H, CH_3), 1.39−1.56 (m, 2H, CH_2), 1.91−1.96 (m, 2H, CH_2), 2.23−2.33 (m, 2H, CH_2N), 2.76−2.82 (m, 2H, CH_2N), 3.19 (s, 2H, CH_2CO), 3.49−3.56 (m, 1H, CHN), 4.06 (q, J = 7.1 Hz, 2H, CH_2O), 7.33 (s, 1H, CHS), 7.73 (d, J = 7.23 Hz, NH), 7.80 (d, J = 8.5 Hz, 2H, Ar), 7.97 (d, J = 8.5 Hz, 2H, Ar).

Ethyl (*R,S*)-2-[4-[[4-(4-Cyanophenyl)-1,3-thiazol-2-yl]amino]piperidino]propionate (12b). This compound was prepared from **11** as described for **12a** but using ethyl (*R,S*)-2-bromopropionate. Column chromatography (95:5 CH_2Cl_2/CH_3OH) gave **12b** as a white solid (77%): mp 113 °C; ^{1}H NMR (DMSO-d_6) δ 1.19−1.24 (m, 6H, $2CH_3$), 1.41−1.49 (m, 2H, CH_2), 1.96−2.00 (m, 2H, CH_2), 2.26−2.46 (m, 2H, CH_2), 2.80−2.86 (m, 2H, CH_2), 3.32 (q, J = 7 Hz, 1H, CHCO), 3.51−3.55 (m, 1H, CHN), 4.07−4.14 (q, J = 7.4 Hz, 2H, CH_2O), 7.34 (s, 1H, CHS), 7.71 (d, J = 7.2 Hz, NH), 7.82 (d, J = 8.4 Hz, 2H, Ar), 7.99 (d, J = 8.4 Hz, 2H, Ar).

Ethyl 2-[4-[[4-(4-cyanophenyl)-1,3-thiazol-2-yl]amino]-piperidino]isobutyrate (12c). This compound was prepared from **11** as described for **12a** but using ethyl 2-bromo-2-methylpropionate. Column chromatography (95:5 CH_2Cl_2/CH_3-OH) gave **12c** as a white solid (63%): mp 134 °C; ^{1}H NMR (DMSO-d_6) δ 1.14−1.21 (m, 9H, $3CH_3$) 1.30−1.49 (m, 2H, CH_2), 1.93−1.98 (m, 2H, CH_2), 2.15−2.25 (m, 2H, CH_2), 2.81−2.87 (m, 2H, CH_2) 3.45−3.50 (m, 1H, CH-N), 7.32 (s, 1H, CHS), 7.70 (d, J = 7.2 Hz, NH), 7.79 (d, J = 8.5 Hz, 2H, Ar), 7.95 (d, J = 8.5 Hz, 2H, Ar).

Methyl (*R,S*)-3-[4-[[4-(4-Cyanophenyl)-1,3-thiazol-2-yl]-amino]piperidino]-3-(methoxycarbonyl)propionate (12d). A solution of dihydrochloride **11** (2 g, 5.6 mmol), Et_3N (1.16 g, 11.5 mmol), and dimethyl fumarate (1.21 g, 8.4 mmol) in CH_3-OH (30 mL) was heated at reflux overnight. After cooling and concentration, column chromatography (95:5 CH_2Cl_2/CH_3OH) gave **12d** as a yellow solid (0.55 g, 23%): mp 134 °C; ^{1}H NMR (DMSO-d_6) δ 1.39−1.44 (m, 2H, CH_2), 1.92−1.98 (m, 2H, CH_2), 2.09−2.19 (m, 1H, CH_2N), 2.52−2.86 (m, 3H, CH_2N and 2H, CH_2CO), 3.57−3.77 (m, 8H, $2CH_3$ and 2CH), 7.32 (s, 1H, CHS), 7.68 (d, J = 7.1 Hz, NH), 7.79 (d, J = 8.3 Hz, 2H, Ar), 7.96 (d, J = 8.3 Hz, 2H, Ar).

Methyl (*R,S*)-2-[4-[[4-(4-cyanophenyl)-1,3-thiazol-2-yl]-amino]piperidino]phenylacetate (12e). This compound was prepared from **11** as described for **12a** but using methyl (*R,S*)-α-bromophenylacetate. Column chromatography (5:1 CH_2Cl_2/AcOEt) gave **12e** as a yellow solid (77%): mp 78 °C; ^{1}H NMR (DMSO-d_6) δ 1.32−1.55 (m, 2H, CH_2), 1.94−2.27 (m, 4H, $2CH_2$), 2.62−2.79 (m, 2H, CH_2), 3.40−3.53 (m, 1H, CH) 3.59 (s, 3H, OCH_3), 4.14 (s, 1H, CHPh), 7.32−7.37 (m, 6H, Ph and CHS), 7.74 (d, J = 7.1 Hz, NH), 7.78 (d, J = 8.5 Hz, 2H, Ar), 7.95 (d, J = 8.5 Hz, 2H, Ar).

Methyl3-[4-[[4-(4-cyanophenyl)-1,3-thiazol-2-yl]amino]-piperidino]propionate (12f). This compound was prepared from **11** as described for **12d** but using methyl acrylate. Column chromatography (95:5 CH_2Cl_2/CH_3OH) gave **12f** as a white solid (72%): mp 154 °C; ^{1}H NMR (DMSO-d_6) δ 1.42−1.47 (m, 2H, CH_2), 1.92−2.13 (m, 4H, $2CH_2$), 2.42−2.58 (m, 4H, $2CH_2$), 2.75−2.81 (m, 2H, CH_2), 3.43−3.58 (m, 1H, CHN), 3.59 (s, 3H, OCH_3), 7.33 (s, 1H, CH-S), 7.70 (d, J = 7.2 Hz, NH), 7.81 (d, J = 8.5 Hz, 2H, Ar), 7.97 (d, J = 8.5 Hz, 2H, Ar).

