pneumoniae. The initial pyrrolidinylquinolines prepared and tested were **9a–c**, which represent the primary amino, methylamino, and 3-[(ethylamino)methyl]-1-pyrrolidinyl analogues of norfloxacin. The [3-[(ethylamino)methyl]-1-pyrrolidinyl]quinoline **9c** showed excellent MICs with very impressive coverage (≤0.2 μg/mL) against Gram-positive organisms. Even the less potent compounds **9a,b** still possessed better Gram-positive activity than the standard drugs (≤1.6 μg/mL). Furthermore, replacement of the piperazine moiety with the substituted 3-(aminomethyl)-1-pyrrolidinyl moiety did not compromise the gyrase inhibition, which is further proof that the piperazine group is not essential for antibacterial activity. The gyrase cleavage value for **9c** of 2.5 μg/mL is equal to that of amifloxacin (**1e**) and superior to that of enoxacin (**1c**) and ofloxacin (**2**). The in vivo activity of **9c**, however, was very poor. In order to increase the in vivo potency of **9c** without sacrificing the MICs and gyrase activity already in hand, small molecular changes to increase solubility and possibly absorption were pursued. The result of this search led to the synthesis of the 6,8-difluoro analogues **9d–f**. The primary amino pyrrolidinyl-6,8-difluoroquinoline **9d** displayed a 5-fold improvement in gyrase activity with improved MICs and in vivo efficacy as well when compared to **9a**. 1-Ethyl-7-[3-[(ethylamino)methyl]-1-pyrrolidinyl]-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (**9f**) showed no enhancement of gyrase inhibition over **9c** but displayed a marked 8-fold improvement in the mouse protection assay. Especially noteworthy are the PD_{50}s vs. *S. aureus* and *S. pneumoniae* when compared to ofloxacin and pefloxacin. This new extended spectrum quinoline **9f** (CI-934) shows the best Gram-positive activity in vitro and in vivo of any quinoline tested in this study.

Registry No. 7 (R = H), 67318-88-1; 7 (R = CH_3), 91187-81-4; 7 (R = CH_3CH_2), 91187-83-6; **8a**, 70032-25-6; **8b**, 68077-26-9; **8c**, 75338-42-0; **9a**, 91187-93-8; **9b**, 91187-94-9; **9c**, 91187-95-0; **9d**, 91187-96-1; **9e**, 99947-82-7; **95**, 91188-00-0.

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Articles

Tranexamic Acid Derivatives with Enhanced Absorption

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Derivatives of the antifibrinolytic drug tranexamic acid [*trans*-4-(aminomethyl)cyclohexanecarboxylic acid] containing one or two tranexamic acid moieties were synthesized. Most of the derivatives have good stability in acidic and neutral solutions but are easily hydrolyzed in plasma. By measuring the amount of tranexamic acid excreted in the urine after an oral dose, relative absorptions of a number of derivatives in the rat were estimated. Most of the derivatives showed greater absorption than tranexamic acid itself. 1-[(Ethoxycarbonyl)oxy]ethyl *trans*-4-(aminomethyl)cyclohexanecarboxylate hydrochloride (1) was chosen for studies in man.

Tranexamic acid [*trans*-4-(aminomethyl)cyclohexanecarboxylic acid, Cyclokapron] is a clinically used antifibrinolytic drug. The haemostatic properties of this drug mainly relate to its ability to inhibit the activation of plasminogen to plasmin,[1,2] thereby preventing excessive loss of blood in hyperfibrinolytic conditions.

Tranexamic acid is incompletely absorbed from the gastrointestinal tract, possibly due to its amphoteric nature. In man, after administration of an oral dose of 10–15 mg/kg of body weight, about 40% was recovered in the urine within 24 h.[3] After a single intravenous injection to two volunteers of 1 g (about 15 mg/kg) of tranexamic acid, 88 and 94%, respectively, of the unchanged drug was excreted in the urine within 24 h.[4] In an attempt to increase the gastrointestinal absorption of the drug, derivatives lacking the amphoteric nature of tranexamic acid were synthesized. As tranexamic acid is used clinically in rather large doses (2–6 g/day), it was desirable to keep the molecular weight of the synthesized compounds low. With this in mind, potential prodrug containing two moieties of tranexamic acid were also synthesized.

Chemistry

The potential prodrugs of tranexamic acid that are described in this paper can be divided into two groups; mono derivatives containing one moiety of tranexamic acid (Table I) and bis derivatives containing two moieties of tranexamic acid per mole of potential prodrug (Table II). All of the potential prodrugs except compounds **9**, **10**, and **20** contain the (acyloxy)methyl ester moiety. They can also be considered bis esters of geminal diols (hydrate forms of aldehydes).

