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Synthesis and structure activity relationships of novel non-peptidic metallo-aminopeptidase inhibitors

Sébastien Albrecht,[a] Albert Defoin,[a,*] Emmanuel Salomon,[a] Céline Tarnus,[a,*] Anders Wetterholm[b] and Jasper Z. Haeggström[b]

[a]*Laboratoite de Chimie Organique et Bioorganique, UMR 7015, ENSCMu, F-68093 Mulhouse Cedex, France*
[b]*Department of Medical Biochemistry and Biophysics, Karolinska Institutet, S-17177 Stockholm, Sweden*

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Abstract—Racemic derivatives of 3-amino-2-tetralone were synthesised and evaluated for their ability to inhibit metallo-aminopeptidase activities. New compounds substituted in position 2 by methyl ketone, substituted oximes or hydroxamic acids as well as heterocyclic derivatives were evaluated against representative members of zinc-dependent aminopeptidases: leucine aminopeptidase (E.C. 3.4.11.1), aminopeptidase-*N* (E.C. 3.4.11.2), *Aeromonas proteolytica* aminopeptidase (E.C. 3.4.11.10), and the aminopeptidase activity of leukotriene A_4 hydrolase (E.C. 3.3.2.6). Several compounds showed K_i values in the low micromolar range against the 'one-zinc' aminopeptidases, while most of them were rather poor inhibitors of the 'two-zinc' enzymes. This interesting selectivity profile may guide the design of new, specific inhibitors of target mammalian aminopeptidases with one active site zinc.
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1. Introduction

Metallo-aminopeptidases (APs) remove amino acids from unblocked N-termini of peptides and proteins. This family of exopeptidases is widely distributed in nature, with representative members present in animal cells, plants, bacteria and fungi. Although some APs are secreted, the vast majority are either cytosolic or membrane-bound enzymes.[1–4]

All metallo-aminopeptidases catalyse the same chemical reaction. Generally cleavage of the scissile peptide bond is dependent upon the chemical structure and composition of amino acid residues that flank the cleavage site ($P_1 * P_1'$).[5] They can be broadly classified into two subfamilies on the basis of the number of their active site zincs. While some of these enzymes contain only one-zinc, others possess a binuclear metal centre, usually referred to as a co-catalytic unit.[5]

These APs are believed to play an important role in many normal or pathophysiological processes.[6–8] Therefore, the design of highly specific, potent inhibitors is of utmost importance in order to gain a deeper understanding of the biological functions of APs and to assess their potential as drug targets. In the present study, we focus on APs that prefer an hydrophobic residue in position P_1. Many of these enzymes show a similar broad specificity, except for a few ones which are highly specific. Although many AP inhibitors are already available,[9–12] most of them are poorly selective. Moreover, the vast majority of these compounds are amino acid or peptide analogues, with a few notable exceptions such as the natural products curcumin and psammaplin A, and synthetic flavonoid derivatives, notably 2′,3-dinitroflavone-8-acetic acid.[12,13]

Unfortunately, since all these APs are zinc-dependent enzymes sharing a broad substrate specificity, the development of specific inhibitors is undoubtedly a daunting task. In the present study, we report on the design and synthesis of 3-amino-2-tetralone derivatives, as well as on their inhibitory activities against a panel of 'one-zinc' and 'two zincs' APs. 3-Amino-2-tetralone **1** has been described as a selective inhibitor of the 'one-zinc' AP-*N*.[14] We have found that **1** is not stable under physiological conditions. In an attempt to identify more stable derivatives of **1** and to gain insights into the selectivity-determining features, we have investigated a number of structural modifications in positions 1–3 of 3-amino-2-tetralone. A comprehensive list of the compounds

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* Corresponding authors. Tel.: +33 389336864; fax: +33 389336875; e-mail addresses: Albert.Defoin@uha.fr; Celine.Tarnus@uha.fr

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synthesised during the course of this work is provided in Scheme 1.

All compounds were evaluated against the following enzymes: the mammalian cytosolic leucine aminopeptidase (LAPc, E.C. 3.4.11.1) and the secreted, bacterial aminopeptidase from *Aeromonas proteolytica* (APaero, E.C. 3.4.11.10) were used as representative members of the 'two-zinc' sub-family. The biological role of the ubiquitous LAPc is not well-understood, nevertheless altered activity is observed with a number of physiological processes.[7] The membrane-bound aminopeptidase M (also referred to as or AP-*N*, E.C. 3.4.11.2) and the aminopeptidase activity of leukotriene A_4 hydrolase (LTA_4H, E.C. 3.3.2.6) were selected as representative of the 'one-zinc' sub-family. Both enzymes belong to the M1 family of zinc-dependent metallopeptidases.[4] AP-*N* is widely expressed at the surface of mammalian cells and up-regulated in a number of pathological processes including cell migration and tumour growth.[12] The precise function of the LTA_4H AP activity is currently not known but it also carries an epoxide hydrolase activity that catalyses the final step in the biosynthesis of leukotriene B4, a potent chemotactic and immune modulating lipid mediator.[14]

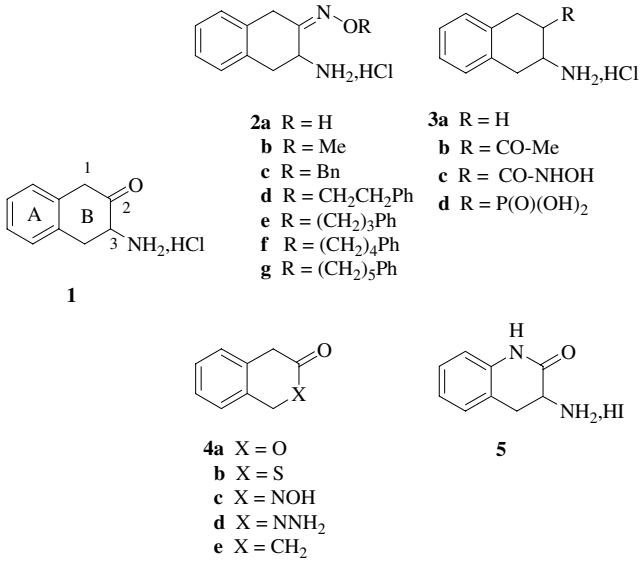
Therefore, inhibitors of this family of enzymes may prove to be interesting biological tools.

In this study, the parent compound 3-amino-2-tetralone **1** and bestatin, a well-known aminopeptidase inhibitor, were used as reference inhibitors.

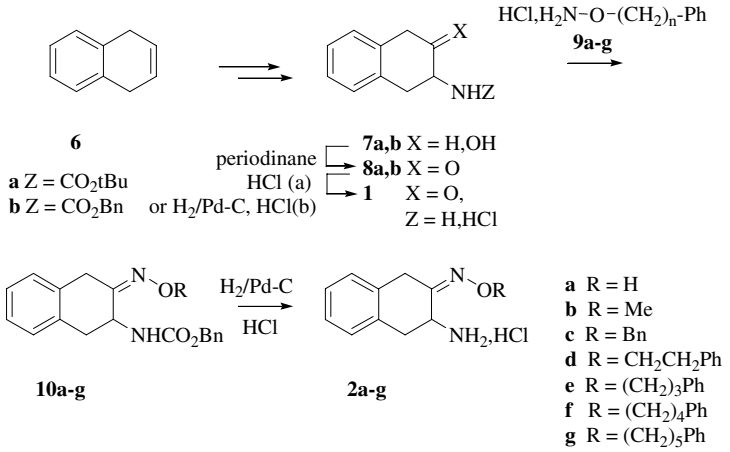
2. Chemistry

2.1. Tetralone-oxime derivatives (2a–g)

Preparation of amino-tetralone **1**[15,16] has already been described from 1,4-dihydronaphthalene **6**[17] by epoxidation, opening of this epoxide with ammonia, N-protection as Boc-derivative **7a**, alcohol oxidation in ketone **8a** and finally acidic N-deprotection (Scheme 2).



Scheme 1.



Scheme 2.

For the synthesis of oximes **2a**–**g**, the same initial reactions were followed but N-protection was best carried out as benzyloxycarbonyl derivative **7b**, to prevent partial hydrolysis of the oxime function to the corresponding ketone, which otherwise occurred during the final acidic deprotection of Boc-derivatives.

Quantitative oxidation of **7b** to ketone **8b** with Dess–Martin periodinane[18] followed with condensation with hydroxylamine **9a** or O-substituted hydroxylamines **9b**–**g**[19] provided N-protected oximes **10a**–**g**, which were quantitatively deprotected to yield final amino-oximes **2a**–**g** by hydrogenolysis over Pd–C 5% in aqueous HCl and ethanol (Scheme 2).

2.2. Aminotetraline (3a)

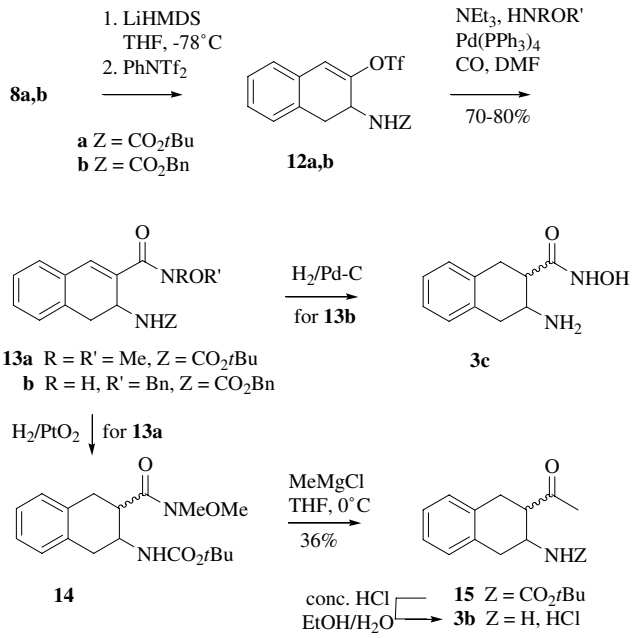
The known amine **3a**[20–22] was prepared according to the Bhattacharyya's method[23] (Scheme 3) by treatment of β-tetralone **11** with ammonia in ethanol and titanium (IV) isopropoxide, followed by *in situ* sodium borohydride reduction in ca. 40% yield from **11**.

2.3. Amino-tetralinecarbonyl derivatives (3b–d)

The synthesis of these compounds is presented in Scheme 4, starting from the aminoketones **8a** and **b** which were transformed into the triflate enol ethers **12a** and **b** according to described method.[24] Their palladium-catalysed carbonylation under CO atmosphere[25,26] with the Weinreb hydroxylamine for the Boc-derivative **12a** or with *O*-benzyl-hydroxylamine for the benzyloxycarbonyl derivative **12b** provided the crystalline dihydro-naphthalene-2-amides **13a** and **b**, respectively, in 68–80% yield from **8a** or **b**. Hydrogenation on Pd–C of the benzyl derivative **13b** led directly to a 60/40 isomeric mixture of hydroxamic acid **3c** with hydrogenolysis of the diverse protecting groups in 71% yield. Hydrogenation over PtO_2 of the Boc-derivative **13a** give quantitatively a 80/20 isomeric mixture of tetrahydronaphthalene **14**.

Addition of the methylmagnesium onto **14** at 0 °C gave a 20/80 mixture of *cis* and *trans* isomers of methylketone **15** in moderate yield (36%) which was then quantitatively acidic N-deprotected into the amino-ketone **3b** (5/95 mixture of *cis* and *trans* isomers).

The triflate enol ether **12a** was phosphonylated (Scheme 5) by palladium catalysed coupling of dimethyl phosphite[27,28] to provide the dihydro-naphthalene-2-phosphonate **16** in 61% yield. Hydrogenation over PtO_2 and acidic hydrolysis of the obtained phosphonate **16** with HBr in AcOH led to amino phosphonic acid **3d** as 70/30 isomeric mixture in 70% overall yield from 16.



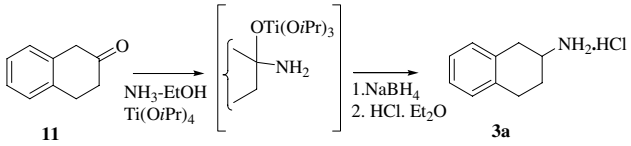
Scheme 4.

