Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 15 (2004) 2415–2420

Carbamoylphosphonate MMP inhibitors. Part 4: The influence of chirality and geometrical isomerism on the potency and selectivity of inhibition

Eli Breuer,[a,*] Yiffat Katz,[a] Rivka Hadar[b] and Reuven Reich[b,*]

[a]*The Department of Medicinal Chemistry, The School of Pharmacy, The Hebrew University of Jerusalem, PO Box 12065, Jerusalem, 91120 Israel*
[b]*The Department of Pharmacology, The School of Pharmacy, The Hebrew University of Jerusalem, PO Box 12065, Jerusalem, 91120 Israel*

Received 24 May 2004; accepted 2 July 2004

Abstract—Matrix metalloproteinases (MMPs) are a family of over twenty zinc-dependent enzymes that hydrolyze connective tissue and are involved in a variety of diseases, which are associated with undesired tissue breakdown. Previously we described the synthesis of a series of achiral alkyl and cycloalkylcarbamoylphosphonic acids and their biological evaluation. Herein we report the effect of chirality and geometrical isomerism on the potency and selectivity of inhibition. The inhibitory potencies of pairs of enantiomeric and stereoisomeric alkyl and cycloalkylcarbamoylphosphonic acids were evaluated on recombinant MMP-1, MMP-2, MMP-3, MMP-8, and MMP-9 enzymes. The results show that the enantiomers and stereoisomers studied differ considerably in their inhibitory potencies and selectivities on the enzyme subtypes studied. Such a result is consistent with the assumption that the carbamoylphosphonates interact with a chiral environment such as an enzyme.

1. Introduction

Matrix metalloproteinases (MMPs), are a family of structurally related zinc enzymes that mediate the breakdown of connective tissue and are therefore targets for therapeutic inhibitors in inflammatory, malignant, and degenerative diseases associated with excessive enzymatic activity.[1] Such conditions include cancer,[2] tumor metastasis,[3] arthritis,[4] and cardiovascular[5] diseases, as well as wound healing.[6] The Zn^{2+} ion present at the active sites of these enzymes is crucial for enzymatic activity, therefore virtually all attempts to develop inhibitors have involved so-called zinc-binding groups (ZBG). We reported recently that alkyl and cycloalkylcarbamoylphosphonates can act as MMP inhibitors, and that several of them show considerable potency and selectivity toward MMP-2, in vitro, as well as considerable activity in a cancer metastasis model in vivo.[7] We have also recently reported that carbamoylphosphonates form zinc complexes of considerable stability, and thus confirm that they are capable of serving as zinc-selective binding groups.[8] Following our previous results, we posed the question whether there is any stereoselectivity in the interaction between the carbamoylphosphonate inhibitors and the MMP enzymes. An affirmative answer to this question would confirm that the inhibitors indeed interact with a chiral environment, such as an enzyme, and not by another kind of mechanism, for example, by simple chelation of a cation crucial to the enzymatic catalysis. In our quest for an answer to this question, we synthesized pairs of enantiomeric and stereoisomeric alkyl and cycloalkylcarbamoylphosphonic acids, and evaluated their inhibitory potencies on five recombinant MMP enzyme subtypes.

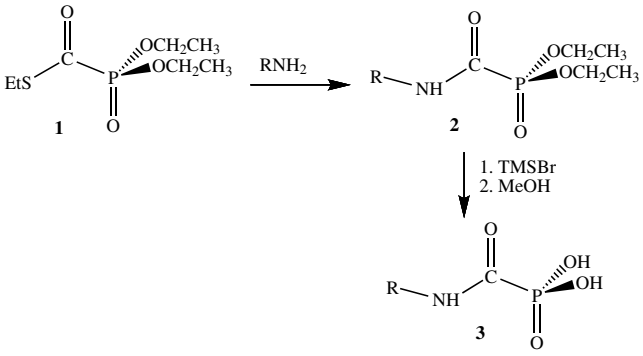
Herein we report the synthesis of two pairs of enantiomeric carbamoylphosphonates, as well as two pairs of geometrical isomers, and the results of studies of their effects on five different MMP subtypes. Our results show that the enantiomers and geometric isomers studied differ considerably in their inhibitory potencies and selectivities on the enzyme subtypes studied.