The key intermediate for the synthesis of the mono derivates **1–4** and **6–8** was an α-chloro- or α-bromoalkyl ester of a carboxylic[5] or carbonic acid,[6] as illustrated for **1** (method A, Chart I). This intermediate was reacted with

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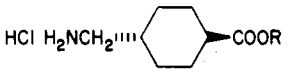
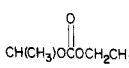
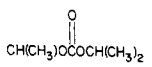
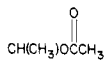
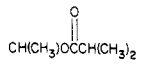
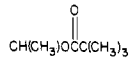
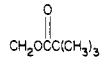
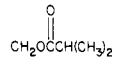
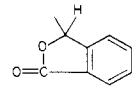
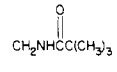
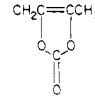
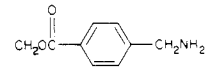
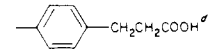
(1) Andersson, L.; Nilsson, I. M.; Nilehn, J. E.; Hedner, U.; Granstrand, B.; Melander, B. *Scand. J. Hematol.* **1965**, *2*, 239.
(2) Ogston, D. "Antifibrinolytic Drugs"; Wiley: New York, 1985; p 48.
(3) Nilsson, I. M. *J. Clin. Pathol., Suppl. (R. Coll. Pathol.)* **1979**, *14*, 41.
(4) Eriksson, O.; Kjellman, H.; Pilbrant, Å.; Schannong, M. *Eur. J. Clin. Pharmacol.* **1974**, *7*, 375.
(5) Ulich, L. H.; Adams, R. *J. Am. Chem. Soc.* **1921**, *43*, 662.
(6) Müller, H. *Ann.* **1890**, *258*, 50.

0022-2623/86/1829-0448$01.50/0

Table I. Potential Prodrugs of Tranexamic Acid and Some Reference Compounds (Compounds Containing One Moiety of Tranexamic Acid Per Mole of Potential Prodrugs)



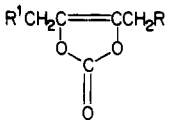
no.	R	method	mp, °C	yield,[a] %	formula[b] of free amine	abs,[c] %
1		A	139	46	$C_{13}H_{23}NO_5$	50 ± 5
2		A	158	8	$C_{14}H_{25}NO_5$	43 ● 4
3		A	126	8	$C_{12}H_{21}NO_4$	59 ± 6
4		A	102	6	$C_{14}H_{25}NO_4$	71 ± 2
5		B	85	20	$C_{15}H_{27}NO_4$	43 ± 4
6		A	165	30	$C_{14}H_{25}NO_4$	36 ± 3
7		A	100	31	$C_{13}H_{23}NO_4$	54 ± 3
8		A	212	53	$C_{16}H_{19}NO_4$	44 ± 7
9		D	90	38	$C_{14}H_{26}N_2O_3$	22 ± 3
10		E	176	27	$C_{13}H_{19}NO_5$	67 ± 17
11		C	242	4	$C_{17}H_{24}N_2O_4$	35 ± 9
12	 [d]		230	8	$C_{17}H_{23}NO_4$	28 ± 3
13	CH_2CH_3		198	86	$C_{10}H_{19}NO_2$	92 ± 5
	tranexamic acid		>290		$C_8H_{15}NO_2$	22 ± 4

[a] From tranexamic acid. For method B from *trans*-4-cyanocyclohexanecarboxylic acid. Yields not optimized. [b] Analyzed for C, H, H, Cl, the results being within ±0.4% of the theoretical values. All compounds hydrochloric acid salts except **9**, which is a benzoic acid salt and tranexamic acid which is the free amine. [c] Percent tranexamic acid recovered in rat urine within 24 h after oral administration of 0.1 mmol/kg of body weight of potential prodrug (n = 4). For tranexamic acid, n = 10. n = number of rats. [d] 4′-(2-Carboxyethyl)phenyl *trans*-4-(aminomethyl)cyclohexanecarboxylate hydrochloride.

the tetrabutylammonium (Q) salt of *tert*-butoxycarbonyl- (Boc-) protected tranexamic acid. Deprotection of the amino group gave the desired product.

For the synthesis of the bis derivatives **15** and **16**, an α-chloroalkyl ester of *trans*-4-cyanocyclohexanecarboxylic acid was used, as illustrated for **15** (method B, Chart I). The 4-cyano groups were directly transformed to the hydrochlorides of the 4-aminomethyl groups by catalytic hydrogenation in the presence of chloroform as a source of hydrogen chloride.[7] The intermediate **26** was also used for the synthesis of the mono derivative **5**. The bis derivatives **14** and **17–19** were obtained by reacting 1,1-dihalo compounds with 2 equiv of Boc-tranexamic acid as the trialkylammonium salt in dimethylformamide as illustrated for **18** (method C, Chart I) or as the Q salt according to Holmberg and Hansen.[8] The mixed compound **11** containing one moiety of tranexamic acid and one moiety of another antifibrinolytic drug namely 4-(aminomethyl)benzoic acid was obtained by reacting (benzyloxy)carbonyl- (Z-) protected tranexamic acid **21** with Boc-4-(aminomethyl)benzoic acid **24** (method C, Experimental Section). The Z- and Boc-protected **11** thus obtained was sequentially deprotected to give the desired compound **11**.

Compound **9** was prepared from (pivaloylamino)methanol (**30**) and Z-protected tranexamic acid **21**, using dicyclohexylcarbodiimide and 4-(*N*,*N*-dimethylamino)pyridine (method D, Experimental Section). After deprotection by hydrogenation under neutral conditions, a benzoic acid salt was prepared. The compounds **10** and **20** were synthesized from the bromodioxolenes **33** and **34**, respectively, using the Q salt of Boc-tranexamic acid (method E, Experimental Section). The bromodioxolenes **33** and **34** were obtained by brominating dimethyldioxolene (**32**) with different amounts of *N*-bromosuccinimide.



