

New Thiol Inhibitors of Neutral Endopeptidase EC 3.4.24.11: Synthesis and Enzyme Active-Site Recognition

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Selective, as well as mixed, inhibitors of the two zinc metallopeptidases, neutral endopeptidase (NEP) and angiotensin converting enzyme (ACE), are of major clinical interest in the treatment of hypertension and cardiac failure. New thiol inhibitors, corresponding to the general formula HS-CH(R₁)-CH₂-CH(R₂)-CONH-CH(R₃)-COOH, were designed in order to explore the putative S₁ subsite of the active site of NEP. The inhibitors were also tested on ACE and the most representative on thermolysin (TLN) for comparison. The relatively low inhibitory potencies exhibited by these compounds (IC₅₀s in the 10⁻⁷ M range for NEP and in the 10⁻⁶ M range for ACE) as compared to that of thiorphan (IC₅₀s 2.10 × 10⁻⁹ M on NEP and 1.40 × 10⁻⁷ M on ACE) clearly indicate the absence of the expected energetically favorable interactions with the active site of both peptidases. A 100-fold loss of potency for these inhibitors was also observed for thermolysin as compared to thiorphan. Using the mutated Glu¹⁰²-NEP, it was possible to demonstrate that the inhibitors do not fit the S₁ subsite of NEP but interact with the S'₁ and S'₂ subsites through binding of their R₁ and R₂ residues and that the C-terminal amino acid is located outside the active site. These results seem to indicate that these thiol inhibitors are not well adapted for optimal recognition of the S₁ subsite of NEP, and probably ACE, and that other zinc-chelating moieties such as carboxylate or phosphonate groups may be preferred for this purpose.

Introduction

Neutral endopeptidase (EC 3.4.24.11, NEP) is a metallopeptidase involved in the metabolism of a variety of physiologically important peptides and its inhibition offers several interesting new therapeutic possibilities (see review in ref 1). Thus, in the brain, the opioid peptides enkephalins are inactivated by the common action of two zinc metallopeptidases, NEP and aminopeptidase N (APN). Mixed inhibitors of both enzymes have been shown to induce potent analgesic responses without the major side effects of morphine.²⁻⁴ In the intestine, the enkephalins, acting at δ opioid receptors, are mainly involved in the regulation of fluid secretion.⁵ The demonstration that their intestinal actions can be blocked by NEP inhibitors has led to the marketing of thiorphan (HS-CH₂-CH(CH₂Φ)-CONH-CH₂-COOH),⁶ under its prodrug form acetorphan, as an antidiarrheal agent designated tiorfan.^{7,8} In addition, the atrial natriuretic peptide ANP is cleaved by NEP into inactive fragments, and numerous inhibitors have been shown to produce natriuresis and diuresis in animals and humans (see review in ref 9). The association of an NEP inhibitor such as retrothiorphan with an angiotensin converting enzyme inhibitor such as enalapril led to a potentiation of the antihypertensive action of the ACE inhibitor,¹⁰ and mixed inhibitors of the two metallopeptidases could therefore represent a new approach in the treatment of hypertension and cardiac failure.¹¹

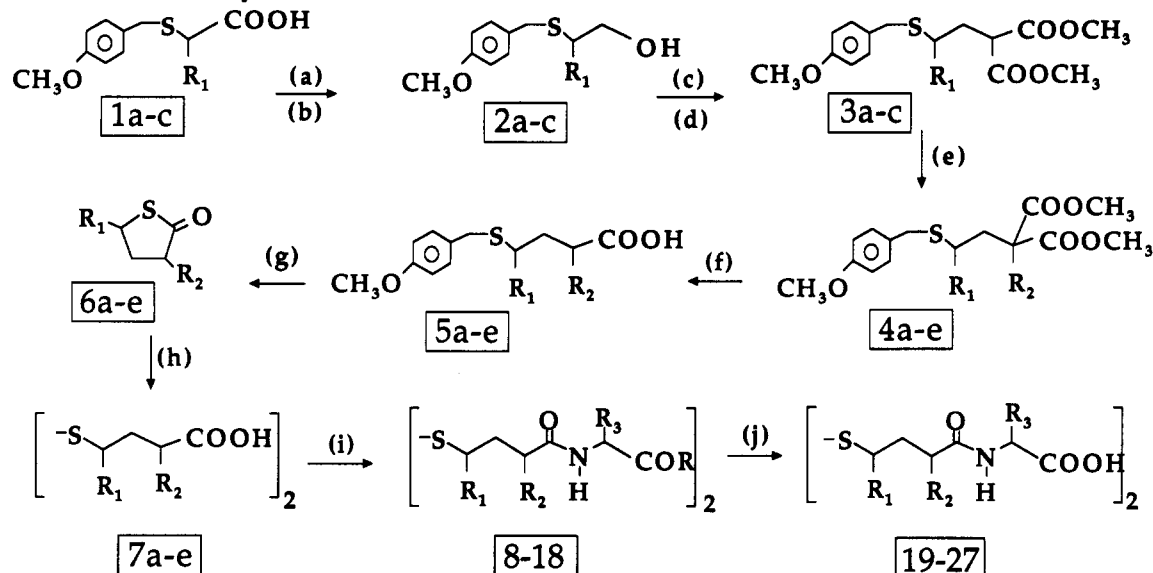
The primary sequence of NEP has been deduced from cDNA clones from various species (rabbit,¹² rat,¹³ and