Methyl (*R,S*)-2-[4-[[4-(4-Cyanophenyl)-1,3-thiazol-2-yl]-amino]piperidino](2-chlorophenyl)acetate (12g). This compound was prepared from **11** as described for **12a** but using methyl (*R,S*)-α-bromo-2-chlorophenylacetate. Salification with hydrogen chloride in acetone afforded **12g** (dihydrochloride) as a white solid (89%): mp 200 °C; ^{1}H NMR (DMSO-d_6) δ 1.80−2.30 (m, 4H, $2CH_2$), 3.11−3.60 (m, 5H, $2CH_2$ and CH), 3.75 (s, 3H, OCH_3), 3.93 (s, 1H, CHPh), 7.39 (s, 1H, CHS), 7.51−7.89 (m, 6H, H, Ar), 7.99 (d, J = 8.5 Hz, 2H, Ar).

Ethyl [4-[[4-[4-(Aminoiminomethyl)phenyl]-1,3-thiazol-2-yl]amino]piperidino]acetate (13a). To a cold (0 °C) saturated solution of HCl in C_2H_5OH (150 mL) was added **12a** (10.33 g, 29 mmol), and the mixture was stirred at 4 °C overnight. The mixture was evaporated to dryness without heating, and then the residue was taken up in C_2H_5OH (150 mL) and ammonia was bubbled through until a basic pH was obtained. The mixture was heated 2 h at reflux and then evaporated. Column chromatography (8:2 CH_2Cl_2/CH_3OH) gave **13a** as a yellow solid (8.15 g, 69%): mp 150 °C; ^{1}H NMR (DMSO-d_6) δ 1.12−1.19 (t, J = 7.1 Hz, 3H, CH_3), 1.4−1.55 (m, 2H, CH_2), 1.91−1.96 (m, 2H, CH_2), 2.24−2.34 (m, 2H, CH_2), 2.76−2.82 (m, 2H, CH_2), 3.14 (s, 2H, CH_2CO), 3.36−3.58 (m, 1H, CHN), 4.05 (q, J = 7.1 Hz, 2H, CH_2O), 7.34 (s, 1H, CHS), 7.75 (d, J = 7.2 Hz, NH), 7.82 (d, J = 8.5 Hz, 2H, Ar), 7.99 (d, J = 8.5 Hz, 2H, Ar), 9.13−9.35 (2bs, 4H, $2NH_2$). Anal. ($C_{19}H_{25}N_5O_2S$·HCl·1.5H_2O) C, H, N, S.

Ethyl (*R,S*)-2-[4-[[4-[4-(aminoiminomethyl)phenyl]-1,3-thiazol-2-yl]amino]piperidino]propionate (13b). 13b was prepared from **12b** as described for **13a**, substituting CH_3OH by C_2H_5OH. Column chromatography (8:2 CH_2Cl_2/CH_3OH) gave **13b** (hydrochloride) as a yellow solid (69%): mp 150 °C; ^{1}H NMR (DMSO-d_6) δ 1.03 (d, J = 7.9 Hz, 3H, CH_3), 1.18 (t, J = 7.0 Hz, 3H, CH_3), 1.21−1.48 (m, 2H, CH_2), 1.87−1.98 (m, 2H, CH_2), 2.20−2.39 (m, 2H, CH_2), 2.72−2.84 (m, 2H, CH_2), 3.30 (q, J = 7.9 Hz, 1H, CHCO), 3.47−3.59 (m, 1H, CHN), 4.07 (q, J = 7.0 Hz, 2H, CH_2O), 7.33 (s, 1H, CHS), 7.74 (d, J = 7.2 Hz, NH), 7.82 (d, J = 8.5 Hz, 2H, Ar), 7.98 (d, J = 8.5 Hz, 2H, Ar), 9.11−9.34 (2bs, 4H, $2NH_2$). Anal. ($C_{20}H_{27}N_5O_2S$·HCl) C, H, S; N: calcd, 15.06; found, 14.56.

Ethyl 2-[4-[[4-[4-(Aminoiminomethyl)phenyl]-1,3-thiazol-2-yl]amino]piperidino]isobutyrate (13c). 13c was prepared from **12c** as described for **13a**, substituting CH_3OH by C_2H_5OH. Column chromatography (8:2 CH_2Cl_2/CH_3OH) gave **13c** (hydrochloride) as a yellow solid (71%): mp 167 °C; ^{1}H NMR (DMSO-d_6) δ 1.06 (t, J = 7.1 Hz, 3H, CH_3), 1.22 (s, 6H, $2CH_3$), 1.34−1.50 (m, 2H, CH_2), 1.81−1.99 (m, 2H, CH_2), 2.17−2.27 (m, 2H, CH_2), 2.83−2.88 (m, 2H, CH_2), 3.40−3.54 (m, 1H, CHN), 4.08 (q, J = 7.1 Hz, 2H, CH_2O), 7.34 (s, 1H, CHS), 7.73 (d, J = 7.2 Hz, NH), 7.83 (d, J = 8.5 Hz, 2H, Ar), 7.99 (d, J = 8.5 Hz, 2H, Ar), 9.25 (bs, 4H, $2NH_2$). Anal. ($C_{21}H_{29}N_5O_2S$·HCl·H_2O) C, H, N, S.

Methyl (*R,S*)-3-[4-[[4-[4-(Aminoiminomethyl)phenyl]-1,3-thiazol-2-yl]amino]piperidino]-3-(methoxycarbonyl)-propionate (13d). 13d was prepared from **12d** as described for **13a**. Column chromatography (8:2 CH_2Cl_2/CH_3OH) gave **13d** (hydrochloride) as a yellow solid (46%): mp 128 °C; ^{1}H NMR (DMSO-d_6) δ 1.30−1.54 (m, 2H, CH_2), 1.87−2.30 (m, 3H, CH_2CH_2N), 2.54−2.95 (m, 3H, CH_2N and 2H, CH_2CO), 3.40−3.80 (m, 8H, $2OCH_3$ and 2CH), 7.34 (s, 1H, CHS), 7.74 (d, J = 6.9 Hz, NH), 7.85 (d, J = 8.2 Hz, 2H, Ar), 7.99 (d, J = 8.2 Hz, 2H, Ar), 9.21−9.39 (bs, 4H, $2NH_2$). Anal. ($C_{21}H_{27}N_5O_4S$·HCl·1.5H_2O) C, H, N, S.