2.4. Hetero-naphthalenones (4a–d)

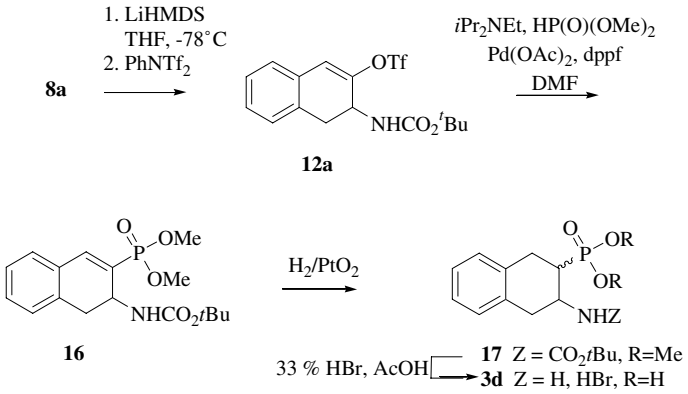
Isochromanone **4a**,[29,30] isothiochromanone **4b**[29,31] and dihydro-isoquinolinones **4d**[32] are known compounds. Synthesis of isochromanone **4a** was carried out from homophthalic acid **18a**. Monoesterification by $SOCl_2$ in MeOH[33] and reduction with borane[34] gave easily a variable mixture of alcohol-ester **19** and isochromanone **4a** which provided pure **4a** by heating in toluene at 80 °C in the presence of *p*-TsOH[35] (Scheme 6).

Isothiochromanone **4b** was synthesised by acidic opening of isochromanone **4a** with HBr in bromo-acid **20a**,[29] but the cyclisation of the corresponding acid chloride with sulfide ion gave unsatisfactory results and was therefore realised via another route (Scheme 6). The bromo-acid **20a** was reacted with thiourea and the thiouronium salt was directly saponified with NaOH into the thiol-acid **21**. Esterification of **21** with $SOCl_2$/MeOH or with diazomethane and cyclisation with $AlMe_3$[36,37] provided isothiochromanone **4b** in 46 % overall yield from **4a**.

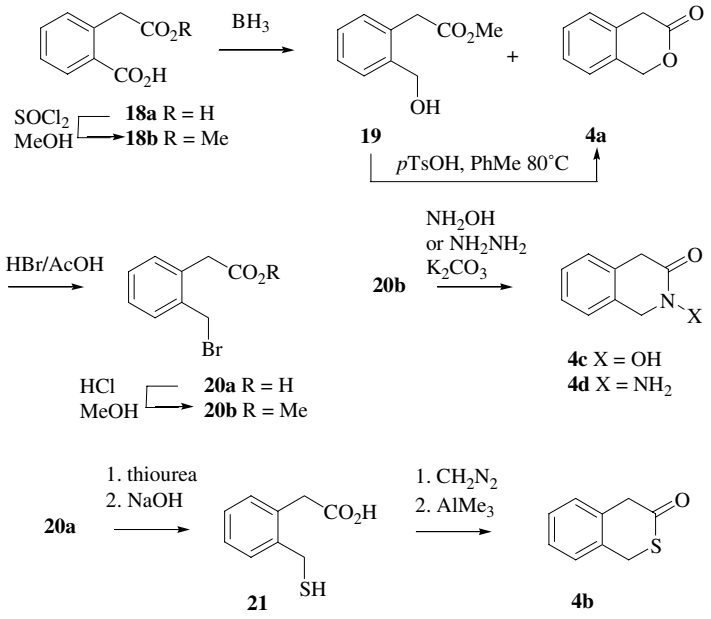
N-Substituted isoquinolinones **4c** and **d** were obtained more simply by the method described for **4d**[32] by action



Scheme 3.



Scheme 5.



Scheme 6.

of hydroxylamine for **4c** or hydrazine for **4d** with bromo-ester **20b** in ethanol.

2.5. Aminoquinolinone (5)

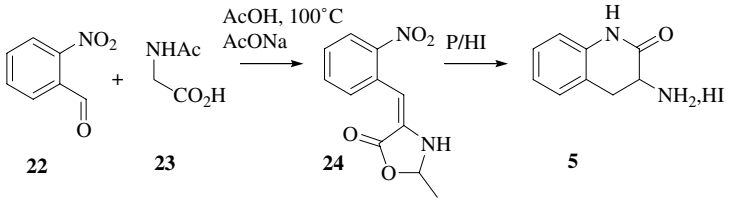
Amine **5** was prepared according to the lit.[38,39] in two steps (Scheme 7), by condensation of *ortho*-nitrobenzaldehyde (**22**) with *N*-acetylglycine (**23**) into aryl-isoxazolone **24** which was then reduced and hydrolysed to **5** as hydroiodide with red phosphor and HI in ca. 40% yield from **22**.

3. Aminopeptidase inhibition and discussion

All compounds were evaluated as racemic mixtures. All active compounds behaved as competitive inhibitors of the panel aminopeptidases. The inhibitory parameters (K_i or IC_{50}) are reported in Table 1.

3.1. Structural requirements for 3-amino-2-tetralone activity

The bicyclic structure **1**, which may be described as a conformationally constrained, cyclised phenylalanine derivative, has previously been reported as a selective inhibitor of the 'one-zinc' AP-*N*. Furthermore, it has been proposed that the amino-tetralone scaffold acts as a bidentate ligand, with both its amino and carbonyl groups contributing to the coordination sphere of the catalytic zinc.[15] The primary amine function in position 3 is clearly an essential feature for inhibitory activity since all N-protected derivatives reported herein were inactive up to 1 M concentration. This result is also in line with the well-known requirement for a free N-terminus in peptide substrates of APs.[15] Hence, the primary amino group of **1** is likely to mimic the aminoterminal amino group of an AP substrate. The carbonyl group in position 2 also appears to be critical, presumably as



Scheme 7.

Table 1. Inhibition of aminopeptidase activity

Compound	LAPc (E.C. 3.4.11.1)	APaero (E.C. 3.4.11.10)	AP-*N* (E.C. 3.4.11.2)	LTA_4H (E.C. 3.3.2.6)
Bestatin	0.0005	0.0016	3.5	0.5
1	120	130	0.5	>1000
2a	>1000	>1000	1800	>1000
2b	>1000	800	**130**[a]	>1000
2c	>1000	210	790	>1000
2d	>100	170	**260**[a]	500
2e	>1000	300	**110**[a]	**6**[a]
2f	>100	110	**55**[a]	**8**[a]
2g	>100	130	**80**[a]	**30**[a]
3a	>1000	>1000	>1000	>1000
3b	>1000	500	>1000	750
3c	**10**[a]	**4**[a]	**4**[a]	>1000
3d	>1000	150	500	>1000
4a	>1000	>1000	>1000	>1000
4b	>1000	**4**[a]	>1000	>1000
4c	>1000	**4**[a]	>1000	>1000
4d	1000	740	>1000	>1000
4e	>1000	>1000	>1000	>1000
5	>1000	**80**[a]	>1000	>1000

All substances were evaluated as racemic mixtures. IC_{50} (μM) values were determined from Dixon plots at a substrate concentration set to the K_m value for the corresponding enzyme (see Section 5). Inactive compounds were tested up to their solubility limit under the assay conditions. K_i (μM, in boldface) were also determined from Dixon plots. LAPc, cytosolic leucine aminopeptidase (E.C. 3.4.11.1); AP-*N*, aminopeptidase-*N* (E.C. 3.4.11.2); APaero, *Aeromonas proteolytica* aminopeptidase (E.C. 3.4.11.10) and LTA_4H, the aminopeptidase activity of leukotriene A_4 hydrolase (E.C. 3.3.2.6).
[a] K_i (μM).

a surrogate of the carbonyl group of the scissile peptide bond in AP substrates. In support of this view, alcohol derivatives, which have been obtained by reduction of the carbonyl function, have been shown to be very weak inhibitors.[15] The lack of binding affinity of compounds **3a** and **4e**, bearing either the primary amino or the carbonyl functionality, respectively, further corroborates this hypothesis. Thus, our design strategy was focused on analogues bearing new functionalities in positions 2 and 3, with the potential to display bidentate zinc-chelating properties. The primary amine was conserved in most, but not all, cases.

3.2. Modifications of the carbonyl group

In a first series, the replacement of the carbonyl group with potential zinc-chelating functions was investigated.

3.2.1. Oxime and O-substituted derivatives. Compounds in the **2** series appeared to be rather poor inhibitors of most APs evaluated. The free oxime was unfortunately not an interesting chelating function in our case, since derivative **2a** was inactive on all four AP enzymes. O-Substituted derivatives **2b**–**g** were totally inactive on the cytosolic porcine kidney leucine aminopeptidase (LAPc), an important member of the 'two-zinc' AP sub-family. Its bacterial twin sister from *A. proteolytica* was only weakly inhibited, with IC_{50} values ranging from 110 to 210 μM, for the best compounds, depending on the length of the alkyl spacer between the oxime-oxygen and the phenyl ring. There was no clear correlation between the chain length and the observed inhibitory potency. By contrast, the selected members of the 'one-zinc' enzymes (AP-*N* and LTA_4H aminopeptidase activity) seemed to be more sensitive to this series of compounds, again depending on the spacer length. AP-*N* was inhibited by **2f** and **g** with K_i values of 55 and 80 μM, respectively. With such spacers of four to five carbon atoms the phenyl ring might be able to reach the S1 hydrophobic binding pocket, simultaneously allowing optimal positioning of the zinc chelating groups. Finally, LTA_4H was inhibited more selectively by **2e** and **f**, with remarkably low K_i values of 6 and 8 μM, respectively. A chain length of at least three carbon atoms was necessary to observe this level of inhibitory potency. Other inhibitors of LTA_4H bearing such an alkylphenyl group have already been reported.[40] The lack of inhibitory activity of the free oxime and its *O*-methyl derivative strongly suggests that, in these structures, the O-substituted oxime function is not involved in zinc-chelation.

3.2.2. Other modifications in position 2. Derivative **3b** bearing a methyl ketone in position 2 was essentially inactive on all sub-classes of aminopeptidases evaluated, with IC_{50} values higher than or equal to 0.5 mM for APaero.

The introduction of an hydroxamic acid, a potent zinc-chelating function widely used for the design of metalloprotease inhibitors,[41–43] led to compound **3c** which inhibited most of the panel enzymes, with K_i values in the low micromolar range. Interestingly, and in sharp contrast to the more typical APs, LTA_4H was not inhibited by this particular structure, again suggesting that zinc-chelation is more difficult to achieve for LTA_4H than for the more typical APs. This may be explained by the distinct shape of the LTA_4H active site, a long and narrow hydrophobic cleft with a deeply buried zinc ion.[44] The active sites of known APs are more open and their zinc ion(s) thus more accessible.[9,45,46]

Phosphonate and phosphinate derivatives have been widely used as transition states analogues for peptidomimetic inhibitors of proteolytic enzymes.[47–49] The application of this concept to the tetralone scaffold led to the design of derivative **3d**. This compound inhibited APaero with a K_i value of 150 μM and was thus equipotent to the parent 3-amino-2-tetralone **1** on this bacterial enzyme. Against the mammalian enzymes, however, compound **3d** was found to be 1000-fold less active than **1** on AP-*N*, and totally inactive on LAP_C and LTA_4H up to 1 mM concentration.

3.2.3. Modification of the B cycle. Finally, we have carried out modifications of the B cycle of **1** in an attempt to increase stability at physiological pH. The heterocyclic compounds in the **4** and **5** series were synthesised and evaluated. None of them inhibited the mammalian aminopeptidases, up to 1 mM concentration. Interestingly, however, compound **4c** exhibited a K_i of 4 μM against the bacterial enzyme from *A. proteolytica*. Thus, this cyclised hydroxamic acid compound turned out to be as active as the exocyclic hydroxamic acid **3c** against APaero. Furthermore, the isothiochromanone derivative **4b** was also a good inhibitor of this enzyme (K_i = 4 μM), equipotent to the hydroxamic acids **4c** and **3c**.