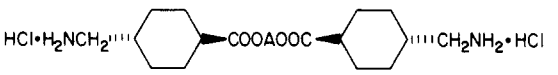
32: R^1=H, R=H
33: R^1=Br, R=H
34: R^1=Br, R=Br

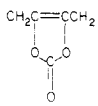
Results and Discussion

Tranexamic acid exerts its antifibrinolytic activity in blood plasma. In order to obtain improved bioavailability

(7) Secrist, J. A., III; Logue, M. W. *J. Org.* Chem. **1972**, *37*, 335.
(8) Holmberg, K.; Hansen, B. *Tetrahedron Lett.* **1975**, 2303.

Table II. Potential Prodrugs of Tranexamic Acid (Compounds Containing Two Moieties of Tranexamic Acid Per Mole of Potential Prodrug)

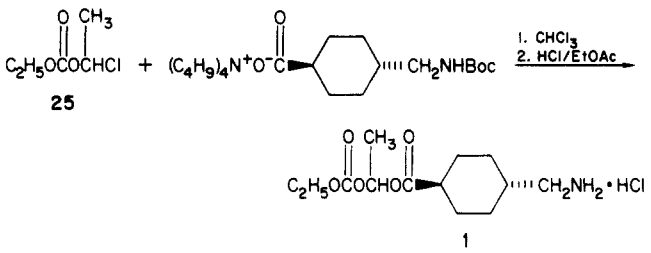


no.	A	method	mp, °C	yield,[a] %	formula of[b] free amine	absorption,[c] % per mole of prodrug	absorption,[c] % per moiety tranexamic acid
14	CH_2	C	269	45	$C_{17}H_{30}N_2O_4$	50 ± 6	25 ± 3
15	$CH(CH_3)$	B	260	50	$C_{18}H_{32}N_2O_4$	42 ± 12	21 ± 6
16	$CH(C_2H_5)$	B	262	27	$C_{19}H_{34}N_2O_4$	26 ± 8	13 ± 4
17		C	150	14	$C_{20}H_{34}N_2O_6$	62 ± 8	31 ± 4
18		C	224	8	$C_{20}H_{35}N_3O_5$	54 ± 18	27 ± 9
19		C	218	4	$C_{22}H_{39}N_3O_5$	34 ± 14	17 ± 7
20		E	254	5	$C_{21}H_{32}N_2O_7$	54 ± 10	27 ± 5

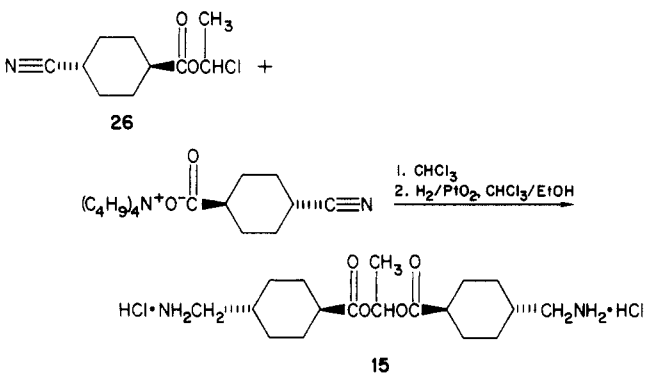
[a] From tranexamic acid. For method B from *trans*-4-cyanocyclohexanecarboxylic acid. Yields not optimized. [b] Analyzed for C, H, N, Cl, the results being within ±0.4% of the theoretical values. All compounds hydrochloric acid salts. [c] Percent tranexamic acid recovered in urine within 24 h after oral administration of 0.1 mmol/kg of body weight of potential prodrug (n = 4). n = number of rats.

Chart I. Principle Methods for Synthesis of Potential Prodrugs of Tranexamic Acid

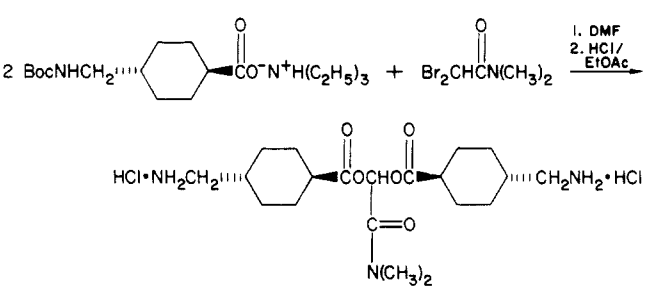
Method A



Method B



Method C



of tranexamic acid, good absorption of the potential prodrugs has to be combined with fast regeneration of the parent drug during its uptake into or within the plasma. Rapid regeneration is also important for avoiding possible adverse affects that might arise from the intact prodrug. The half-lives of some potential prodrugs in 90% human heparinized plasma at 37 °C were therefore determined (Table III). Some compounds, e.g. **1**, **7**, and **14**, had a very short half-life in human plasma whereas others, **3**, **6**, and **16**, showed a somewhat longer half-life; the most stable compound was **13**. When compound **14** was incubated in human heparinized plasma two moieties of tranexamic acid per mole of potential prodrug were released. By a more sensitive method for determination of compound **1** in whole blood, the half-life at an initial concentration of 2.1–4.4 μM was found to be 1.5 min in blood at 37 °C, 4 min in dog blood at 37 °C, and 1 min in rat blood at 20 °C.[9]