human¹⁴), but its three-dimensional structure remains unknown. However, its mechanism of action and its subsite specificity are well documented, due to its overall analogy with thermolysin (TLN), a bacterial metalloendopeptidase whose structure was established from X-ray crystallography.¹⁵ These analogies include not only the hydrophobicity of the binding subsites surrounding the catalytic domain¹⁶⁻¹⁹ and the three zinc coordinating ligands²⁰⁻²² but also the amino acids involved in the stabilization of the Michaelis complex.²³⁻²⁶ However, the main difference between NEP and TLN is the presence in the S'₂ subsite of the former of an arginine residue (Arg¹⁰²) which was shown to interact with the free carboxyl group of substrates such as the enkephalins.⁶ In spite of large similarities in the active site of both enzymes, the potency of a large number of inhibitors is about 2 or 3 orders of magnitude lower for TLN than for NEP. This is particularly evident for inhibitors interacting with the S'₁ and S'₂²⁷ subsites of both enzymes. For example, the K_i of (S)-thiorphan (HS-CH₂-CH(CH₂Φ)-CONH-CH₂-COOH) is 1.8 × 10⁻⁶ M for TLN and 1.9 × 10⁻⁹ M for NEP.²⁸ However, the difference is smaller for inhibitors able to interact with the S₁, S'₁, and S'₂ subsites of each enzyme. For example, the K_i of (1-carboxy-3-phenylpropyl)Leu-Trp is 5 × 10⁻⁸ M for TLN,²⁹ and an analogous compound such as SCH 39370 ((1-carboxy-3-phenylpropyl)Phe-β-Ala) has a K_i of 1.1 × 10⁻⁸ M for NEP.³⁰ Taken together, these results seem to indicate that the occupancy of the S₁ subsite is more important in TLN than in NEP for strong inhibition of the enzyme.

The S₁ subsite of NEP has been investigated with various carboxyalkyl dipeptides³⁰⁻³³ or related compounds, such as UK 69578,³⁴ constructed on the model of enalapril,³⁵ and the results obtained seem to indicate that the S₁ subsite

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Scheme 1. Scheme for the Synthesis of Inhibitors 17–27^a

^a (a) SOCl₂, MeOH; (b) NaBH₄, LiCl; (c) NaI, (CH₃)₃SiCl; (d) NaH, CH₂(COOCH₃)₂; (e) NaH, R₂X; (f) DMSO–20% KOH; (g) CF₃COOH, reflux; (h) NaOH/EtOH, O₂; (i) H₂N-CH(R₃)-COR, BOP, DIEA; (j) OH⁻ then H₃O⁺.

range, whatever the degree of the hydrophobicity of the P₁ moiety, a result which does not permit a clear characterization of the S₁ subsite.

Recently, we have reported two new series of NEP inhibitors containing a thiol group as the zinc-chelating agent and designed to interact with the S₁, S'₁, and S'₂ subsites of the enzyme.³⁶ Some of these compounds were found to be very efficient, essentially those corresponding to the general formula HS-CH(R₁)-CH(R₂)-CONH-CH(R₃)-COOH with IC₅₀ values in the nanomolar range for the most active stereoisomer. Nevertheless, none of these inhibitors is more active than thiorphan (HS-CH₂-CH(CH₂Φ)-CONH-CH₂-COOH),⁶ which interacts only with the S'₁ and S'₂ subsites of NEP. Several hypotheses have been proposed to account for this result. The inhibitors might be unable to interact with the S₁ subsite for steric reasons, or the interaction of the R₁ chain in the S₁ subsite might decrease the strength of the zinc complexation. On the other hand, the S₁ subsite of NEP might not be well defined, leaving the inhibitor R₁ side chain to be located in the aqueous medium or at the surface of the enzyme active site.