3.3. Stability of 3-amino-2-tetralone (1) and its active analogues

Enzyme assays were run at 25 °C in 20 mM Tris–HCl buffer pH 7.5, with leucine-*para*-nitroanilide (0.2 mM) as substrate, in a total reaction volume of 1 mL. The formation of *para*-nitroaniline was followed at 405 nm (ε = 10,800 $mol^{-1}\,l\,cm^{-1}$). The reaction was started by addition of 3 mU of porcine kidney AP-*N*. Under these experimental conditions linear kinetics were observed for at least 10 h. Dotted line A corresponds to control (no inhibitor; V_o = 4.3 nmol h^{-1}). In experiments B and C 1 μM of **1** and 200 μM of **2b**, respectively, were used. In experiment B, 40% of inhibition (V_i = 2.4 nmol h^{-1}) was observed during the first hour. After 4 h, the enzyme activity was back to control ($V_i = V_o$ = 4.25 nmol h^{-1}). In contrast, 50% inhibition (V_i = 2.1 nmol h^{-1})was observed throughout experiment C.

We found that the stability of the 3-amino-2-tetralone **1** in aqueous solution at physiological pH is limited, with an approximate half life of 2 h. This prompted us to devise a simple experimental approach to evaluate compound stability under our assay conditions. By continuously monitoring AP-*N* reaction rates over a period of 10 h we were able to assess and compare the stability of the various compounds reported herein. An example is shown in Figure 1, where **1** is compared to the more stable analogue **2b**. While inhibition of AP-*N* activity by the oxime analogue **2b** remained constant during at

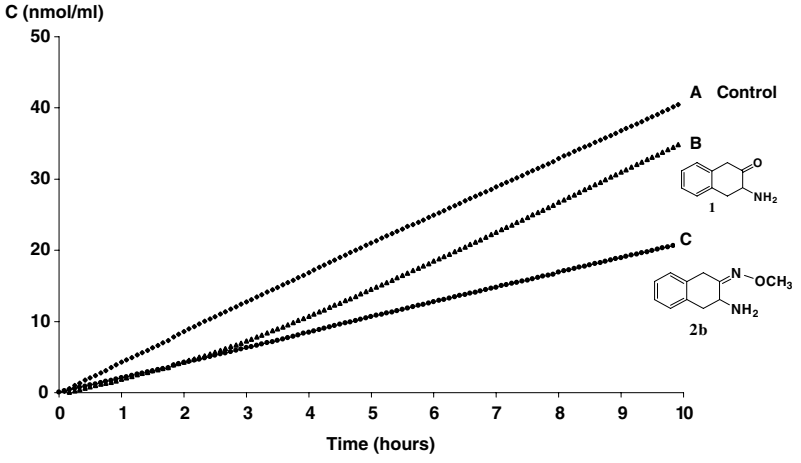


Figure 1. Enzyme assays were run at 25 °C in 20 mM Tris–HCl buffer, pH 7.5, with leucine-*para*-nitroanilide (0.2 mM) as substrate, in a total reaction volume of 1 mL. The formation of *para*-nitroaniline was followed at 405 nm (ε = 10,800 $mol^{-1}\,l\,cm^{-1}$). The reaction was started by addition of 3 mU of porcine kidney AP-*N*. Under these experimental conditions linear kinetics were observed for at least 10 h. Dotted line A corresponds to control (no inhibitor; V_o = 4.3 nmol h^{-1}). In experiments B and C 1 μM of **1** and 200 μM of **2b**, respectively, were used. In experiment B, 40% of inhibition (V_i = 2.4 nmol h^{-1}) was observed during the first hour. After 4 h, the enzyme activity was back to control ($V_i = V_o$ = 4.25 nmol h^{-1}). In contrast, 50% inhibition (V_i = 2.1 nmol h^{-1}) was observed throughout experiment C.

least 10 h, inhibition by **1** levelled off after about 2 h, the observed reaction rate returning slowly to control values after this period of time. Similar results were observed with all active compounds, which were all stable for at least 10 h under our assay conditions.

4. Conclusion

The development of novel metallo-protease inhibitors in general represents an important scientific endeavour because of the pharmaceutical relevance of many of these enzymes. While this work was concentrated on aminopeptidases and the 3-amino-2-tetralone scaffold, recent published work on matrix metallo-protease inhibitors illustrates the need to explore novel chemotypes with zinc binding properties.[50] Although 3-amino-2-tetralone and bestatin remain the best inhibitors to date, both in terms of specificity and potency, against the 'one-zinc' and 'two-zinc' aminopeptidase sub-families, respectively, we successfully identified 3-amino-2-tetralone derivatives with improved stability. Moreover, O-substituted oxime derivatives with large hydrophobic groups were shown to be micromolar inhibitors of the 'one-zinc' AP-*N* and LTA_4H aminopeptidase activities. These compounds were inactive against the mammalian LAPc, a member of the 'two-zinc' sub-family, and, hence, may have an interesting selectivity profile for the further development of inhibitors of mammalian aminopeptidases with only one active site zinc. Not unexpectedly, hydroxamic acid derivatives were devoid of specificity, but LTA_4H was found to be surprisingly insensitive to such inhibitors. During this study, we also identified three compounds, the cyclised hydroxamic acid **4c**, the isothiochromanone **4b** and aminoquinolinone **5**, which were selective, micromolar inhibitors of the bacterial, 'two-zinc' APaero. Although these compounds failed to inhibit LAPc, the mammalian representative of the 'two-zinc' sub-family, they might, nevertheless, prove useful in the future for the inhibition of other metalloenzymes with a co-catalytic unit.

5. Experimental

5.1. General

Flash chromatography (FC), silica gel (*Merck 60*, 230–400 mesh). TLC, Al-roll silica gel (*Merck 60*, F_{254}). Mp, Kofler hot bench, corrected. IR spectra (ν, cm^{-1}), *Nicolet 405 FT-IR*. $[\alpha]_D$, Schmidt–Haensch Polartronic Universal or Perkin-Elmer 341 LC polarimeter. ^1H, ^{31}P and ^{13}C NMR (400, 161.9 and 100.6 MHz, respectively). Spectra: Bruker Avance 400, or in some cases Bruker AC-F 250, tetramethylsilane (TMS), or sodium (D_4)-trimethylsilylpropionate (D_4-TSP) in D_2O (^1H NMR), extern 80% aqueous PO_4H_3 (^{31}P NMR) and $CDCl_3$, or (in D_2O) dioxane [$\delta(CDCl_3) = 77.0$, in D_2O δ(dioxane) = 67.4 with respect to TMS] (^{13}C NMR) as internal references; δ in parts per million and J in Hertz. High resolution MS were measured in Spectroscopy Laboratory of Strasbourg University or on a Waters Micromass Q-Tof Ultima API spectrometer in Basilea Pharmaceuticals, Basel. Microanalyses were carried out by the Service Central de Microanalyses du CNRS, F-69390 Vernaison.

5.2. Reagents and solvents

1,4-Dihydronaphthalene (**6**) was synthesised according to Ref. 17, 2,3-epoxy-1,2,3,4-tetrahydronaphthalene according to Refs. 16 and 17, 2-methyl-4-(2-nitro-benzylidene)-4*H*-oxazol-5-one (**24**) according to Ref. 38 and 3-amino-3,4-dihydro-1 *H*-quinolin-2-one **(5)** according to Ref. 39. Dess–Martin periodinane was obtained as 1 M solution in CH_2Cl_2 from Aldrich or synthesised according to Refs. 18 and 53. O-Substituted hydroxylamines **9d**–**g** were prepared according to Ref. 19. Commercial products were purchased from usual suppliers, 1,1'-bis(diphenylphosphino) ferrocene (dppf) from Alfa Aesar. Usual solvents were freshly distilled, dry EtOH and MeOH distilled over Mg/MgI_2, dry THF over Na and benzophenone, dry Et_2O was distilled and stored over Na, CH_2Cl_2 was distilled over P_2O_5 and kept over Na_2CO_3. NEt_3 was distilled before use.

5.3. trans-3-tert-Butoxycarbonyl-amino-1,2,3,4-tetrahydronaphthalen-2-ol (7a)

A suspension of 2,3-epoxy-1,2,3,4-tetrahydronaphthalene[16,17] (2.9 g, 19.9 mmol) in MeOH (40 mL) and 25% concd ammonia (50 mL) was heated at 95 °C in a bomb-enrohr for 18 h. The solvent was evaporated to give the crude amino-alcohol.

To a solution of the crude amino-alcohol in MeOH (40 mL) was added Boc_2O (5.2 g, 23.9 mmol, 1.2 equiv) and the mixture was stirred under Ar at rt 16 h. The solvent was evaporated, and the residue purified by FC (cyclohexane/AcOEt, 8/2–6/4) to give **7a** (2.84 g, 54%).

Colorless crystals, mp 122–4 °C (lit.[16] 149–150 °C).

^1H NMR ($CDCl_3$): 7.20–7.05 (m, 4Har); 4.72 (d, J = ca. 6.0, NH); 3.88 (m, H–C(2), H–C(3)); 3.25 (dd, J = 16.4, 5.0 Hz, 1H); 3.20 (dd, J = 16.4, 4.8 Hz, 1H); 2.86 (dd, J = 16.4, 8.3 Hz, 1H); 2.71 (dd, J = 16.4, 8.7 Hz, 1H); 1.47 (s, CMe_3).

5.4. 3-Benzyloxycarbonyl-amino-1,2,3,4-tetrahydronaphthalen-2-ol (7b)

To a solution of the crude above amino-alcohol (prepared from 2,3-epoxy-1,2,3,4-tetrahydronaphthalene,[16,17] 1.0 g, 6.84 mmol) in THF (10 mL) and water (2 mL) were successively added at 0 °C Na_2CO_3 (1.6 g, 15 mmol) and benzyl chloroformate (1.4 mL, 9.81 mmol, 1.5 equiv) and the mixture was stirred under Ar at rt for 1 h. Water and Et_2O were added and the precipitated **7b** was filtered and washed with $^iPr_2O$ (1.6 g, 79%).

Colorless needles, mp 143–5 °C (toluene).

IR (KBr), ν: 3369, 3308, 3063, 2926, 2895, 2840, 1687, 1548, 1453, 1435, 1316, 1303, 1255, 1212, 1108, 1067, 1049, 1022, 747, 726, and 694 cm^{-1}.

^{1}H NMR ($CDCl_3$): 7.37–7.33 (m, 5Har); 7.16–7.06 (m, 4Har); 5.14 (s, CH_2Ph); 4.91 (s, NH); 3.94 (m, H–C(2), H–C(3)); 3.29 (dd, Ha–C(4)); 3.21 (dd, Ha–C(3); 2.87 (dd, Hb–C(1)); 2.72 (dd, Hb–C(4)); 2.60 (s, OH). J(1a, 1b) = 16.8, J(1a, 2) = 4.6, J(1b, 2) = 7.6, J(3, 4a) = 3.6, J(3, 4b) = 8.6, J(4a, 4b) = 16.4 Hz.

^{13}C NMR ($CDCl_3$): 157.2 (NCO_2); 136.4 (Cs(Bn)); 133.8, 133.4 (C(4a), C(8a)); 129.1, 128.8, 128.7, 128.4, 128.3, 126.6, 126.4 (7Car); 70.7 (C(2)); 67.2 (OCH_2Ph); 53.5 (C(3)); 37.2 (C(1)); 34.6 (C(4)).

Anal. Calcd for $C_{18}H_{19}NO_3$ (297.35): C, 72.71; H, 6.44; N, 4.71. Found: C, 72.6; H, 6.5; N, 4.7.

5.5. 3-Benzyloxycarbonyl-amino-3,4-dihydro-1*H*-naphthalen-2-one (8b)

To a solution of **7b** (1.0 g, 3.36 mmol) in wet CH_2Cl_2 (60 mL) was added Dess–Martin periodinane (3.14 g, 7.4 mmol) and the mixture was stirred at rt for 3 h. The reaction mixture was diluted with AcOEt (100 mL), reduced with $Na_2S_2O_3 \cdot 5H_2O$ (9.2 g, 37 mmol, 5 equiv) and 1 N aq $NaHCO_3$ and stirred at room temperature for 1 h. The organic solution was washed successively with 1 N aq $NaHCO_3$ and brine, and dried over $MgSO_4$. The solvent was evaporated, and the residue purified by FC (cyclohexane/AcOEt, 9/1 then 8/2) to give **8b** (0.80 g, 80%).

Colorless needles, mp 89–90 °C (^{i}Pr$_2$O).

IR (KBr), *v*: 3325, 2934, 1730, 1693, 1517, 1494, 1384, 1360, 1300, 1238, 1071, 998, 779, 753, 744, and 696 cm^{-1}.

