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HUMAN β_3 ADRENERGIC RECEPTOR AGONISTS CONTAINING CYCLIC UREIDOBENZENESULFONAMIDES

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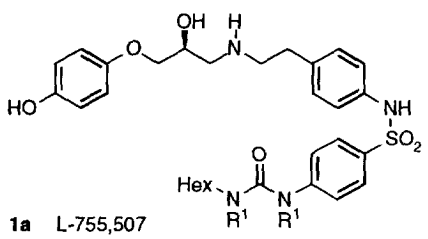
Abstract: Human β_3 adrenergic receptor agonists containing 5-membered ring ureas were shown to be potent partial agonists with excellent selectivity over β_1 and β_2 binding. L-760,087 (**4a**) and L-764,646 (**5a**) (β_3 EC_{50} = 18 and 14 nM, respectively) stimulate lipolysis in rhesus monkeys (ED_{50} = 0.2 and 0.1 mg/kg, respectively) with minimal effects on heart rate. Oral absorption in dogs is improved over other urea analogs.

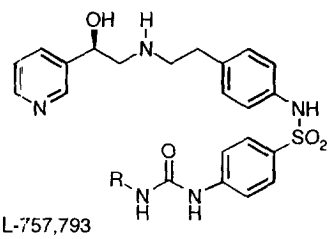
Increasing metabolic rate by activation of the human β_3 adrenergic receptor (β_3 AR) is an attractive approach toward the treatment of obesity.[2] We have recently reported several series of selective human β_3 AR agonists containing a benzenesulfonamide moiety, for example phenol **1a** and pyridines **2**.[3] In the phenolic series, L-755,507 (**1a**) is one of the most potent and selective β_3 AR agonists reported to date with a β_3 EC_{50} value of 0.43 nM, and over 400-fold selectivity over binding to or activation of the β_1 and β_2 ARs.[3b] This compound has also been shown to increase metabolic rate by 30% with minimal effects on heart rate when administered intravenously at a dose of 0.1 mg/kg to anesthetized rhesus monkeys.[4] The highly polar urea moiety, however, is detrimental to oral absorption, and also, the phenolic derivatives have been shown to undergo substantial in vivo glucuronidation.[3c] Cyclic derivatives of L-755,507 (**1b** and **1c**) were prepared in an attempt to reduce the polarity of the molecule whilst maintaining the activity conferred by the urea.[5a] The 6-membered ring analog **1b** was nearly 20-fold less potent than L-755,507 (β_3 EC_{50} = 8.3 nM); however, the imidazolidinone **1c** was only four-fold less potent than the parent urea (β_3 = EC_{50} 1.7 nM) and more selective over binding to the β_1 and β_2 ARs than the 6-membered ring analog (>80-fold selective vs 20-fold).[6,7]



1a L-755,507 [R^1 = H]

1b [R^1 = –$(CH_2)_3$–]

1c [R^1 = –$(CH_2)_2$–]



2a L-757,793 [R = Hex]

2b [R = Oct]

