

Supporting Information

Side chain cyclized aromatic amino acids: great tools as local constraints in peptide and peptidomimetic design

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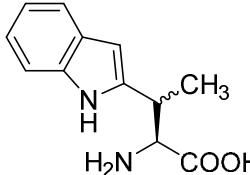
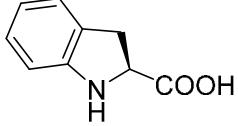
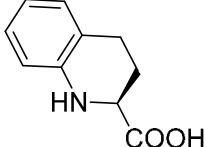
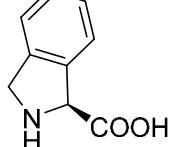
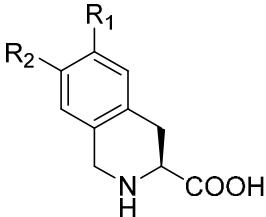
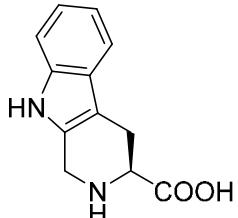
[§] O.V.d.P and A.K contributed equally to this work.

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Table S1: Structures, names and used abbreviations of the constrained amino acids discussed in this review, with representative references for their synthesis and applications

Structure	Name	Abbreviation	Representative synthesis: reference	Use and references	Commercial availability
	(2 <i>S</i> ,3 <i>R</i>)-2-(1-indanyl)glycine	Ing ¹	¹	Substance P ¹ Arginine vasopressin ²	yes
	2-(9-fluorenyl)glycine	Flg ¹	¹	Substance P ¹	yes
	2,3-methanophenylalanine	VPhe ³ c ₃ Phe ⁴	⁴	Substance P ⁵ Enkephalin ⁶ Carboxypeptidase inhibitor ⁷ Aspartame ⁸	yes
	α,β-dehydrophenylalanine	Δ ^Z Phe ¹	^{9,10}	Substance P ¹ Enkephalin ¹¹ Reviews ^{9,12}	yes
	R = H 3-prolinophenylalanine <i>trans</i> -3-phenylproline	P ^c ₃ Phe ¹³	^{14,15}	Melanocortin ¹⁵	yes
	R = OH 3-prolinotyrosine <i>trans</i> -3-(4'-hydroxy phenyl)proline	t-Hpp ¹⁶	¹⁶	Opioid ¹⁶	no
	β-methylphenylalanine	β-MePhe	Reviews _{1,6,17}	Reviews ^{17,18} Melanocortin, Opioids, CCK, Oxytocin, Glucagon, Opioid ¹⁹	yes

				Somatostatin ²⁰	
	β-methyltryptophan	β-MeTrp	^{17,18}	Reviews ^{17,18} , Melanocortin ¹⁸ Somatostatin ^{20,21,22}	no
	indoline-2-carboxylic acid	loc ²³	²⁴	FT-inhibitors ²⁵ ACE-inhibitors ²⁶ ACE/NEP inhibitors ²⁷ Melanocortin ²³	yes
	1,2,3,4-tetrahydroisoquinoline-2-carboxylic acid	-	^{24,28}	ACE inhibitor ²⁶	yes
	isoindoline-1-carboxylic acid	-	²⁶	ACE inhibitor ²⁶	yes
	R ₁ = R ₂ = H: 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid	Tic	Review ²⁹	Review ³⁰ FT inhibitors ^{25,31} ACE inhibitor ²⁶ ACE/NEP inhibitors ^{27,32} Bradykinin ^{33,34} AngIV ³⁵ Substance P ^{1,36,37} Melanocortin ²³ Opioids ^{10,29,38,39,40,41,} ^{42,43,44} Syk kinase ligand ⁴⁵	yes
	R ₁ = OH, R ₂ = H:	6-HO-Tic,* 6-Htc ³⁸	Review ²⁹ ^{,38}	Opioid ³⁸ AngIV ³⁵	yes
	R ₁ = H, R ₂ = O H	7-HO-Tic,* Htc ⁴⁶	Review ²⁹ ^{,46,47}	Hen egg lysozyme[52-61] ⁴⁸ AngIV ³⁵	yes
	1,2,3,4-tetrahydrocarboline-3-carboxylic acid	Tcc ⁴⁹ Tpi ^{50,51} Tca ¹⁸	^{29,49}	ACE inhibitor ²⁶ NK1 ^{36,37} Nociceptin ⁵² Bombesin ⁵¹ Neurotensin ⁵³	yes