^{1}H NMR ($CDCl_3$): 7.38–7.31 (m, 5Har); 7.24 (m, 3Har); 7.12 (m, 1Har); 5.89 (br s, NH); 5.14 (s, OCH_2Ph); 4.52 (m, H–C(3)); 3.79, 3.78 (2 d, CH_2C(1)); 3.64 (dd, Ha–C(4)); 2.91 (dd, Hb–C(4)). J(1a,1b) = 21.6, J(3,4a) = ca. 6.0, J(3,4b) = 13.0, J(3,NH) = ca. 6.0, J(4a, 4b) = 14.9 Hz.

^{13}C NMR ($CDCl_3$): 205.5 (C(2)); 156.0 (NCO_2); 136.4 (Cs(Bn)); 133.6, 132.3 (C(4a),C(8a)); 128.9, 128.7, 128.5, 128.4, 128.3, 127.5, 127.3 (7Car); 67.1 (OCH_2Ph); 57.6 (C(3)); 42.9 (C(1)); 36.3 (C(4)).

Anal. Calcd for $C_{18}H_{17}NO_3$ (295.33): C, 73.20; H, 5.80; N, 4.74. Found: C, 73.1; H, 5.9; N, 4.7.

5.6. 3-*tert*-Butoxycarbonyl-amino-3,4-dihydro-1*H*-naphthalen-2-one (8a)

Same procedure as **8b** with **7a** (2.733 g, 10.38 mmol) in CH_2Cl_2 (90 mL) and Dess–Martin periodinane (6.6 g, 15.57 mmol). The crude crystallised **8a** was washed three times with ^{i}Pr$_2$O (2.23 g, 82%).

Colorless needles, mp 100–4 °C (^{i}Pr$_2$O) (lit.[16] 104–5 °C).

IR (KBr), *v*: 3327, 3012, 2981, 1733, 1679, 1528, 1366, 1311, 1163, 1020, and 744 cm^{-1}.

^{1}H NMR ($CDCl_3$): 7.22 (s, 3Har); 7.12 (m, 1Har); 5.63 (br s, NH), 4.47 (m, H–C(3)); 3.78 (d, Ha–C(1)); 3.77 (d, Hb–C(1)); 3.62 (dd, Ha–C(4)); 2.89 (t, Hb–C(4)), 1.47 (s, O^{t}Bu). J(1a, 1b) = 21.4, J(3, 4a) = 5.8, J(3, 4b) = 12.5, J(3, NH) = ca. 7.0, J(4a, 4b) = 15.5 Hz.

5.7. General procedure for the synthesis of 3-benzyloxycarbonylamino-3,4-dihydro-1*H*-naphthalen-2-one O-substituted-oximes (10a–g)

To a solution of **8b** in dry pyridine (15 mL/mmol) was added O-substituted-hydroxylamine hydrochloride **9a–g** (1.2 equiv) and the mixture was stirred under Ar at rt for 1–9 h. The reaction was monitored by TLC. The reaction mixture was diluted with AcOEt, washed successively with 2 N aq NH_4Cl and brine and dried over $MgSO_4$. After evaporation of the solvent, the title product crystallised in cool ^{i}Pr$_2$O or ^{i}PrOH and washed with cool ^{i}Pr$_2$O.

5.7.1. 3-Benzyloxycarbonylamino-3,4-dihydro-1*H*-naphthalen-2-one oxime (10a). From **8b** (300 mg) was obtained **10a** (256 mg, 81%).

Colorless crystals, mp 171–2 °C (^{i}PrOH).

IR (KBr), *v*: 3302, 3065, 3033, 2955, 2897, 1701,1685,1667, 1534, 1496, 1456, 1363, 1327, 1309, 1283, 1233, 1262, 1070, 996, 939, 741, and 696 cm^{-1}.

^{1}H NMR (CD_3OD): 7.35–7.28 (m, 5 Har); 7.19–7.14 (m, 4 Har); 5.09 (s, OCH_2Ph); 4.45 (dd, H–C(3)); 3.93 (d, Ha–C(1)); 3.78 (d, Hb–C(1)); 3.14 (dd, Ha–C(4)); 2.91 (dd, Hb–C(4)). J(1a, 1b) = 21.6, J(3, 4a) = 4.5, J(3, 4b) = 9.6, J(4a, 4b) = 15.0 Hz.

^{13}C NMR (CD_3OD): 158.2 (C(2)); 156.0 (NCO_2); 138.3 (Cs(Bn)); 135.4, 134.1 (C(4a), C(8a)); 129.8, 129.6, 129.5, 129.0, 128.8, 128.1, 127.4 (7Car); 67.5 (CH_2Ph); 51.5 (C(3)); 37.2 (C(4)); 29.1(C(1)).

Anal. Calcd for $C_{18}H_{18}N_2O_3$ (310.35): C, 69.66; H, 5.85; N 9.03. Found: C, 69.4; H, 5.9; N, 9.0.

5.7.2. 3-Benzyloxycarbonylamino-3,4-dihydro-1*H*-naphthalen-2-one *O*-methyloxime (10b). From **8b** (300 mg) was obtained **10b** (260 mg, 66%).

Colorless crystals, mp 115-7 °C (^{i}PrOH).

IR (KBr), *v*: 3295, 3062, 3033, 2953, 2896, 1688, 1545, 1356, 1307, 1283, 1261, 1072, 1046, 991, 891, 744, and 696 cm^{-1}.

^{1}H NMR (CD_3OD): 7.38–7.29 (m, 5 Har); 7.20–7.12 (m, 4 Har); 5.11 (s, OCH_2Ph); 4.45 (dd, H–C(3)); 3.89 (s, NOMe), 3.89 (d, Ha–C(1)); 3.74 (d, Hb–C(1)); 3.13 (dd, Ha–C(4)); 2.92 (dd, Hb–C(4)). J(**1a**,**1b**) = 21.6, J(**3**,**4a**) = 4.6, J(**3**,**4b**) = 9.8, J(**4a**,**4b**) = 15.1 Hz.

^{13}C NMR (CD_3OD): 158.1 (C(2)); 156.5 (NCO_2); 138.4 (Cs(Bn)); 135.3, 133.8 (C(4a), C(8a)); 129.8, 129.6, 129.5, 129.0, 128.8, 128.1, 127.5 (7Car); 67.4 (CH_2Ph); 62.3 (OMe); 51.5 (C(3)); 37.0 (C(4)); 29.7 (C(1)).

Anal. Calcd for $C_{19}H_{20}N_2O_3$ (324.37): C, 70.35; H, 6.21; N, 8.64. Found: C, 70.4; H, 6.4; N, 8.6.

5.7.3. 3-Benzyloxycarbonylamino-3,4-dihydro-1*H*-naphthalen-2-one *O*-benzyloxime (10c). From **8b** (100 mg) was obtained **10c** (66 mg, 50%).

Colorless crystals, mp 116–8 °C (^{i}PrOH).

IR (KBr), *v*: 3305, 3032, 2923, 2462, 1685, 1537, 1494, 1438, 1351, 1254, 1071, 1040, 1008, 875, 741, and 695 cm^{-1}.

^{1}H NMR ($CDCl_3$): 7.36–7.27 (m, 10Har); 7.19–709 (m, 4Har); 5.85 (br d, NH), 5.13–5.10 (m, 2OCH_2Ph); 4.48 (dd, H–C(3)); 4.03 (d, Ha–C(1)); 3.68 (d, Hb–C(1)); 3.41 (dd, Ha–C(4)), 2.74 (dd, Hb–C(4)). J(1a, 1b) = 21.9, J(3, 4a) = 4.6, J(3, 4b) = 10.4, J(3, NH) = ca. 5.0, J(4a, 4b) = 14.8 Hz.

^{13}C NMR ($CDCl_3$): 155.9 (C(2)); 155.1 (NCO_2); 137.5 (Cs(Bn)); 136.4 (Cs(NOBn)); 133.8, 132.2 (C(4a), C(8a)); 129.0, 128.6, 128.5, 128.3, 128.1, 127.2, 126.7 (Car); 76.5, 67.0 (2CH_2Ph); 50.5 (C(3)); 36.5 (C(4)); 29.4 (C(1)).

Anal. Calcd for $C_{25}H_{24}N_2O_3$ (400.47): C, 74.98; H, 6.04; N, 7.00. Found: C, 75.1; H, 6.2; N, 6.9.

5.7.4. 3-Benzyloxycarbonylamino-3,4-dihydro-1*H*-naphthalen-2-one *O*-(2-phenylethyl)oxime (10d). From **8b** (50 mg) was obtained **10d** (66 mg, 83%).

Colorless crystals, mp 96–8 °C (^{i}PrOH).

IR (KBr), *v*: 3321, 3027, 2935, 1686, 1534, 1495, 1455, 1439, 1282, 1259, 1065, 1043, 1027, 986, 897, 745, and 697 cm^{-1}.

^{1}H NMR ($CDCl_3$): 7.40–7.11 (m, 14 Har); 5.74 (br s, NH); 5.14 (s, OCH_2Ph); 4.49 (m, H–C(3)); 4.33 (t, CH_2(1′)); 3.96 (d, Ha–C(1)); 3.63 (d, Hb–C(1)); 3.47 (dd, Ha–C(4)); 2.99 (t, CH_2(2′)); 2.74 (dd, Hb–C(4)). J(1a, 1b) = 21.8, J(3, 4a) = 4.6, J(3, 4b) = 10.6, J(3, NH) = ca. 6.0, J(4a, 4b) = 15.0, J(1′, 2′) = 6.8 Hz.

^{13}C NMR ($CDCl_3$): 155.8 (C(2)); 154.7 (NCO_2); 138.8 (Cs(Bn)); 136.6 (Cs(Ph)); 133.9, 132.4 (C(4a), C(8a)); 129.1, 128.7, 128.6, 128.5, 128.3, 127.3, 126.7, 126.4 (Car); 75.0 (C(1′)); 67.0 (CH_2Ph); 50.5 (C(3)); 36.7 (C(4)); 36.0 (C(2′); 29.4 (C(1)).

Anal. Calcd for $C_{26}H_{26}N_2O_3$ (414.50): C, 75.34; H, 6.32; N 6.76. Found: C, 75.2; H, 6.4; N 6.7.

5.7.5. 3-Benzyloxycarbonylamino-3,4-dihydro-1*H*-naphthalen-2-one *O*-(3-phenylpropyl)oxime (10e). From **8b** (84 mg) was obtained **10e** (72 mg, 60%).

Colorless crystals, mp 93–5 °C (^{i}PrOH).

IR (KBr), *v*: 3326, 2949, 1685, 1533, 1261, 1041, 914, 746, and 697 cm^{-1}.

^{1}H NMR ($CDCl_3$): 7.40–7.14 (m, 14Har); 5.84 (br d, NH); 5.12 (s, OCH_2Ph); 4.48 (m, H–C(3)); 4.13 (t, CH_2(1′)); 3.97 (d, Ha–C(1)); 3.63 (d, Hb–C(1)); 3.46 (dd, Ha–C(4)); 2.75 (dd, Hb–C(4)); 2.70 (t, CH_2(3′)); 2.00 (quint, CH_2(2′)). J(1a, 1b) = 22.4, J(3, 4a) = ca. 5.0, J(3, 4b) = 10.5, J(3, NH) = ca. 6.0, J(4a, 4b) = 15.0, J(1′, 2′) = 6.6, J(2′, 3′) = 7.6 Hz.

^{13}C NMR ($CDCl_3$): 155.9 (C(2)); 154.3 (NCO_2); 141.9 (Cs(Bn)); 136.5 (Cs(Ph)); 133.9, 132.4 (C(4a), C(8a)); 129.1, 128.7, 128.6, 128.6, 128.5, 128.4, 127.3, 126.7, 126.0 (10Car); 73.8 (C(1′)); 67.0 (CH_2Ph); 50.5 (C(3)); 36.7 (C(4)); 32.4 (C(3′)); 30.7 (C(2′); 29.2 (C(1)).

Anal. Calcd for $C_{27}H_{28}N_2O_3$ (428.52): C, 75.68; H, 6.59; N, 6.54. Found: C, 75.6; H, 6.7; N, 6.5.

5.7.6. 3-Benzyloxycarbonylamino-3,4-dihydro-1*H*-naphthalen-2-one *O*-(4-phenylbutyl)oxime (10f). From **8b** (85 mg) was obtained **10f** (105 mg, 83%).

Colorless crystals, mp 115–7 °C (^{i}PrOH).

