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Modelling relationship between angiotensin-(I)-converting enzyme inhibition and the bitter taste of peptides

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Abstract

Relationships between angiotensin-(I)-converting enzyme inhibition and the bitter taste of peptides were studied. In cases where ACE inhibition or bitter taste had not been experimentally determined, their activity was estimated using several different peptide quantitative structure–activity relationship (QSAR) models. Significant correlations between increased ACE inhibition and bitterness were found for dipeptides using both observed and QSAR-predicted values. The relationship between ACE inhibition and bitter taste was attributed to the importance of hydrophobicity for both properties. Limited structural variations for dipeptides could make it difficult to have features that limit the effect of C-terminal hydrophobicity, necessary for ACE inhibition, on bitter taste. A similar modelling approach was also done on data from observed bitter oligopeptides derived from milk proteins. The relationship between QSAR-predicted ACE inhibition and observed bitter taste was not as strong as that found for dipeptides. Larger structural variation possibilities for oligopeptides than for dipeptides may thus make it, more feasible to find a highly efficient ACE inhibitory oligopeptide with a negligible bitter taste than a dipeptide.

Keywords: ACE inhibition; Bitterness; Peptides; QSAR

1. Introduction

Proteolysis and formation of peptides in foods contribute to physical and sensory characteristics as well as being a source of energy and essential amino acids required for growth and maintenance of the body. Recent research has also emphasised that some peptides in foods may have health-related physiological activities connected with the cardiovascular, nervous, immune or nutritional systems (FitzGerald & Meisel, 2003; Silva & Malcata, 2005). Among such health-related effects, much interest has been focused on bioactive peptides that inhibit the angiotensin-(I)-converting enzyme (ACE) associated with the renin-angiotensin system, which regulates peripheral blood pressure. The enzyme can increase blood pressure by converting angiotensin I to the potent vasoconstrictor, angiotensin II, and catalyse the degradation of bradykinin and enkephalins. Inhibition of ACE may therefore exert an antihypertensive effect and potent synthetic inhibitors of ACE are used in the treatment of hypertension (Wyvratt & Patchet, 1985). Efficient ACE inhibitory peptides derived from food proteins may therefore be an alternative or supplement to pharmaceutical agents (Korhonen & Pihlanto, 2003). However, if foods should be enriched with such bioactive peptides, the taste aspect should be considered. Peptides with strong umami or bitter taste have been identified in protein hydrolysates and foods (Roudot-Algaron, 1996). If highly potent, ACE inhibitory peptides also have a strong unwanted taste, their use as neutraceuticals in functional foods could be limited by their taste. It is, therefore, highly relevant to study relationships between ACE inhibition and tastes of peptides.

A purely experimental approach to examine the relationship between health-related bioactivities such as ACE inhibition and bitter taste, would be to measure these two properties simultaneously on large sets of pure peptides.

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Peptide purification or synthesis and workloads with analysis of ACE inhibition and bitterness should be carefully considered, especially, if one takes into account the total number of possible active peptide structures derived from food proteins. An alternative and somewhat more theoretical approach, before large experimental screening studies of peptides are to be considered, could be to draw on the advantage of previously found relationships between peptide bioactivities (i.e., ACE-inhibition or bitter taste) and chemical structures (i.e., amino acid sequence). Quantitative structure–activity modelling (QSAR) is helpful in that respect. The principle behind QSAR modelling is that activities or properties, as a function of chemical structures, can be described by molecular or physicochemical descriptors, e.g., electronic attributes, hydrophobicity, and steric properties (Hansch & Leo, 1995). It has been demonstrated as a useful method for several activities and properties of peptides in foods (Pripp, Isaksson, Stepaniak, Sørhaug, & Ardö, 2005) and for evaluating food proteins as sources of bioactive peptides (Pripp, 2005). To explore possible relationships, QSAR models could predict an unmeasured bioactivity, e.g., ACE inhibition, and compared it with observed values for another bioactivity, e.g., bitter taste. This approach would be highly relevant for peptides, since considerable research about either bitterness or ACE inhibition has been reported, but the two properties have seldom been systematically compared.

The present objective was thus to use, in combination, experimental measurements and QSAR models for ACE inhibition and bitter taste of peptides to model relationships between these two bioactivities.