A potential prodrug should also have reasonable stability. The half-lives of potential prodrugs were therefore determined in phosphate buffer at pH 7.5 and in sodium chloride–hydrochloride buffer at pH 1.2. Most of the

Table III. Half-Lives at 37 °C of Potential Prodrugs in 90% Human Heparinized Plasma, in Phosphate Buffer at pH 7.5 and in Sodium Chloride–Hydrochloride Buffer at pH 1.2

no.	$t_{1/2}$ human plasma, min	$t_{1/2}$ buffer, h: pH 1.2	$t_{1/2}$ buffer, h: pH 7.5
1	1.5, 1.5[a]	54	90
2		58	144
3	6–12	14	68
4		22	140
6	2–9	164	147
7	0.5	18	36
8			5
9		2[b]	10[b]
10		25	2
13	240[a]		c
14	1.5	31	26
16	6–17	29	70
17		11	0.9
18		38	6.7

[a] In human blood.[9] [b] Minutes. [c] 88% intact after 21 days.

(9) Abrahamsson, M. *J. Pharm. Biomed. Anal.*, in press.

Table IV. Percent Recovery of Tranexamic Acid in Urine from Rats within 24 h after Oral Administration of Two Different Doses of Potential Prodrugs of Tranexamic Acid[a]

	dose	
no.	0.1 mol/kg of body wt	1 mmol/kg of body wt
1	50 ± 5	62 ± 7[b]
2	43 ± 4	86 ± 16
6	36 ± 3	58 ± 11
8	44 ± 7	54 ± 12
14	25 ± 3[c]	32 ± 5[c]
tranexamic acid	22 ± 4[d]	11 ± 1

[a] $n = 4$. [b] $n = 8$. [c] Per moiety 10. [d] $n = 10$. n = number of rats.

potential prodrugs showed good stability in buffers at pH 1.2 and 7.5. The least stable compound was **9** (Table III).

In the rat the absorbed tranexamic acid is excreted through the kidneys mainly as unchanged drug. The absorption is rather low (Table IV), and only about 1% of a dose of 10 mg/kg is metabolized.[10] The rat was therefore chosen for determining potential increased absorption, which was correlated with the amount of tranexamic acid excreted in the urine during 24 h, and these values are given in Tables I, II, and IV. The urine was collected for a further two 24-h intervals (to a total of 72 h), but less than an additional 2% of tranexamic acid was excreted in the 24–72-h time period. The dose administered was 0.1 mmol/kg of body weight, corresponding to 15.7 mg of tranexamic acid/kg for the mono derivatives (Table I) or 31.4 mg of tranexamic acid/kg for the bis derivatives (Table II). The lower dose was similar to the dose used in studies of absorption of tranexamic acid in man.[3,4] A 10 times higher dose was also used for a few potential prodrugs (Table IV).

From Tables I and IV it is seen that most of the potential prodrugs containing one moiety of tranexamic acid gave an increased absorption compared with tranexamic acid itself. Compound **9** is less stable in acid (Table III) than the other potential prodrugs and might therefore be hydrolyzed in the stomach before being absorbed. Compound **12** is a clinically available derivative of tranexamic acid,[11] used as an antiulcer drug in Japan. Its absorption of 28% is close to the value of 32% given by Ono et al.[12] The tranexamic acid ester **12** still retains its amphoteric character, which may explain this rather low absorption in the rat. Although the ethyl ester of tranexamic acid **13** was well absorbed in the rat, it is only slowly hydrolyzed by human blood (Table III); consequently, it was not considered a suitable prodrug of tranexamic acid.

In order to keep the weight of the potential prodrugs low, the additional part of the compounds was kept at low weight (Table I). In an attempt to reduce the extra weight of the potential prodrugs still further, some compounds were also prepared in which two moieties of tranexamic acid were combined in the molecule (Table II). Considering the amount of tranexamic acid absorbed per mole of these bis derivatives of tranexamic acid, good enhancement of absorption was obtained for several compounds, namely **14**, **15**, **17**, **18**, and **20**. However, if the absorption is expressed per moiety of tranexamic acid, no significant improvement was observed. Although the amphoteric nature of tranexamic acid has been eliminated also in these bis derivatives, they still contain two charged groups that may render them too polar for facile absorption. The same level of absorption was also found for the mixed compound **11** that contained one moiety of tranexamic acid and one moiety of the poorly absorbed antifibrinolytic drug, 4-(aminomethyl)benzoic acid.[2,13]

When the dose–absorption relationship was studied, a statistically significant ($p > 0.02$) increase of absorption was found when the dose was raised from 0.1 to 1 mmol/kg for compounds **1**, **2**, and **6** (Table IV). The reason for this increase is not known, but it might be due to a more rapid gastric emptying into the duodenum, thus favoring absorption. For tranexamic acid, in contrast, a decrease in absorption was seen when the dose was increased (Table IV).

From the potential prodrugs synthesized, compound **1** was chosen for further preclinical evaluation because of a short half-life in blood, good stability in buffer solutions, and good absorption in the rat. At present, the absorption of compound **1** is being evaluated in man.