* Corresponding authors. Tel.: +972-2-6758704; fax: +972-2-6758934; e-mail: breuer@cc.huji.ac.il

0957-4166/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2004.07.002

2. Results and discussion

The *N*-alkylcarbamoylphosphonates were synthesized using the approach previously described, based on the reaction of triethyl phosphonothiolformate[9] **1** with commercially available amines, followed by bromotrimethylsilane mediated dealkylation to the corresponding *N*-(cyclo)alkylcarbamoylphosphonic acids **3** (Scheme 1).[7] The final products were isolated as crystalline free acids. The synthesis of *N*-(*S*)-(+)-2-butylcarbamoylphosphonic acid is given as a representative procedure. All other products were prepared using the same method.



Scheme 1.

The only exception was the case of 4-methylcyclohexylamine, which was available commercially as an (*E*) and (*Z*) mixture and was reacted with **1** as such. Separation of the reaction mixture yielded the pure (*E*) and (*Z*) products, **3i** and **3j**, as described in Experimental section. The structure of the higher melting product was determined by X-ray crystallography and found to be the *trans*-isomer, namely, *N*-(*E*)-(4-methylcyclohexyl)carbamoylphosphonic acid, **3i**.[10]

All carbamoylphosphonic acids, **3**, were characterized by elemental analysis and by their ^{1}H and ^{31}P NMR spectra, the results of which fully confirmed their structures and purity. The homochiral compounds were also characterized by their optical rotation.

Inhibition constants (IC_{50} values) of all compounds were determined on five recombinant MMP subtypes, namely MMP-1, MMP-2, MMP-3, MMP-8, and MMP-9.[11] The IC_{50} values obtained from the new compounds, and of some previously reported ones for comparison, are displayed in Table 1.

It is noteworthy that among the MMPs, gelatinases (MMP-2 and MMP-9) are especially important in connection with the processes of tumor growth, invasion, and metastasis.[12] Thus, gelatinase inhibitors have been studied extensively as new types of anticancer drugs. Furthermore, special attention has been paid to the discovery of MMP-2 (and/or MMP-9) inhibitors. Achieving highly selective inhibition of MMP-2, the enzyme involved and mainly responsible for the breaching of basement membranes, would especially be advantageous, as selectivity might help to evade the undesirable side effects as a result of nonspecific inhibition of other MMPs. Therefore, the selectivity of an inhibitor is an asset.

Herein, we examine two pairs of enantiomeric carbamoylphosphonates, one derived from optically active, commercially available (*R*)- and (*S*)-2-butylamines and the other from (*R*)- and (*S*)-1-cyclohexylethylamines.

Examination of the results in Table 1 revealed that the two optically active 2-butylcarbamoylphosphonic acids, **3b** and **3c**, differ greatly in their inhibitory potencies on the three enzymes, MMP-1, -2, and -8, and that they also differ from those of the racemate **3a**, in such a way that in each case, one enantiomer is more potent from the racemate while the other is less (inactive). Neither **3b** nor **3c** have any significant activity on MMP-3 and -9. The (*S*)-isomer, **3b**, was a selective and potent inhibitor of MMP-2, while the (*R*)-isomer, **3c**, was a selective and potent inhibitor of MMP-8. The latter (also known as neutrophile collagenase) is associated