2. Materials and methods

2.1. Data sets and QSAR models for peptides with bitter taste or ACE inhibition

Two classical dataset on ACE inhibition (Table 1) or bitter taste (Table 2) of dipeptides, compiled by Cushman, Cheung, Sabo, and Ondetti (1981) and Asao, Iwamara, Akamatsu, and Fujita (1987), respectively, have been extensively used in development and verification of peptide QSAR methodology. They were, therefore, used in this study to model relationships between ACE inhibition and bitter taste of dipeptides. QSAR modelling, using amino acid descriptors has the advantage that it facilitates prediction of activity directly from the sequence (Pripp et al., 2005). The QSAR models used for prediction of ACE inhibition or bitter taste of dipeptides (Tables 1 and 2) were from the six studies (Collantes & Dunn, 1995; Hellberg, Sjöström, Skagerberg, & Wold, 1987; Jonsson, Eriksson, Hellberg, Sjöström, & Wold, 1989; Mei, Liao, Zhou, & Shengshi, 2005; Sandberg, Eriksson, Jonsson, Sjöström, & Wold, 1998; Zaliani & Gancia, 1999) on development of amino acid descriptors for QSAR modelling. The dipeptide datasets in Tables 1 and 2 were used in those six studies for experimental evaluation of derived amino acid descriptors for peptide QSAR modelling. A summary of development and characteristics of descriptors is provided in Table 3. Regression models for determination of bitterness or ACE inhibition using the amino acid descriptors were recalculated by partial least square (PLS) regression (Tables 4 and 5), using the Unscrambler software (Camo A/S, Oslo, Norway).

Observed bitter oligopeptides derived from casein was compiled by Roudot-Algaron (1996) (Table 6). ACE inhibition of these oligopeptides was predicted using the QSAR models (Table 4) on the C-terminal dipeptide region and with models from Pripp, Isaksson, Stepaniak, and Sørhaug (2004). Compiled bitter oligopeptides by Roudot-Algaron (1996) longer than six amino acids were excluded from

Table 1
Biological activity of angiotensin-(I)-converting enzyme (ACE) inhibitory dipeptides (data from Cushman et al., 1981)

Peptide	Obsd log $1/IC_{50}$	Peptide	Obsd log $1/IC_{50}$	Peptide	Obsd log $1/IC_{50}$
PG	1.77	FG	2.43	VP	3.38
DG	1.85	GR	2.49	KA	3.42
EA	2.00	HL	2.49	LA	3.51
EG	2.00	KG	2.49	AP	3.64
TG	2.00	GH	2.51	RF	3.64
GD	2.04	AG	2.60	GY	3.68
LG	2.06	GL	2.60	AF	3.72
SG	2.07	GA	2.70	RP	3.74
QG	2.13	YG	2.70	IP	3.89
GG	2.14	GM	2.85	AY	4.06
GQ	2.15	GI	2.92	VF	4.28
HG	2.20	IG	2.92	GW	4.52
WG	2.23	VG	2.96	VY	4.66
GT	2.24	IF	3.03	RW	4.80
GE	2.27	FR	3.04	AW	5.00
GK	2.27	GF	3.20	IY	5.43
MG	2.32	AA	3.21	IW	5.70
GV	2.34	RA	3.34	VW	5.80
DA	2.42	YA	3.34		
GS	2.42	GP	3.35		

Table 2
Biological activity of bitter tasting dipeptides expressed by their threshold value (T) (data from Asao et al., 1987)

Peptide	Obsd log $1/T$	Peptide	Obsd log $1/T$	Peptide	Obsd log $1/T$
GV	1.13	IA	1.68	II	2.26
AV	1.16	IG	1.68	IL	2.26
VA	1.16	AL	1.70	PI	2.33
VG	1.19	GI	1.70	LL	2.35
PA	1.32	VV	1.71	IP	2.40
GP	1.35	AF	1.72	YL	2.40
ID	1.37	LA	1.72	LY	2.46
IE	1.37	LG	1.72	FP	2.70
IN	1.49	FG	1.77	LF	2.75
IQ	1.49	GY	1.77	PF	2.80
IS	1.49	GF	1.80	FL	2.87
IT	1.49	PY	1.80	IW	3.05
SL	1.49	GW	1.89	FF	3.10
WE	1.56	VL	2.00	FY	3.13
IK	1.65	IV	2.05	LW	3.40
GL	1.68	PL	2.22	WW	3.60

Table 3
Summary of amino acid descriptors used for QSAR modelling

Amino acid descriptors developed by	Properties of amino acid descriptors used for QSAR modelling
Hellberg et al., 1987	They were derived using multivariate analysis of 29 physiochemical variables for the 20 coded amino acids and interpreted as being related to hydrophilicity (z_1), bulk (z_2) and electronic (z_3) properties.
Jonsson et al., 1989	They were derived using multivariate analysis of seven thin-layer chromatographic, three NMR and two theoretical variables for 55 amino acids and interpretation of z_1, z_2 and z_3 was similar as for descriptors by Hellberg et al. (1987).
Collantes and Dunn, 1995	Descriptors isotropic surface area (ISA) and the electronic charge index (ECI) were derived from calculation of side chain surface area and atomic charges of optimized three-dimensional amino acid structures. ISA was interpreted as an expression of size/hydrophobicity and ECI was interpreted as an expression of chain polarity.
Sandberg et al., 1998	They were derived using multivariate analysis of 26 physicochemical variables for 87 amino acids and interpreted as being related to hydrophilicity (z_1), steric bulk/polarizibility (z_2) and polarity (z_3). Descriptors z_4 and z_5 were found difficult to interpret in physiochemical terms and were more related to theoretical and NMR values.
Zaliani and Gancia, 1999	They were derived using multivariate analysis on 36 calculated steric and electrostatic variables of the 3D molecular structure in an extended side-chain conformation. Descriptors classified amino acids into different groups, but a clearly stated physicochemical interpretation of them was found difficult.
Mei et al., 2005	They were derived using multivariate analysis on 50 physicochemical variables for the 20 coded amino acids. Interpretation showed that descriptors v1 and v2 were related to hydrophobic properties, v3 and v4 to steric properties and v5–v8 to electronic properties.