Methyl (*R,S*)-2-[4-[[4-[4-(Aminoiminomethyl)phenyl]-1,3-thiazol-2-yl]amino]piperidino]phenylacetate (13e). 13e was prepared from **12e** as described for **13a.** Column chromatography (8:2 CH_2Cl_2/CH_3OH) gave **13e** (hydrochloride)

as a yellow solid (85%): mp 169 °C; ^{1}H NMR (DMSO-d_6) δ 1.42−1.52 (m, 2H, CH_2), 1.94−2.28 (m, 4H, $2CH_2$), 2.63−2.80 (m, 2H, CH_2), 3.40−3.59 (m, 1H, CHN), 3.59 (s, 3H, OCH_3), 4.37 (s, 1H, CHCO), 7.31−7.35 (m, 6H, Ph and CHS), 7.78 (d, J = 7.1 Hz, NH), 7.83 (d, J = 8.4 Hz, 2H, Ar), 7.98 (d, J = 8.4 Hz, 2H, Ar), 9.28 (bs, 4H, $2NH_2$). Anal. ($C_{24}H_{27}N_5O_2S$·HCl) C, H, N, S.

Methyl 3-[4-[[4-[4-(Aminoiminomethyl)phenyl]-1,3-thiazol-2-yl]amino]piperidino]propionate (13f). 13f was prepared from **12f** as described for **13a**. Column chromatography (8:2 CH_2Cl_2/CH_3OH) gave **13f** (hydrochloride) as a yellow solid (88%): mp 110 °C; ^{1}H NMR (DMSO-d_6) δ 1.40−1.68 (m, 2H, CH_2), 1.90−2.30 (m, 4H, $2CH_2$), 2.60−2.95 (m, 6H, $3CH_2$), 3.40−3.60 (m, 1H, CHN), 3.59 (s, 3H, OCH_3), 7.34 (s, 1H, CHS), 7.78 (d, J = 7 Hz, NH), 7.87 (d, J = 8.5 Hz, 2H, Ar), 8.01 (d, J = 8.5 Hz, 2H, Ar), 9.33 (bs, 4H, $2NH_2$). Anal. ($C_{19}H_{25}N_5O_2S$·HCl) C, H, N, S.

Methyl (*R,S*)-2-[4-[[4-[4-(Aminoiminomethyl)phenyl]-1,3-thiazol-2-yl]amino]piperidino](2-chlorophenyl)acetate (13g). 13g was prepared from **12g** as described for **13a**. Column chromatography (8:2 CH_2Cl_2/CH_3OH) gave **13g** (hydrochloride) as a yellow solid (83%): mp 180 °C; ^{1}H NMR (DMSO-d_6) δ 1.40−1.70 (m, 2H, CH_2), 1.90−2.08 (m, 2H, CH_2), 2.22−2.42 (m, 2H, CH_2), 2.68−2.92 (m, 2H, CH_2), 3.44−3.63 (m, 1H, CHN), 3.64 (s, 3H, OCH_3), 4.63 (s, 1H, CHCO), 7.32−7.60 (m, 5H, 4H Ar and CHS), 7.78 (d, J = 7.2 Hz, NH), 7.83 (d, J = 8.5 Hz, 2H, Ar), 8.01 (d, J = 8.5 Hz, 2H, Ar), 9.10−9.34 (2bs, 4H, $2NH_2$). Anal. ($C_{24}H_{26}ClN_5O_2S$·HCl·$2H_2O$) C, H, N, S.

[4-[[4-[4-(Aminoiminomethyl)phenyl]-1,3-thiazol-2-yl]-amino]piperidino]acetic Acid (14a). A solution of **13a** (1 g, 2.44 mmol) in 6 N HCl (20 mL) was heated 5 h at reflux. Evaporation then crystallization from acetone gave **14a** (trihydrochloride) as a white solid (1.1 g, 96%): mp 216 °C; ^{1}H NMR (DMSO-d_6) δ 1.75−2.32 (m, 4H, $2CH_2$), 3.13−3.70 (m, 4H, $2CH_2$), 3.82−4.05 (m, 1H, CHN), 4.10 (s, 2H, CH_2CO), 7.41 (s, 1H, CHS), 7.88 (d, J = 8.5 Hz, 2H, Ar), 8.02 (d, J = 8.5 Hz, 2H, Ar), 9.22−9.43 (2bs, 4H, $2NH_2$). Anal. ($C_{17}H_{21}N_5O_2S$·3HCl) C, H, N; S: calcd, 6.34; found, 5.92.

(*R,S*)-2-[4-[[4-[4-(Aminoiminomethyl)phenyl]-1,3-thiazol-2-yl]amino]piperidino]propionic Acid (14b). This compound was prepared from **13b** as described for **14a**. Crystallization from acetone gave **14b** (trihydrochloride) as a white solid (68%): mp 226 °C; ^{1}H NMR (DMSO-d_6) δ 1.52 (d, J = 7.1 Hz, 3H, CH_3) 1.80−2.40 (m, 4H, $2CH_2$), 3.13−3.70 (m, 4H, $2CH_2$), 3.90−4.28 (m, 2H, CHCO and CHN), 7.42 (s, 1H, CHS), 7.88 (d, J = 8.5 Hz, 2H, Ar), 8.03 (d, J = 8.5 Hz, 2H, Ar), 9.25−9.48 (2bs, 4H, $2NH_2$). Anal. ($C_{18}H_{23}N_5O_2S$·3HCl) C, H, N, S.