Table 1. Inhibition constants of carbamoylphosphonates on different MMPs

Symbol	Structure of R in R–NHCOPO$_3$H$_2$	MMP-1 IC_{50} (μM)[a]	MMP-2 IC_{50} (μM)[a]	MMP-3 IC_{50} (μM)[a]	MMP-8 IC_{50} (μM)[a]	MMP-9 IC_{50} (μM)[a]
3a[b]	(*RS*)-2-Butyl–	40	30	80	5	>100
3b	(*S*)-2-Butyl–	25	0.8	100	20	>100
3c	(*R*)-2-Butyl–	80	>100	100	0.4	>100
3d[b]	2-Propyl–	50	5	>100	50	2
3e[b]	3-Pentyl–	80	30	>100	10	>100
3f	(*S*)-1-Cyclohexylethyl–	2	1	0.1	>100	10
3g	(*R*)-1-Cyclohexylethyl–	>100	0.2	>100	>100	>100
3h[b]	Cyclohexylmethyl	30	0.2	1	80	1
3i	(*E*)-4-Me-Cyclohexyl–	>100	4	>100	1	>100
3j	(*Z*)-4-Me-Cyclohexyl–	100	20	50	20	20
3k[b]	Cyclohexyl–	0.1	3	3	>100	>100
3l	*exo*-2-Norbornyl–	1	15	>100	>100	>100
3m	*endo*-2-Norbornyl–	>100	0.1	>100	>100	>100
3n[b]	Cyclopentyl–	0.5	0.080	>100	>100	>100

[a] Errors for these measurements are 5% of the mean values.
[b] Reported in Ref. 7.

with inflammatory conditions. Furthermore, the latter two compounds were distinctly superior to the two closely analogous and achiral 2-propyl and 3-pentylcarbamoylphosphonic acids, **3d** and **3e**, respectively. The structures of these compounds and their inhibition constants on MMP-2 and MMP-8 are shown in Figure 1.

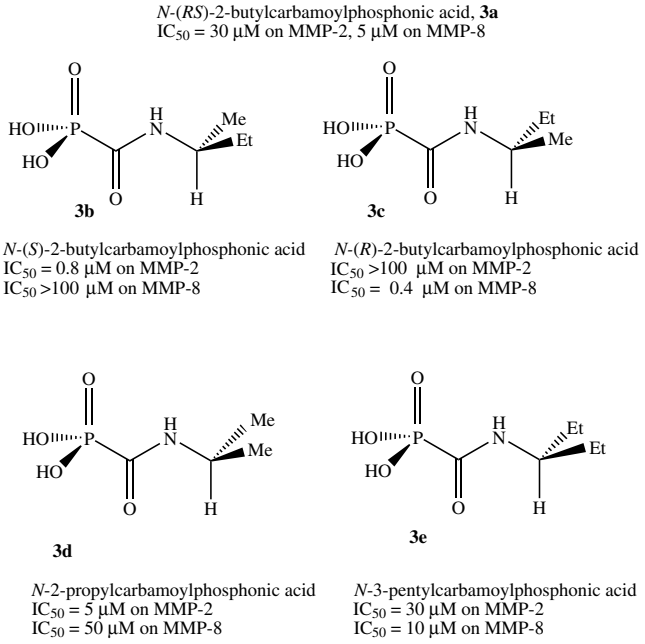


Figure 1.

A somewhat similar situation was seen in case of the enantiomeric 1-cyclohexylethylcarbamoylphosphonates **3f** and **3g**. While the (*S*)-enantiomer **3f** is a potent inhibitor of MMP-3 (an enzyme associated with mammary development and tumor progression), the (*R*)-enantiomer **3g** inhibited MMP-2 with high selectivity. Interestingly, the inhibition constant (IC_{50}) of **3g**, on MMP-2 is identical to that of the achiral analogue **3h**, which is lacking the methyl group. However homochiral **3g** was much better in its selectivity for MMP-2 relative to the other MMP subtypes examined. The structures of **3f**, **3g**, and **3h**, and their inhibition constants on MMP-2 and MMP-3 are shown in Figure 2.

In addition to the two pairs of enantiomers, we have also examined the effect of geometrical isomerism on the inhibitory characteristics of carbamoylphosphonates. Examination of the (*E*)- and (*Z*)-4-methylcyclohexylcarbamoylphosphonates (**3i** and **3j**, respectively), revealed that they differ in their inhibitory profiles. Both 4-methylcyclohexyl derivatives (Fig. 3) are less active than the parent cyclohexyl compound, **3k,** on all enzymes, except on MMP-8, which is inhibited only by **3i**.