In order to test the hypothesis that the potency of the previously discussed series is limited by steric hindrance, we have developed new compounds of general formula HS-CH(R₁)-CH₂-CH(R₂)-CONH-CH(R₃)-COOH, in which a methylene spacer has been introduced between the R₁ and R₂ chains. For R₁, R₂, and R₃, hydrophobic chains were chosen which have previously been found to fit well into the active site of NEP. For comparison, these compounds have also been tested on ACE and some of them on TLN.

Results

(1) Synthesis. The compounds 17–27 were prepared following the scheme summarized in Scheme 1. The protected 2-mercaptoalkanoic acids **1a-c** were obtained under optically pure forms from the corresponding α-amino acids through desamino halogenation of D-amino acids following the Fischer procedure,³⁷ yielding the corresponding 2-bromo analogs with retention of configuration

by the potassium salt of *p*-methoxybenzyl sulfide gave intermediates **1a-c** with inversion of configuration. These protected α-mercapto acids were reduced by lithium borohydride to the corresponding β-mercapto alcohols **2a-c**.

The following synthetic pathway involved three key steps. The first was the formation of the malonate derivatives **3a-c**, which necessitated the transformation of the alcohols **2a-c** to iodinated derivatives³⁸ before reaction with the sodium salt of dimethyl malonate. The second critical step was the decarboxylation of the hindered intermediates obtained, **4a-e**, which was achieved only by heating these compounds in DMSO–20% KOH to give **5a-e**. The third difficult step was the deprotection of the thiol group, which could not be performed at the last step of the synthesis either by the classical Hg(CF₃COO)₂ and H₂S treatment or by reflux in CF₃COOH³⁹ without major degradation of the final compounds. This problem was bypassed in an intermediate step of the synthesis. Thus, the thiol deprotection was easily obtained from **5a-e** by refluxing the compounds in CF₃COOH, owing to the high stability of the thiolactones **6a-c** which were spontaneously formed during this step. The synthesis was continued by opening the cyclic structures **6a-e** by alkaline treatment and with bubbling O₂ to obtain the disulfides **7a-e**. The synthesis was achieved by condensation of α-amino esters or α-amino amides of defined stereochemistry using BOP reagent and final deprotection. The final compounds were isolated as mixtures of diastereoisomers in about equal proportions as shown by NMR and, in some cases, by HPLC. This is due to a racemization of the carbon bearing the protected thiol group, which occurred probably during the drastic treatment with KOH of the intermediates **3a-c**.

Compound **32** was obtained by a different pathway (Scheme 2), using the procedure leading to the preparation of α-β-substituted β-mercapto acids.³⁶ Thus, condensation of triethyl 2-benzyl phosphonoacetate with phenylacetaldehyde led to a mixture of α-β and β-γ unsaturated esters (compounds **28** and **29**). Saponification of this mixture yielded only the β-γ unsaturated acid **30** by transposition of the double bond. Addition of thioacetic acid to **30**