2-[4-[[4-[4-(Aminoiminomethyl)phenyl]-1,3-thiazol-2-yl]amino]piperidino]isobutyric Acid (14c). This compound was prepared from **13c** as described for **14a**. Crystallization from acetone gave **14c** (trihydrochloride) as a white solid (73%): mp 256 °C; ^{1}H NMR (DMSO-d_6) δ 1.56 (s, 6H, $2CH_3$), 1.90−2.42 (m, 4H, $2CH_2$), 3.22−3.50 (m, 4H, $2CH_2$), 3.92−4.15 (m, 1H, CHN), 7.42 (s, 1H, CHS), 7.91 (d, J = 8.4 Hz, 2H, Ar), 8.04 (d, J = 8.4 Hz, 2H, Ar), 9.31−9.53 (2bs, 4H, $2NH_2$). Anal. ($C_{19}H_{25}N_5O_2S$·3HCl) C, H, N, S.

(*R,S*)-3-[4-[[4-[4-(Aminoiminomethyl)phenyl]-1,3-thiazol-2-yl]amino]piperidino]-3-(hydroxycarbonyl)propionic Acid (14d). This compound was prepared from **13d** as described for **14a**. Crystallization from acetone gave **14d** (trihydrochloride) as a white solid (74%): mp 105 °C; ^{1}H NMR (DMSO-d_6) δ 1.85−2.40 (m, 4H, $2CH_2$), 3.20−3.65 (m, 4H, $2CH_2$), 3.90−4.45 (m, 4H, CH_2CO and 2CH), 7.39 (s, 1H, CHS), 7.86 (d, J = 8.4 Hz, 2H, Ar), 8.02 (d, J = 8.4 Hz, 2H, Ar), 9.16−9.39 (2bs, 4H, $2NH_2$). Anal. ($C_{19}H_{23}N_5O_4S$·3HCl·$3H_2O$) C, H, S; N: calcd, 12.06; found, 11.35.

(*R,S*)-2-[4-[[4-[4-(Aminoiminomethyl)phenyl]-1,3-thiazol-2-yl]amino]piperidino]phenylacetic Acid (14e). This compound was prepared from **13e** as described for **14a**. Crystallization from acetone gave **14e** (trihydrochloride) as a white solid (79%): mp 250 °C; ^{1}H NMR (DMSO-d_6) δ 2.07−2.14 (m, 2H, CH_2), 2.24−2.30 (m, 2H, CH_2), 3.20−3.42 (m, 3H, CH_2), 3.55−3.68 (m, 1H, CH_2), 3.97−4.00 (m, 1H, CHN), 5.26 (s, 1H, CHCO), 7.32 (s, 1H, CHS), 7.50−7.54 (m, 3H, Ar), 7.67−7.70 (m, 2H, Ar), 7.91 (d, J = 8.5 Hz, 2H, Ar), 8.02 (d, J = 8.5 Hz, 2H, Ar), 9.32 (bs, 4H, $2NH_2$). Anal. ($C_{23}H_{25}N_5O_2S$·3HCl·$1.5H_2O$) C, H, N, S.

3-[4-[[4-[4-(Aminoiminomethyl)phenyl]-1,3-thiazol-2-yl]amino]piperidino]propionic Acid (14f). This compound was prepared from **13f** as described for **14a**. Crystallization from acetone gave **14f** (trihydrochloride) as a white solid (88%): mp 230 °C; ^{1}H NMR (DMSO-d_6) δ 1.87−2.25 (m, 4H, $2CH_2$), 2.84−2.91 (m, 2H CH_2), 3.07−3.52 (m, 6H, $3CH_2$), 3.90−4.05 (m, 1H, CHN), 7.42 (s, 1H, CHS), 7.92 (d, J = 8.5 Hz, 2H, Ar), 8.04 (d, J = 8.5 Hz, 2H, Ar), 9.30−9.51 (2bs, 4H, $2NH_2$). Anal. ($C_{18}H_{23}N_5O_2S$·3HCl) C, H, N, S.

(*R,S*)-2-[4-[[4-[4-(Aminoiminomethyl)phenyl]-1,3-thiazol-2-yl]amino]piperidino](2-chlorophenyl)acetic Acid (14g). This compound was prepared from **13g** as described for **14a**. Crystallization from acetone gave **14g** (trihydrochloride) as a white solid (25%): mp 244 °C; ^{1}H NMR (DMSO-d_6) δ 1.55−1.80 (m, 2H, CH_2), 1.93−2.18 (m, 2H, CH_2), 2.55−2.90 (m, 3H, CH_2), 3.15−3.30 (m, 1H, CH_2), 3.65−3.82 (m, 1H, CHN), 4.61 (m, 1H, CHCO), 7.33−7.70 (m, 5H, 4H Ar and CHS), 7.84 (d, J = 8.5 Hz, 2H, Ar), 8.02 (d, J = 8.5 Hz, 2H, Ar), 9.32−9.42 (2bs, 4H, $2NH_2$). Anal. ($C_{23}H_{24}ClN_5O_2S$·3HCl) C, H, N, S.

4-[2-[*N*-(1-Benzylpiperid-4-yl)-*N*-methylamino]-1,3-thiazol-4-yl]benzonitrile (15a). To a stirred suspension of NaH (146 mg, 3.64 mmol; 60% dispersion in oil) in DMF (13 mL), at room temperature, was added dropwise a solution of **10** (1.3 g, 3.47 mmol) in DMF (5 mL). After 15 min methyl iodide (0.23 mL, 3.64 mmol) was added. After 4 h at room temperature, the mixture was poured over water and extracted with AcOEt. The organic phase was washed with water, dried (Na_2SO_4), and concentrated. Column chromatography (CH_2Cl_2) gave **15a** as a yellow solid (0.9 g, 67%): mp 136 °C; ^{1}H NMR (DMSO-d_6) δ 1.62−1.92 (m, 4H, $2CH_2$), 1.97−2.18 (m, 2H, CH_2), 2.82−2.95 (m, 2H, CH_2), 2.96 (s, 3H, CH_3N), 3.49 (s, 2H, CH_2Ph), 3.82−4.03 (m, 1H, CHN), 7.31 (s, 5H, Ph), 7.48 (s, 1H, CHS), 7.83 (d, J = 8.5 Hz, 2H, Ar), 8.02 (d, J = 8.5 Hz, 2H, Ar).