Finally, examination of the two isomeric bicyclic derivatives the *exo*- and *endo*-2-norbornylcarbamoylphosphonates, **3l** and **3m**, respectively, revealed that, although the *exo*-derivative, **3l**, inhibits MMP-1 (the classical collagenase thought to be involved in chronic wound formation and healing as well as in arthritis) with an IC_{50} of 1 μM, the *endo*-compound, **3m**, is somewhat more interesting, as it is 150 times more potent on MMP-2 than the *exo*-phosphonate **3l**, coupled with impressive selectivity. As the norbornane system can be viewed both as a substituted cyclopentane or cyclohexane derivative, the comparison with these two can tell us the effect of substitution in cyclopentane (or cyclohexane) on the potency and selectivity. From this

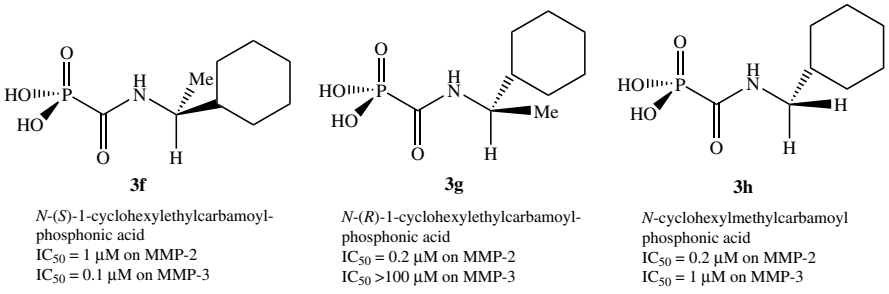


Figure 2.

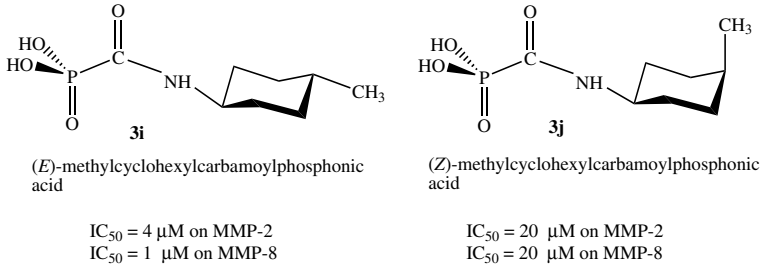
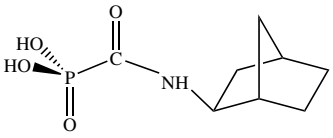
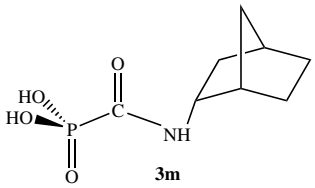


Figure 3.



3l

exo-2-Norbornylcarbamoylphosphonic acid
IC_{50} = 15 μM on MMP-2
IC_{50} = 1 μM on MMP-1



3m

endo-2-Norbornylcarbamoylphosphonic acid
IC_{50} = 0.1 μM on MMP-2
IC_{50} > 100 μM on MMP-1

Figure 4.

comparison we see that the potencies of bicyclic **3m** and monocyclic **3n** on MMP-2 are comparable, but the bicyclic **3m** is more selective than either of the monocyclic derivatives, **3n** or **3k**. Finally, it is important to emphasize that as both norbornane derivatives are racemic mixtures, it is quite likely that resolution of **3m** to the two enantiomers will yield one less potent and one more potent and probably highly selective MMP-2 inhibitor. The structures of **3l** and **3m** and their inhibition constants on MMP-1 and MMP-2 are shown in Figure 4.

