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NONPEPTIDE BRADYKININ ANTAGONIST ANALOGS BASED ON A MODEL OF A STERLING-WINTHROP NONPEPTIDE BRADYKININ ANTAGONIST OVERLAPPED WITH CYCLIC HEXAPEPTIDE BRADYKININ ANTAGONIST PEPTIDES

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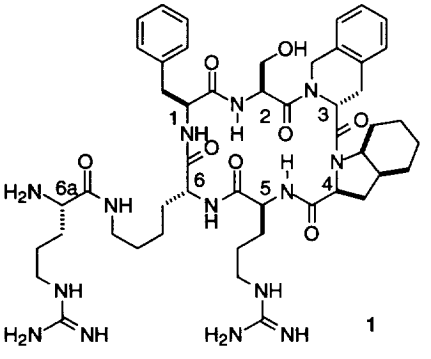
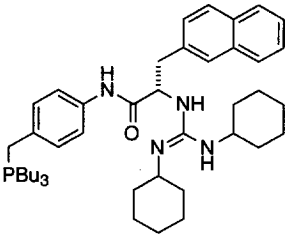
Abstract: A proposed overlap between cyclic hexapeptide Bradykinin antagonists and nonpeptide Bradykinin antagonists is discussed. Structural variations on both the peptides and nonpeptides support the proposed overlap based on an increase or decrease in the biological activities of the antagonists. © 1997 Elsevier Science Ltd.

Bradykinin (Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg) is a nonapeptide hormone that is released upon tissue injury or trauma by the action of kallikrein on kininogen. It has been implicated in a number of pathophysiological processes, including pain and inflammation.[1] There are a number of peptide antagonists of the B2 receptor of bradykinin, however relatively few nonpeptide antagonists have been described.[2,3]



1



2

Our investigation of bradykinin antagonists involved designing small molecule, nonpeptide antagonists based on potent cyclic hexapeptide antagonists. During our investigation of Bradykinin antagonists, Sterling-Winthrop disclosed a potent nonpeptide Bradykinin antagonist **2** (WIN 64338).[3] We have prepared a number of

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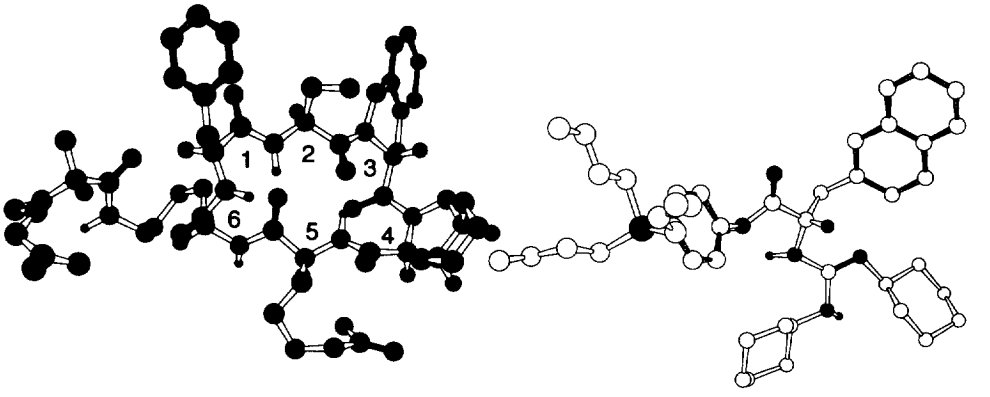
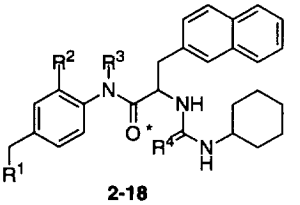
structurally similar compounds and are proposing an overlap of these compounds with our cyclic hexapeptide Bradykinin antagonists **1**.[4]



We are proposing that the naphthalene ring of **2** (right structure) lays over the tetrahydroisoquinoline[3] moiety of the cyclic hexapeptide **1** (left structure). This then places one of the cyclohexyl rings near the octahydroisoquinoline[4] and the positively charged guanidine over the Arg[5] of the cyclic peptide. The positively charged phosphonium then would mimic the Lys[6] of the cyclic peptide.

This manuscript illustrates the synthetic effort towards the naphthylalanine derivatives **2–18**.