Ethyl 3-[*N*-(1-Benzylpiperid-4-yl)-*N*-[4-(4-cyanophenyl)-1,3-thiazol-2-yl]amino]propionate (15d). A solution of **10** (44.8 g, 120 mmol), ethyl acrylate (25.92 mL, 239 mmol), K_2CO_3 (32.98 g, 239 mmol), and tetrabutylammonium bromide (7.7 g, 23.9 mmol) in toluene (960 mL) was heated at reflux overnight. After the solution was cooled to room temperature, water was added, and the mixture was allowed to settle. The organic phase was separated, dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography (diisopropyl ether). Salification with oxalic acid in acetone afforded **15d** (oxalate form) as a white solid (56.9 g, 84%): mp 225 °C; ^{1}H NMR (DMSO-d_6) δ 1.15−1.20 (t, J = 7.1 Hz, 3H, CH_3), 1.73−1.85 (m, 4H, $2CH_2$), 2.02−2.09 (m, 2H, CH_2), 2.66−2.71 (m, 2H, CH_2), 2.89−2.93 (m, 2H, CH_2), 3.50 (s, 2H, CH_2Ph), 3.50−3.67 (m, 1H, CHN), 3.68−3.73 (m, 2H, CH_2), 4.03−4.10 (q, J = 7.1 Hz, 2H, CH_2O), 7.32 (s, 5H, Ph), 7.50 (s, 1H, CHS), 7.84 (d, J = 8.5 Hz, 2H, Ar), 8.01 (d, J = 8.5 Hz, 2H, Ar).

4-[[2-[*N*-Methyl-*N*-(piperid-4-yl)amino]-1,3-thiazol-4-yl]-benzonitrile (16a). 16a was prepared from **15a** as described for **11**. Crystallization from diethyl ether gave **16a (**dihydrochloride) as a beige solid (67%): mp 175 °C; ^{1}H NMR (DMSO-d_6) δ 1.85−2.12 (m, 4H, $2CH_2$), 2.95 (s, 3H, NCH_3), 3.06−3.13 (m, 2H, CH_2), 3.30−3.40 (m, 2H, CH_2), 4.22−4.40 (m, 1H, CHN), 7.52 (s, 1H, CHS), 7.84 (d, J = 8.4 Hz, 2H, Ar), 8.06 (d, J = 8.4 Hz, 2H, Ar), 8.85 (bs, 2H, NH).

4-[2-[*N*-Benzyl-*N*-(piperid-4-yl)amino]-1,3-thiazol-4-yl]-benzonitrile (16b). The compound **15b** was prepared from **10** as described for **15a** using benzyl bromide. Crude **15b** was then debenzylated as described for **11** to give **16b** (dihydrochloride) as a white solid (69%): mp 195 °C; ^{1}H NMR (DMSO-d_6) δ 1.87−1.93 (m, 2H, CH_2), 2.09−2.26 (m, 2H, CH_2), 2.99−3.03 (m, 2H, CH_2N), 3.27−3.40 (m, 2H, CH_2N), 4.30−4.52 (m, 1H, CHN), 4.63 (s, 2H, CH_2Ph), 5.67 (bs, NH_2), 7.31 (bs, 5H, Ar), 7.51 (s, 1H, CHS), 7.81 (d, J = 8.5 Hz, 2H, Ar), 8.04 (d, J = 8.5 Hz, 2H, Ar).

Methyl 3-[*N*-[4-(4-Cyanophenyl)-1,3-thiazol-2-yl]-*N*-(piperid-4-yl)amino]acetate (16c). The compound **15c** was prepared from **10** as described for **15a** using methyl bromoacetate. Crude **15c** was then debenzylated as described for **11** to give **16c** (dihydrochloride) as a white solid (58%): mp 213

°C; ^{1}H NMR (DMSO-d_6) δ 1.72−2.17 (m, 4H, $2CH_2$), 3.03−3.10 (m, 2H, CH_2N), 3.26−3.44 (m, 2H, CH_2N), 3.69 (s, 3H, OCH_3), 3.94−4.12 (m, 1H, CHN), 4.25 (s, 2H, CH_2CO), 6.27 (bs, 2H, NH), 7.57 (s, 1H, CHS), 7.82 (d, J = 8.5 Hz, 2H, Ar), 8.00 (d, J = 8.5 Hz, 2H, Ar).

Ethyl 3-[*N*-[4-(4-Cyanophenyl)-1,3-thiazol-2-yl]-*N*-(piperid-4-yl)amino]propionate (16d). This compound was prepared from **15d** as described for **11**. Crystallization from diethyl ether gave **16d** (dihydrochloride) as a white solid (70%): mp 140 °C; ^{1}H NMR (DMSO-d_6) δ 1.16 (t, J = 7.1 Hz, CH_3), 1.59−1.78 (m, 4H, $2CH_2$), 2.49−2.74 (m, 3H, CH_2), 2.99−3.22 (m, 4H, $2CH_2$), 3.63−3.71 (m, 2H, CH_2), 4.05 (q, J = 7.1 Hz, CH_2O), 7.49 (s, 1H, CHS), 7.82 (d, J = 8.4 Hz, 2H, Ar), 8.00 (d, J = 8.4 Hz, 2H, Ar)

Methyl [4-[*N*-[4-(4-Cyanophenyl)-1,3-thiazol-2-yl]-*N*-methylamino]piperidino]acetate (17a). This compound was prepared from **16a** as described for **12a** but using methyl bromoacetate to give **17a** as a beige solid (70%): mp 107 °C; ^{1}H NMR (DMSO-d_6) δ 1.64−1.90 (m, 4H, $2CH_2$), 2.26−2.37 (m, 2H, CH_2N), 2.85−2.94 (m, 2H, CH_2N), 2.95 (s, 3H, CH_3N), 3.25 (s, 2H, CH_2CO), 3.61 (s, 3H, OCH_3), 3.82−3.98 (m, 1H, CHN), 7.45 (s, 1H, CHS), 7.82 (d, J = 8.4 Hz, 2H, Ar), 8.01 (d, J = 8.4 Hz, 2H, Ar).