Scheme 2. Scheme for the Synthesis of Inhibitor 32

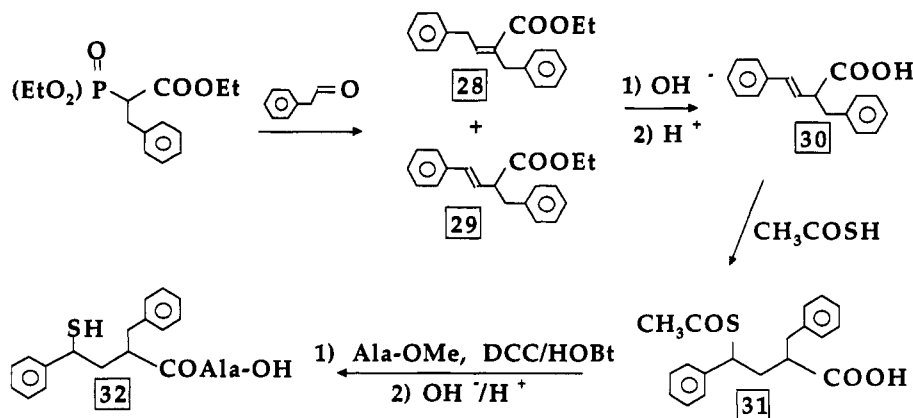


Table 1. Inhibitory Potency of Compounds 17–32 on NEP and ACE Activities

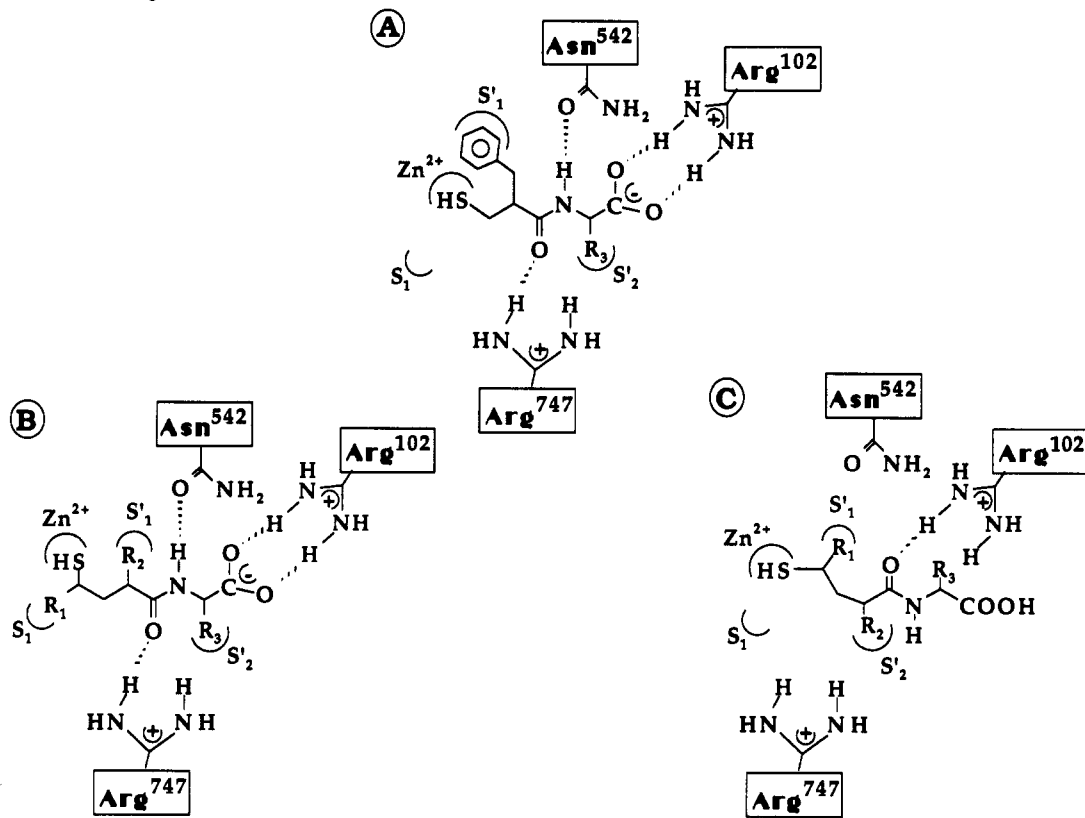
compound	IC ₅₀ (μM) ^a		compound	IC ₅₀ (μM) ^a	
	NEP ^b	ACE ^c		NEP ^b	ACE ^c
	0.044 ± 0.012 ^d	4.0 ± 0.5 ^d		0.018 ^e	
	0.19 ± 0.07	3.8 ± 0.8		0.38 ± 0.02	3.4 ± 0.6
	0.29 ± 0.05	3.5 ± 1.5		0.36 ± 0.02	4.0 ± 1.0
	0.32 ± 0.06	3.6 ± 0.5		0.27 ± 0.02	4.4 ± 0.4
	0.15 ± 0.06	2.4 ± 0.7		0.32 ± 0.05	8.0 ± 0.6
	0.22 ± 0.03	0.8 ± 0.05		0.35 ± 0.05	3.5 ± 0.5
	0.35 ± 0.05	2.8 ± 0.6		0.22 ± 0.05	2.3 ± 0.6
	0.13 ± 0.05	3.5 ± 0.5		0.25 ± 0.06	4.0 ± 0.6
				0.26 ± 0.04	2.9 ± 0.5