	6-carboxy-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine	-	54,55	ACE inhibitors ²⁶ FT inhibitors ⁵⁵ Metalloproteinase inhibitors ⁵⁴	yes
	6-carboxy-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine, spinacine	Spi ⁵⁶	Review ²⁹	Opioid ⁵⁶ AngIV ⁵⁷	yes
	1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid	Tiq	26	Urotensin ⁵⁰ ACE inhibitors ²⁶	yes
	R = H: 2-amino-1,2,3,4-tetrahydro-2-carboxylic acid	Atc	40,58,59	Opioid ^{10,16,39,40,59} AngIV ³⁵	yes
	R = OH: 6-hydroxy-2-amino-1,2,3,4-tetrahydro-2-carboxylic acid	Hat ⁶⁰ , 6-HO-Atc*	60	Syk kinase ligand ⁴⁵ AngIV ³⁵ Hen egg lysozyme[52-61] ⁴⁸ Neurotensin ⁵³ Opioid ⁶⁰	yes
	3-amino-1,2,3,4-tetrahydrocarbazole-3-carboxylic acid	Thc	36,61,62	NK1/NK2 ligand ³⁶ Neuromedin B ⁶¹ GnRH antagonist ⁶³	yes
	R = H : 2-aminoindan-2-carboxylic acid	Aic ⁴⁰	40	Opioid ^{10,16,39,40} FT inhibitor ²⁵ AngIV ³⁵ Melanocortin ²³	yes
	R = OH : 5-hydroxy-2-aminoindan-2-carboxylic acid	5-HO-Aic,* Hai ^{16,64}	64,65	Neurotensin ⁵³ Syk kinase ligand ⁴⁵ Hen egg lysozyme[52-61] ⁴⁸	yes
	R = H 4-amino-1,2,4,5-tetrahydro-2-benzazepine-3-one-(2-acetic acid)	Aba-(Gly) ⁶⁶	Review ⁶⁶	ACE/NEP inhibitors ³² Renin inhibitors ⁶⁷ Opioids ⁶⁸ NK1 antagonist ³⁷ Opioid/NK1 hybrid ³⁷	yes

				Melanocortin ⁶⁹ Bradykinin ⁷⁰	
	R = OH 4-amino-1,2,4,5-tetrahydro-8-hydroxy-2-benzazepine-3-one (-2-acetic acid)	Hba-(Gly) ⁷¹ , 8-HO-Aba-(Gly)*	^{71,72}	Syk kinase ligand ^{45,71} Opioid ⁷³ Hen egg lysozyme[52-61] ⁴⁸	no
	4-amino-3-oxo-3,4,5,10-tetrahydro-azepino[3,4-b]indol(-2(1H)-acetic acid)	Aia-(Gly) ⁷⁴	^{74,75}	Somatostatin ⁷⁶ AngIV ⁵⁷ NK1 antagonist ³⁷ Melanocortin ^{69b} Opioids ⁷⁷	no
	7-amino-6-oxo-7,8-dihydro-4H-[1,2,3]triazolo[1,5-a]diazepino-5(6H)-acetic acid	Ata-(Gly) ⁷⁸	⁷⁸	AngIV ⁷⁸ Melanocortin ^{69b}	no
	X = CH ₂	-	⁷⁹	ACE inhibitor ⁷⁹ ACE/NEP inhibitor ^{80,81}	no
	X = O	-	⁸²	ACE inhibitor ⁸²	no
	2-aza-bicyclo-[3.3.0]-octane-3-carboxylic acid	-	^{83,84}	ACE inhibitor ⁸⁵	yes
	octahydroindole-2-carboxylic acid	Oic	⁸⁶	Bradykinin ^{33,87} ACE inhibitor ^{85,88} Melanocortin ²³	yes
	3-amino-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid	-	^{89,90}	ACE inhibitor ⁹¹ ACE/NEP inhibitor ³² Thrombin inhibitor ⁸⁹	yes

	(2 <i>S</i> ,5 <i>S</i>)-5-amino-1,2,4,5,6,7-hexahydro-4-oxo-azepino[3,2,1- <i>h</i>]indole-2-carboxylic acid	Haic ⁹²	28,92,93	ACE inhibitor ⁹³ Stat3 activator ⁹² Thrombin inhibitor ⁸⁹ Granzyme B inhibitor ⁹⁴ Bradykinin ⁹⁵	yes
	(<i>S</i>)-[3-amino-4-oxo-2,3-dihydro-5 <i>H</i> -benzo[<i>b</i>][1,4]thiazepin-5-yl]acetic acid	DBT ⁹⁶	96,97,98	Review ⁹⁹ Bradykinin ^{95,100} Cholecystokinin ¹⁰¹ Growth hormone secretagogue ¹⁰² Elastase inhibitor ¹⁰³ ACE inhibitor ^{97,98} ACE/NEP inhibitor ¹⁰⁴	yes
	(<i>S</i>)-3-amino-5-(carboxymethyl)-2,3-dihydro-1,5-benzoxazepin-4(5 <i>H</i>)-one	DBO ⁹⁵	98,101	Bradykinin ⁹⁵ ACE inhibitor ⁹⁸	yes

* For the ease of reading, we recommend this notation to indicate the hydroxy-substitution of the parent compound, rather than using an arbitrary new abbreviation.

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