IR (KBr), *v*: 3317, 2937, 1688, 1530, 1453, 1362, 1281, 1260, 1069, 961, 921, 748, 733, and 697 cm^{-1}.

^{1}H NMR ($CDCl_3$): 7.40–7.12 (m, 14Har); 5.83 (br d, NH); 5.14 (s, OCH_2Ph); 4.48 (m, H–C(3)); 4.12 (br t, CH_2(1′)); 4.01 (d, Ha–C(1)); 3.65 (d, Hb–C(1)); 3.48 (dd, Ha–C(4)); 2.73 (dd, Hb–C(4)); 2.65 (t, CH_2(4′)); 1.71 (m, CH_2(2′), CH_2(3′)). J(1a, 1b) = 22.0, J(3, 4a) = 4.6, J(3, 4b) = 11.0, J(3, NH) = ca. 6.0, J(4a, 4b) = 15.2 Hz.

^{13}C NMR ($CDCl_3$): 155.8 (C(2)); 154.1 (NCO_2); 142.4 (Cs(Bn)); 136.6 (Cs(Ph)); 134.0, 132.4 (C(4a), C(8a)); 129.1, 128.7, 128.6, 128.5, 128.4, 128.4, 128.3, 127.3, 126.7, 125.9 (10Car); 74.3 (C(1′)); 67.0 (CH_2Ph); 50.5 (C(3)); 36.7 (C(4)); 35.8 (C(4′)); 29.3 (C(1)); 28.8, 27.9 (C(2′), (C(3′)).

Anal. Calcd for $C_{28}H_{30}N_2O_3$ (442.55): C, 75.99; H, 6.83; N, 6.33. Found: C, 76.1; H, 7.0; N, 6.3.

5.7.7. 3-Benzyloxycarbonylamino-3,4-dihydro-1*H*-naphthalen-2-one *O*-(5-phenylpentyl)oxime (10g). From **8b** (90 mg) was obtained **10g** (121 mg, 87%).

Colorless crystals, mp 78–80 °C (^{i}PrOH).

IR (KBr), *v*: 3329, 2959, 2936, 2882, 1692, 1529, 1494, 1451, 1361, 1307, 1281, 1069, 998, 931, 749, 733, and 697 cm^{-1}.

^{1}H NMR ($CDCl_3$): 7.40–7.12 (m, 14Har), 5.85 (br d, NH); 5.13 (s, OCH_2Ph); 4.48 (m, H–C(3)); 4.10 (t, CH_2(1′)); 3.99 (d, Ha–C(1)); 3.63 (d, Hb–C(1)); 3.48 (dd, Ha–C(4)); 2.75 (dd, Hb–C(4)); 2.62 (t, CH_2(5′)); 1.68 (m, CH_2(2′), CH_2(4′)), 1.41 (quint, CH_2 (3′)). J(1a, 1b) = 21.8, J(3, 4a) = 4.6, J(3, 4b) = 11.2, J(3, NH) = 5.8, J(4a, 4b) = 14.8, J(1′, 2′) = 6.4, J(2′, 3′) = J(3′, 4′) = 7.7, J(4′, 5′) = 7.6 Hz.

^{13}C NMR ($CDCl_3$): 155.8 (C(2)); 154.1 (NCO_2); 142.7 (Cs(Bn)); 136.6 (Cs(Ph)); 134.0, 132.4 (C(4a), C(8a)); 129.1, 128.7, 128.6, 128.5, 128.4, 128.4, 128.3, 127.2, 126.7, 125.8 (10Car); 74.5 (C(1′)); 67.0 (CH_2Ph); 50.5 (C(3)); 36.7 (C(4)); 36.0 (C(5′)); 31.4 (C(2′)); 29.3 (C(1)); 29.0 (C(4′)); 25.7 (C(3′)).

Anal. Calcd for $C_{29}H_{32}N_2O_3$ (456.58): C, 76.29; H, 7.06; N, 6.14. Found: C, 76.5; H, 7.3; N, 6.0.

5.8. General procedure for the synthesis of 3-amino-3,4-dihydro-1*H*-naphthalen-2-one *O*-phenylalkyloximes hydrochloride (2a–g)

Oxime **10a–g** was hydrogenolysed in EtOH (20 mL/mmol) and 1 N aq HCl (1.0 equiv) over 5% Pd–C (20 mg/mmol) at rt. The reaction was monitored by TLC. Pd–C was centrifuged off and the solvent evaporated. The obtained compound was recrystallised in ^{i}PrOH/Et_2O.

5.8.1. 3-Amino-3,4-dihydro-1*H*-naphthalen-2-one oxime hydrochloride (2a). From oxime **10a** (50 mg) was obtained **2a** (26 mg, 76%).

Colorless crystals, mp 230–40 °C (dec) (^{i}PrOH/Et_2O).

IR (KBr), *v*: 3240, 3000, 1586, 1494, 1457, 1422, 978, 757, and 739 cm^{-1}.

^{1}H NMR (CD_3OD): 7.25–7.21 (m, 4Har); 4.14 (dd, H–C(3)); 4.08 (d, Ha–C(1)); 3.76 (d, Hb–C(1)); 3.24 (dd, Ha–C(4)); 3.03 (dd, Hb–C(4)). J(1a,1b) = 22.0, J(3,4a) = 4.6, J(3,4b) = 11.8, J(4a,4b) = 14.6 Hz.

^{13}C NMR (CD_3OD): 152.6 (C(2)); 133.5, 133.2 (C(4a),C(8a)); 129.9, 129.7, 128.8, 127.9 (4Car); 50.4 (C(3)); 34.9 (C(4)); 28.9 (C(1)).

HR-MS (FAB$^+$) calcd for $C_{10}H_{13}N_2O$, [M+H]$^+$: 177.1028; found: 177.1034.

5.8.2. 3-Amino-3,4-dihydro-1*H*-naphthalen-2-one *O*-methyloxime hydrochloride (2b). From oxime **10b** (50 mg) was obtained **2b** (26 mg, 74%).

Colorless crystals, mp 200–10 °C (dec) (^{i}PrOH/Et_2O). IR (KBr) *v*: 3506, 3426, 3006, 2928, 1605, 1522, 1493, 1458, 1411, 1055, 919, and 756 cm^{-1}.

^{1}H NMR (CD_3OD): 7.23–7.21 (m, 4Har); 4.18 (dd, H–C(3)); 4.05 (d, Ha–C(1)); 4.00 (s, NOMe); 3.76 (d, Hb–C(1)); 3.27 (dd, Ha–C(4)); 3.04 (dd, Hb–C(4)). J(1a,1b) = 22.0, J(3,4a) = 5.0, J(3,4b) = 11.8, J(4a,4b) = 14.8 Hz.

^{13}C NMR (CD_3OD): 153.6 C(2); 133.1, 133.0 (C(4a),C(8a));129.8, 129.7, 128.9, 128.0 (4Car); 62.9 (OCH_3); 50.2 (C(3)); 34.7 (C(4)); 29.5 (C(1)).

HR-MS (FAB$^+$) calcd for $C_{11}H_{15}N_2O$, [M+H]$^+$: 191.1184; found: 191.1184.

5.8.3. 3-Amino-3,4-dihydro-1*H*-naphthalen-2-one *O*-benzyloxime hydrochloride (2c). From oxime **10c** 49 mg) was obtained **2c** (27 mg, 73%).

Colorless crystals, mp 230 °C (dec) (^{i}PrOH/Et_2O).

IR (KBr), *v*: 3450, 3030, 2856, 2616, 1584, 1514, 1495, 1356, 983, 980, 758, 752, 739, and 697 cm^{-1}.

^{1}H NMR (CD_3OD): 7.42–7.20 (m, 9H), 5.24 (s, OCH_2Ph), 4.19 (dd, H–C(3)), 4.10 (d, Ha–C(1)), 3.82 (d, Hb–C(1)), 3.27 (dd, Ha–C(4)), 3.04 (dd, Hb–C(4)). J(1a,1b) = 22.1, J(3,4a) = 5.0, J(3,4b) = 11.8, J(4a,4b) = 14.6 Hz.

^{13}C NMR (CD_3OD): 154.4 (C(2)); 138.8 (Car-s); 133.1, 133.0 (C(4a),C(8a)); 129.8, 129.7, 129.5, 129.3, 129.1, 128.9, 128.0 (7Car); 77.8 (CH_2Ph); 50.3 (C(3)); 34.7 (C(4)); 29.8 (C(1)).

HR-MS (FAB$^+$) calcd for $C_{17}H_{19}N_2O$, [M+H]$^+$: 267.1497; found: 267.1483.

5.8.4. 3-Amino-3,4-dihydro-1*H*-naphthalen-2-one *O*-(2-phenylethyl)oxime hydrochloride (2d). From oxime **10d** (58 mg) was obtained **2d** (30 mg, 68%).

Colorless crystals, mp 182–6 °C (^{i}PrOH/Et_2O).

IR (KBr), *v*: 3430, 3026, 2865, 1578, 1496, 1454, 1066, 1021, 755, and 699 cm^{-1}.

^{1}H NMR (CD_3OD): 7.29–7.19 (m, 9Har), 4.39 (t, CH_2(1′)), 4.18 (dd, H–C(3)), 3.99 (d, Ha–C(1)), 3.73 (d, Hb–C(1)), 3.26 (dd, Ha–C(4)), 3.03 (m, Hb–C(4), CH_2(2′)). J(1a,1b) = 22.0, J(3,4a) = 5.0, J(3,4b) = 11.6, J(4a,4b) = 14.8, J(1′,2′) = 6.8 Hz.

^{13}C NMR (CD_3OD): 154.0 (C(2)); 139.9 (Car-s); 133.2, 133.0 (C(4a),C(8a)); 130.0 (Car-m); 129.8, 129.7 (2Car); 129.4 (Car-o); 128.9, 128.0, 127.3 (3Car); 76.5 (C(1′)); 50.3 (C(3)); 36.5 (C(2′)); 34.8 C(4)); 29.7 C(1)).

HR-MS (ESI-Q-Tof) calcd for $C_{18}H_{20}N_2O$, [M]$^+$: 280.1576; found: 280.1588.

5.8.5. 3-Amino-3,4-dihydro-1*H*-naphthalen-2-one *O*-(3-phenylpropyl)oxime hydrochloride (2e). From oxime **10e** (49 mg) was obtained **2e** (26 mg, 68%).

Colorless crystals, mp 162–70 °C (^{i}PrOH/Et_2O).

IR (KBr), *v*: 3450, 3027, 2865, 1583, 1505, 1496, 1454, 1408, 1384, 1066, 1032, 1013, 918, 757, 743, and 700 cm^{-1}.

^{1}H NMR (CD_3OD): 7.27–7.20 (m, 8Har), 7.15 (m, 1Har), 4.22 (t, CH_2(1′)), 4.17 (dd, H–C(3)), 4.00 (d, Ha–C(1)), 3.73 (d, Hb–C(1)), 3.27 (dd, Ha–C(4)), 3.03 (dd, Hb–C(4)), 2.75 (t, CH_2(3′)), 2.07 (quint, CH_2(2′)). J(1a,1b) = 22.0, J(3,4a) = 5.0, J(3,4b) = 11.9, J(4a,4b) = 14.8, J(1′,2′) = 6.4, J(2′,3′) = 7.6 Hz.

^{13}C NMR (CD_3OD): 153.5 C(2); 143.1 (Car-s); 133.2, 133.0 (C(4a), C(8a)); 129.9, 129.7 (2Car);129.5, 129.4 (Car-m, Car-o); 128.9, 128.0, 126.9 (3Car); 75.2 (C(1′)); 50.3 (C(3)); 34.8 (C(4)); 33.3 (C(3′)); 31.7 (C(2′)); 29.6 (C(1)).

HR-MS. (FAB$^+$) calcd for $C_{19}H_{23}N_2O$, $[M+H]^+$: 295.1810; found: 295.1802.

5.8.6. 3-Amino-3,4-dihydro-1*H*-naphthalen-2-one *O*-(4-phenylbutyl)oxime hydrochloride (2f). From oxime **10f** (88 mg) was obtained **2f** (54 mg, 78%).

Colorless crystals, mp 150–4 °C (^{i}PrOH/Et_2O).

IR (KBr), *v*: 3450, 3025, 2858, 2616, 1578, 1512, 1495, 1453, 1406, 1384, 1025, 1018, 756, 741, and 698 cm^{-1}.