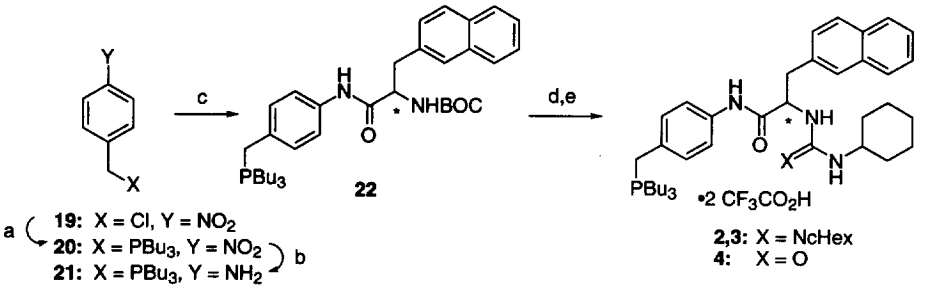


2-18

#	R^1	R^2	R^3	R^4	*	BK Kd (nM)	SP Kd (nM)	#	R^1	R^2	R^3	R^4	*	BK Kd (nM)	SP Kd (nM)
2	nBu_3P^+	H	H	NcHx	L	44	370	**11**	$H_2NC(NH)NH$	H	H	NcHx	L	200	860
3	nBu_3P^+	H	H	NcHx	D	340	670	**12**	$H_2NC(NH)NH$	H	H	NcHx	D	330	1100
4	nBu_3P^+	H	H	O	D	1600	1300	**13**	EtHNC(NEt)NH	H	H	NcHx	D	460	1800
5	nBu_3N^+	H	H	NcHx	L	79	290	**14**	H-L-Arg-NH	H	H	NcHx	D	390	1500
6	nBu_3N^+	H	H	NcHx	D	98	540	**15**	H-D-Arg-NH	H	H	NcHx	D	230	
7	H_2N-	H	H	NcHx	L	450		**16**	aca-D-Arg-NH	H	H	NcHx	D	990	
8	H_2N-	H	H	NcHx	D	800	1300	**17**	H_2N-	CO_2H	H	NcHx	D	690	3800
9	HO-	H	H	NcHx	L	1500		**18**	H_2N-	H	$EtCO_2H$	NcHx	D	1500	
10	HO-	H	H	NcHx	D	2100									

A variety of naphthylalanine derivatives were prepared to test our proposed overlap, most importantly those lacking the necessary positively charged interactions (**4**, **9**, and **10**) and those bearing functionality that enhance activity in the cyclic hexapeptide (**15**).

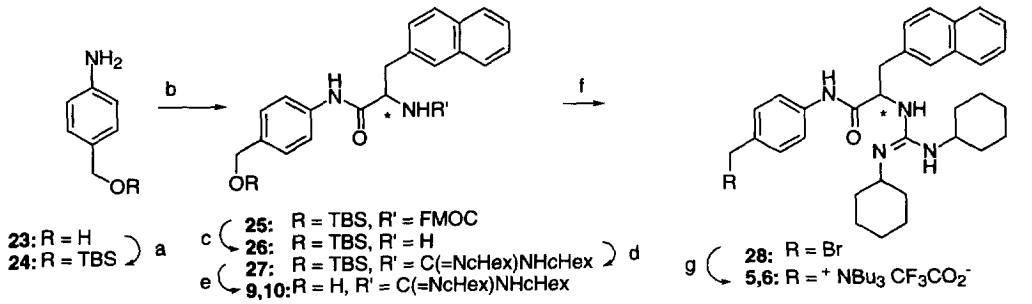
Since the synthesis of **2** had not been disclosed when we initiated this work, we set out to prepare both enantiomers of the known compound to test in our own assays. Scheme 1 illustrates our synthetic procedure. Prolonged exposure of **3** to aqueous acid yielded **4**, which shows a loss in activity.



Scheme 1

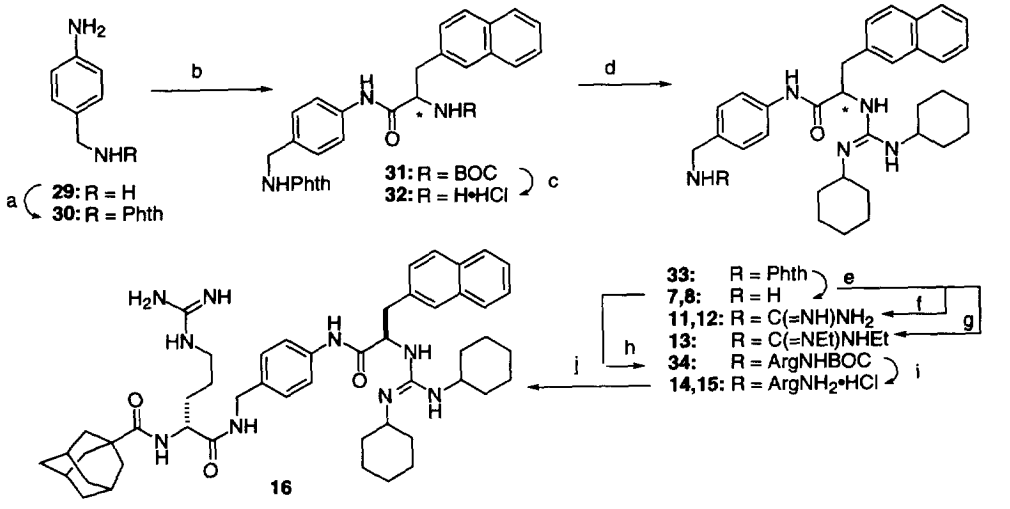
Reagents: (a) PBu_3, $CHCl_3$; (b) $SnCl_2 \cdot 2H_2O$, HCl, THF; (c) DCC, HOBT, Et_3N, CH_2Cl_2, DMF, DMSO; (d) HCl, EtOAc; (e) DCC, Et_3N, *t*-BuOH.

