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HUMAN β3 ADRENERGIC RECEPTOR AGONISTS CONTAINING IMIDAZOLIDINONE AND IMIDAZOLONE BENZENESULFONAMIDES

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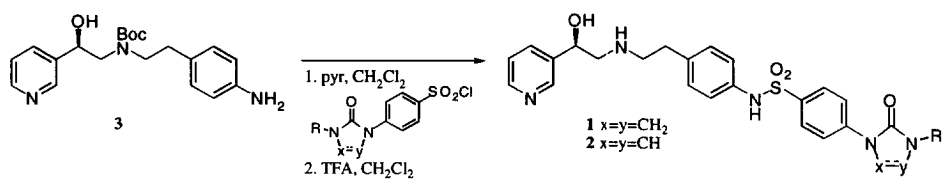
Abstract: The cyclopentylpropylimidazolidinone L-766,892 is a potent β_3 AR agonist (EC_{50} 5.7 nM, 64% activation) with 420- and 130-fold selectivity over binding to the β_1 and β_2 ARs, respectively. In anesthetized rhesus monkeys, L-766,892 elicited dose-dependent hyperglycerolemia (ED_{50} 0.1 mg/kg) with minimal effects on heart rate.

The preceding paper outlines the discovery of cyclic ureidobenzenesulfonamides as potent and selective β_3 adrenergic receptor agonists (AR).[2] In particular, the hexyl imidazolidinone L-760,087 (**1d**) and hexyl imidazolone L-764,646 (**2a**) produced a dose-dependent lipolytic response (ED_{50} values for glycerolemia were 0.2 and 0.1 mg/kg, respectively) in anesthetized rhesus monkeys following iv administration. In dogs, L-760,087 and L-764,646 exhibited modest oral bioavailability (both 7%). In an effort to improve the pharmacological characteristics of these cyclic ureidobenzenesulfonamides, we decided to investigate modification of the alkyl side chain.

Scheme. Synthesis of Imidazolidinones **1** and Imidazolones **2**



The imidazolidinones **1** and imidazolones **2** were prepared from aniline **3**.[3] Reaction with the appropriate sulfonyl chloride[4] afforded the sulfonamides that were deprotected with trifluoroacetic acid (TFA) to give the desired (*R*)-ethanolamines **1** and **2**.[5] In vitro data for these compounds are shown in Tables 1 and 2.[6]

The β_3 AR agonist potency of a series of *n*-alkyl imidazolidinones **1a–f** showed that increasing the length of the alkyl chain led to enhanced potency for the β_3 AR, as was observed in the earlier urea series.[3] The

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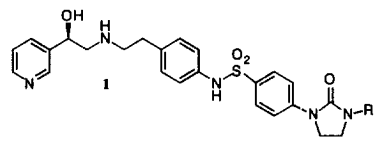
most potent of these compounds was the octyl derivative **1f** (β_3 EC_{50} = 2.2 nM) with 260- and 170-fold selectivity over binding to the β_1 and β_2 ARs, respectively. Imidazolidinone **1g**, with a gem dimethyl substituent at the C-2 position of the hexyl chain, was threefold more active than the parent compound **1d** for the β_3 AR.

Table 1. Comparison of the β_3 AR Agonist Activity and β_1 and β_2 Binding Affinity for Imidazolidinones **1**



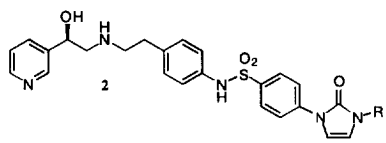
Compound	R	β_3 EC_{50}, nM (%act)[a]	β_1 Binding IC_{50}, nM[b]	β_2 Binding IC_{50}, nM[b]
1a	Me	85 (31)	10,000	2,000
1b	nBu	37 (75)	10,000	5,300
1c	nPent	21 (66)	10,000	5,000
1d	nHex	18 (62)	5,000	2,300
1e	nHept	20 (74)	3,000	1,000
1f	nOct	2.2 (62)	580	380
1g	$Me(CH_2)_3CMe_2CH_2$	5.9 (67)	8,500	5,000
1h	$MeO(CH_2)_4$	67 (40)	50,000	50,000
1i	$(CH_2)_4NCO(CH_2)_2$	130 (75)	100,000	100,000
1j	$Ph(CH_2)_3$	4.2 (76)	4,000	2,000
1k	$4\text{-}ClPh(CH_2)_3$	4.4 (65)	2,000	2,000
1l	$3,4diFPhCH_2$	9.5 (86)	5,000	3,500
1m	$CF_3(CH_2)_3$	18 (64)	10,000	6,500
1n	$CF_3CF_2(CH_2)_3$	14 (69)	10,000	9,000
1o	$cPent(CH_2)_3$	5.7 (64)	2,400	760
1p	$cPent(CH_2)_2$	13 (72)	10,000	5,000
1q	$cHex(CH_2)_3$	2.5 (63)	1,000	1,000
1r	$cHex(CH_2)_2$	5.8 (69)	4,000	1,000

[a]Adenylyl cyclase activation given as % of the maximal stimulation with isoproterenol. [b]Receptor binding assays were carried out with membranes prepared from CHO cells expressing the cloned human receptor in the presence of ^{125}I-iodocyanopindolol.