Table 4
Prediction models from the 58 ACE inhibitory dipeptides (Table 1) with coefficients of amino acids in N-terminal (*aa*1) and C-terminal (*aa*2) position, number of PLS components, correlation coefficient (R^2) and with full-cross validation (Q^2), and reference to amino acid descriptors used

Regression model			PLS comp.	R^2	Q^2	Descriptors
	*aa*1	*aa*2				
$y = 3.28$	$-0.11z_{11} + 0.05z_{21} - 0.07z_{31}$	$-0.14z_{12} + 0.15z_{22} + 0.04z_{32}$	2	0.77	0.72	Hellberg et al., 1987
$y = 3.30$	$-0.12z_{11} + 0.05z_{21} - 0.05z_{31}$	$-0.16z_{12} + 0.17z_{22} + 0.06z_{32}$	2	0.76	0.71	Jonsson et al., 1989
$y = 1.39$	$+0.006\mathrm{ISA}_1 + 0.12\mathrm{ECI}_1$	$+0.01\mathrm{ISA}_2 + 0.52\mathrm{ECI}_2$	2	0.70	0.63	Collantes and Dunn, 1995
$y = 3.16$	$-0.11z_{11} + 0.03z_{21} - 0.08z_{31} + 0.02z_{41} + 0.01z_{51}$	$-0.14z_{12} + 0.14z_{22} + 0.05z_{32} + 0.08z_{42} - 0.03z_{52}$	2	0.80	0.75	Sandberg et al., 1998
$y = 2.90$	$-0.41x_{11} + 0.27x_{21} + 0.23x_{31}$	$+0.73x_{12} + 0.59x_{22} + 0.13x_{32}$	1	0.67	0.62	Zaliani and Gancia, 1999
$y = 3.21$	$-0.16v_{41} + 0.25v_{51}$	$0.45v_{12} + 0.35v_{22} + 018v_{62}$	1	0.77	0.73	Mei et al., 2005

Table 5
Prediction models from the 48 bitter dipeptides (Table 1) with coefficients of amino acids in N-terminal (*aa*1) and C-terminal (*aa*2) position, number of PLS components, correlation coefficient (R^2) and with full-cross validation (Q^2), and reference to amino acid descriptors used

Regression coefficients			PLS comp.	R^2	Q^2	Descriptors
	*aa*1	*aa*2				
$y = 1.64$	$-0.11z_{11} + 0.09z_{21} - 0.004z_{31}$	$-0.13z_{12} + 0.09z_{22} - 0.02z_{32}$	2	0.82	0.78	Hellberg et al., 1987
$y = 1.75$	$-0.11z_{11} + 0.10z_{21} - 0.01z_{31}$	$-0.12z_{12} + 0.09z_{22} + 0.02z_{32}$	2	0.81	0.76	Jonsson et al., 1989
$y = -0.05$	$+0.007\mathrm{ISA}_1 + 0.21\mathrm{ECI}_1$	$+0.009\mathrm{ISA}_2 + 0.10\mathrm{ECI}_2$	2	0.85	0.80	Collantes and Dunn, 1995
$y = 1.55$	$-0.13z_{11} + 0.08z_{21} - 0.02z_{31} + 0.005z_{41} - 0.02z_{51}$	$-0.14z_{12} + 0.05z_{22} + 0.01z_{32} + 0.07z_{42} - 0.02z_{52}$	3	0.90	0.87	Sandberg et al., 1998
$y = 1.62$	$+0.32x_{11} + 0.64x_{21} + 0.42x_{31}$	$+0.27x_{12} + 0.76x_{22} + 0.14x_{32}$	3	0.73	0.65	Zaliani and Gancia, 1999
$y = 1.46$	$0.37v11 + 0.22v_{21} + 0.07v_{51} + 0.03v_{81}$	$0.50v_{12} + 0.20v_{22} + 0.05v_{42} + 0.14v_{82}$	3	0.91	0.86	Mei et al., 2005

modelling, since the relationship between C-terminal dipeptide sequence and ACE inhibition for such large peptides have been reported to be poorer than those for shorter peptides (Pripp et al., 2004).