Experimental Section

Chemistry. Unless otherwise stated, melting points were determined on a Kofler bench, and IR and proton NMR spectra were measured on Perkin-Elmer instruments 599B and R12, respectively. The spectra were in accordance with the expected structures. Microanalyses were carried out at the Chemical Center, University of Lund, Sweden. Analytical results are indicated by the symbols of the elements, the results being within ±0.4% of the theoretical values. TLC was carried out on silica gel $60F_{254}$ (Merck), eluants EtOAc–pyridine–H_2O–HOAc (5:5:3:1) and $CHCl_3$–MeOH–HOAc (5:2:1). *trans*-4-(Aminomethyl)cyclohexanecarboxylic acid (tranexamic acid) was KabiVitrum batch 18045-17. 4-(2-Carboxyethyl)phenyl *trans*-4-(aminomethyl)-cyclohexanecarboxylate (**12**),[14] *trans*-4-[[[(benzyloxy)carbonyl]-amino]methyl]cyclohexanecarboxylic acid (**21**)[14] (yield 92%), *trans*-4-cyanocyclohexanecarboxylic acid (**22**),[15] mp 156–157 °C, and ethyl *trans*-4-(aminomethyl)cyclohexanecarboxylate hydrochloride (**13**),[16] mp 198 °C (Fus-O-Mat Hereaus) were synthesized according to known procedures.

***trans*-4-[[(*tert*-Butoxycarbonyl)amino]methyl]cyclohexanecarboxylic Acid (23).** Tranexamic acid (78.6 g, 0.50 mol) was dissolved in a mixture of water (390 mL) and *tert*-butyl alcohol (880 mL) containing sodium hydroxide (20.8 g, 0.52 mol). Di-*tert*-butyl dicarbonate (113 g, 0.52 mol) was added. After the mixture was stirred for 18 h at room temperature, water (1500 mL) was added and the solution was extracted with hexane. After the water solution was cooled to +5 °C, the pH was adjusted to 3 with a saturated citric acid solution. The acidified solution was extracted with ethyl acetate. The solvent was evaporated, giving a crystalline product in 94% yield; mp 135 °C. Anal. ($C_{13}H_{23}NO_4$) C, H, N.

4-[[(*tert*-Butoxycarbonyl)amino]methyl]benzoic Acid (24). This compound was similarly prepared from 4-(aminomethyl)benzoic acid:[17] yield 63%; mp 166 °C. Anal. ($C_{13}H_{17}NO_4$) C, H, N.

Method A. 1-[(Ethoxycarbonyl)oxy]ethyl *trans*-4-(Aminomethyl)cyclohexanecarboxylate Hydrochloride (1). A solution of compound **23** (25.7 g, 0.1 mol) and tetrabutylammonium hydrogen sulfate ($QHSO_4$) (34 g, 0.1 mol) in 2 M NaOH (100 mL) was extracted with ethanol-free chloroform. The chloroform solution was dried and evaporated to give 50 g of product. This was dissolved in trichloroethylene (200 mL), and chloro carbonate **25**[6] (16.8 g, 0.11 mol) was added. After refluxing

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for 3 h, the solution was washed with 0.2 M H_2SO_4, $NaHCO_3$ solution, and H_2O and dried. After evaporation of the solvent, the residue was dissolved in ethyl acetate (50 mL) and cooled to 0 °C. This was treated with a cold solution of anhydrous HCl in ethyl acetate (100 mL, 3.8 M). After 3 h in an ice bath the solvent was evaporated to give 23 g. This residue was dissolved in isopropyl alcohol and precipitated with diisopropyl ether: yield 15 g (49%); mp 139 °C; ^1H NMR ($CDCl_3$; JEOL GX-400; 400 MHz) δ 1.32 (t, 3, J = 7.1 Hz, CH_3CH_2), 1.53 (d, 3, J = 5.4 Hz, CH_3CH), 1.04–2.30 (m, 10, C_6H_{10}), 2.86 (m, 2, CH_2N), 4.22 (q, 2, J = 7.1 Hz, CH_2O), 6.74 (q, 1, J = 5.4 Hz, CHO_2) 8.34 (m, 3, NH_3^+).

Method B. 1-Chloroethyl *trans*-4-Cyanocyclohexanecarboxylate (26). Compound **22** (7.7 g, 0.05 mol) was dissolved in sulfurous oxychloride (8.0 g, 0.066 mol), refluxed for 30 min, and concentrated in vacuo. Paraldehyde (2.5 g, 0.62 mol) and a catalytic amount of anhydrous zinc chloride were added, and the mixture was kept at 90 °C for 1.5 h.[5] After cooling, it was extracted with ether, and the ethereal solution was washed with 5% w/v $NaHCO_3$ solution and saturated NaCl, dried over $MgSO_4$, and fractionated, yielding 6.5 g (66%) of oil, bp 112 °C (1 Pa).

1,1-Ethylidene Bis(*trans*-4-cyanocyclohexanecarboxylate) (27). Compound **22** (11.5 g, 0.075 mol) and $QHSO_4$ (25.5 g, 0.075 mol) were dissolved in 2 M NaOH and extracted with ethanol-free chloroform. The chloroform solution was dried and the solvent evaporated. The residue was dissolved in trichloroethylene (600 mL), and the α-chloro ester **26** (10.8 g, 0.05 mol) was added. The solution was refluxed for 8 h. It was then washed with 5% w/v cold $NaHCO_3$, H_2O, and saturated NaCl solution and dried over $MgSO_4$, and the solvent was evaporated, yielding 16.6 g (100%) of a thick oil that slowly crystallized; mp 75–76 °C.

