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Nipecotic and *iso*-Nipecotic Amides as Potent and Selective Somatostatin Subtype-2 Receptor Agonists

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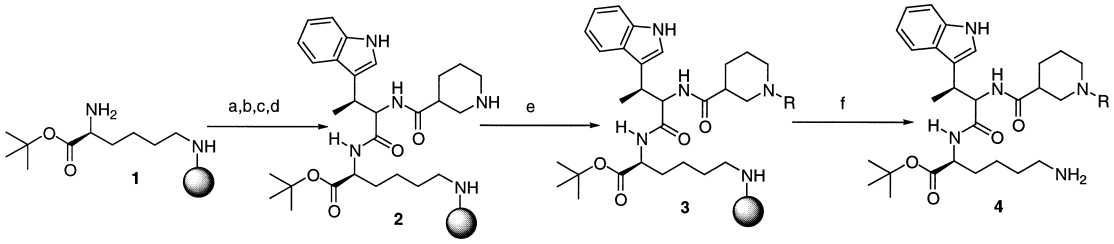
Abstract—*N*-Substituted nipecotic and *iso*-nipecotic amides of β-methylTrpLys *tert*-butyl ester were found to be novel, selective and potent agonists of the somatostatin subtype-2 receptor in vitro. For example *iso*-nipecotic amide **8a** showed high hsst2 binding affinity ($K_i = 0.5$ nM) and good selectivity ($h_5/h_2 = 832$). © 2001 Elsevier Science Ltd. All rights reserved.

Introduction

Somatostatin (sst) is a widely distributed cyclic peptide occurring in two forms, SRIF-14 (with 14 amino acids) and SRIF-28 (with 28 amino acids). SST has multiple functions including modulation of growth hormone, insulin, glucagon, and gastric acid secretion, in addition to having potent antiproliferative effects.[1] Five somatostatin receptors (sst1–5) are known.[2] The availability of these receptors now makes it possible to determine selectivities among the subtypes to guide potential clinical applications. For example, studies utilizing subtype selective peptides have shown that somatostatin subtype-2 receptors (sst2) mediate the inhibition of growth hormone release from the anterior pituitary gland and glucagon release from the pancreas whereas sst5 selective analogues inhibit insulin release. Due to the low stability of somatostatin in vivo, more stable peptide-based analogues such as octreotide and MK-678 have been developed; however, they still suffer from poor oral absorption and some limitations in receptor subtype specificity.[3] Our group has previously described potent nonpeptide somatostatin receptor subtype-2 (sst2) specific agonists such as **A**.[4] Agonist **A** and its urea analogues, prepared from a *t*-butyl capped dipeptide (β-methylTrpLys-O-*t*-Bu) and a 4-substituted piperidine 'privileged structure',[5] show low oral bioavailability.[6] One hypothesis responsible for low



Scheme 1. (a) *N*-Fmoc-β-MethylTrp/PyBOP/HOBt/DIEA/DMF; (b) 25% piperidine/DMF (45 min); (c) *N*-Fmoc-nipecotic acid/PyBOP/HOBt/DIEA/DMF; (d) 25% piperidine/DMF; (e) RX/DIEA/DCM/60 °C or carboxylic acid/PyBOP/DIEA/DCM or sulfonyl chloride/DIEA/DCM or isocyanate/DCM; (f) HOAc/40 °C, overnight, then lyophilization. The yield ranged from 74–92%. The purity (94–98%) was analyzed by HPLC.