2.2. Modelling approach to examine relationship between ACE inhibition and bitter taste of peptides

The observed or QSAR model predicted ACE inhibition were compared to observed or QSAR-model predicted bitter taste. Relationship between the two bioactivities was expressed by the correlation coefficient. A spreadsheet with databases for amino acid descriptors was made in Microsoft Office Excel 2003 to predict activities using the QSAR models.

3. Results and discussion

3.1. ACE inhibition and bitter taste of dipeptides

The two dipeptide datasets (Tables 1 and 2) had 15 identical sequences where both bitter taste and ACE inhibition

Table 6
Biological activities of bitter tasting oligopeptides expressed by their threshold values (T) compiled from Roudot-Algaron (1996)

Peptide	Obsd log $1/T$	Peptide	Obsd log $1/T$
LGG	1.12	FFG	2.66
PGR	1.60	GGGGL	2.66
GGLG	1.60	PPP	2.70
GPG	1.70	RRPP	2.70
GTG	1.72	LVL	2.70
GLGG	1.72	FFPE	2.76
RGP	1.89	GGF	2.82
LGGG	1.89	GGT	2.82
GGGLG	1.89	GLL	2.82
GGLGG	1.89	RPF	2.82
GLGGG	1.89	FFPGG	2.82
LGGGG	1.89	GGFF	2.85
GGL	2.00	FGFG	2.90
GLG	2.00	FGGF	2.90
LEL	2.00	FFPG	2.90
GGP	2.02	FGF	2.92
PGP	2.02	LLL	2.92
PPG	2.02	GRP	3.10
GGVVV	2.10	RPG	3.10
LQL	2.19	TGT	3.10
LGL	2.30	GFF	3.22
LLG	2.30	TTG	3.22
FGG	2.35	LLLL	3.22
FPP	2.35	FPF	3.40
PGG	2.35	GTT	3.40
VVV	2.35	KPF	3.40
GGGL	2.35	PFP	3.40
PFPP	2.35	TPF	3.52
RRR	2.40	VTPF	3.52
GLT	2.52	FFF	3.70
FPK	2.52	TTT	3.70
GFG	2.52	GGFFGG	3.70
KPK	2.52	LPFDQL	3.82
VTP	2.52	LPFSQL	3.82
FFGG	2.52	RPFFGG	3.92
FFPP	2.52	GGRPFF	4.05
GPPF	2.52	RPFF	4.40
PGI	2.64	RRPFF	4.70
PPF	2.64	RRPPFF	5.15
YGG	2.64		

had been experimentally determined. It was therefore possible to study relationships for these dipeptides without using QSAR models (Fig. 1). A squared correlation coefficient of $R^2 = 0.57$ between increased ACE inhibition and bitter taste, indicating a possible general relationship, was found. The complete datasets contained 58 dipeptides measured for ACE inhibition and 48 dipeptides measured for bitter taste. Further direct comparison was hindered since most of these dipeptides were only measured for either ACE inhibition or bitter taste. However, peptide QSAR models (Tables 4 and 5) can predict unmeasured activities from the chemical structure. Models using different amino acid descriptors (Table 3) gave a significant relationship between observed and predicted values (Tables 4 and 5). The predicted values for both ACE inhibition and bitter taste were slightly different, in the prediction models obtained in this study using descriptors developed by Zaliani and Gancia (1999), from those reported in the original

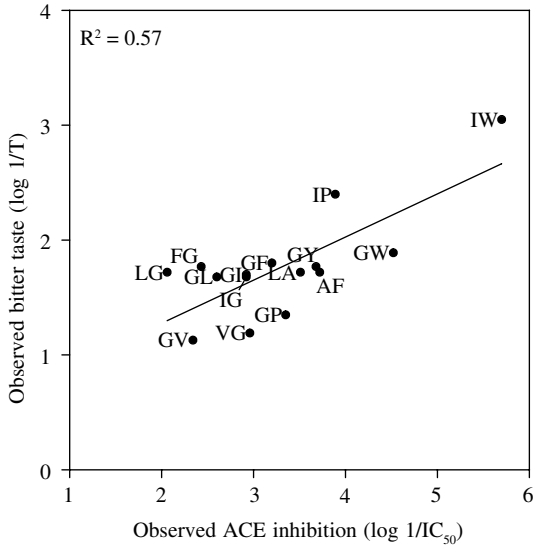

Fig. 1. Relationship between observed ACE inhibition and bitter taste for dipeptide structures in Tables 1 and 2 where both properties have been determined experimentally.