1,1-Ethylidene Bis[*trans*-4-(aminomethyl)cyclohexanecarboxylate] Dihydrochloride (15). The dinitrile **27** (6.0 g, 0.018 mol) was dissolved in a mixture of anhydrous ethanol (600 mL) and chloroform (20 mL). Platinum oxide (1 g) was added, and the mixture was hydrogenated[7] in a Parr apparatus at 3.4 MPa and 22 °C for 15 h. The catalyst was filtered off and the solvent evaporated. The product was crystallized from a mixture of isopropyl alcohol and methyl alcohol, yielding 5.5 g (74%) of salt, mp 260 °C.

Method C. (*N*,*N*-Dimethylcarbamoyl)methylene Bis[*trans*-4-[[(*tert*-butoxycarbonyl)amino]methyl]cyclohexanecarboxylate] (28). Sodium bromide (10.2 g, 0.1 mol) and 1,1-dichloro-*N*,*N*-dimethylacetamide (7.8 g, 0.05 mol) were added to dry dimethylformamide (100 mL), and the mixture was stirred for 4 h. Triethylamine (20.7 g, 0.2 mol) and compound **23** (25.7 g, 0.1 mol) dissolved in dimethylformamide were added. The mixture was stirred for 84 h at 50 °C, the solvent was evaporated, and the residue was taken up into diethyl ether, which was washed with H_2O, dried over $MgSO_4$, and evaporated. The oily residue was stirred with pentane, affording 7 g (23%) of a crystalline product, mp 110 °C.

(*N*,*N*-Dimethylcarbamoyl)methylene Bis[*trans*-4-(aminomethyl)cyclohexanecarboxylate] Dihydrochloride (18). Compound **28** (3 g, 0.005 mol) was dissolved in ethyl acetate (50 mL), and ethyl acetate containing anhydrous HCl (50 mL, 3.8 M) was added. After 2 h the solvent was evaporated and the residue dissolved in methyl alcohol. Addition of ether afforded 0.9 g (38%) of salt, mp 224 °C.

Methylene Bis[*trans*-4-[[(*tert*-butoxycarbonyl)amino]methyl]cyclohexanecarboxylate] (29). A solution of compound **23** (25.7 g, 0.1 mol) and $QHSO_4$ (34 g, 0.1 mol) in 2 M NaOH (100 mL) was extracted with methylene chloride. The organic solution was dried over $MgSO_4$ and then refluxed for 6 days.[8] The solvent was evaporated, H_2O was added, and the mixture was extracted with ether. The ethereal solution was washed with H_2O and saturated NaCl solution, dried over $MgSO_4$, and concentrated in vacuo. The solid obtained (23.2 g) was recrystallized from isopropyl ether to give 18.3 g (70%) of crystals, mp 132 °C. Anal. ($C_{27}H_{46}N_2O_8$) C, N, H.

Methylene Bis[*trans*-4-(aminomethyl)cyclohexanecarboxylate] Dihydrochloride (14). Compound **29** (5.4 g, 0.01 mol) was dissolved in ethyl acetate (100 mL), cooled to +10 °C, and treated with a cold solution of anhydrous HCl in ethyl acetate (150 mL, 3.8 M). After the mixture was stirred for 2.5 h, 2.5 L of ether was added and the precipitate was filtered off and dried, giving 3.7 g of crude product. This was dissolved in methyl alcohol, filtered with charcoal, and precipitated with acetone, yielding 2.7 g (68%) of crystals, mp 269 °C.

Methylene *trans*-4-(Aminomethyl)cyclohexanecarboxylate 4-(Aminomethyl)benzoate Dihydrochloride (11). A mixture of Q salt of **21** (42.5 g, 0.08 mol) and Q salt of **24** (39.4 g, 0.08 mol) in dichloromethane (800 mL) was refluxed for 120 h. After washing, drying, and evaporation of solvent, 31 g of an oil was obtained. This oil contained methylene bis[4-[[(*tert*-butoxycarbonyl)amino]methyl]benzoate], bis[Z-**14**], and methylene *trans*-4-[[[(benzyloxy)carbonyl]amino]methyl]cyclohexanecarboxylate 4-[[(*tert*-butoxycarbonyl)amino]methyl]benzoate (Z,Boc-**11**). To remove the Boc groups the oil was dissolved in glacial acetic acid, and anhydrous HCl in acetic acid was added. After 3 h, a precipitate (11.7 g) consisting of crude methylene bis[4-(aminomethyl)benzoate] dihydrochloride was collected. The mother liquor was treated with diethyl ether, giving 7.0 g of precipitate. This product was recrystallized from isopropyl alcohol several times to yield 2.3 g of methylene *trans*-4-[[[(benzyloxy)carbonyl]amino]methyl]cyclohexanecarboxylate 4-(aminomethyl)benzoate hydrochloride, mp 162 °C. A 0.7-g portion of this product was dissolved in 50 mL of acetic acid and hydrogenated at atmospheric pressure using 10% palladium on carbon as catalyst. After 20 h the catalyst was filtered off and anhydrous HCl in ethyl acetate was added. The solvent was evaporated, and the produt was crystallized from isopropyl alcohol–diisopropyl ether mixture, yielding 0.3 g (4%) of salt, mp 242 °C.

