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Novel Bifunctional Peptides as Opioid Agonists and NK-1 Antagonists

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Introduction

Inadequate treatment of pain is an important and urgent problem, which needs to be addressed. Opiates are still the drugs of choice for the treatment of moderate to severe acute pain; however their use are generally accompanied by undesired side effects like analgesic tolerance. Several pharmacological studies have suggested the role of substance P, in pain transmission [1]. It has been observed that co-administration of neurokinin-1 receptor antagonists and opioid agonists augmented the acute effects of opioids and also prevented opioid induced tolerance [2]. In view of these and other observations we have designed novel bifunctional peptides with mixed opioid μ/δ agonist activity and neurokinin-1 antagonist activity [3]. Earlier reports of molecules with opioid μ/δ agonist activity and neurokinin-1 antagonist activity did not have balanced activity at both the receptor's systems [4]. In our studies the opioid pharmacophore chosen has the sequence H-Tyr-DAla-Gly-Phe which is a substructure of biphalin, a highly potent agonist at both δ and μ opioid receptors [5]. A 3,5-(bistrifluoromethyl) benzyl ester of *N*-acylated tryptophans was chosen as the NK1 pharmacophore [6]. These two pharmacophores were combined with amino acids acting as possible address moieties they could be part of the two pharmacophores.

Sequences of some of the bifunctional peptides synthesized are represented below (Fig. 1)

Results and Discussion

The bifunctional peptide ligands were synthesized using solution phase chemistry. The synthetic strategy was started with coupling of tryptophan 3,5-(bistrifluoromethyl)benzyl ester with the respective Boc protected amino acid followed by subsequent chain elongation using BOP/HOBT/NMM method. The N^{α}-Boc groups were deprotected by 100% TFA. The final crude peptides were purified by C_{18} RP-HPLC (Vydac 10 mm x 250 mm, 10 μM) with a gradient of 30–70% CH_3CN in aq. 0.1% TFA.

NP30, with Gly as the linker showed excellent binding affinity at both δ and μ opioid receptors and rat NK1 receptors (K_i = 4.7 nM, δ opioid; 0.29 nM, μ opioid; 4.2 nM, rNK1). It also showed potent δ and μ opioid agonist efficacies in the MVD and GPI assays binding assays with the IC_{50} values of 21 and 26 nM, respectively.

GPI assay clearly showed that NP30 was an antagonist against substance P stimulation with K_e = 59 nM. NP34 with γAbu (Aminobutyric) at position 5 turned out to be the most potent at the GPI assay (K_e = 0.96nM) among all the compounds synthesized. On the other hand substitution with DAla (NP40) at the same position resulted in drastic lowering of antagonistic activity in the GPI assays (K_e = 610nM). However both NP34 and NP40 were highly potent in the binding affinity studies at the opioid and rat NK1 receptors.

Conclusion

Several bifunctional peptides with δ/μ opioid agonist pharmacophore and NK1 antagonist pharmacophore were designed and synthesized. Binding assays performed showed potent activities as an opioid agonist and as NK1 antagonists thus exhibiting the potential of these compounds to act as bifunctional ligands (Table 1).

Acknowledgments

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NP30 H-Tyr-DAla-Gly-Phe-**Gly**-Trp-O-3,5-Bzl(CF_3)$_2$
NP32 H-Tyr-DAla-Gly-Phe-**βAla**-Trp-O-3,5-Bzl(CF_3)$_2$
NP34 H-Tyr-DAla-Gly-Phe-**γAbu**-Trp-O-3,5-Bzl(CF_3)$_2$
NP40 H-Tyr-DAla-Gly-Phe-***D*Ala**-Trp-O-3,5-Bzl(CF_3)$_2$

Fig. 1.
Sequences of the peptides with opioid agonist and NK-1 antagonist activity.

Table 1

Binding affinities.

Peptide	Binding affinities			Functional assay		
	K_i(nM)			IC_{50} (nM) (agonist)	K_e (nM)	
	hDOR	rMOR	rNK1	MVD	GPI	SP(GPI) (antagonist)
NP30	4.7	0.29	4.2	21	26	59
NP32	58	11	1.6	13	430	250
NP34	25	2.2	7.4	68	200	0.96
NP40	3.9	2.8	2.4	58	530	610