study. It is likely that some different conditions, during PLS regression, were applied in the original study. Observed measurements of ACE inhibitory dipeptides (Table 1) were plotted against their QSAR model-predicted values for bitter taste, and observed measurement for bitter dipeptides (Table 2) were plotted against their QSAR model-predicted values for ACE inhibition (Fig. 2). Significant correlations between increased ACE inhibition and stronger bitter taste (lower threshold values for bitterness) of dipeptides were found using all six different sets of amino acid descriptors in QSAR predictions. To find whether dipeptide sequences not in the dataset may have a preferable efficient ACE inhibition coupled with low bitterness, QSAR model-predicted ACE inhibition were compared with predicted bitter taste for all 400 theoretically possible dipeptides composed of the 20 coded amino acids. Significant relationships between increased ACE inhibition and stronger bitter taste for all 400 dipeptides were found using the QSAR prediction models (Fig. 3). The prediction models, based on amino acid descriptors from Zaliani and Gancia (1999), gave the poorest relationship between the bioactivities while the models using descriptors from Collantes and Dunn (1995) gave the strongest relationship. As also stated in the original publication of Zaliani and Gancia (1999), their approach for deriving the amino acid descriptors had the drawback that it was impossible to obtain a physical interpretation of a QSAR model. A straightforward or "visualized" physicochemical interpretation of their descriptors was not possible. The other QSAR models had descriptors that were, to a larger extent, related to common physicochemical characteristics such as hydrophobicity, size and polarity. It might be that modelling, using descriptors from Zaliani and Gancia (1999) emphasised other amino acid properties than the common physicochemical ones and that this could be a reason for