Method D. *N*-(Hydroxymethyl)-2,2-dimethylpropanamide[18] (30). A mixture of pivalamide (17.7 g, 0.17 mol), potassium carbonate (600 mg) in water (21 mL), and 37% aqueous formaldehyde solution (15 mL) was stirred at 40 °C until the solution became clear. After cooling, it was concentrated in vacuo, and the dry solid was recrystallized from trichloroethylene, affording 19.2 g (87%) of a product, mp 84 °C.

(2,2-Dimethylpropanamido)methyl *trans*-4-[[[(Benzyloxy)carbonyl]amino]methyl]cyclohexanecarboxylate (31). A mixture of methylene chloride (200 mL), compound **30** (5.8 g, 0.044 mol), compound **21** (11.7 g, 0.040 mol), dicyclohexylcarbodiimide (9.1 g, 0.044 mol), and 4-(*N*,*N*-dimethylamino)pyridine (0.5 g, 0.044 mol) was stirred at room temperature for 48 h. The crystals formed were filtered off, and the filtrate was concentrated in vacuo to give 15.9 g of crude product that was recrystallized from isopropyl ether to yield 13.3 g (83%) of crystals, mp 102 °C.

(2,2-Dimethylpropanamido)methyl *trans*-4-(Aminomethyl)cyclohexanecarboxylate Benzoic Acid Salt (9). Compound **31** (8.0 g, 0.0198 mol) was hydrogenated at 0.1 MPa and 22 °C in isopropyl alcohol (400 mL) with Pd/C (10%, 1 g) as catalyst for 3 h. The catalyst was filtered off, and the filtrate was concentrated in vacuo to give an oil (5 g). This was dissolved in isopropyl alcohol (50 mL) and treated with benzoic acid (4.9 g, 0.040 mol) in isopropyl ether (200 mL), giving a crystalline compound (1.4 g). From the mother liquor, a further 1.7 g was obtained: totally 3.1 g (41%); mp 90 °C.

Method E. 4,5-Dimethyl-2-oxo-1,3-dioxolene (**32**) was obtained from acetoin and phosgene.[19] 4-(Bromomethyl)-5-methyl-2-oxo-1,3-dioxolene (**33**) was obtained from **32** with *N*-bromosuccinimide and a catalytic amount of α,α-azobis(isobutyronitrile) in carbon tetrachloride.[20]

(5-Methyl-2-oxo-1,3-dioxolen-4-yl)methyl *trans*-4-[[(*tert*-Butoxycarbonyl)amino]methyl]cyclohexanecarboxylate (35). A mixture of compound **23** (14.2 g, 0.055 mol), compound **33** (9.65 g, 0.05 mol), anhydrous K_2CO_3 (14.5 g, 0.083 mol), QBr (1.6 g, 0.005 mol), and trichloroethylene (150 mL) was stirred in an oil bath at 60 °C for 20 h. It was cooled to 20 °C and shaken with H_2O (200 mL) and the organic layer separated. The organic solution was washed with 0.2 M H_2SO_4, H_2O, 5% w/v $NaHCO_3$, and H_2O, then dried over $MgSO_4$, and concentrated in vacuo to an oil that solidified. It was recrystallized from isopropyl ether to give 7.7 g (41%) of crystals, mp 68 °C. Anal. ($C_{18}H_{27}NO_7$) C, H, N.

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(5-Methyl-2-oxo-1,3-dioxolen-4-yl)methyl *trans*-4-(Aminomethyl)cyclohexanecarboxylate Hydrochloride (10). Compound **35** (5.2 g, 0.014 mol) was dissolved in ethyl acetate (15 mL) and cooled to 10 °C. A 3.8 M solution of anhydrous HCl in ethyl acetate (15 mL) was added and the mixture stirred at 0 °C for 30 min and then at room temperature for 2 h. The white precipitate formed was filtered off, washed with cold ethyl acetate, and recrystallized from isopropyl alcohol; yield 3.0 g (70%); mp 176 °C.

Stability in Vitro. For HPLC determinations a miniPump (Milton Roy Co.) was used at a flow rate of 1.0 mL/min. A variable-wavelength detector LC-55 (Perkin-Elmer) was operated at 210 nm.

The degradation of the potential prodrug in a phosphate buffer of pH 7.5 (μ = 0.1) and in a NaCl/HCl buffer of pH 1.2 (μ = 0.1) was monitored by reversed-phase HPLC. The initial concentration of all the potential prodrugs was 1 mg/mL, corresponding to 2–4.5 mM. The solutions were stored in a water bath at 37 ± 0.5 °C. At different time intervals samples were withdrawn, and 100 μL was injected on a HPLC column. The HPLC column was a Chromegabond MC-18 (ES Industries) 250 mm × 4.6 mm i.d. 10-μm particles. The mobile phase consisted of 55%, v/v, of methyl alcohol in phosphate buffer (μ = 0.1). The apparent pH of this mixture was adjusted to 3.0. For compounds **9** and **10**, 0.1 M $NaClO_4$ was added. For **14** and **18**, the content of methyl alcohol was 25%, and for **16** and **17**, 32.5%, v/v.