^{1}H NMR (CD_3OD): 7.26–7.14 (m, 9Har); 4.22 (t, CH_2(1′)); 4.17 (dd, H–C(3)); 4.04 (d, Ha–C(1)); 3.77 (d, Hb–C(1)); 3.26 (dd, Ha–C(4)); 3.03 (dd, Hb–C(4)); 2.67 (t, CH_2(4′)); 1.80–1.70 (m, CH_2(2′), CH_2(4′)). J(1a, 1b) = 22.0, J(3, 4a) = 5.0, J(3, 4b) = 12.0, J(4a, 4b) = 14.6, J(1′, 2′) = 6.0, J(3′, 4′) = 6.8 Hz.

^{13}C NMR ($CDCl_3$): 150.9, 142.5, 132.1, 131.8, 129.0, 128.8, 128.5, 128.4, 127.8, 127.0, 125.8, 75.0, 49.7, 35.7, 34.1, 29.0, 28.6, 27.9.

^{1}H NMR ($CDCl_3$): 7.27–7.17 (m, 9Har), 4.23 (m, H–C(1′)), 4.20 (m, H–C(3)), 4.03 (d, J = 22.1 Hz, Ha–C(1)); 3.70 (d, J = 22.1 Hz, Hb–C(1)); 3.63 (dd, J = 4.0, 15.1 Hz, Ha–C(4)); 3.34 (t, J = 13.5 Hz, Hb–C(4)); 2.66 (t, J = 7.1 Hz, CH_2(4′)).

HR-MS (ESI-Q-Tof) calcd for $C_{20}H_{24}N_2O$, $[M]^+$: 308.1889; found: 308.1906.

5.8.7. 3-Amino-3,4-dihydro-1*H*-naphthalen-2-one *O*-(5-phenylpentyl)oxime hydrochloride (2g). From oxime **10g** (62 mg) was obtained **2g** (37 mg, 76%).

Colorless crystals, mp 152–5 °C (^{i}PrOH/Et_2O).

IR (KBr), *v*: 3450, 2936, 2854, 2614, 1578, 1509, 1495, 1459, 1451, 1051, 1039, 1004, 743, 739, and 697 cm^{-1}.

^{1}H NMR (CD_3OD): 7.27–7.08 (m, 9Har), 4.20 (t, CH_2(1′)), 4.16 (dd, H–C(3)), 4.00 (d, Ha–C(1)), 3.72 (d, Hb–C(1)), 3.26 (dd, Ha–C(4)), 3.02 (dd, Hb–C(4)), 2.63 (t, CH_2(5′)), 1.77 (quint, CH_2(2′)), 1.68 (quint, CH_2(4′)), 1.44 (quint, CH_2(3′)). J(1a, 1b) = 22.0, J(3, 4a) = 5.0, J(3, 4b) = 11.8, J(4a, 4b) = 14.8, J(1′, 2′) = 6.5, J(2′, 3′) = J(3′, 4′) = J (4′, 5′)=7.6 Hz.

^{13}C NMR (CD_3OD): 153.3, 143.7, 133.2, 133.0, 129.8, 129.7, 129.4, 129.3, 128.9, 128.0, 126.7, 75.8, 50.3, 36.7, 34.8, 32.4, 29.8, 29.6, 26.5.

HR-MS (ESI-Q-Tof) calcd for $C_{22}H_{26}N_2O$, $[M]^+$: 322.2045; found: 322.2041.

5.9. 1,2,3,4-Tetrahydronaphthalen-2-amine, hydrochloride (3a)

A mixture of β-tetralone **11** (1 mL, 10 mmol), Ti(O^iPr)$_4$ (5.85 mL, 20 mmol, 2 equiv) and saturated ammonia in EtOH (10 mL) was stirred under Ar at rt for 16 h. $NaBH_4$ (0.46 mg, 12 mmol, 1.2 equiv) was then added and the resulting mixture was stirred at rt for an additional 3 h. The solvents were evaporated, the residue diluted with AcOEt and treated with 1 N aq NH_4OH (20 mL). The inorganic precipitate was filtered off and washed with AcOEt (3× 20 mL). The organic layer was separated and the remaining aqueous layer was extracted with AcOEt (3× 20 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. HCl, 2.2 M, in dry Et_2O (5 mL) was added and the precipitated hydrochloride **3a** was filtered and recrystallised in ^{i}PrOH/Et_2O (0.75 g, 40%).

Colorless crystals, mp 230–2 °C (^{i}PrOH/Et_2O) (lit.[20] 236–8 °C).

IR (KBr), *v*: 3432, 3055, 2990, 2895, 1605, 1498, 1477, and 744 cm^{-1}.

Same ^{1}H NMR and ^{13}C NMR spectra (D_2O) as in lit.[21,22]

5.10. 2-Trifluoromethylsulfonyloxy-3-benzyloxycarbonylamino-3,4-dihydronaphthalene (12b) and *O*-benzyl 3-benzyloxycarbonylamino-3,4-dihydronaphthalene-2-carbohydroxamate (13b)

To a solution of LiHMDS (prepared from HMDS and BuLi, 0.57 mmol, 2.2 equiv) in dry THF (1 mL) was added dropwise a solution of **8b** (78 mg, 0.26 mmol) in THF (1 mL) and the mixture was stirred under Ar at −78 °C for 45 min, then $PhNTf_2$ (223 mg, 0.62 mmol, 2.4 equiv) in THF (1 mL) was added at −78 °C and the reaction mixture was stirred at 0 °C for 2.5 h. The reaction mixture was quenched with 2 M aq NH_4Cl, extracted with Et_2O and washed with brine. The organic solution was dried over $MgSO_4$ and the solvent was evaporated to give crude **12b** which was used without purification.

A solution of crude **12b** (0.26 mmol), Et_3N (220 μL, 1.58 mmol, 6 equiv), $BnONH_2 \cdot HCl$ (210 mg, 1.32 mmol, 5 equiv), $Pd(PPh_3)_4$ (22 mg) in DMF (5 mL) was purged with CO and stirred under CO (1 atm) at 60 °C for 4 h. The reaction mixture was diluted with Et_2O, quenched with 2 M aq NH_4Cl and washed with brine. The organic solution was dried over $MgSO_4$, the solvent was evaporated and the residue purified by FC (cyclohexane/AcOEt, 7/3) to give **13b** (90 mg, 80%).

Compound **12b**, only characterised by NMR: ^{1}H NMR ($CDCl_3$): 7.40–7.17 (m, 9Har); 6.64 (s, H–C(1)); 5.11 (s, OCH_2Ph); 5.01 (d, NH); 4.79 (m, H–C(3)); 3.33 (dd, Ha–C(4)); 3.13 (dd, Hb–C(4)). J(3, 4a) = 6.5, J(3, 4b) = 3.5, J(4a, 4b) = 16.6 Hz.

Compound **13b**: Colorless crystals, mp 150–2 °C (^{i}PrOH).

IR (KBr), *v*: 3304, 3196, 1689, 1655, 1626, 1541, 1257, 1047, 746, 736, and 697 cm^{-1}.

^1H NMR ($CDCl_3$): 10.75 (s, N*H*OBn); 7.71 (s, H–C(1)); 7.50–7.21 (m, 14Har); 5.27 (d, NH); 5.04–4.91 (m, 2 OCH_2Ph); 4.52 (m, H–C(3)); 3.20 (dd, Ha–C(4)); 2.93 (dd, Hb–C(4)). $J(3,NH) = 9.6$, $J(3,4a) = 5.9$, $J(3,4b) = 1.5$, $J(4a,4b) = 16.3$ Hz.

^{13}C NMR ($CDCl_3$): 164.3 (CON–C(2)); 156.9 (NCO_2); 135.8, 135.6, 132.2, 131.7, 130.0, 129.5, 129.2, 129.1, 128.9, 128.7, 128.6, 128.5, 128.4, 127.9 (14Car); 78.0 (NO*C*H_2Ph); 67.8 (O*C*H_2Ph); 43.3 (C(3)); 35.1 (C(4)).

Anal. Calcd for $C_{26}H_{24}N_2O_4$ (428.48): C, 72.88; H, 5.65; N, 6.54. Found: C, 72.6; H, 5.5; N, 6.3.

5.11. 2-Trifluoromethylsulfonyloxy-3-*tert*-butoxycarbonylamino-3,4-dihydronaphthalene (12a) and *N,O*-Dimethyl 3-*tert*-butoxycarbonyl-amino-3,4-dihydronaphthalene-2-carbohydroxamate (13a)

Same procedure as for **13b** with **8a** (50 mg, 0.19 mmol) to give crude **12a** which was used without purification.

Same procedure as for **13b** with crude **12a** (0.19 mmol), HCl · HN(OMe)Me (93 mg, 0.95 mmol), Et_3N (140 μL, 0.95 mmol) and $Pd(PPh_3)_4$ (22 mg, 10% mol) in DMF (5 mL). The reaction mixture was stirred under CO (1 atm) at 60 °C for 24 h. The reaction mixture was diluted with Et_2O, quenched with 2 M aq NH_4Cl and washed with brine. The organic solution was dried over $MgSO_4$ and the solvent was evaporated and the residue purified by FC (cyclohexane/AcOEt, 7/3) to give **13a** (40 mg, 68%).

Compound **12a**, only characterised by NMR: ^1H NMR ($CDCl_3$): 7.40–7.17 (m, 4Har); 6.62 (s, H–C(1)); 4.75 (m, NH, H–C(3)); 3.31 (dd, Ha–C(4)), 3.11 (d, Hb–C(4)); 1.26 (s, CMe_3). $J(3,4a) = 6.3$, $J(4a,4b) = 16.8$ Hz.

Compound **13a**: Colorless crystals, mp 70–4 °C (^{i}PrOH).

IR (KBr), *v*: 3282, 3266, 2981, 2972, 1700, 1696, 1642, 1531, 1364, 1164, 1049, 1018, and 764 cm^{-1}.

^1H NMR ($CDCl_3$): 7.25–7.20 (m, 4 Har); 6.97 (s, H–C(1)); 4.83 (m, NH, H–C(3)); 3.69 (s, OMe); 3.31 (s, NMe); 3.10 (m, 2H–C(4)).

^{13}C NMR ($CDCl_3$): 169.4 (CON–C(2)); 155.2 (NCO_2); 133.7, 133.5 (C(4a), C(8a)); 131.6 (C(2)); 131.5 (C(1)); 129.3, 129.0, 128.1, 127.3 (4Car); 79.7 (*C*Me_3); 61.4 (OMe); 45.1 (C(3)); 35.0 (NMe); 33.5 (C(4)); 28.5 (C*Me*$_3$).

Anal. Calcd for $C_{18}H_{24}N_2O_4$, 1/2H_2O: C, 63.32; H, 7.23; N, 8.21. Found: C, 63.3; H, 7.3; N, 8.3.

5.12. 3-Amino-1,2,3,4-tetrahydronaphthalene-2-carbohydroxamic acid (3c)

Compound **13b** (54 mg, 0.126 mmol) was hydrogenolysed in EtOH (3 mL) over 5% Pd–C (10 mg) at rt 8 h. Then Pd–C was centrifuged off and the solution was concentrated. The crude compound was recrystallised in ^{i}PrOH/Et_2O to give **3c** as (40/60) mixture of *cis* and *trans* isomers (22 mg, 71%).

Colorless crystals, mp 130–5 °C (dec) (^{i}PrOH/Et_2O).

IR (KBr), *v*: 3418, 3171, 3025, 2927, 1665, 1496, 1455, 1043, and 748 cm^{-1}.

^1H NMR (CD_3OD): 7.19–7.17 (m, 8Har); 3.96 (m, H–C(3), isomer 1); 3.82 (dt, $J = 5.2$, 10.6 Hz, H–C(3), isomer 2); 3.30–2.75 (m, 5H, isomer 1, 4H, isomer 2); 2.71 (dt, $J = 5.6$, 10.8 Hz, H–C(2), isomer 2).

^{13}C NMR (CD_3OD): 172.4, 171.0, 134.5, 133.9, 132.8, 131.6, 130.6, 130.2, 129.8, 129.4, 128.1, 128.0, 127.9, 127.8, 49.8, 48.8, 43.1, 38.8, 34.1, 34.1, 31.1, 28.7.

HR-MS (ESI-Q-Tof) calcd for $C_{11}H_{14}N_2O_2$, $[M]^+$: 206.1055; found: 206.1054.