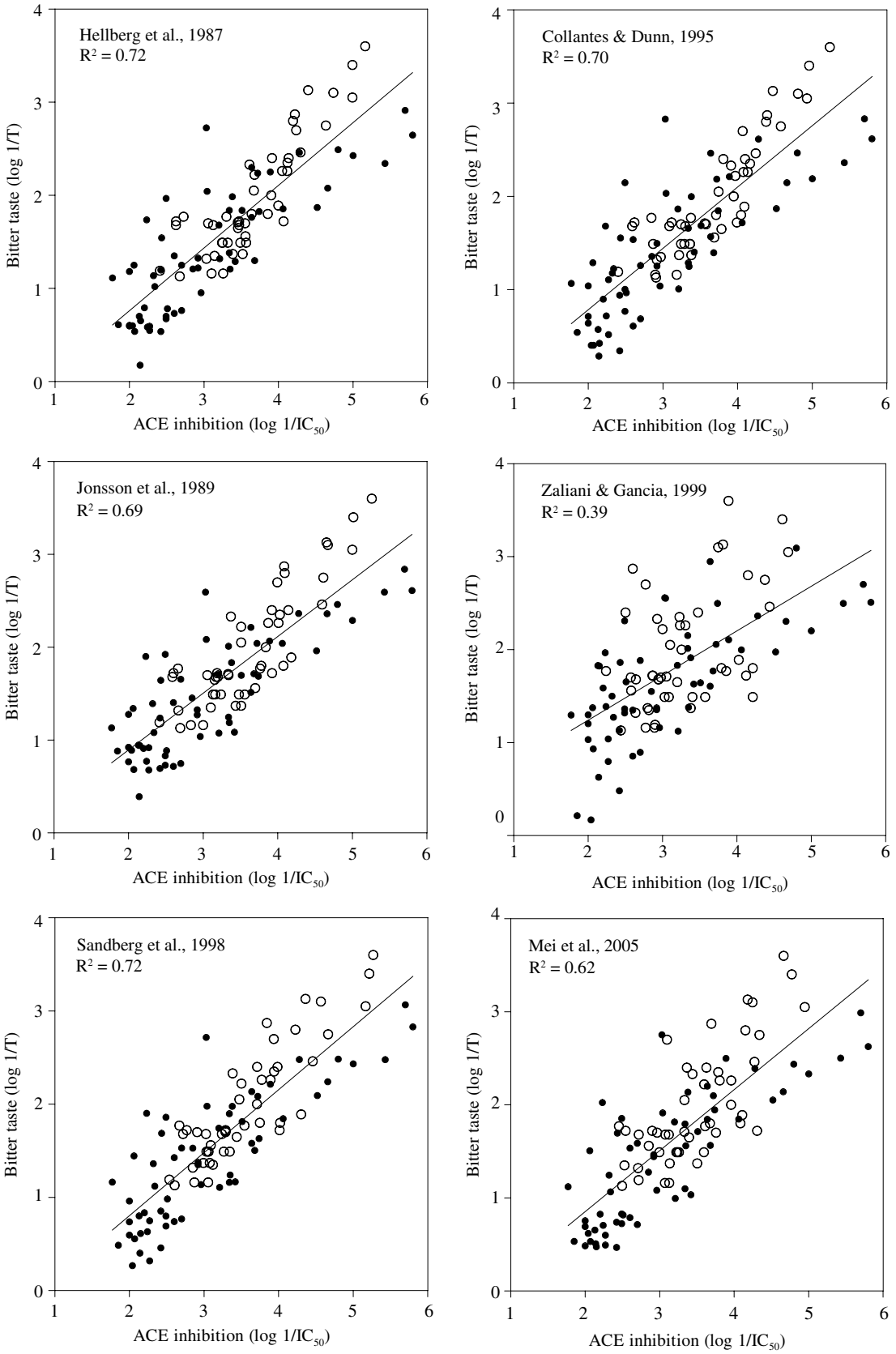

Fig. 2. Combined relationship between observed ACE inhibition and QSAR-predicted bitter taste for dipeptides in Table 1 (●) and between QSAR-predicted ACE inhibition and observed bitter taste for dipeptides in Table 2 (○) with reference to QSAR models are used from Tables 4 and 5.

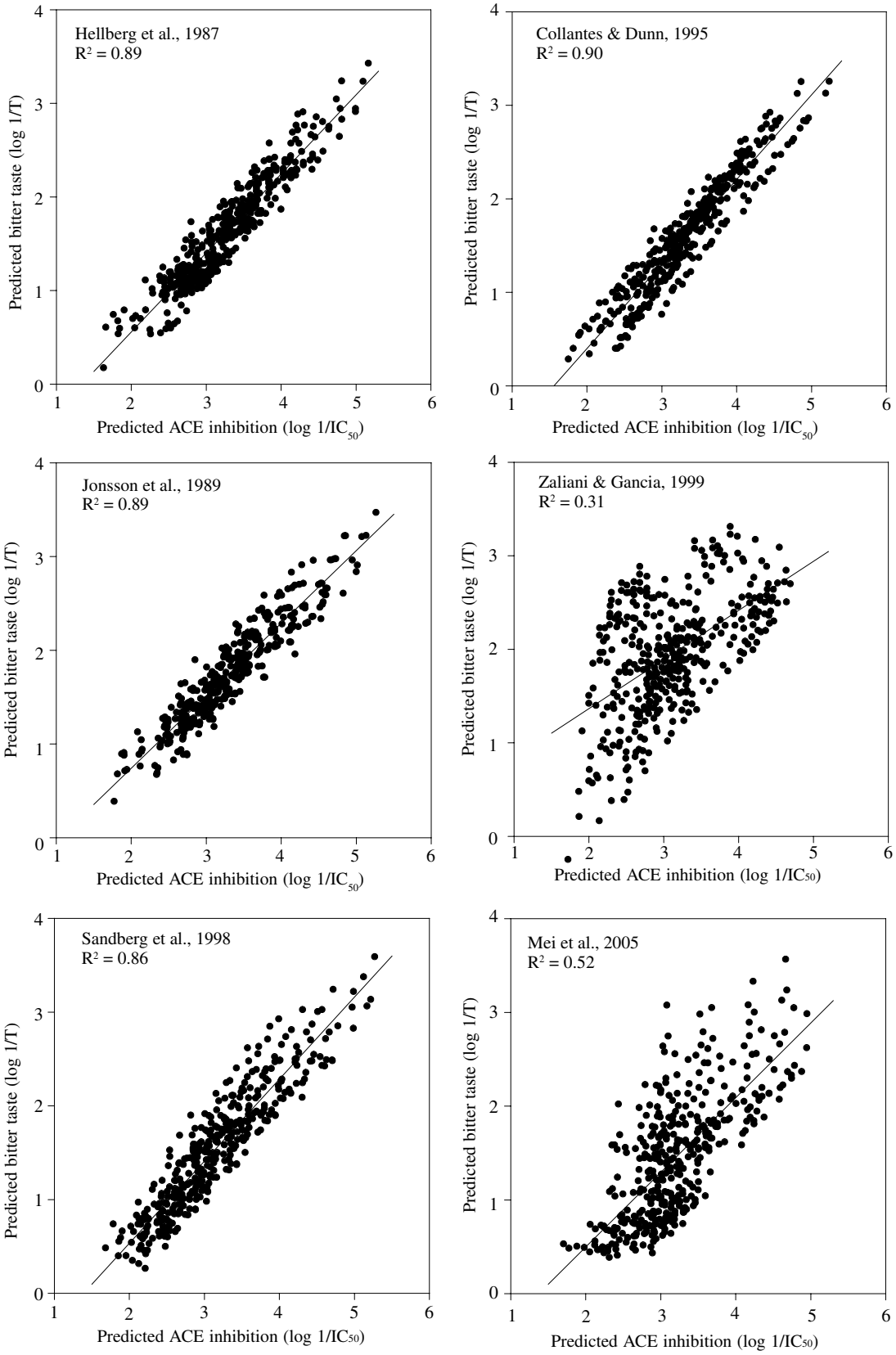

Fig. 3. Relationship between QSAR-predicted ACE inhibition and bitter taste for all 400 theoretically possible dipeptide sequences using the 20 common amino acids with reference to QSAR models are used from Tables 4 and 5.

the poorer relationship between ACE and bitterness. Such findings reflect the complexity between molecular structure and biological or functional properties.