Methyl [4-[*N*-Benzyl-*N*-[4-(4-cyanophenyl)-1,3-thiazol-2-yl]amino]piperidino]acetate (17b). This compound was prepared from **16b** as described for **12a** but using methyl bromoacetate. Crystallization from diisopropyl ether gave **17b** as a white solid (80%): mp 138 °C; ^{1}H NMR (DMSO-d_6) δ 1.65−1.85 (m, 4H, $2CH_2$), 2.20−2.40 (m, 2H, CH_2N), 2.84−2.90 (m, 2H, CH_2N), 3.22 (s, 2H, CH_2CO), 3.58 (s, 3H, OCH_3), 3.85−4.05 (m, 1H, CHN) 4.69 (s, 2H, CH_2Ph), 7.20−7.32 (m, 5H, Ar), 7.47 (s, 1H, CHS), 7.81 (d, J = 8.2 Hz, 2H, Ar), 7.98 (d, J = 8.2 Hz, 2H, Ar).

Methyl [4-[*N*-[4-(4-Cyanophenyl)-1,3-thiazol-2-yl]-*N*-[(methoxycarbonyl)methyl]amino]piperidino]acetate (17c). This compound was prepared from **16c** as described for **12a** using methyl bromoacetate. Column chromatography (95:5 CH_2Cl_2/CH_3OH) gave **17e** as a yellow solid (58%): mp 93 °C; ^{1}H NMR (DMSO-d_6) δ 1.68−1.86 (m, 4H, $2CH_2$), 2.24−2.36 (m, 2H, CH_2), 2.86−2.93 (m, 2H, CH_2), 3.24 (s, 2H, CH_2N), 3.50−3.65 (m, 1H, CHN), 3.59 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 4.28 (s, 2H, CH_2N), 7.51 (s, 1H, CHS), 7.82 (d, J = 8.5 Hz, 2H, Ar), 7.99 (d, J = 8.5 Hz, 2H, Ar).

Ethyl 3-[*N*-[4-(4-Cyanophenyl)-1,3-thiazol-2-yl]-*N*-[1-[(ethoxycarbonyl)methyl]piperid-4-yl]amino]propionate (17d). This compound was prepared from **16d** as described for **12a**. Column chromatography (98:2 CH_2Cl_2/CH_3OH) gave **17d** as a foam (85%): ^{1}H NMR (DMSO-d_6) δ 1.08−1.21 (m, 6H, $2CH_3$), 1.65−1.90 (m, 4H, $2CH_2$), 2.25−2.36 (m, 2H, CH_2), 2.62−2.70 (m, 2H, CH_2N), 2.85−3.00 (m, 2H, CH_2N), 3.24 (s, 2H, CH_2), 3.45−3.60 (m, 1H, CHN), 3.63−3.71 (m, 2H, CH_2N), 3.99−4.12 (m, 4H, $2CH_2O$), 7.48 (s, 1H, CHS), 7.82 (d, J = 8.5 Hz, 2H, Ar), 7.99 (d, J = 8.5 Hz, 2H, Ar).

Ethyl 4-[*N*-[4-(4-Cyanophenyl)-1,3-thiazol-2-yl]-*N*-[1-(ethoxycarbonylmethyl)piperid-4-yl]amino]butyrate (17e). The compound **15e** was prepared from **10** as described for **15a** using ethyl 4-bromobutyrate. Crude product **15e** was then debenzylated as described for **11** to give **16e**, which was alkylated as described for **15a** using ethyl bromoacetate. Column chromatography (98:2 CH_2Cl_2/CH_3OH) and then salification with hydrogen chloride in AcOEt gave **17e** (dihydrochloride) as a white solid (13%): mp 100 °C; ^{1}H NMR (DMSO-d_6) δ 1.16 (t, J = 7.1 Hz, 3H, CH_3), 1.24 (t, J = 7.1 Hz, 3H, CH_3), 1.88−2.03 (m, 4H, $2CH_2$), 2.27−2.42 (m, 4H, $2CH_2$), 4.00−4.27 (m, 7H, CH_2N, $2CH_2O$, CHN), 7.54 (s, 1H, CHS), 7.83 (d, J = 8.3 Hz, 2H, Ar), 8.04 (d, J = 8.3 Hz, 2H, Ar).

Methyl [4-[*N*-[4-[4-(Aminoiminomethyl)phenyl]-1,3-thiazol-2-yl]-*N*-methylamino]piperidino]acetate (18a). **18a** was prepared from **17a** as described for **13a**. Column chromatography (8:2 CH_2Cl_2/CH_3OH) gave **18a** (hydrochloride) as a yellow solid (68%): mp 107 °C; ^{1}H NMR (DMSO-d_6) δ 1.66−1.87 (m, 4H, $2CH_2$), 2.25−2.45 (m, 2H, CH_2N), 2.85−2.95 (m, 2H, $2CH_2N$), 2.98 (s, 3H, CH_3N), 3.27 (s, 2H, CH_2N), 3.62 (s, 3H, OCH_3), 3.78−3.98 (m, 1H, CHN), 7.48 (s, 1H, CHS), 7.85 (d, J = 8.4 Hz, 2H, Ar), 8.05 (d, J = 8.4 Hz, 2H, Ar), 9.21 (bs, 4H, NH_2). Anal. ($C_{19}H_{25}N_5O_2S$·HCl·1.5H_2O) C, H, S; N: calcd, 15.53; found, 15.10.