Replacement of the C-5 methylene group by an oxygen produced the methoxybutyl analog **1h** that was fourfold less potent than the hexyl derivative **1d**. The cyclic amide **1i** also exhibited modest β_3 AR potency, suggesting that polar groups near the terminus of the side chain are deleterious. Incorporation of a phenyl moiety into the imidazolidinone side chain was well tolerated. The phenylpropyl derivative **1j** and its 4-chloro analog **1k** were equipotent β_3 AR agonists (EC_{50} = 4.2 and 4.4 nM, respectively) with excellent selectivity (> 450-fold) over binding to both the β_1 and β_2 ARs. When the phenylpropyl group was replaced by a 3,4-difluorobenzyl moiety, the resulting β_3 AR agonist was twofold less potent. In the β_3 AR assay, the trifluorobutyl- and the pentafluoropentylimidazolidinones **1m** and **1n** were at least equipotent with their parent compounds **1b** and **1c**, respectively. We also examined the effect of cycloalkyl groups upon β_3 AR agonist

potency. The cyclopentylpropyl derivative **1o** was twofold more potent than the cyclopentylethyl analog **1p** (β_3 EC_{50} = 5.7 and 13 nM, respectively). A similar trend was seen in the cyclohexyl series; the cyclohexylpropyl- and cyclohexylethylimidazolidinones **1q** and **1r** had β_3 EC_{50} values of 2.5 and 5.8 nM, respectively. The cycloalkyl analogs **1o–r** exhibited good selectivity (> 130-fold) for β_3 AR agonist potency over binding to the β_1 and β_2 ARs. All these imidazolidinones **1** were either inactive or exhibited weak partial agonist activity (< 30% activation at 10 μM) at both the β_1 and β_2 ARs.

Table 2. Comparison of the β_3 AR Agonist Activity and β_1 and β_2 Binding Affinity for Imidazolones **2**



Compound	R	β_3 EC_{50}, nM (%act)[a]	β_1 Binding IC_{50}, nM[b]	β_2 Binding IC_{50}, nM[b]
2a	nHex	14 (56)	18,000	12,000
2b	nOct	3.4 (63)	5,500	330
2c	3,4diFPhCH_2	2.6 (84)	27,000	13,000
2d	$CF_3(CH_2)_3$	25 (53)	100,000	10,000
2e	cPent$(CH_2)_3$	1.6 (61)	5,300	760

[a]Adenylyl cyclase activation given as % of the maximal stimulation with isoproterenol. [b]Receptor binding assays were carried out with membranes prepared from CHO cells expressing the cloned human receptor in the presence of ^{125}I-iodocyanopindolol.

Five imidazolones **2** were synthesized and examined in the β AR assays. Data for these compounds indicated a similar trend to that observed in the imidazolidinone series. Enhancing the lipophilicity of the side chain by either increasing the length of the alkyl chain or adding a hydrophobic group such as phenyl or cyclopentyl produced β_3 AR agonists with improved potency. These compounds all exhibited good to excellent selectivity (97- to 10,000-fold) for β_3 AR agonist potency over β_1 and β_2 AR binding affinities. The imidazolones, like the imidazolidinones, were either inactive or weak partial agonists for the β_1 and β_2 ARs (< 30% activation at 10 μM).

A number of the more potent imidazolidinones and imidazolones were administered (10 mg/kg po, vehicle PEG400/EtOH/0.9% saline, 60/20/20 v/v/v) to fasted dogs and drug levels measured for those that produced a glycerol response. Drug levels were either similar to or lower than those of their respective hexyl derivatives **1d** and **2a**. The oral bioavailability for the cyclopentylpropylimidazolidinone **1o** (dosed 10 mg/kg po, 3 mg/kg iv) was 5%. The aqueous solubilities of imidazolidinone **1o** and the hexylimidazolone **2a** were found to be highly pH dependent, with both compounds showing greatly increased solubility below pH 3.[7] Thus, we decided to measure the bioavailability of these two cyclic ureas in an acidic vehicle. Dogs were dosed with either imidazolidinone **1o** (10 mg/kg po, vehicle 0.1 M citric acid, 3 mg/kg iv) or imidazolone **2a** (10 mg/kg po, vehicle 0.05 M citric acid/0.05 M hydrochloric acid, 3 mg/kg iv) and the bioavailabilities determined to be 17 and 12%, respectively.

The efficacy of the cyclopentylpropylimidazolidinone, L-766,892 (**1o**) was examined in a rising dose infusion study in anesthetized rhesus monkeys.[6b] L-766,892 elicited hyperglycerolemia (ED_{50} = 0.1 mg/kg)

and produced a maximum response equivalent to 75% of that of isoproterenol. No significant change in heart rate was observed up to the highest dose (30 mg/kg) when a 12% increase was measured.

