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NON-PEPTIDE OXYTOCIN ANTAGONISTS: IDENTIFICATION AND SYNTHESIS OF A POTENT CAMPHOR AMINOSUCCINIMIDE

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Abstract: The structure activity relationships of a series of non-peptide oxytocin antagonists containing a camphor aminosuccinimide as a key structural element were investigated. A potent and selective analog was identified and prepared in diastereomerically pure form starting from aspartic acid.

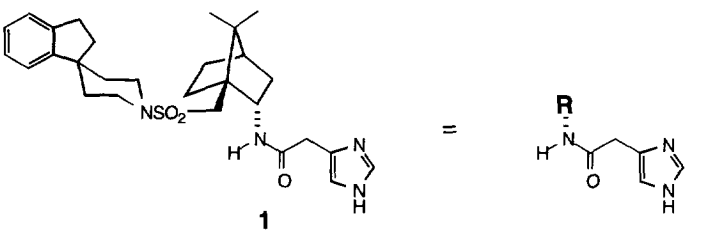
Introduction:

Preterm birth remains a leading cause of infant mortality in most developed countries despite significant medical advances made in the last few decades. Since the peptide hormone oxytocin has been implicated in the natural onset and maintenance of labor,[1] inhibition of oxytocin has recently emerged as one of the most promising mechanisms for the treatment of preterm labor.[2] In this context, several reports have appeared describing novel camphor containing non-peptide antagonists of oxytocin.[3] In a previous report from these laboratories, imidazole acetamide **1**, a typical member of this class, was highlighted due to its high affinity for the oxytocin receptor, its selectivity versus the vasopressin V_{1a} and V_2 receptors, and its oral bioavailability.[3b] In the same manuscript it was noted that while hydantoins and imides of the camphor endo amine generally have higher oxytocin receptor affinity than similar amides, none were identified as having overall superior properties compared to **1**. Specifically, many of the compounds with increased receptor affinity have poor oral bioavailability. In this communication we extend the work on imide containing oxytocin antagonists, and outline the discovery of a compound with better affinity for the oxytocin receptor than **1**, while retaining oral bioavailability.

Chemistry:

All the compounds discussed in this letter contain as a common structural feature an acylated camphor endo amine, such as the imidazole acetamide **1**, whose preparation has been described elsewhere.[3b]

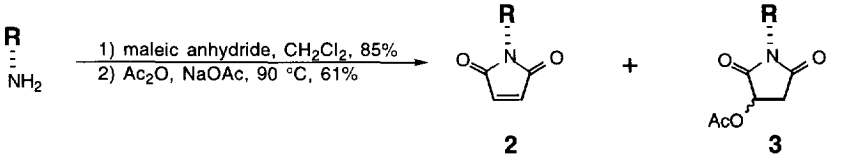
Figure 1: Endo imidazole acetamide **1**



1

For the preparation of the imides discussed herein, the endo amine was treated with maleic anhydride and then cyclized to the maleimide **2** using acetic anhydride and sodium acetate (scheme 1). Also isolated from the cyclization reaction was a mixture of the malimide acetates **3** (6% yield). The acetates could be saponified using lithium hydroperoxide in THF to give a separable mixture of the (R) and (S) malimides, **4R** and **4S** (the stereochemistry was assigned by proton NMR. See discussion below).

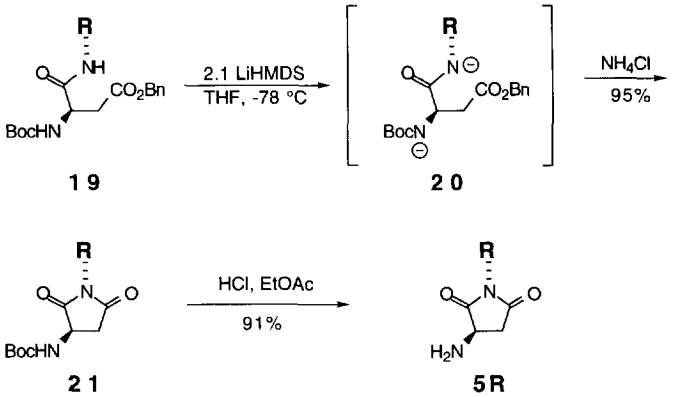
Scheme 1:



The remaining compounds in Table 1 could be prepared from maleimide **2** through conjugate addition. The conjugate addition reactions proceeded in yields ranging from 50% to 80%. In some cases the individual epimers could be separated, but for most of the compounds biological evaluation was performed on a 1:1 mixture of stereoisomers.

While the yields of the conjugate addition reaction were satisfactory for providing material for initial in vitro screening, we found it to be inefficient for the preparation of the quantities needed for in vivo evaluation. An alternative preparation of the unsubstituted aminosuccinimides **5R** and **5S** is outlined in Scheme 2. The endo amine was acylated with Boc-D-aspartic acid β-benzyl ester to afford the amide ester **19**. Treatment of **19** with 2.1 equivalents of lithium hexamethyldisilylazide in THF at -78 °C, followed by the addition of ammonium chloride and work up afforded the cyclized product **21** in excellent yield. On the basis of proton NMR data, we were able to conclude that less than 5% of the other diastereomer was formed. Presumably the excess base leads to the formation of the dianion **20**, which effectively protects the α-amino center from deprotonation.[4] The Boc group was removed with HCl in ethyl acetate to afford **5R**. Compound **5S** was similarly prepared from L-aspartic acid. By using aspartic acid as the source of chirality, we were able to conveniently prepare multigram quantities of either **5R** or **5S** in high yield. In addition, by analogy with characteristic differences in the proton NMR spectra of **5R** and **5S**, we were able to assign the absolute stereochemistry of several of the other compounds in Table 1.