Use of both observed and QSAR-predicted values gave a significant relationship between efficient ACE inhibition and strong bitter taste, i.e., low threshold, for dipeptides. This is a result with applied relevance, since it strongly indicates that using ACE inhibitory dipeptides derived from food proteins as neutraceuticals in functional foods, with claimed blood pressure-reducing effect, may also give it a bitter taste. Structural studies into the mechanism of ACE inhibition of dipeptides have shown that aromatic side chains and proline are favoured in C-terminal positions and branched aliphatic side amino acids are preferred in N-terminal positions. Both positions have hydrophobic interaction with ACE (Cheung, Wang, Ondetti, Sabo, & Cushman, 1980). The importance of hydrophobic residues for efficient ACE inhibition of dipeptides has also been confirmed by QSAR modelling on the specific dipeptides in Table 1 (Collantes & Dunn, 1995; Hellberg et al., 1987; Jonsson et al., 1989; Mei et al., 2005; Sandberg et al., 1998; Zaliani & Gancia, 1999). Structure–activity studies of bitter peptides have also related hydrophobicity directly to bitterness (Ney, 1971, 1979). Specific QSAR modellings of bitter dipeptides in Table 2 have also identified hydrophobicity and size as main factors affecting the bitter taste (Asao et al., 1987; Collantes & Dunn, 1995; de Armas, Diaz, Molina, González, & Uriarte, 2004; Hellberg et al., 1991; Jonsson et al., 1989; Liu, Yin, Cai, & Li, 2001; Opris & Diudea, 2001). There seems thus to be, on a molecular structural level, a strong relationship between bitter taste and ACE inhibition of dipeptides. Based on modelling results (Figs. 1–3) and structural–activity studies on bitterness or ACE inhibition of dipeptides, a derived hypothesis is that limited structural variation possibilities for dipeptides make it difficult to obtain a sequence with strong hydrophobicity needed for efficient ACE inhibition combined with other structural properties, e.g., size or electrostatic, to counteract the effect of hydrophobicity on bitterness.

3.2. Predicted ACE inhibition of observed bitter oligopeptides

Since other structural properties seem to be needed to counteract the effect of hydrophobicity of ACE inhibitory peptides on bitterness, oligopeptides might be better candidates with efficient ACE inhibition and low bitterness. Studies on the ACE inhibition mechanism have emphasis the C-terminal region as important for inhibition activity (Cheung et al., 1980; Ondetti & Cushman, 1982; Pripp et al., 2004). The QSAR models used to predict ACE inhibition of dipeptides and models reported by Pripp et al. (2004) were therefore applied to the C-terminal dipeptide sequence of a compiled dataset of observed bitter oligopeptides (Table 5) to predict their ACE inhibition. Plots representing relationships between observed bitterness and predicted ACE inhibition, using different QSAR models, are shown in Fig. 4. The relationship between predicted ACE inhibition and observed bitter taste is not as prominent as that found for dipeptides. Some of the oligopeptides with observed low bitterness also had a high QSAR-predicted ACE inhibition. This may indicate that it is more likely to find oligopeptides with efficient ACE inhibition that are not very bitter.

Extensive research in Japan, involving synthesis of hundreds of peptides to establish a structure-bitterness relationship (for recent review of this work see Raksakulthai & Haard, 2003), also found that the impact of bitterness of hydrophobic amino acids in the C-terminal position depends on adjacent residues and total length along the peptide backbone. Hydrophobic amino acids located at the C-terminal and, conversely, basic amino acids located at the N-terminal have been found to strengthen the bitterness in di- and tripeptides. Strong bitter taste was also observed in peptides where arginine was contiguous to proline residues (Otagiri, Nosho, Shinoda, Fukui, & Okai, 1985). A mechanism was proposed for how peptides bind to bitterness receptors. Bitter peptides have two active sites – a ''binding unit'' with hydrophobic groups and a ''stimulating unit'' with hydrophobic or basic groups (Ishibashi, Kouge, Shinoda, Kanehisa, & Okai, 1988). Shinoda, Fushima, Kato, Okai, and Fukui (1985) also found intense bitterness to be associated with peptides having at least two hydrophobic amino acids in the C-terminal position (Shinoda et al., 1985). Interestingly, introducing the Gly–Gly sequence after N-terminal position of some of the peptides reduced their bitter taste. It was suggested that the Gly–Gly sequence in the N-terminal position, prior to potentially bitter peptide sequences, might prevent the hydrophobic group from binding to taste receptors (Shinoda et al., 1987). Whether it would also influence the ACE inhibition of peptides needs to be further experimentally investigated. Even though the C-terminal hydrophobicity of peptides is related to both bitterness and ACE inhibition, the found effect of peptide size and properties of the ''stimulating unit'' in bitter peptides, provide a structural basis for finding potent ACE inhibitory oligopeptides with low bitterness.