5.13. *N,O*-Dimethyl 3-*tert*-butoxycarbonylamino-1,2,3,4-tetrahydronaphthalene-2-carbohydroxamate (14)

Amide **13a** (154 mg, 0.46 mmol) was hydrogenated in EtOH (3.5 mL) over PtO_2 (5 mg) at rt for 48 h. PtO_2 was centrifuged off and the solution was concentrated to give **14** as a 80/20 isomeric mixture (155 mg, quant.).

Colorless resin.

^1H NMR ($CDCl_3$): 7.14–7.07 (m, 4Har); 4.91 (d, $J = 8.0$ Hz, NH); 4.50 (m, H–C(3)); 3.73 (s, OMe); 3.30–3.28 (m, Ha–C(1), H–C(2)); 3.21 (s, NMe); 3.08 (m, 2H–C(4)); 2.84 (m, Hb–C(1)); 1.40 (s, ^{t}Bu).

^{13}C NMR ($CDCl_3$): 162.6 (CON–C(2)); 155.7 (NCO_2); 134.2, 133.2 (C(4a), C(8a)); 129.6, 129.1, 126.3, 126.3 (4Car); 79.4 (*C*Me_3); 61.6 (OMe); 45.9 (C(3)); 39.2 (C(2)); 35.2 (C(4)); 32.9 (NMe); 28.5 (C*Me*$_3$); 27.2 (C(1)).

HR-MS (ESI-Q-Tof) calcd for $C_{18}H_{26}N_2O_4$, $[M]^+$: 334.1849; found: 334.1853.

5.14. 3-*tert*-Butoxycarbonylamino-1,2,3,4-tetrahydronaphthalene-2-ethanone (15)

To a solution of amide **14** (0.46 mmol) in dry THF (4 mL) was added 3 M MeMgCl in THF (710 μL, 2.13 mmol) under Ar at 0 °C. The reaction mixture was stirred at rt for 4 h, diluted with Et_2O, quenched with 2 M aq NH_4Cl, washed with brine and dried over $MgSO_4$. The organic solution was concentrated and purified by FC (cyclohexane/ethyl acetate, 8/2) to give **15** as a 80/20 diastereoisomeric mixture (36 mg, 27%).

Colorless crystals, mp 130–6 °C (^{i}PrOH).

IR (KBr), *v*: 3447, 3345, 2975, 2930, 1713, 1686, 1502, 1367, 1344, 1253, 1167, 1060, and 760 cm^{-1}.

Major isomer. ^{1}H NMR ($CDCl_3$): 7.15–7.07 (m, 4Har); 4.83 (d, J = 8.5 Hz, NH); 4.61 (m, H–C(3)); 3.21–3.15 (m, Ha–C(1)), Ha–C(4)); 2.97–2.92 (m, Hb–C(1), Hb–C(4), H–C(2),); 2.31 (s, Me); 1.39 (s, ^{t}Bu).

^{13}C NMR ($CDCl_3$): 209.0 (C═O); 155.6 (NCO_2); 133.7, 132.9 (C(4a), C(8a)); 129.8, 129.3, 126.6, 126.5 (4Car); 79.8 (CMe$_3$); 50.3 (C(2)); 46.4 (C(3)); 35.7 (C(4)); 28.9 (Me); 28.4 (CMe_3); 26.6 (C(1)).

Minor isomer. ^{1}H NMR ($CDCl_3$): 7.15–7.07 (m, 4Har); 4.83 (d, J = 8.5 Hz, NH); 4.24 (m, H–C(3)); 3.12–3.04 (m, Ha–C(1), Ha–C(4)); 2.92–2.87 (m, Hb–C(1), H–C(2)); 2.73 (dd, J = 8.1, 16.4 Hz, Hb–C(4)); 2.26 (s, Me); 1.43 (s, ^{t}Bu).

^{13}C NMR ($CDCl_3$): 209.0 (C═O); 155.3 (NCO_2); 133.9, 133.6 (C(4a), C(8a)); 129.2, 128.6, 126.6, 126.5 (4Car); 79.8 (CMe$_3$); 53.5 (C(2)); 47.9 (C(3)); 35.0 (C(4)); 30.0 (C(1)); 28.4 (CMe_3); 28.1 (Me).

HR-MS (ESI-Q-Tof) calcd for $C_{17}H_{23}NO_3$, $[M]^+$: 289.1678; found: 289.1672.

5.15. 3-Amino-1,2,3,4-tetrahydronaphthalene-2-ethanone hydrochloride (3b)

A mixture of **15** (26 mg, 90 μmol) and concd HCl (75 μL, 900 μmol, 10 equiv) in EtOH (1.2 mL) and water (55 μL) was stirred at rt under Ar for 16 h. The solvent was evaporated and the solid recrystallised in ^{i}PrOH/Et_2O to give **3b** as a 5/95 mixture of *cis* and *trans* isomers (16 mg, 80%).

Colorless crystals, mp 198–200 °C (^{i}PrOH/Et_2O).

IR (KBr), *v*: 3435, 3220, 3165, 2977, 2935, 2897, 2846, 2823, 1703, 1593, 1490, 1398, 1175, and 747 cm^{-1}.

Major isomer. *trans*, ^{1}H NMR (CD_3OD): 7.19–7.16 (m, 4Har); 3.83 (dt, H–C(3)); 3.39 (dd, Ha–C(1)); 3.22 (dd, Ha–C(4)); 3.11 (dt, H–C(2)); 2.89 (dd, Hb–C(4)); 2.84 (dd, Hb–C(1)); 2.35 (s, Me). J(1a,1b) = 16.0, J(1a,2) = 5.4, J(1b,2) = 11.4, J(2,3) = 8.6, J(3,4a) = 5.6, J(3,4b) = 10.7, J(4a,4b) = 15.7 Hz.

^{13}C NMR (CD_3OD): 210.3 (C═O); 134.6, 133.1 (C(4a), C(8a)); 129.7, 129.5, 128.1, 127.9 (4Car); 51.6 (C(2)); 48.9 (C(3)); 33.8 (C(4)); 32.0 (C(1)); 28.6 (Me).

HR-MS (ESI-Q-Tof) calcd for $C_{12}H_{16}NO$, $[M]^+$: 189.1154; found: 189.1182.

5.16. Dimethyl 3-*tert*-butoxycarbonylamino-3,4-dihydronaphthalene-2-phosphonate (16)

A mixture of **12a** (0.38 mmol), $^{i}Pr_2EtN$ (210 μL, 2.29 mmol, 6 equiv), $HP(OMe)_2$ (175 μL, 1.91 mmol, 5 equiv), $Pd(OAc)_2$ (17 mg, 0.2 equiv) and dppf (85 mg, 0.4 equiv) in DMF (5 mL) was stirred under Ar at 100 °C for 24 h. The reaction mixture was diluted with Et_2O, quenched with 2 M aq NH_4Cl and washed with brine. The organic solution was dried over $MgSO_4$ and the solvent was evaporated and the residue purified by FC (cyclohexane/AcOEt, 3/7) to give **16** (82 mg, 61%).

Brownish oil.

IR (KBr), *v*: 3440, 2976, 2956, 1702, 1636, 1522, 1366, 1246, 1168, 1053, 1028, 829, 765, and 531 cm^{-1}.

^{1}H NMR ($CDCl_3$): 7.50 (d, J = 19.6 Hz, H–C(1)); 7.33–7.22 (m, 4Har); 4.70 (m, NH, H–C(3)); 3.79 (d, J = 10.1 Hz, OMe); 3.77 (d, J = 10.1 Hz, OMe); 3.06 (m, 2H–C(4)); 1.41 (s, ^{t}Bu).

^{31}P NMR ($CDCl_3$): 22.2.

^{13}C NMR ($CDCl_3$): 154.8 (NCO_2); 143.0 (d, J = 11 Hz, C(1)); 134.1 (C(4a)); 130.8 (d, J = 18 Hz, C(8a)); 130.5, 129.3, 128.7, 127.5 (4Car); 125.3 (d, J = 188 Hz, C(2)); 79.7 (CMe$_3$); 52.8, 52.8 (2OMe); 43.0 (d, J = 8.5 Hz, C(3)); 35.0 (d, J = 8.5 Hz, C(4)), 28.4 (CMe_3).

HR-MS (ESI-microTof) calcd for $C_{17}H_{24}NNaO_5P$, $[M]^+$: 376.1284; found: 376.1289.

5.17. Dimethyl 3-*tert*-butoxycarbonylamino-1,2,3,4-tetrahydronaphthalene-2-phosphonate (17)

The phosphonate **16** (80 mg, 0.22 mmol) was hydrogenated in MeOH (3.5 mL) over PtO_2 (5 mg) at rt for 48 h. PtO_2 was centrifuged off and the solution concentrated to give **17** as a 70/30 diastereoisomeric mixture (80 mg, quant.).

Colorless oil.

Major isomer. ^{1}H NMR ($CDCl_3$): 7.15–7.07 (m, 4Har); 5.15 (br s, NH); 4.12 (m, H–C(3)); 3.79 (d, J = 10.6 Hz, OMe); 3.74 (d, J = 10.6 Hz, OMe); 3.30 (br d, Ha–C(4)); 3.16–2.97 (m, 2H–C(1)); 2.74 (dd, J = 8.0, 16.1 Hz, Hb–C(4)); 2.41 (m, H–C(2)); 1.45 (s, CMe_3).

^{31}P NMR ($CDCl_3$): 33.2.

^{13}C NMR ($CDCl_3$): 155.1 (NCO_2); 134.0, 133.7 (d, J = 12 Hz, (C(4a), C(8a)); 129.2, 128.3, 126.5 (2) (4Car); 79.5 (CMe$_3$); 53.0 (d, J = 7 Hz), 52.8 (d, J = 7 Hz) (2 OMe)); 46.8 (C(3)); 36.6 (d, J = 143 Hz, C(2)); 35.9 (d, J = 10 Hz, C(4)); 28.3 ((C(1), CMe_3).

Minor isomer. ^{1}H NMR ($CDCl_3$): 7.15–7.07 (m, 4Har); 5.42 (br d, NH); 4.42 (m, H–C(3)); 3.76 (d, J = 10.6 Hz, OMe); 3.61 (d, J = 10.6 Hz, OMe); 3.16–2.97 (m, 2H–C(1), 2H–C(4)); 2.52 (ddt, J = 19.2, 2.8, 7.0 Hz, H–C(2); 1.44 (s, ^{t}Bu).

^{31}P NMR ($CDCl_3$): 33.7.

^{13}C NMR ($CDCl_3$): 155.1 (NCO_2); 133.5, 133.1 (d, J = 10 Hz, (C(4a), C(8a)); 130.0, 128.7, 126.4 (2) (4Car); 79.5 (CMe_3); 52.8 (d, J = 7 Hz), 52.6 (d, J = 7 Hz) (2 OMe); 45.2 (C(3)); 35.5 (d, J = 143 Hz, C(2)); 35.2 (d, J = 8 Hz, C(4)); 28.3 (CMe_3); 27.0 (C(1)).

HR-MS (ESI-microTof) calcd for $C_{17}H_{26}NNaO_5P$, $[M]^+$: 378.1441; found: 378.1442.

5.18. 3-Amino-1,2,3,4-tetrahydronaphthalene-2-phosphonic acid, hydrobromide (3d)

Compound **17** (45 mg, 0.12 mmol) was heated with an excess of 33% HBr in AcOH (2 mL) at 100 °C for 2 h. The mixture was evaporated to dryness and the solid recrystallised in ^{i}PrOH/Et_2O to give **3d** as a 70/30 isomeric mixture (26 mg, 70%).

Colorless crystals, mp 144–6 °C (^{i}PrOH/Et_2O).

IR (KBr), *v*: 3408, 3217, 3025, 2934, 1620, 1604, 1496, 1234, 1210, 1154, 985, 958, 948, 909, 753, and 525 cm^{-1}.

Major isomer. ^{1}H NMR (CD_3OD): 7.25–7.15 (m, 4Har); 4.03 (m, H–C(3)); 3.26–3.10 (m, 2H–C(1), 2H–C(4)); 2.59 (m, H–C(2)).

^{31}P NMR (CD_3OD): 26.3.