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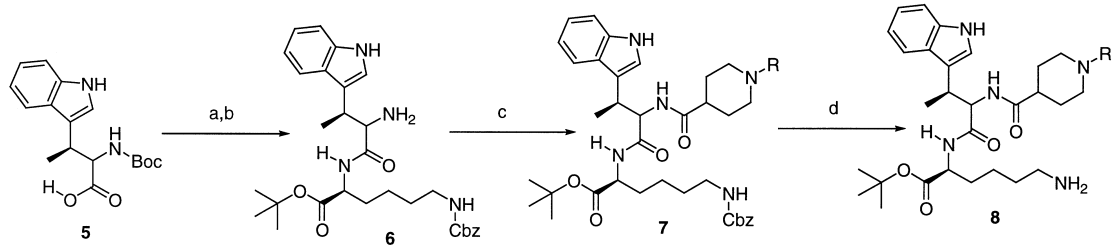
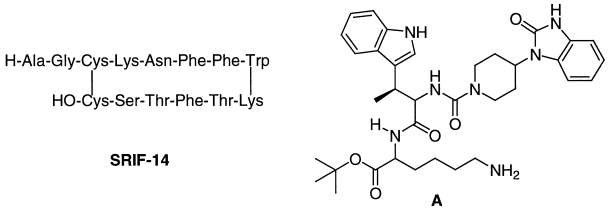
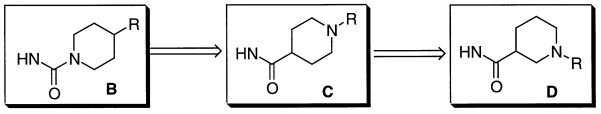


Scheme 2. (a) ω-*N*-Cbz-Lys-*t*-Bu/EDC/HOAt/DIEA/DCM; (b) $MeSO_3H$ (3.0 equiv)/MeOH; (c) *N*-substituted *iso*-nipecotic acid/EDC/DIEA/DCM; (d) 10% Pd/C, H_2/MeOH.

bioavailability might be the urea part which is metabolically labile. Therefore, novel leads without urea structure are deserved to be exploited in the hope to improve the pharmacokinetic profiles.



Herein we disclose our efforts in generating new potent and sst2 selective agonists with highly modular amide scaffolds. Our rationale was based on the structural similarity of urea (**B**) and *iso*-nipecotic (**C**) as well as nipecotic (**D**) moieties. Thus amides derived from β-methylTrpLys-O-*t*-Bu were expected to have intrinsic activities similar to the compound **A** series and to generate possible potent sst2 agonists with improved pharmacokinetic properties.



Chemistry

Two general methods for preparing nipecotic and *iso*-nipecotic amides are illustrated in Schemes 1 and 2. The first route was based on solid-phase chemistry (Scheme 1). The key step involved preparation of resin-bound Lys-O-*t*-Bu **1** by treatment of Lys-O-*t*-Bu with chloro-2-chlorotrityl resin in the presence of diisopropyl ethylamine (DIEA). Only the sterically less hindered ω-amino group reacted with the trityl resin. Chain elongation of **1** with *N*-Fmoc-β-MethylTrp and then Fmoc-*iso*-nipecotic acid was performed by standard solid-phase Fmoc chemistry to yield intermediate **2**. Reactions of **2** with alkyl halides (+DIEA), acids (DIEA/PyBOP), sulfonyl chlorides (+DIEA) and isocyanates introduced *N*-substituted groups. Final products as the AcOH salts were obtained by cleavage of **3** with hot acetic acid.

The second route started from a standard solution-phase condensation of ω-*N*-Cbz-Lys-O-*t*-Bu and *N*-Boc-β-MethylTrp **5** (Scheme 2). The resulting intermediate was treated with $MeSO_3H$ (3.0 equiv) in

Table 1. Nipecotic amide **4** and hsst2 binding affinity[7]