^a Values are the mean ± SEM from three independent experiments computed by log probit of five inhibitor concentrations. ^b Concentration inhibiting 50% of NEP activity using 20 nM [³H]-D-Ala²-Leu-enkephalin as substrate. ^c Concentration inhibiting 50% of ACE activity using 50 μM N-Cbz-Phe-His-Leu as substrate. ^d From ref 36. ^e From ref 40.

proportions, and the final compound 32 was obtained by condensation of alanine methyl ester followed by alkaline hydrolysis of both protective groups.

(2) **Inhibitory Activity.** The inhibitory potencies of

summarized in Table 1. The effects of five structural modifications were investigated (i) amidification of the free C-terminal carboxyl group (compound 26 versus 17 or 27S versus 18); (ii) modification of the C-terminal amino acid with a thioester introduction of an alanine (compound

Chart 1. Schematic Representation of NEP Active Site^a

^a (A) Complex NEP-thiorphan as deduced from X-ray analysis of the complex TLN-thiorphan. (B) Possible model of interaction of inhibitors 17-32 with NEP active site. In this model, the R₁, R₂, and R₃ side chains fit the S₁, S₁' and S₂' subsites of the enzyme, respectively. (C) Possible model of interaction of inhibitors 17-32 with NEP active site deduced from experiments with the Glu¹⁰²-mutated enzyme. In this model, the R₁ and R₂ side chains fit the S₁' and S₂' subsites of NEP and R₃ is outside the active site.

or a tyrosine (compound 22) moiety; (iii) change in the stereochemistry of the C-terminal amino acid with 27*S* and 27*R*; (iv) replacement of the benzyl group, assumed to interact with the S₁' subsite by an isobutyl chain (compounds 22 and 23 or 26 and 27); and finally (v) exploration of the putative S₁ subsite using successively a phenyl (compound 32 versus 19), a benzyl, and phenethyl and isobutyl chains (compounds 23, 25, and 26).

Regarding NEP inhibition, all compounds showed similar potencies, with IC₅₀s in the 1-4 × 10⁻⁷ M range, whatever the chemical modifications introduced in these molecules. For ACE inhibition, the same potency was also obtained for all compounds studied with IC₅₀s in the micromolar range. Furthermore, the synthetic intermediates 6b and 7b were also tested on both enzymes, and their activities were found to be in the 10⁻⁷ M range on NEP and in the micromolar range on ACE. The potencies of the compounds tested on TLN were found in the 10⁻⁴ M range.

Discussion

With the aim of improving NEP active-site recognition, a new series of thiol inhibitors expected to interact with the S₁, S₁' and S₂' subsites of the enzyme was synthesized (Table 1). The development of these compounds was based on the structure of a recently described³⁶ thiol inhibitor (compound A, Table 1) and of NEP inhibitors of general formula HOOC-CH(CH₂Ph)-CH₂-CH(CH₂Ph)-CO-AA (compound B, Table 1).⁴⁰ Some of these latter compounds were shown to have IC₅₀s for NEP in the nanomolar range, suggesting that their interaction with the three subsites

In contrast to these results, all the compounds described here exhibited surprisingly similar IC₅₀s for NEP, which were in the 10⁻⁷ M range (Table 1). These data show a significant decreased efficiency of these compounds in binding NEP as compared to that of the thiol inhibitor A³⁶ or the dibenzylglutaryl derivative B. In contrast, the IC₅₀ values for ACE, which were found to be in the 10⁻⁶ M range for all compounds, are not significantly different from those reported for A (Table 1) and derivatives.³⁶ In order to understand in terms of active-site occupancy, the decreased activity of these new compounds as compared to that of other thiol inhibitors such as thiorphan or compound A and its analogs, the activities of 19, 21, 23, 26, 27*S*, and 27*R*, chosen as models for this series, were checked on TLN (data not shown). Their IC₅₀s (in the 10⁻⁴ M range) were increased by 3 orders of magnitude as regard to their IC₅₀s for NEP (10⁻⁷ M range). This ratio already found for thiorphan (IC₅₀ on NEP 1.9 × 10⁻⁹ M, IC₅₀ on TLN 1.8 × 10⁻⁶ M) or for constrained thiols such as HS-CH(CH₂CHiPr)-CH(CH₂Ph)-CONHCH(CH₃)-COOH (IC₅₀ on NEP 3.6 × 10⁻⁹ M, IC₅₀ on TLN 4.0 × 10⁻⁶ M) indicates again that the TLN active site can be used as a model to investigate recognition of the active site of NEP. From the crystallographic data of the complex TLN-thiorphan,⁴¹ the assumed interactions of this inhibitor with the active site of NEP are shown in Chart 1A. This model allows two possible types of binding to be proposed. Firstly, the inhibitors bind to the active site of NEP as shown in Chart 1B, i.e., with the three side chains fitting the S₁, S₁' and S₂' subsites. In this case, the decreased affinity of these compounds related to the

