

# Peptides

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# A simple synthesis of 1,2,3,4,-tetrahydro-7-hydroxyisoquinoline-3-carboxylic acid (HO-Tic) a conformationally constrained tyrosine analog and its incorporation into opioid peptides

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## Introduction

Topographical considerations in the design of highly selective and potent peptide ligands indicate that fixing or biasing the side chain of critical amino acids to specific conformers should provide new insight into peptide conformation-activity relationships [1]. As an example, the phenylalanine side chain can be fixed into the gauche (-) ( $\chi_1 = -60$ ) or gauche (+) ( $\chi_1 = +60$ ) conformation by cyclization to 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic) **1** [2], depending on whether it is in the N-terminal or in an internal position. Since many opioid peptides have an N-terminal tyrosine residue, the corresponding tetrahydroisoquinoline derivative **2** (HO-Tic) is very useful for investigating the topographical requirements of this residue for the different opiate receptors.

## Results and Discussion

The preparation of HO-Tic by a Pictet-Spengler reaction using formaldehyde in acidic conditions, as is used for Tic, does not succeed due to a polymerization reaction [3]. A very tedious, low yield preparation has been reported [4]. We have prepared HO-Tic in 2 steps, starting from 3',5'-diiodo- or 3',5'-dibromotyrosine and formaldehyde, by using a lower reaction temperature (72–75°C) and longer reaction time (18 h), which avoids dehalogenation and racemization, yields 55% and 30%, respectively. Deiodination/debromination is performed by catalytic hydrogenolysis before or after Boc-protection (avg. yield ca. 70%). Boc-HO-Tic was incorporated into the  $\mu$ -selective dermorphin analog **2**, and into the  $\delta$ -selective deltorphin **5** and DPDPE analog **8**. Their binding affinities to rat brain membranes and their activities in the MVD and GPI bioassays are collected in Table 1. A substantial loss of potency is observed for each

Table 1 Biological activities ( $IC_{50}$ , nM) and chemical shift of D-Ala<sup>2</sup> methyl signal (DMSO)

Compound		GPI	MVD	[ <sup>3</sup> H] $\mu^a$	[ <sup>3</sup> H] $\delta^b$	$\delta(\text{CH}_3)$
dermorphin	1	6.18	79.2	-	-	0.67(7)
[HO-Tic <sup>1</sup> ]dermorphin	2	-	-	1 615	>10 000	0.90
[Tic <sup>3</sup> ]dermorphin	3	1 166	>10 000	-	-	1.02 + 1.04 <sup>c</sup>
deltorphin B	4	3 000	0.97	16 795	0.4	0.69(9)
[HO-Tic <sup>1</sup> ]deltorphin B	5	>30 000	89.8	>10 000	304	0.91
[Tic <sup>3</sup> ]deltorphin B	6	>30 000	116.8	26 500	740	1.05 + 1.05 <sup>c</sup>
DPDPE	7	9 214	1.24	609	5.25	
[HO-Tic <sup>1</sup> ]DPDPE	8	>40 000	265	93 044	346	

<sup>a</sup>[<sup>3</sup>H]CTOP, <sup>b</sup>[<sup>3</sup>H]p-CIDPDPE, <sup>c</sup>cis-trans rotamers.

compound. For the  $\delta$  receptor, topographical considerations suggest a close proximity of the Tyr<sup>1</sup> and Phe<sup>4</sup> sidechains in DPDPE [5], which explains the present drop in potency of 8. For dermorphin 1 and analogs a shielding of the D-Ala<sup>2</sup> methyl signal by the Tyr<sup>1</sup> and Phe<sup>2</sup> sidechains is observed (Table 1), which is further confirmed by the presence of NOE's between the methyl and both aromatic rings [6,7], and a tilted stacking interaction was proposed as an important structural requirement for  $\mu$ -affinity [8]. Similar NMR observations were made for deltorphin B 4 [9]. The [HO-Tic<sup>1</sup>] analogs cannot adopt the required sidechain orientation in agreement with the low potencies observed. In view of these observations it can be concluded that the g(-) conformation for the Tyr<sup>1</sup> sidechain is not favorable for interaction with both the  $\mu$ - and the  $\delta$ -opiate receptors. For the  $\mu$ -receptor specific octapeptide D-Tic-Cys-Tyr-D-Trp-Lys-Thr-Pen-Thr-NH<sub>2</sub> however, it was concluded that the bioactive model required some distance between the aromatic ring pharmacophores in position 1 and 3 [10]. The requirements for this antagonist appear to be different from those for the dermorphin agonists. The loss of potency in [Tic<sup>3</sup>]-analogs 3 and 5 may be due to a g(+) conformation of the sidechain [2], as indicated by the upfield shift of the methyl<sup>2</sup> signal.

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