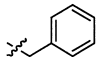
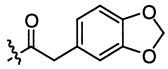
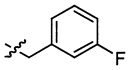
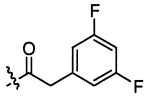
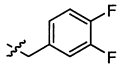
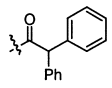
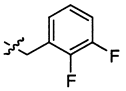
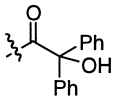
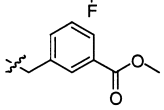
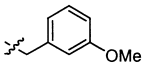
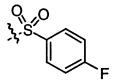
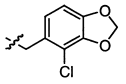
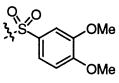
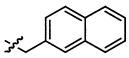
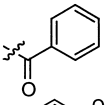
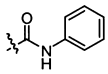
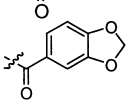
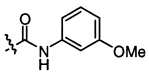
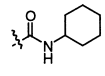
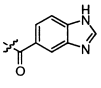
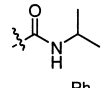
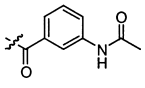
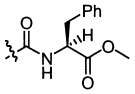
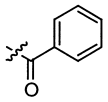
Entry	Nipecotic amide **4**: R	hsst2 K_i (nM)	Entry	R	hsst2 K_i (nM)
1		4.6	16		10
2		5.0	17		2.3
3		2.9	18		5.0
4		5.7	19		2.8
5		11	20		23
6		21	21		178
7		10	22		11
8		12	23		23
9		31	24		14
10		17	25		35
11		10	26		11
12		36	27		9.0
13		85	28		7.2
14		85	29		95
15		47	30		8.6

Table 2. *iso*-Nipecotic amide **8** and binding affinity[7]

Entry	*iso*-Nipecotic amide **8**: R	hsst2 K_i (nM)	hsst3 K_i (nM)	hsst5 K_i (nM)	h_5/h_2 Ratio
a		0.5	2660	416	832
b		15	5250	2,858	190
c		120	3750	>10,000	83
d		2.5	NA	333	133

methanol to selectively remove the *N*-Boc group without altering the *t*-butyl ester. Intermediate **6** was then reacted with *N*-substituted *iso*-nipecotic acid to give **7**. Removal of the Cbz protecting group afforded final product **8** as the HCl salt suitable for bioassay.

Results and Discussion

A small nipecotic amide library **4** (30 compounds) was prepared from solid-phase syntheses and the in vitro binding affinities of these compounds were evaluated. As expected, many compounds derived from nipecotic acid showed low nanomolar hsst2 affinity ($K_i < 10$ nM). The most important feature of the nipecotic amide template was that various *N*-substitutions of the nipecotic ring were tolerated and necessary for high affinity. A low affinity (K_i: 178 nM) was observed without any substitution (entry 21 in Table 1). *N*-Arylmethyl (entries 1–10) and *N*-arylacetyl (entries 16–19) substitutions were among the best and fluoro substitution(s) on the phenyl ring had favorable effects on potency. Benzamides (entries 11–15), sulfonamides (entries 21–25) and ureas (entries 26–30) were slightly less active. It is noteworthy that racemic nipecotic acid was used in these syntheses and it is expected that more active compounds would be obtained if single enantiomers were used.

Several *N*-substituted *iso*-nipecotic amides were prepared by solution-phase chemistry and the in vitro affinities of these compounds were also quite encouraging; a very potent (hsst2: $K_i = 0.5$ nM) and highly selective ($h_5/h_2 = 832$) compound **8a** were obtained from *N*-benzoylated *iso*-nipecotic acid (entry a in Table 2). In contrast to the nipecotic amide series, *N*-benzylated *iso*-nipecotic amide (entry d in Table 2) was less potent than the corresponding *N*-benzoylated amide. Replacement of *N*-benzoyl with *N*-isopropylcarbonyl or sulfonyl groups decreased both potency and selectivity. The above results indicate slightly different SARs in the *iso*-nipecotic and nipecotic amide series.

Quite unfortunately, the *iso*-nipecotic amide **8a** showed low bioavailability ($F = 3\%$) in rats. Considering the general low bioavailability associated with lysine moiety, further replacement of Lys *tert*-butyl ester with other metabolically more stable diamines[6b] has been performed and the results will be reported in due course.

In summary, novel sst2 selective agonists possessing *iso*-nipecotic and nipecotic amide structures were discovered.

Acknowledgements

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7. Binding affinities were measured as described in ref 4. The data have been corrected for the actual concentration of the active principle according to the corresponding purity quantified by HPLC.