In conclusion, we have shown that enhancing the lipophilicity of the side chain of either the imidazolidinone or imidazolone resulted in more potent β_3 AR agonists whilst still maintaining good selectivity over binding to the β_1 and β_2 ARs. In particular, the cyclopentylpropylimidazolidinone, L-766,892 is a potent β_3 AR agonist (EC_{50} = 5.7 nM, 64% activation) with 420- and 130-fold selectivity over binding to the β_1 and β_2 ARs, respectively. L-766,892 binds to the β_3 AR with an IC_{50} value of 110 nM. L-766,892 was evaluated in a wide range of other receptor and enzyme assays and found to have excellent specificity for the β_3 AR. The data amassed from the SAR study outlined in this paper set the stage for the discovery of a compound that combined the superior potency and selectivity achieved here with excellent bioavailability. This work will be published in the near future.

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References and Notes

1. Present address: Schering Plough Research Institute, Kenilworth, NJ 07033, U.S.A.

2. Parmee, E. R.; Naylor, E. M.; Perkins, L.; Colandrea, V. J.; Ok, H. O.; Candelore, M. R.; Cascieri, M. A.; Deng, L.; Feeney, W. P.; Forrest, M. J.; Hom, G. J.; MacIntyre, D. E.; Miller, R. R.; Stearns, R. A.; Strader, C. D.; Tota, L.; Wyvratt, M. J.; Fisher, M. H.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 749.

3. The enantiomeric excess of aniline **3** was estimated to be 90%. For details of the synthesis and the determination of the enantiomeric excess see Naylor, E. M.; Colandrea, V. J.; Candelore, M. R.; Cascieri, M. A.; Colwell, Jr., L. F.; Deng, L.; Feeney, W. P.; Forrest, M. J.; Hom, G. J.; MacIntyre, D. E.; Strader, C. D.; Tota, L.; Wang, P.-R.; Wyvratt, M. J.; Fisher, M. H.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3087.

4. The sulfonyl chlorides, with the exception of those required for the synthesis of sulfonamides **1j–k**, were prepared according to the procedure outlined in the preceding paper. The sulfonyl chorides, required for the synthesis of sulfonamides **1j–k**, were prepared from the appropriately substituted 4-bromophenylimidazolidinone according to the procedure described in Graham, S. L.; Hoffman, J. M.; Gautheron, P.; Michelson, S. R.; Scholz, T. H.; Schwam, H.; Shepard, K. L.; Smith, A. M.; Smith, R. L.; Sondey, J. M.; Sugrue, M. F. *J. Med. Chem.* **1990**, *33*, 749.

5. The 3-pyridylethanolamines **1** and **2** were prepared as optically active *(R)*-enantiomers. Several pairs of *(R)*- and *(S)*-enantiomers in this 3-pyridylethanolamine series have been synthesized and their β_3 AR agonist activity examined. In each case, in line with expectation, the *(R)*-isomer was 5- to 190-fold more potent than the respective *(S)*-isomer. All final compounds were characterized by NMR, mass spectrometry and HPLC. For experimental details see: Fisher, M. H.; Naylor, E. M.; Weber, A. E. U.S. Patent 5 541 197, 1996; *Chem. Abstr.* **1996**, *125*, 221588.

6. (a) Compounds were assayed for their ability to stimulate increases in cAMP in Chinese hamster ovary (CHO) cells expressing the cloned human β_3 AR. The activity of an agonist at the β_3 AR is best described by its ability to stimulate adenylyl cyclase in a functional assay, since this method measures affinity for the high affinity, G-protein coupled state of the receptor. This assay accurately predicts the lipolytic potential of compounds in native adipocytes.[6b] The β_3 AR IC_{50} values are a measure of the compounds binding affinity for both the high and low affinity states of the β_3 AR, thus are lower than the respective EC_{50} values. The imidazolidinones and imidazolones exhibited very low efficacy at the β_1 and β_2 ARs (< 30% activation at 10 μM), hence the selectivity of the compounds is most accurately represented by comparing the β_3 EC_{50} values with the β_1 and β_2 IC_{50} values. (b) For experimental details see Fisher, M. H.; Amend, A. M.; Bach, T. J.; Barker, J. M.; Brady, E. J.; Candelore, M. R.; Carroll, D.; Cascieri, M. A.; Chiu, S.-H. L.; Deng, L.; Forrest, M. J.; Hegarty-Friscino, B.; Guan, X.-M.; Hom, G. J.; Hutchins, J. E.; Kelly, L. J.; Mathvink, R. J.; Metzger, J. M.; Miller, R. R.; Ok, H. O.; Parmee, E. R.; Saperstein, R.; Strader, C. D.; Stearns, R. A.; Thompson, G. M.; Tota, L.; Vicario, P. P.; Weber, A. E.; Woods, J. W.; Wyvratt, M. J.; Zafian, P. T.; MacIntyre, D. E. *J. Clin. Invest.* **1998**, *101*, 2387.

7. Personal communication from Dr. Karen A. Owens and Ms. Dorothy A. Levorse.