Schemes 2 and 3 illustrate our route for the replacement of the tributylphosphonium salt with other cationic groups. Both enantiomers of the tributylammonium salt **5** and **6** are slightly less active than their corresponding phosphorus analogs **1** and **2**; but interestingly, both enantiomers are about equally active. The trifluoroacetic acids salts of amines **7** and **8** are significantly less potent than their more lipophilic tributylammonium salts **5** and **6**. Using an uncharged replacement (i.e., alcohols **9** and **10**) resulted in the least active of these analogs. Guanylation of **7** or **8** does not improve affinity (**11**, **12**, or **13**). A $DArg^0$ extension of bradykinin has been shown to increase its affinity for the B2 receptor.[5] Correspondingly, an Arg group appended to the Lys on the cyclic hexapeptide has been shown to improve the activity of the antagonist.[3] This effect was also observed for our nonpeptide analogs. A 2- to 3-fold improvement in the antagonist was observed when L or D Arg was appended onto the benzylic amine (**14** and **15**). An adamantane carboxylic acid attached to Arg^0 of bradykinin gives further improvement in activity;[6] however, this effect was not observed for analog **16**.



Scheme 2

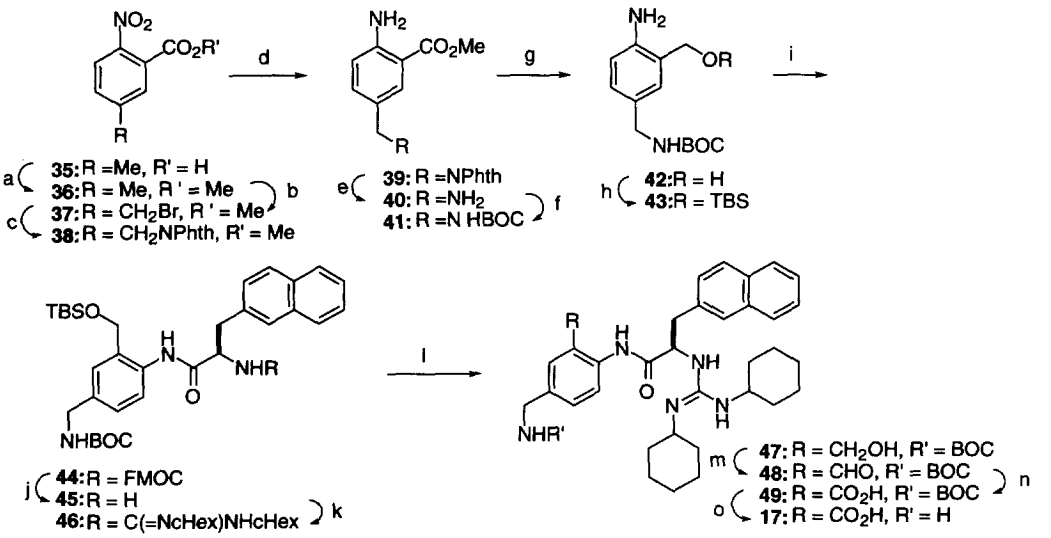
Reagents: (a) TBSCl, imidazole, CH_2Cl_2; (b) FMOC-D-3-(2-naphthyl)alanine, EDC, HOBT, DMF; (c) piperidine, DMF; (d) dicyclohexylthiourea, $HgCl_2$, Et_3N, CH_3CN, 80 °C; (e) $Bu_4N^+F^-$, aq THF; (f) NBS, Me_2S, CH_2Cl_2; (g) Bu_3N, $CHCl_3$.