The degradation of the potential prodrug in human heparinized plasma was also monitored by reversed-phase HPLC. To 1000 μL of plasma in a water bath at 37 ± 0.5 °C was added 100 μL of an aqueous solution of 23 mM of potential prodrug. A 20-μL portion of the sample containing an initial concentration of 2.3 mM of potential prodrug in 90% plasma was directly injected on the precolumn Perisorb RP8 50 mm × 4.6 mm i.d. 30–40 μm particles followed by a column Nucleosil C_8 150 mm × 4.6 mm i.d. 5 μm particles. It was assumed that the enzymatic activity was stopped immediately at the injection onto the column. The mobile phase was methyl alcohol in phosphate buffer of apparent pH 3.0. The v/v content of methyl alcohol was for **3** 25%, for **7** 30%, for **1** 35%, for **6** 40%, and for **14** and **16** 25% including 0.2 M $NaClO_4$. The release of tranexamic acid from compound **14** was monitored by GC. To 10 mL of heparinized human plasma was added 11.3 mg of **14**, giving an initial concentration of 2.8 mM. This solution was stored in a water bath at 37 ± 0.5 °C. A sample of 5 μL was withdrawn and analyzed by GC[21] at the following time intervals: 0.5, 3, 6, 9, 15, 30, and 60 min. The amount of tranexamic acid released per mole of **14** was 9.5, 28, 58, 76, 88, 95, and 100% of theoretical.

Pharmacology. Male rats, Sprague–Dawley, weighing about 200 g, were obtained from ALAB, Sollentuna, Sweden. After overnight fasting, 2.5 mL of distilled water was given 5 min prior to administration of the potential prodrugs. These were dissolved in distilled water immediately before administration and given by gavage (1 or 0.1 mmol/kg) in a volume of 2 mL/kg. During the experiment the rats were kept in ordinary metabolism cages with free access to food and water. The urine was collected for three consecutive 24-h intervals. At the end of each period the cages were rinsed with 20 mL of distilled water. The collected urines and rinsing waters were kept frozen until they were analyzed by gas chromatography.[21]

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Registry No. 1, 100165-48-8; **2**, 100165-49-9; **3**, 87589-30-8; **4**, 100165-50-2; **5**, 100165-51-3; **6**, 87589-22-8; **7**, 87589-32-0; **8**, 100165-52-4; **9**, 100165-53-5; **10**, 100165-54-6; **11**, 87589-52-4; **11** (Z, BOC), 100165-59-1; **12**, 27724-96-5; **13**, 19878-18-3; **14**, 87638-56-0; bis(Z-14), 100165-58-0; **15**, 87589-39-7; **16**, 87589-43-3; **17**, 87589-46-6; **18**, 87589-45-5; **19**, 100227-65-4; **20**, 100165-55-7; **21**, 27687-12-3; **21** (q salt), 87635-73-2; **22**, 15177-68-1; **23**, 27687-14-5; **24**, 33233-67-9; **24** (q salt), 87611-44-7; **25**, 50893-36-2; **26**, 87589-40-0; **27**, 87589-42-2; **28**, 100227-66-5; **29**, 100227-67-6; **30**, 66297-46-9; **31**, 100165-56-8; **32**, 37830-90-3; **33**, 80715-22-6; **35**, 100165-57-9; tranexamic acid, 1197-18-8; 4-(aminomethyl)-benzoic acid, 56-91-7; tetrabutylammonium hydrogen sulfate, 32503-27-8; paraldehyde, 123-63-7; 1,1-dichloro-*N*,*N*'-dimethylacetamide, 5468-76-8; pivalamide, 754-10-9; acetoin, 513-86-0; tetrabutylammonium bromide, 1643-19-2; methylene bis[4-(aminoethyl)benzoate] dihydrochloride, 100165-60-4; methylene *trans*-4-[[[(benzyloxy)carbonyl]amino]methyl]cyclohexane-carboxylate 4-(aminomethyl)benzoate hydrochloride, 87589-51-3.

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A Common Structural Model for Central Nervous System Drugs and Their Receptors

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On the basis of the hypothesis that there is a common structural basis for central nervous system (CNS) drug action consisting primarily of an aromatic group and a nitrogen atom, a four-point model for a common pharmacophore is defined with use of five semirigid CNS-active drug molecules: morphine, strychnine, LSD, apomorphine, and mianserin. Two of the points of the model represent possible hydrophobic interactions between the aromatic group and the receptor, while the other two represent hydrogen bonding between the nitrogen atom and the receptor. The model is then extended by the inclusion of nine additional CNS-active drug molecules: phenobarbitone, clonidine, diazepam, bicuculline, diphenylhydantoin, amphetamine, imipramine, chlorpromazine, and procyclidine, each being chosen as a key representative of a different CNS-active drug class or neurotransmitter system. Consideration of all phenyl group and nitrogen atom combinations, as well as all feasible conformations, shows that all nine molecules closely fit the common model in low-energy conformations. It is proposed that the model may eventually be used to design CNS-active drugs by mapping the relative locations of secondary binding sites. It can also be used to predict whether a given structure is likely to show CNS activity: a search over 1000 entries in the Merck Index shows a high probability of CNS activity in compounds fitting the common structural model.

In the area of central nervous system (CNS) active drugs, many studies have resulted in proposals of receptor requirements for separate CNS classes. Although these requirements vary in detail, it has become clear than an aromatic group and a nitrogen atom are common features of the majority of CNS-active drugs. Specific topographical arrangements of these groups have therefore been proposed as basic requirements for analgesic, hallucino-

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