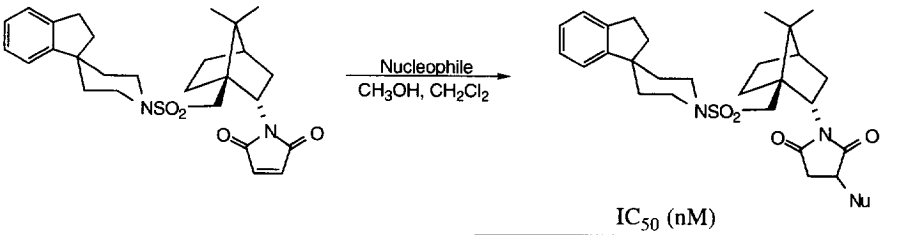
Scheme 2:



Results and Discussion:

The binding affinities listed in Table 1 are for half-maximal inhibition of binding of [^{3}H]oxytocin to rat uterine tissue (OT), or [^{3}H]vasopressin to rat liver (V_{1a}), or rat kidney (V_2) tissues as described by Pettibone et al.[5]

Table 1:



Compound	Nu	IC_{50} (nM) OT *	V_{1a}	V_2
1	-	52	5,600	17,000
2	-	240	4,140	8,700
3	OAc	25	1,300	2,500
4R	OH	17	1,500	2,300
4S	OH	20	945	1,500
5R	NH_2	12	610	1,300
5S	NH_2	7	970	2,800
6R	NEt_2	124	2,340	7,140
6S	NEt_2	150	2,970	8,370
7	NHEt	32	860	4,100
8R	NHBn	64	2,900	3,930
8S	NHBn	200	2,300	11,600
9	$NHCH_2CH_2NH_2$	40	2,750	5,450
10	$NHCH_2CH_2N(CH_3)_2$	18	160	1,300
11	$NHCH_2CH_2CH_2N(CH_3)_2$	15	170	1,100
12	$SCH_2CH_2N(CH_3)_2$	20	110	880
13	$NHCH_2CO_2CH_3$	13	1,850	1,620
14	$NHCH_2CO_2H$	44	4,100	7,200
15	$NHCH_2CH_2OH$	9	490	6,167
16	$N(CH_3)CH_2CH_2OH$	20	1,300	3,060
17	$NHCH(R\text{-}CH_3)CH_2OH$	20	990	3,000
18	$NHCH_2CH(R\text{-}CH_3)OH$	10	520	2,300

* Standard deviation ≈ ± 5.

Comparison of **4R** and **4S** with **5R** and **5S** indicates that the primary amines have a modest advantage over hydroxyl. Continuing in the amine series, we substituted the amino group with various alkyl chains. In the series **5R**, **5S**, **6R**, **6S**, **7**, **8R**, and **8S**, the trend approximates decreasing potency with increasing steric bulk, and there is a clear preference for the unsubstituted amines. Since the monoethyl analog was the best tolerated of the alkyl amines, we prepared some additional substituted ethyl amines.

Examining the effect of basic substituents led to compounds **9-12**. The three dimethyl amines **10-12** had an

advantage in oxytocin receptor affinity over the primary amine **9**. However with these compounds, the vasopressin V_{1a} affinity was also increased. While vasopressin antagonist activity is not necessarily a problem for the proposed therapeutic application, in order to simplify safety issues we were interested in obtaining greater selectivity than the 1:10 ratio seen in **10-12**. Comparing **10** and **11** suggested that chain length was not critical for high affinity, nor was it necessary that the heteroatom attached to the succinimide be a nitrogen (cf. **12**).

In general, neutral polar groups were among the best substituents examined. The ester **13** showed some promise, but when the ester was hydrolyzed to the acid **14**, a likely metabolite, the affinity dropped off three-fold.

The ethyl alcohol **15** was found to have promising affinity and selectivity, and some additional examples were prepared in that series. Similar to the trend observed in compounds **5-8**, increased steric bulk had an adverse effect on receptor affinity. More specifically, it was steric bulk near the succinimide ring that was poorly tolerated. If a methyl group was added to the amine to give a tertiary amine (**16**), or to the carbon adjacent to the amine (**17**), a two-fold loss in affinity was observed. However, moving the methyl group one carbon further away from the ring (to the hydroxyl-bearing carbon) led to a compound with the same receptor affinity as the unsubstituted ethyl alcohol (compound **18**).

On the basis of in vivo experiments, in addition to the data presented in Table 1, **5R** proved to have the best balance of properties. It was found to inhibit oxytocin stimulated uterine contractions in the rat after either intravenous and intraduodenal administration (AD_{50} i.v. = 0.43 mg/kg; AD_{50} i.d. = 5.1 mg/kg). Compared to compound **1**, **5R** has approximately a three-fold improvement in oxytocin antagonism as measured by its AD_{50}, which is consistent with its four-fold improvement in in vitro receptor affinity.

In conclusion, by preparing a series of substituted camphor succinimides, we were able to identify **5R** which represents an improvement over compound **1** in vitro and in vivo.

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