interaction of the three side chains with their respective subsites, inhibiting the perfect alignment of the thiol groups with the zinc atom, required for optimal coordination.⁴² In the case of dibenzylglutaryl derivatives, such as **B**, this problem could be overcome by the enhanced degree of freedom of the carboxylate group and its possibility of interacting with the zinc atom, by using one or two of its oxygen atoms, as amply demonstrated by crystallographic analysis of complexes between various carboxyl inhibitors and TLN.¹⁵

However, another explanation may account for the data reported in Table 1. For both compound **A** and its analogs,³⁶ or for compound **B** and its analogs,⁴⁰ the nature of the C-terminal residue is of great importance for the inhibitory activity. In Table 1 it can be seen that IC₅₀s for NEP were the same for compounds **17** and **26** or **18** and **27S**, which differed by the presence of a free carboxylate in **26** and **27S** and an amide group in **17** and **18**. However, it is now well known that, due to the presence of Arg¹⁰² in the active site of NEP, lower IC₅₀s are obtained for inhibitors containing a free C-terminal carboxylate rather than a carboxamide group.²⁶ More significant was the fact that compounds **21** and **24**, which contain a C-terminal proline, have the same IC₅₀ for NEP as **19** or **20** which are terminated by an alanine or a β -alanine residue, as it has also been demonstrated that the S'₂ subsite of NEP poorly recognizes a proline ring.^{16,43} Moreover, the IC₅₀ values of **27R** and **27S** on both NEP and ACE were almost identical (Table 1), although the S'₂ subsite of these enzymes has a 100–1000 times better affinity for amino acids of S configuration.^{17,44,45}

Likewise, the comparison of the inhibitory potencies of compounds **20** and **21** on ACE surprisingly showed that they are identical, although it is also well known that ACE does not accept a β -amino acid in its S'₂ subsite, due to its strong carboxy dipeptidase nature.³² Finally, compound **7b** and its cyclic analog **6b**, which is transformed to **7b** during the incubation time at pH 7.4, also have the same inhibitory potencies on NEP and ACE, although they do not contain a C-terminal amino acid. All these arguments seem to favor the mode of interaction with the active site of NEP (and ACE) in which the residues R₁ and R₂ interact with the S'₁ and S'₂ subsites of the enzyme as shown schematically in Chart 1C, with the C-terminal amino acid outside the active site. In this model, the stabilizing hydrogen bonds between the amide group of the inhibitor and the side chains of Arg⁷⁴⁷ and Asn⁵⁴², which are assumed to be important for the formation of stable complexes with NEP's active site, do not occur.

This proposal seems to be confirmed by experiments performed with **7b** and **25** on the mutated enzyme Glu¹⁰²-NEP^{25,26} that we have previously used as an index of inhibitor positioning in the enzyme's active site.^{46,36} As shown in Chart 1, Arg¹⁰² is thought to be positioned to interact with the C-terminal carboxyl of a P'₂ residue. When Arg¹⁰² was replaced by Glu, the K_i of thiorphan for the mutated enzyme increased by over 2 orders of magnitude, due to the ionic repulsion between the two negatively charged groups. Under the same conditions, the K_i of thiorphan amide which has no free carboxylate was increased only by a factor of 6. The IC₅₀s of **7b** and **25** on the mutated enzyme were respectively 3×10^{-5} and 2×10^{-6} M. These values correspond to a loss of affinity,

strongly suggest that both compounds interact with S'₁ and S'₂ subsites of NEP and that the C-terminal tyrosine of **25** is outside the active site of the enzyme.