3. Conclusion

Herein we have examined the effect of chirality and geometrical isomerism in some alkyl and cycloalkylcarbamoylphosphonic acids on the potency and selectivity of MMP inhibition. The inhibitory potencies of pairs of enantiomeric and diastereoisomeric alkyl and cycloalkylcarbamoylphosphonic acids were evaluated on recombinant MMP-1, MMP-2 MMP-3, MMP-8, and MMP-9 enzymes. The results show that pairs of enantiomers and diastereoisomers had in all cases different inhibitory potencies and different selectivity profiles on the enzymes studied. Such results are consistent with the assumption that the carbamoylphosphonates indeed interact with a chiral environment such as an enzyme. We are currently continuing our efforts to elucidate the mode of interaction of carbamoylphosphonates with MMPs.

4. Experimental section

4.1. Diethyl *N*-[(*S*)-2-butyl]carbamoylphosphonate, 2b (representative procedure)

A solution of triethyl phosphonothiolformate **1** (1.74 g, 7.7 mmol) and (*S*)-(+)-2-butylamine (0.77 mL, 7.61 mmol) in MeCN (15 mL) was kept at room temperature for 3 days. The volatiles were removed and the residue dried in high vacuum to yield 1.67 g colorless oil (92%), which was purified by column chromatography (AcOEt/PE, 8:2) to give 1.48 g, 82% of oil. NMR ($CDCl_3$) ^{31}P −0.88 ppm, ^{1}H, 0.88 (t, J = 7.5 Hz, 3H), 1.13 (d, J = 6.9 Hz, 3H), 1.32 (t, J = 7.2 Hz, 6H), 1.47 (quin, 2H, J = 7.2 Hz), 3.97 (m, 1H), 4.18 (m, 4H), 6.90 (br s 1H). Anal. Calcd for $C_9H_{20}NO_4P$: C, 45.49; H, 8.42; N, 5.89. Found: C, 45.23; H, 8.45; N, 5.75.

4.2. *N*-(*S*)-(+)-2-Butylcarbamoylphosphonic acid, 3b (representative procedure)

A solution of diethyl *N*-[(*S*)-2-butyl]carbamoylphosphonate, **2b**, obtained in the previous step (1.013 g, 4.27 mmol) and bromotrimethylsilane (TMSBr, 2.76 mL, 21.3 mmol) in MeCN (10 mL) was kept at room temperature overnight. The volatiles were evaporated and the residue taken up in MeOH (10 mL), which was evaporated to leave behind a white solid, which was recrystallized from EtOH to yield 0.48 g (62%) crystals mp 149–151 °C, $[\alpha]_D = +13.5$ (c 0.0185, MeOH). NMR (D_2O) ^{31}P −2.66 ppm, ^{1}H, 0.66 (t, J = 7.2 Hz, 3H), 0.95 (d, J = 6.6 Hz, 3H), 1.30 (m, 2H), 3.55 (m, 1H). Anal. Calcd for $C_5H_{12}NO_4P$: C, 33.15; H, 6.63; N, 7.73. Found: C, 33.21; H, 6.71; N, 7.38.

4.3. Diethyl *N*-[(*R*)-2-butyl]carbamoylphosphonate 2c

Oil (0.74 g, 91%). NMR ($CDCl_3$) ^{31}P −0.90 ppm, ^{1}H, 0.88 (t, J = 7.5 Hz, 3H), 1.15 (d, J = 6.9 Hz, 3H), 1.34 (t, J = 7.2 Hz, 6H), 1.49 (quin, 2H, J = 7.2 Hz), 3.98 (m, 1H), 4.18 (m, 4H), 6.88 (br s, 1H).

4.4. *N*-[(*R*)-(−)-2-Butyl]carbamoylphosphonic acid 3c

White solid 0.5 g (99%) mp 142–145 °C, $[\alpha]_D = -12.6$ (c 0.0193, MeOH). NMR (D_2O) ^{31}P −2.66 ppm, ^{1}H, 0.68 (t, J = 7.2 Hz, 3H), 0.97 (d, J = 6.6 Hz, 3H), 1.30 (m, 2H), 3.55 (m, 1H). Anal. Calcd for: $C_5H_{12}NO_4P$: C, 33.15; H, 6.63; N, 7.73. Found: C, 30.61; H, 6.42; N, 6.77.