^{13}C NMR (CD_3OD): 134.1 (d, J = 10.6 Hz, C(8a)); 131.7 (C(4a)); 130.6, 130.2, 128.1, 127.8 (Car); 47.7 (d, J = 5.0 Hz, C(3)); 35.2 (d, J = 139.2 Hz, C(2)); 33.5 (d, J = 10.6 Hz, C(4)); 26.0 (C(1)).

Minor isomer. ^{1}H NMR (CD_3OD): 7.25–7.15 (m, 4Har); 3.77 (m, H–C(3)); 3.26–3.10 (m, 2H–C(1),Ha–C(4)); 2.95 (dd, J = Hb–C(4)); 2.31 (m, H–C(2)).

^{31}P NMR (CD_3OD): 25.7.

^{13}C NMR (CD_3OD): 134.9 (d, J = 11.3 Hz, C(1a)); 132.8 (C(8a)); 129.8, 129.4, 128.2, 127.8 (Car); 48.9 (C(3)); 37.3 (d, J = 140.6 Hz, C(2)); 34.3 (d, J = 13.6 Hz, C(4)); 29.0 (d, J = 3.5 Hz, C(1)).

HR-MS (ESI-Q-Tof) calcd for $C_{10}H_{14}NO_3P$, $[M]^+$: 227.0711; found: 227.0669.

5.19. Methyl 2-carboxyphenylacetate (18b)

$SOCl_2$ (1 mL, 13.8 mmol) was slowly added to a solution of homophthalic acid (10 g, 55.5 mmol) in dry methanol (100 mL) and the solution was stirred under Ar at rt for 6 h. The reaction mixture was poured in brine (30 mL), extracted with CH_2Cl_2 and the organic phase washed with water, dried over $MgSO_4$, and the solvent was evaporated to give **18b** (10.8 g, quant.).

Colorless crystals, mp 96–8 °C (lit.[33] 96–8 °C).

^{1}H NMR ($CDCl_3$): 8.15 (d, H–C(3)), 7.54 (t, H–C(5)), 7.41 (t, H–C(4)), 7.29 (d, H–C(6)), 4.06 (s, 2H–C(1)), 3.71 (s, OMe). $J(3,4)$ = 7.8, $J(3,5)$ = 1.2, $J(4,5)$ = 7.6, $J(4,6)$ = 1.4, $J(5,6)$ = 7.6 Hz.

5.20. Isochroman-3-one (4a) and methyl 2-hydroxymethylphenylacetate (19)

A solution of BH_3 1 M in THF (60 mL, 60 mmol) was slowly added to a solution of **18b** (10.8 g, 55.5 mmol) in dry THF (80 mL) at −15 °C and the mixture was stirred under Ar at −15 °C to rt for 16 h. The reaction mixture was diluted with Et_2O, washed successively with 1 N aq $NaHCO_3$ and brine and dried over $MgSO_4$. The solvent was evaporated to give a variable mixture of **19** and **4a** (10.1 g).

A solution of this crude mixture in toluene (20 mL) and *p*-TsOH (0.5 g, 2.5 mmol) was heated at 80 °C for 3 h. The reaction mixture was diluted with Et_2O, washed with brine and dried over $MgSO_4$. After evaporation **4a** was crystallised in toluene (5.36 g, 66%).

Compound **19**: Colorless resin, only characterised by ^{1}H NMR ($CDCl_3$): 7.41 (m, 1Har); 7.30 (m, 2Har); 7.24 (m, 1Har); 4.69 (s, 2H–C(2)); 3.78 (s, 2H–C(1)); 3.71 (s, OMe).

Compound **4a**: Colorless crystals, mp 82–4 °C (toluene) (lit.[52] 82–3 °C).

IR (KBr), *v*: 3020, 2990, 2893, 1749, 1486, 1458, 1406, 1392, 1252, 1225, 1187, 1148, 1037, 1028, 992, 959, 819, 777, 762, 743, 693, 551, and 458 cm^{-1}.

^{1}H NMR ($CDCl_3$): same data as in lit.[30]

5.21. 2-Bromomethylphenylacetic acid (20a)

Same procedure as in the literature.[30] A solution of **4a** (1 g, 6.7 mmol) in 33% HBr in acetic acid (9.1 mL) was stirred at rt for 2 h and then at 70 °C for 1 h. Dilution with cold water and filtration affords **20a** which was recrystallised in ^{i}Pr$_2$O (1.35 g, 88%).

Colorless crystals, mp 133–4 °C (^{i}Pr$_2$O); (lit.[29] 139–140 °C, lit.[51] 129–132 °C)).

IR (KBr), *v*: 2923, 2954, 2740, 2637, 1694, 1425, 1415, 1338, 1248, 1226, 936, 918, 769, 675, 618, and 601 cm^{-1}.

^{1}H NMR ($CDCl_3$): same data as in lit.[51]

5.22. Methyl 2-bromomethylphenylacetate (20b)

A solution of 2.1 N HCl in Et_2O (1 mL, 2.1 mmol) was slowly added to a solution of **20a** (1 g, 4.4 mmol) in MeOH (10 mL). The reaction mixture was stirred at rt for 12 h and the solvent evaporated to give the crude product as a 66/33 mixture of **20b** and the corresponding chloro-derivative (540 mg, quant.).

Only characterised by ^{1}H NMR ($CDCl_3$): 7.37–7.36 (m, 1Har); 7.30–7.20 (m, 3Har); 4.68 (s, CH_2Cl); 4.58 (s, CH_2Br); 3.81 (s, 2H–C(1)); 3.71 (s, OMe).

5.23. Isothiochroman-3-one (4b)

Thiourea (0.20 g, 2.61 mmol, 1.2 equiv) was added to a stirred solution of **20a** (500 mg, 2.18 mmol) in dry acetone (5.5 mL) under Ar at rt for 0.5 h. The precipitate of thiouronium salt was filtered and washed with dry acetone (0.544 g, 83%).

The crude thiouronium salt was hydrolysed in water (3 mL) and aqueous 1 N aq NaOH (2.5 mL) at 100 °C for 2 h. The solution was acidified with aqueous 1 N HCl (pH ~1) and extracted with CH_2Cl_2. The organic solution was dried over $MgSO_4$, and the solvent was evaporated to give crude thiol-acid **21.** Esterification of **21** with an excess of solution of diazomethane in THF gave the crude methyl ester after evaporation. To a solution of this crude methyl ester in dry toluene (20 mL) was slowly added a solution of 2 M $AlMe_3$ (1.1 mL, 2.18 mmol) in toluene. The reaction mixture was stirred under Ar at rt for 16 h, hydrolysed at 0 °C with aqueous 1 N HCl and extracted with AcOEt. The organic solution was washed with brine, dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified by sublimation (60 °C, 20 Torr) to give **4b** (165 mg, 46% from **20a**).

Compound **4b**: Colorless crystals, mp 102–4 °C (subl.) (lit.[29] 105–6 °C).

IR (KBr), *v*: 1662, 1652, 1051, 773, 744, and 644 cm^{-1}.

Same ^1H NMR and ^{13}C NMR spectra ($CDCl_3$) as in lit.[29,31]

Anal. Calcd for C_9H_8OS (164.23): C, 65.82; H, 4.91; S, 19.53. Found: C, 65.6; H, 5.1; S, 19.5.

HR-MS (FAB^+) calcd for C_9H_9OS, $[M+H]^+$: 165.0374; found: 165.0377.

Thiouronium salt, ^1H NMR (CD_3OD): 7.45 (m, 1Har); 7.32 (m, 3Har); 4.52 (s, 2H); 3.79 (s, 2H).

Compound **21**, only characterised by ^1H NMR ($CDCl_3$): 7.31–7.23 (m, 4Har); 3.82 (s, 2H); 3.79 (d, 2H); 1.72 (t, SH). $J(CH_2, SH)$ = 7.0 Hz.

5.24. 2-Hydroxy-1,4-dihydro-2*H*-isoquinolin-3-one (4c)

A solution of crude **20b** (400 mg, 1.64 mmol) in MeOH (15 mL) was stirred with Na_2CO_3 (523 mg, 4.93 mmol) and $NH_2OH \cdot HCl$ (138 mg, 1.97 mmol, 1.2 equiv) under Ar at 80 °C for 22 h. The hot solution was filtered and the filtrate concentrated, acidified with 1 N aq HCl (pH ~1), and extracted with CH_2Cl_2. The organic solution was dried over $MgSO_4$, and the solvent was evaporated. The crude product was purified by sublimation (140 °C, 20 Torr) to give **4c** (188 mg, 75%).

Colorless crystals, mp 198–200 °C (subl.).

IR (KBr), *v*: 3037, 2810, 1656, 1620, 1530, 1503, 1331, 755, and 745 cm^{-1}.

^1H NMR ($CDCl_3$): 7.29–7.26 (m, 2Har); 7.20–7.16 (m, 2Har); 4.88 (s, 2H–C(1)); 3.79 (s, 2H–C(4)).

^{13}C NMR ($CDCl_3$): 162.6 (C(3)); 129.9, 128.8 (C(4a), C(8a)); 128.1, 128.0, 127.2, 125.9 (4Car); 51.3 (C(1)); 34.6 (C(4)).

Anal. Calcd for C_9H_9NO: (163.17): C, 66.25; H, 5.56; N, 8.58. Found: C, 66.3; H, 5.7; N, 8.5.

HR-MS (FAB^+) calcd for $C_9H_{10}NO_2$, $[M+H]^+$: 164.0711; found: 164.0712.

5.25. 2-Amino-1,4-dihydro-2-isoquinolin-3-one (4d)

A solution of **20b** (215 mg, 0.87 mmol) in MeOH (5 mL) was stirred with Na_2CO_3 (376 mg, 3.55 mmol, 4 equiv) and $NH_2NH_2 \cdot 2HCl$ (102 mg, 0.98 mmol, 1.2 equiv) under Ar at 80 °C for 48 h. The hot solution was filtered and the filtrate concentrated, diluted with CH_2Cl_2 and washed with 1 N aq NaOH (0.9 mL), and brine. The organic solution was dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified by sublimation (100 °C, 20 Torr) to give **4 d** (100 mg, 70%).

Yellowish crystals, mp 115–7 °C (subl.) (lit.[32] 114–117 °C).

IR (KBr), *v*: 3305, 3200, 2894, 1652, 1632, 1609, 1493, and 739 cm^{-1}.

^1H NMR ($CDCl_3$): 7.25–7.17 (m, 4Har); 4.73 (s, 2H–C(1)); 4.59 (s, NH_2); 3.71 (s, 2H–C(4)).

^{13}C NMR ($CDCl_3$): 167.5 (C(3)); 131.2, 130.7 (C(4a), C(8a)); 127.7, 127.6, 126.9, 125.5 (4Car); 54.3 (C(1)); 36.3 (C(4)).

Anal. Calcd for $C_9H_{10}N_2O$ (162.19): C, 66.65; H, 6.21; N, 17.27. Found: C, 66.6; H, 5.7; N, 16.1.

HR-MS (FAB^+) calcd for $C_9H_{11}N_2O$, $[M+H]^+$: 163.0871; found: 163.0871.

5.26. Enzyme assays

Enzyme source: Bovine kidney LAPc and *A. proteolytica* aminopeptidase were purchased from Sigma Chemical Co. Porcine kidney AP-*N* was purified as a soluble form according to a published procedure.[54] Human recombinant LTA_4H was provided by our collaborator J. Z. Haeggström.

Typical assay conditions: Spectrophotometric assays were performed with L-leucine-*para*-notroanilide as a substrate for LAPc (K_m = 2 mM), AP-*N* (K_m = 0.2 mM), and APaero (K_m = 0.03 mM), alanine-*para*-nitroanilide was used for LTA_4H (K_m = 2 mM). All kinetic studies were performed at 30 °C and the reactions were started by the addition of enzyme in 1 mL assay medium: LAPc, 5 U in 10 mM Tris–HCl, 0.1 mM $ZnCl_2$, 5 mM $MnCl_2$, 1 M KCl, pH 8.0; APaero, 3 mU in 10 mM Tris–HCl, 0.05 mM $ZnCl_2$, pH 8.0; AP-*N*,

25 mU in10 mM Tris–HCl, pH 7.5, and LTA_4H, 5 μg in 10 mM Tris–HCl, 0.1 mM KCl, pH 7.5.

The release of *para*-nitroaniline ($\varepsilon = 10{,}800\ M^{-1}cm^{-1}$) at 405 nm was measured to determine initial velocities. K_i values were determined using a Dixon plot.[55]

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