Methyl [4-[*N*-[4-[4-(Aminoiminomethyl)phenyl]-1,3-thiazol-2-yl]-*N*-benzylamino]piperidino]acetate (18b). **18b** was prepared from **17b** as described for **13a**. Column chromatography (8:2 CH_2Cl_2/CH_3OH) gave **18b** (hydrochloride) as a yellow solid (85%): mp 190 °C; ^{1}H NMR (DMSO-d_6) δ 1.68−1.87 (m, 4H, $2CH_2$), 2.20−2.42 (m, 2H, CH_2N), 2.82−2.98 (m, 2H, CH_2N), 3.23 (s, 2H, NCH_2CO), 3.58 (s, 3H, OCH_3), 3.83−4.02 (m, 1H, CHN), 4.71 (s, 2H, CH_2Ph), 7.18−7.33 (m, 5H, Ar), 7.48 (s, 1H, CHS), 7.82 (d, J = 8.4 Hz, 2H, Ar), 8.01 (d, J = 8.4 Hz, 2H, Ar), 9.22 (bs, 4H, NH_2). Anal. ($C_{25}H_{29}N_5O_2S$·HCl·1H_2O) C, H, N, S.

Methyl [4-[*N*-[4-[4-(Aminoiminomethyl)phenyl]-1,3-thiazol-2-yl]-*N*-[(methoxycarbonyl)methyl]amino]piperidino]acetate (18c). **18c** was prepared from **17c** as described for **13a**. Column chromatography (8:2 CH_2Cl_2/CH_3OH) gave **18c** (hydrochloride) as a yellow solid (74%): mp 247 °C; ^{1}H NMR (DMSO-d_6) δ 1.66−1.88 (m, 4H, $2CH_2$), 2.20−2.43 (m, 2H, CH_2N), 2.82−3.00 (m, 2H, CH_2N), 3.26 (s, 2H, NCH_2CO), 3.50−3.65 (m, 1H, CHN), 3.59 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 4.29 (s, 2H, NCH_2CO), 7.53 (s, 1H, CHS), 7.86 (d, J = 8.4 Hz, 2H, Ar), 7.98 (d, J = 8.4 Hz, 2H, Ar). Anal. ($C_{21}H_{27}N_5O_4S$·HCl·1.5H_2O) C, H, N, S.

Ethyl 3-[4-[*N*-[4-[4-(Aminoiminomethyl)phenyl]-1,3-thiazol-2-yl]-*N*-[1-[(ethoxycarbonyl)methyl]piperid-4-yl]-amino]propionate (18d). **18d** was prepared from **17d** as described for **13a**. Column chromatography (8:2 CH_2Cl_2/CH_3OH) gave **18d** (hydrochloride) as a yellow solid (76%): mp 156 °C; ^{1}H NMR (DMSO-d_6) δ 1.12−1.21 (m, 6H, $2CH_3$), 1.65−1.95 (m, 4H, $2CH_2$), 2.24−2.35 (m, 2H, CH_2N), 2.63−2.70 (m, 2H, CH_2CO), 2.85−3.00 (m, 2H, CH_2N), 3.23 (s, 2H, NCH_2CO), 3.43−3.62, (m, 1H, CHN), 3.63−3.79 (m, 2H, CH_2N), 3.99−4.12 (m, 4H, $2CH_2O$), 7.51 (s, 1H, CHS), 7.86 (d, J = 8.5 Hz, 2H, Ar), 8.02 (d, J = 8.5 Hz, 2H, Ar), 9.23 (bs, 2H, NH_2), 9.40 (bs, 2H, NH_2). Anal. ($C_{24}H_{33}N_5O_4S$·HCl·H_2O) C, H, N, S.

Ethyl 4-[*N*-[4-[4-(Aminoiminomethyl)phenyl]-1,3-thiazol-2-yl]-*N*-[1-[(ethoxycarbonyl)methyl]piperid-4-yl]amino]butyrate (18e). **18e** was prepared from **17e** as described for **13a**. Column chromatography (8:2 CH_2Cl_2/CH_3OH) gave **18e** (hydrochloride) as a yellow solid (80%); mp 120 °C; ^{1}H NMR (DMSO-d_6) δ 1.12−1.21 (m, 6H, $2CH_3$), 1.68−2.00 (m, 6H, $3CH_2$), 2.20−2.45 (m, 4H, $2CH_2N$), 2.85−3.05 (m, 2H, CH_2N), 3.25 (s, 2H, NCH_2CO), 3.32−3.41 (m, 2H, CH_2), 3.58−3.80 (m, 1H, CHN), 3.99−4.13 (m, 4H, $2CH_2O$), 7.48 (s, 1H, CHS), 7.83 (d, J = 8.4 Hz, 2H, Ar), 8.04 (d, J = 8.4 Hz, 2H, Ar), 9.06 (bs, 2H, NH_2), 9.34 (bs, 2H, NH_2). Anal. ($C_{25}H_{35}N_5O_4S$·HCl·$2H_2O$) C, H, N, S.

[4-[*N*-[4-[4-(Aminoiminomethyl)phenyl]-1,3-thiazol-2-yl]-*N*-methylamino]piperidino]acetic Acid (19a). **19a** was prepared from **18a** as described for **14a**. Crystallization from acetone gave **19a** (trihydrochloride) as a white solid (88%): mp 226 °C; ^{1}H NMR (DMSO-d_6) δ 1.84−2.04 (m, 2H, CH_2), 2.13−2.40 (m, 2H, CH_2), 2.96 (s, 3H, NCH_3), 3.20−3.45 (m, 2H, CH_2N), 3.52−3.70 (m, 2H, CH_2N), 4.12 (bs, 2H, CH_2-CO), 4.25−4.45 (m, 1H, CHN), 7.53 (s, 1H, CHS), 7.90 (d, J = 8.5 Hz, 2H, Ar), 8.07 (d, J = 8.5 Hz, 2H, Ar), 9.23 (bs, 2H, NH_2), 9.47 (bs, 2H, NH_2), 10.43 (bs, OH). Anal. ($C_{18}H_{23}N_5O_2S$·3HCl·$4H_2O$) C, H, N, S.