The complexity of bitterness of oligopeptides has made it very difficult to develop suitable QSAR models for this property. We therefore based our approach only on predicting ACE inhibition of observed bitter oligopeptides and not the other way around. This prevents us from obtaining reliable estimations of bitterness of potent ACE inhibitory peptides, e.g., VPP and IPP. Improvement of QSAR modelling for bitterness and/or ACE inhibition of tri- and oligopeptides is an area of ongoing investigation.

3.3. Perspectives for finding potent ACE inhibitory peptides with low bitterness

Oligopeptides provide greater structural variation than dipeptides. Thus, it should be more possible to find oligo-

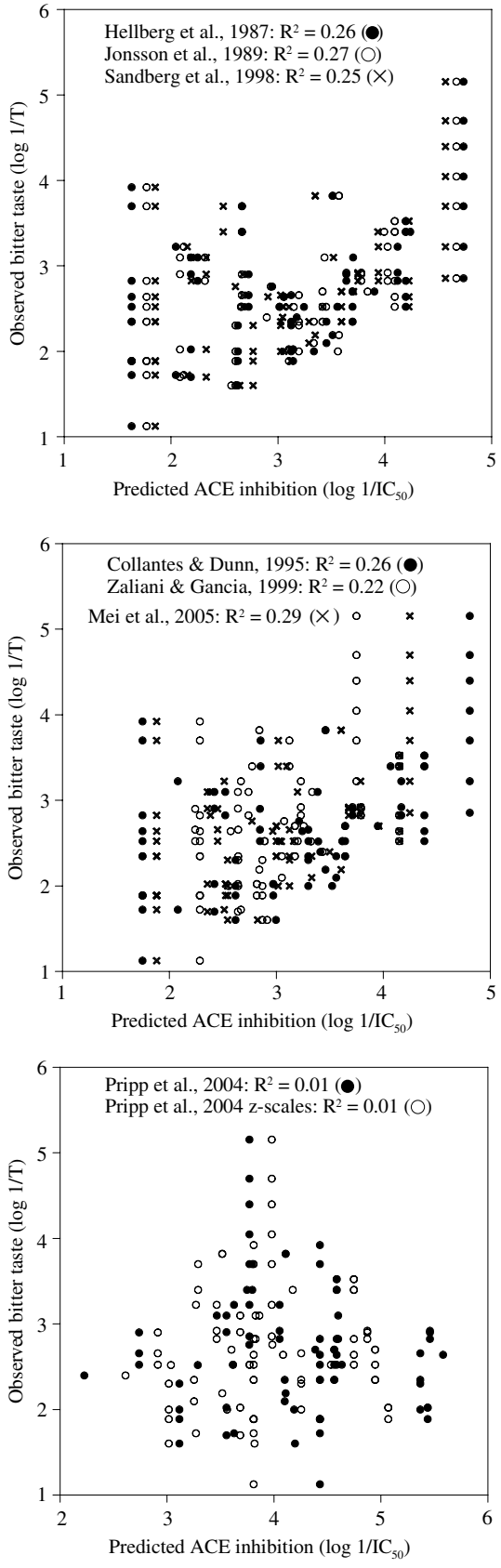

Fig. 4. Relationship between QSAR-predicted ACE inhibition and observed bitter taste for compiled oligopeptides in Table 6 with reference to QSAR models are used from Tables 4 and 5.

peptide structures than dipeptides with potent ACE inhibition (largely related to molecular structure of the C-terminal region), but with size and steric properties adjacent to the C-terminal region that reduce bitterness perception. However, a limitation of ACE inhibitory oligopeptides as neutraceuticals might be their bioavailability, since small peptides are more efficiently absorbed from the intestine and into the bloodstream (Yang, Dantzig, & Pidgeon, 1999) and possibly undergo degradation during gastrointestinal proteolysis. Modelling the relationship between ACE inhibition and bitter taste using QSAR prediction models is a valuable approach. An important contribution of the modelling is that it provides a tool for identifying promising peptide structures with potent health-related properties and desirable taste characteristics that can be further evaluated experimentally. The recent development of extensive databases as e.g., that on bioactive peptides in foods (Dziuba, Minkiewicz, Nalęcz, & Iwaniak, 1999; Iwaniak, Dziuba, & Niklewicz, 2005) provides a further valuable tool for finding such sequences. Thus, structural properties other than those related to the C-terminal region of oligopeptides seem to be important for finding ACE inhibitory peptides with suitable taste characteristics. Improved understanding and development of QSAR models for ACE inhibition and bitter taste of oligopeptides is therefore an important research area.

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