Scheme 3

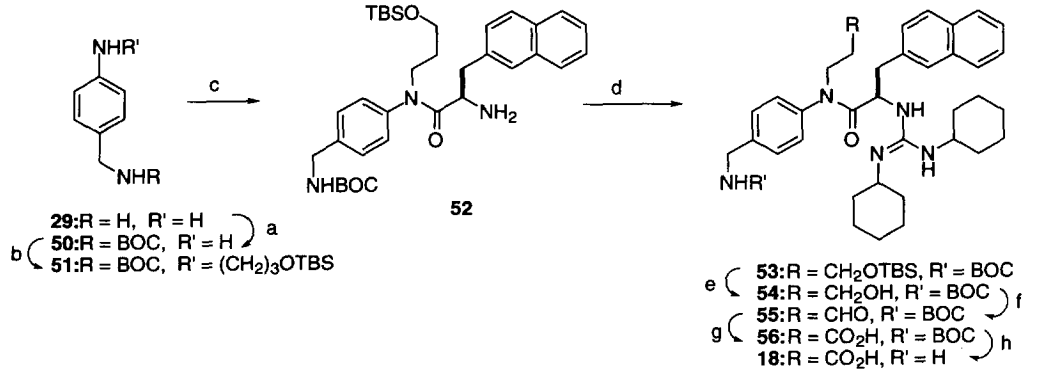
Reagents: (a) carbethoxyphthalimide, aq $NaHCO_3$, cat. Bu_4NHSO_4, CH_2Cl_2; (b) BOC-D or L-3-(2-naphthyl)alanine, EDC, HOBT, DMF; (c) HCl, EtOAc; (d) DCC, Et_3N, *t*-BuOH, 80 °C; (e) $NH_2NH_2•H_2O$, CH_3OH; (f) $H_2NC(=NH)SO_3H$, aq NaOH, CH_3CN; (g) $HEtNC(=NEt)SO_3H$, aq NaOH, CH_3CN; (h) BOC-D or L-arginine•HCl, *i*-Pr_2NEt, EDC, HOBT, DMF; (i) HCl, EtOAc; (j) adamantane carboxylic acid, i-Pr_2NEt, EDC, HOBT, DMF.

Carboxylic acid analogs **17** and **18** (Schemes 4 and 5) were designed in an attempt to pick up an extra charged interaction with the bradykinin receptor. Since the carboxylate of bradykinin is critical for high affinity binding to its receptor, we also hoped that such an interaction would improve the selectivity verses the Substance P receptor. Some improvement in selectivity was observed for analog **17** without a loss in activity, however acid **18** showed a dramatic loss in activity.



Scheme 4

Reagents: (a) HCl, CH_3OH, 65 °C; (b) NBS, cat. AIBN, CCl_4, 80 °C; (c) potassium phthalimide, $Bu_3P^+(C_{16}H_{33})Br^-$, toluene, 60 °C; (d) $SnCl_2{\cdot}2H_2O$, HCl, THF; (e) $NH_2NH_2{\cdot}H_2O$, CH_3OH; (f) BOC-ON, THF; (g) DIBAL, CH_2Cl_2; (h) TBSCl, imidazole, CH_2Cl_2; (i) FMOC-D-3-(2-naphthyl)alanine, EDC, HOBT, DMF; (j) piperidine, DMF; (k) dicyclohexylthiourea, $HgCl_2$, Et_3N, CH_3CN, 80 °C; (l) $Bu_4N^+F^-$, aq THF; (m) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2; (n) $NaClO_2$, NH_2SO_3H, aq THF; (o) HCl, EtOAc.



Scheme 5

Reagents: (a) $(BOC)_2O$, THF; (b) $Br(CH_2)_3OTBS$, KF/Celite, CH_3CN, 80 °C; (c) FMOC-D-3-(2-naphthyl)alanine, $SOCl_2$, CH_2Cl_2, remove volatiles, then **52**, DMAP, Et_3N, CH_2Cl_2, then, piperidine, DMF; (d) dicyclohexylthiourea, $HgCl_2$, Et_3N, CH_3CN, 80 °C; (e) $Bu_4N^+F^-$, aq THF; (f) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2; (g) $NaClO_2$, NH_2SO_3H, aq THF; (h) HCl, EtOAc.

In summary, we have proposed an overlap between two structurally diverse compounds, a cyclic hexapeptide and a small organic molecule. The overlap provides some predictive power since the pharmacophore presented in the cyclic hexapeptide series can be translated into the small molecule framework, as illustrated in this work. This may provide the potential to the develop novel non-peptide bradykinin antagonists from a cyclic peptide.

References and Notes

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