[4-[*N*-[4-[4-(Aminoiminomethyl)phenyl]-1,3-thiazol-2-yl]-*N*-benzylamino]piperidino]acetic Acid (19b). **19b** was prepared from **18b** as described for **14a**. Crystallization from acetone gave **19b** (trihydrochloride) as a white solid (92%): mp 245 °C; ^{1}H NMR (DMSO-d_6) δ 1.90−2.05 (m, 2H, CH_2), 2.32−2.59 (m, 2H, CH_2), 3.25−3.48 (m, 2H, CH_2N), 3.53−3.70 (m, 2H, CH_2N), 3.97 (bs, 2H, CH_2CO), 4.43−4.60 (m, 1H, CHN), 4.61 (s, 2H, NCH_2Ph), 7.16−7.25 (m, 5H, Ph), 7.71 (s, 1H, CHS), 7.80 (d, J = 8.4 Hz, 2H, Ar), 7.93 (d, J = 8.4 Hz, 2H, Ar), 8.93 (bs, 2H, NH_2), 9.31 (bs, 2H, NH_2), 10.86 (bs, OH). Anal. ($C_{27}H_{27}N_5O_2S$·3HCl) C, H; N: calcd, 12.53; found, 12.11. S: calcd, 5.73; found, 5.28.

[4-[*N*-[4-[4-(Aminoiminomethyl)phenyl]-1,3-thiazol-2-yl]-*N*-(carboxymethyl)amino]piperidino]acetic Acid (19c). **19c** was prepared from **18c** as described for **14a**. Crystallization from acetone gave **19c** (trihydrochloride) as a white solid (91%): mp 216 °C; ^{1}H NMR (DMSO-d_6) δ 1.85−2.08 (m, 2H, CH_2), 2.15−2.43 (m, 2H, CH_2), 3.18−3.45 (m, 2H, CH_2N), 3.50−3.70 (m, 2H, CH_2N), 4.00−4.45 (m, 5H, $2CH_2CO$ and CHN),

7.56 (s, 1H, CHS), 7.91 (d, J = 8.5 Hz, 2H, Ar), 8.04 (d, J = 8.5 Hz, 2H, Ar), 9.31 (bs, 2H, NH_2), 9.53 (bs, 2H, NH_2), 10.42 (bs, OH). Anal. ($C_{19}H_{23}N_5O_4S \cdot 3HCl \cdot 1H_2O$) C, H, N, S.

3-[*N*-[4-[4-(Aminoiminomethyl)phenyl]-1,3-thiazol-2-yl]-*N*-[1-(carboxymethyl)piperid-4-yl]amino]propionic Acid (19d). 19d was prepared from **18d** as described for **14a**. The product was crystallized from acetone and filtered. The precipitate was dissolved in water and freeze-dried to afford **19d** (trihydrochloride) as a white solid (80%): mp 215 °C; ^{1}H NMR (DMSO-d_6) δ 1.90−2.08 (m, 2H, CH_2), 2.22−2.43 (m, 2H, CH_2), 2.60−2.73 (m, 2H, CH_2N), 3.18−3.45 (m, 2H, CH_2N), 3.59−3.75 (m, 4H, CH_2CO and CH_2N), 4.00−4.28 (m, 3H, CH_2-CO and CHN), 7.55 (s, 1H, CHS), 7.91 (d, J = 8.3 Hz, 2H, Ar), 8.07 (d, J = 8.3 Hz, 2H, Ar), 9.30 (bs, 2H, NH_2), 9.51 (bs, 2H, NH_2), 10.41 (bs, OH). Anal. ($C_{20}H_{25}N_5O_4S \cdot 3HCl \cdot 1.5H_2O$) C, H, N, S.

4-[*N*-[4-[4-(Aminoiminomethyl)phenyl]-1,3-thiazol-2-yl]-*N*-[1-(carboxymethyl)piperid-4-yl]amino]butyric Acid (19e). 19e was prepared from **18e** as described for **14a**. The product was crystallized from acetone and filtered. The precipitate was dissolved in water and freeze-dried to afford **19e** (trihydrochloride) as a white solid (78%): mp 100 °C; ^{1}H NMR (DMSO-d_6) δ 1.75−2.10 (m, 4H), 2.18−2.43 (m, 4H), 3.15−3.48 (m, 4H), 3.53−3.73 (m, 2H), 4.02−4.30 (m, 3H, CH_2-CO and CHN), 7.54 (s, 1H, CHS), 7.88 (d, J = 8.5 Hz, 2H, Ar), 8.08 (d, J = 8.5 Hz, 2H, Ar), 9.22 (bs, 2H, NH_2), 9.46 (bs, 2H, NH_2), 10.30 (bs, OH). Anal. ($C_{21}H_{27}N_5O_4S \cdot 3HCl \cdot 5H_2O$) C, H, N, S.

Ethyl 3-[*N*-[4-[4-[Amino[(ethoxycarbonyl)imino]methyl]phenyl]-1,3-thiazol-2-yl]-*N*-[1-[(ethoxycarbonyl)methyl]piperid-4-yl]amino]propionate (6). To a solution of **18d** (3.5 g, 6.68 mmol) and triethylamine (1.95 mL, 14 mmol) in DMF (35 mL) at 5 °C was added dropwise ethyl chloroformate (0.67 mL, 7 mmol). After 3 h at room temperature, the mixture was poured over water and extracted with AcOEt. The organic phase was washed with water, dried (Na_2SO_4), and concentrated. Crystallization from diisopropyl ether gave **6** as a white solid (2.9 g, 78%): mp 130 °C; ^{1}H NMR (DMSO-d_6) δ 1.12−1.23 (m, 9H, $3CH_3$), 1.63−1.95 (m, 4H, $2CH_2$), 2.24−2.35 (m, 2H, CH_2N), 2.63−2.71 (m, 2H, CH_2CO), 2.85−2.98 (m, 2H, CH_2N), 3.23 (s, 2H, NCH_2CO), 3.45−3.61 (m, 1H, CHN), 3.63−3.72 (m, 2H, CH_2N), 3.99−4.12 (m, 6H, $3CH_2O$), 7.37 (s, 1H, CHS), 7.89 (d, J = 8.6 Hz, 2H, Ar), 7.97 (d, J = 8.6 Hz, 2H, Ar), 9.07 (bs, 2H, NH_2). Anal. ($C_{27}H_{37}N_5O_6S$) C, H, N, S.

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