In conclusion, the new series of thiol inhibitors described in this paper was not able to clarify the nature of the S₁ subsite of NEP and ACE. Indeed, it seems that both the hydrophobic character of the S'₁ subsite and the high tendency of the thiol group to optimize the complexation of the Zn²⁺ ion direct the positioning of the inhibitors in such a way that these two interactions are greatly privileged to the prejudice of any other stabilizing interactions, i.e., with Arg⁷⁴⁷, Asn⁵⁴², or Arg¹⁰². Consequently, it seems more easy to explore the S₁ subsite of NEP with inhibitors which do not contain a thiol group as a zinc ligand. Carboxylates have been intensively used, but hydroxamates or phosphoryl groups may also be useful.

Experimental Section

I. Biological Tests. [³H]Tyr-D-Ala²-Leu-enkephalin (52 Ci/mmol) was obtained from CEA (Saclay, France). N-Cbz-Phe-His-Leu was from Bachem (Bubendorf, Switzerland). Neutral endopeptidase was purified to homogeneity from rabbit kidney as previously described.⁴⁷ Recombinant human angiotensin converting enzyme obtained as described⁴⁸ was a generous gift from Prof. Corvol (Collège de France, Paris, France).

Assay for Neutral Endopeptidase Activity. IC₅₀ values were determined as previously described.³⁶ NEP (final concentration 1 pmol/100 μ L, specific activity for [³H]-D-Ala²-Leu-enkephalin 0.3 nmol/mg/min) was preincubated for 15 min at 25 °C with or without increasing concentrations of inhibitor in a total volume of 100 μ L in 50 mM Tris-HCl buffer, pH 7.4. [³H]-D-Ala²-Leu-enkephalin ($K_m = 30 \mu$ M) was added to a final concentration of 20 nM, and the reaction was stopped after 30 min by adding 10 μ L of 0.5 M HCl. The tritiated metabolites formed were separated on polystyrene beads. The mutated enzyme Glu¹⁰²-NEP was obtained as previously described.²⁶ The inhibitory potency of the inhibitors tested on this enzyme was determined by the method described for NEP.

Assay for Angiotensin Converting Enzyme Activity. Enzymatic studies on ACE were performed using N-Cbz-Phe-His-Leu as substrate ($k_m = 50$ mM) as previously described.⁴⁹ ACE (final concentration 0.02 pmol/100 μ L, specific activity on Cbz-Phe-His-Leu 13 nmol/mg/min) was preincubated for 15 min at 37 °C with various concentrations of the tested inhibitors in 50 mM Tris-HCl buffer, pH 8.0. N-Cbz-Phe-His-Leu was added to a final concentration of 0.05 mM. The reaction was stopped after 15 min by adding 400 μ L of 2 M NaOH. After dilution with 3 mL of water, the concentration of His-Leu was determined following the fluorimetric assay described by Cheung et al.⁵⁰ with a MPF 44 A Perkin-Elmer spectrofluorimeter (excitation 365 nm, emission 495 nm). The calibration curve for His-Leu was obtained by addition of increasing concentrations of His-Leu into 0.1 mL of 5.0 M Tris-HCl buffer, pH 8.0, containing the denaturated enzyme.

As the compounds tested were synthesized under their disulfide forms, 100 equiv of DTT was added to the stock solutions of the inhibitors before dilution.

II. Chemistry. The amino acids were from Bachem (Bubendorf, Switzerland). Chlorotrimethylsilane, dimethyl malonate, benzyl bromide, 2-iodobutane, and (4-methoxyphenyl)methyl mercaptan, were from Aldrich (Strasbourg, France). BOP reagent was from Propeptide (Vert le Petit, France).

The solvents (Normapur label) were from SDS (Peypin, France). The purity of the synthesized compounds was checked by thin-layer chromatography on silica gel plates (Merck 60F 254) in the following solvent systems (v/v): A, EtOAc/hexane = 1/1; B, EtOAc/hexane = 1/4; C, CH₂Cl₂/MeOH = 14/1; D, EtOAc/hexane = 1/2; E, CHCl₃/MeOH/HOAc = 9/1/0.1; F, CHCl₃/MeOH = 9/1; G, EtOAc/hexane = 2/3. Plates were revealed with UV, iodine vapor, or ninhydrin. The purity of the final compounds was checked by HPLC on a reverse-phase Nucleosil C₈ column

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