4.5. Diethyl *N*-[(*S*)-(+)-1-cyclohexylethyl]carbamoylphosphonate 2f

Colorless oil (76%). NMR ($CDCl_3$) ^{31}P −0.78 ppm, ^{1}H, 0.80–1.80 (m's, 11H), 1.10 (t, J = 6.9 Hz, 3H), 1.34 (t, J = 7.2 Hz, 6H), 3.90 (m, 1H), 4.20 (m, 4H), 6.86 (br, 1H).

4.6. *N*-(*S*)-(−)-(1-Cyclohexylethyl)carbamoylphosphonic acid 3f

White solid (99%) mp 155–156 °C, $[\alpha]_D = -20.2$ (c 0.07, MeOH). NMR (D_2O) ^{31}P −2.62 ppm, ^{1}H, 0.60–1.56 (m's, 11H), 0.90 (t, J = 6.9 Hz, 3H), 3.52 (quin, J = 6.9 Hz, 1H). Anal. Calcd for $C_9H_{18}NO_4P$: C,

45.96; H, 7.66; N, 5.96. Found: C, 46.09; H, 7.66; N, 5.79.

4.7. Diethyl *N*-[(*R*)-1-cyclohexylethyl]carbamoylphosphonate 2g

Oil, NMR ($CDCl_3$) ^{31}P −0.78 ppm, ^{1}H, 0.80–1.80 (m's, 11H), 1.08 (d, $J = 6.9$ Hz, 3H), 1.32 (t, $J = 7.2$ Hz, 6H), 3.90 (m, 1H), 4.17 (m, 4H), 6.90 (br d).

4.8. *N*-[(*R*)-1-Cyclohexylethyl]carbamoylphosphonic acid 3g

Crystals from EtOH, mp 154–155 °C, $[\alpha]_D = +21.0$ (*c* 0.07, MeOH). NMR (D_2O) ^{31}P −2.60 ppm, ^{1}H, 0.60–1.56 (m's, 11H), 0.94 (d, $J = 6.9$ Hz, 3H), 3.56 (quin, $J = 6.9$ Hz, 1H). Anal. Calcd for $C_9H_{18}NO_4P$: C, 45.96; H, 7.66; N, 5.96. Found: C, 45.69; H, 7.55; N, 5.66.

4.9. Diethyl *N*-(*E*)-(4-methylcyclohexyl)carbamoylphosphonate 2i

A solution of triethyl phosphonothiolformate **1** (2.12 g, 9.38 mmol) and 4-methylcyclohexylamine (a mixture of *cis* and *trans*, 1.27 mL, 9.57 mmol) in MeCN (15 mL) was kept at room temperature overnight. Examination of the reaction mixture by ^{31}P NMR spectroscopy showed two peaks at −0.82 (*trans*) and −0.89 (*cis*) ppm. The volatiles were removed and the residue dried in high vacuum to yield a semi-solid residue, which was dissolved in hexane to yield white crystalline needles, 0.625 g (24%), mp 77–79 °C. NMR ($CDCl_3$) ^{31}P −0.82 ppm, ^{1}H, 0.89 (d, $J = 6.5$ Hz, 3H), 1.04 (dq, $J = 11.9$, 3 Hz, 2H), 1.12 (dq, $J = 11.9$, 3.5 Hz, 2H), 1.37 (dt, $J = 6.5$, 0.55 Hz, 6H), 1.73 (m, 3H), 1.95 (m, 2H), 3.80 (m, 1H), 4.29–4.15 (m, 4H), 6.85 (br d, 1H). Anal. Calcd for: $C_{12}H_{24}NO_4P$: C, 51.98; H, 8.66; N, 5.05. Found: C, 51.76; H, 8.53; N, 5.35.

4.10. Diethyl *N*-(*Z*)-(4-methylcyclohexyl)carbamoylphosphonate 2j

The hexane solution obtained after separation of the *trans*-isomer, described in the previous experiment, was evaporated to a semi-solid mass, which was shown by ^{1}H NMR to contain a minor proportion of the *trans*-ester and a different product. The mixture was separated on silica column (ether/petroleum ether) to give the *cis*-ester, the less polar component, followed by fractions containing a *cis*–*trans*-mixture and finally, the pure *trans*-product. The *cis*-ester was an oil, NMR ($CDCl_3$) ^{31}P −0.89 ppm.

4.11. *N*-(*E*)-(4-Methylcyclohexyl)carbamoylphosphonic acid 3i

Compound **3i** was made solid from EtOH by allowing it to evaporate slowly, mp 169–171 °C. NMR (D_2O) ^{31}P −2.61 ppm, ^{1}H, 0.60 (d, $J = 5.7$ Hz, 3H), 0.77 (m, 2H), 1.05 (m, 3H), 1.46 (d, $J = 12.9$ Hz), 1.57 (d, $J = 11.4$ Hz, 2H), 13.36 (m, 1H). Anal. Calcd for $C_8H_{16}NO_4P$: C, 43.44; H, 7.24; N, 6.33. Found: C, 43.04; H, 7.38; N, 5.97.

4.12. *N*-(*Z*)-4-(Methylcyclohexyl)carbamoylphosphonic acid 3j

Solid, mp 149–151 °C. NMR (D_2O) ^{31}P −2.63 ppm, ^{1}H, 0.73 (d, $J = 6$ Hz, 3H), 0.98–1.15 (m, 2H), 1.3–1.58 (m, 7H), 3.74 (broad, 1H). Anal. Calcd for $C_8H_{16}NO_4P$: C, 43.44; H, 7.24; N, 6.33. Found: C, 43.72; H, 7.52; N, 6.03.

4.13. Diethyl [*exo*-2-norbornyl]carbamoylphosphonate 2l

Oil, NMR ($CDCl_3$) ^{31}P −1.09 ppm, ^{1}H, 1.00–1.50 (m's), 1.75 (m, 1H), 2.18 (d, $J = 3.3$ Hz, 1H), 2.24 (s, 1H), 3.74 (m, 1H), 4.10–4.25 (m, 4H), 6.97 (br d (1H).

4.14. *N*-[*exo*-2-Norbornyl]carbamoylphosphonic acid 3l

Crystals from EtOH (1 g, 86%) mp 170–172 °C. NMR (D_2O) ^{31}P −2.79 ppm, ^{1}H, 0.85–1.05 (m's, 3H), 1.05–1.47 (m, 4H), 1.50–1.60 (m, 1H), 1.98 (d, $J = 3$ Hz, 1H), 2.07 (s, 1H), 3.41 (br d, 1H). Anal. Calcd for $C_8H_{14}NO_4P$: C, 43.83; H, 6.39; N, 6.39. Found: C, 43.87; H, 6.67; N, 6.22.

4.15. Diethyl *N*-[*endo*-2-norbornyl]carbamoylphosphonate 2m

Solid, mp 48–50 °C. NMR ($CDCl_3$) ^{31}P −1.13 ppm, ^{1}H, 0.82 (dt, $J = 13.5$, 4.5 Hz, 1H), 1.10–1.65 (m, 12H), 2.06 (tt, $J = 13.5$, 4.5 Hz, 1H), 2.22 (t, 1H), 2.45 (s, 1H), 4.10–4.25 (m, 5H), 7.05 (br d (1H, N*H*). Anal. Calcd for $C_{12}H_{22}NO_4P$: C, 52.28; H, 7.98; N, 5.08. Found: C, 52.01; H, 7.85; N, 5.32.

4.16. *N*-[*endo*-2-Norbornyl]carbamoylphosphonic acid 3m

A solid from EtOH (0.727 g, 73%) mp 164–165 °C. NMR (D_2O) ^{31}P −2.79 ppm, ^{1}H, 0.76 (dt, $J = 13.2$, 3.3 Hz, 1H), 1.0–1.4 (m's, 6H), 1.81 (m, 1H), 2.02 (s, 1H), 2.21 (s, 1H), 3.80 (br d, 1H). Anal. Calcd for $C_8H_{14}NO_4P$: C, 43.83; H, 6.39; N, 6.39. Found: C, 43.79; H, 6.18; N, 6.19.

4.17. Analysis of MMP activity: use of recombinant MMPs and relevant substrates

Commercial recombinants MMP-1, MMP-2, MMP-3, MMP-8, and MMP-9 (R&D Systems, Minneapolis, MN) were incubated at four different concentrations (1–50 ng) with their respective substrates for 3 h. Fluorogenic Peptide Substrate I (ES001, R&D Systems) was used for MMP1 and MMP-8. Fluorogenic Peptide Substrate II ES002, R&D Systems) was used for MMP-3. EnzChek gelatinase Assay Kit was used as the substrate for MMP-2 and MMP-9. The examined compounds were added at four to six different concentrations (0.1–100 μM) to the recombinant enzymes and the inhibitory potencies expressed in a colorimetric change, were measured by an ELISA reader. The inhibitory potency (IC_{50}) was calculated from the kinetic data obtained.

Acknowledgements

This work was supported in part by the Ministry of Science of Israel and by the Israel Science Foundation. E.B. and R.R. are affiliated with the Bloom center for Pharmacy, and with the Alex Grass Center for Drug Design and Delivery in the School of Pharmacy at The Hebrew University of Jerusalem.

References

1. For recent reviews, see: Whittaker, M.; Floyd, C. D.; Brown, P.; Gearing, A. J. H. *Chem. Rev.* **1999**, *99*, 2735–2776; Wojtowicz-Praga, S. *Drugs R&D* **1999**, *1*, 117–129; De, B.; Natchus, M. G.; Cheng, M.; Pikul, S.; Almstead, N. G.; Taiwo, Y. O.; Snider, C. E.; Chen, L.; Barnett, B.; Gu, F.; Dowty, M. *Ann. N.Y. Acad. Sci.* **1999**, *878*, 40–60; Johnson, L. L.; Dyer, R.; Hupe, D. J. *Curr. Opin. Chem. Biol.* **1998**, *2*, 466.
2. Hidalgo, M.; Eckhardt, S. G. *J. Nat. Cancer Inst.* **2001**, *93*, 178–193.
3. Kleiner, D. E.; Stetler-Stevenson, W. G. *Cancer Chemother. Pharmacol.* **1999**, *43*(Suppl.), S42–51.
4. Billinghurst, R. C.; Dahlberg, L.; Ionescu, M.; Reiner, A.; Tanzer, M.; Zukor, D.; Chen, J.; Van Wart, H.; Poole, A. R. *Arthritis Rheum.* **2000**, *43*, 673.
5. Ikeda, U.; Shimada, K. *Clin. Cardiol.* **2003**, *26*, 55–59.
6. Pilcher, B. K.; Wang, M.; Qin, X.-J.; Parks, W. C.; Senior, R. M.; Welgus, H. G. *Ann. N.Y. Acad. Sci.* **1999**, *878*, 12–24.
7. Breuer, E.; Salomon, C. J.; Katz, Y.; Chen, W.; Lu, S.; Röschenthaler, G.-V.; Hadar, R.; Reich, R. *J. Med. Chem.* **2004**, *47*, 2826–2832.
8. Farkas, E.; Katz, Y.; Bhusare, S.; Reich, R.; Röschenthaler, G.-V.; Königsmann, M.; Breuer, E. *J. Biol. Inorg. Chem.* **2004**, *9*, 307–315.
9. Salomon, C. J.; Breuer, E. *Synlett* **2000**, 815–816.
10. Cohen, S.; Katz, Y.; Reich, R.; Breuer, E. In preparation.
11. Baragi, V. M.; Shaw, B. J.; Renkiewicz, R. R.; Kuipers, P. J.; Welgus, H. G.; Mathrubutham, M.; Cohen, J. R.; Rao, S. K. *Matrix Biol.* **2000**, *19*, 267–273.
12. Overall, C.; Lopez-Otin, C. *Nature Rev. Cancer* **2002**, *9*, 657–672.