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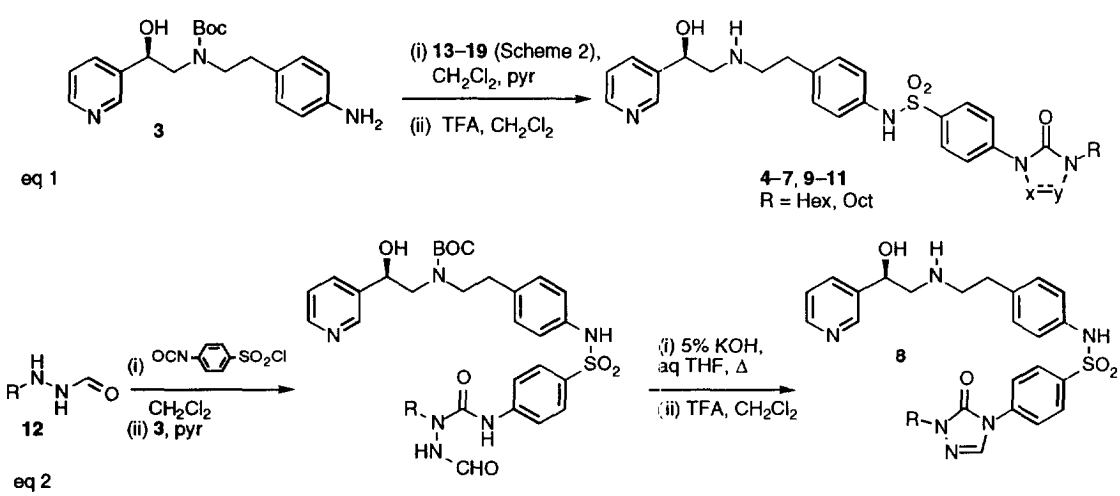
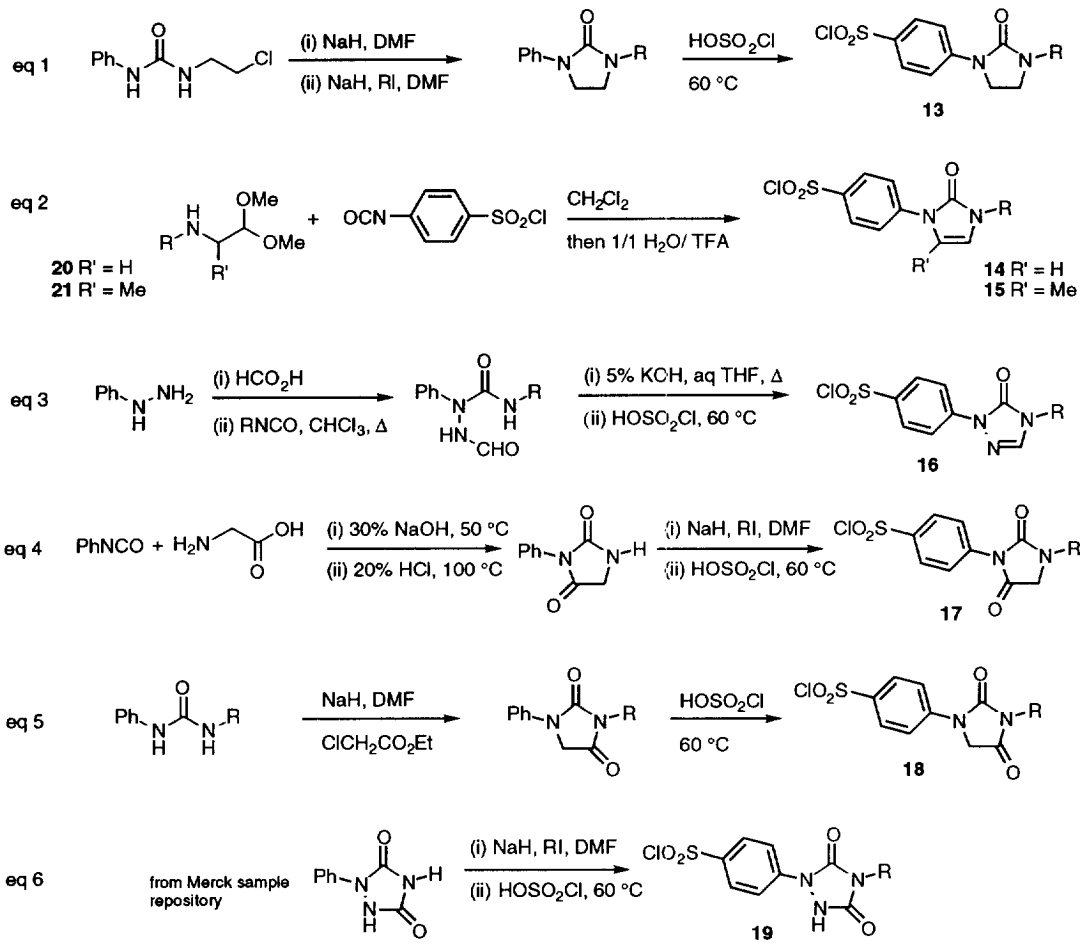
Unlike the phenolic derivatives, the pyridylethanolamines **2** are not prone to glucuronidation. These compounds are selective for the β_3 AR over the β_1 and β_2 ARs, but the ureidobenzenesulfonamide is crucial for β_3 potency. The hexyl and octyl analogs **2a** and **2b**, for example, have EC_{50} values of 6.3 nM and 1.4 nM, respectively.[3d] Oral absorption of the urea containing derivatives was again negligible.[3d] As in the phenol series, we wished to reduce the polarity of these compounds and in this paper we describe the preparation of the more potent imidazolidinones in the (*R*)-pyridylethanolamine series. The study was also extended to include other 5-membered ring urea analogs. As the straight chain hexyl and octyl ureas were among the most potent and selective derivatives, the initial investigation focused only on these two side chains.[3d] Compounds containing a variety of cyclic ureidobenzenesulfonamides were prepared and tested in our cloned human β AR assays.[6,7]

Eight different cyclic urea analogs were chosen [Table 1]; their preparation is shown in Scheme 1.[5] For imidazolidinones **4**, imidazolones **5** and **6**, triazolones **7**, hydantoins **9** and **10**, and triazolidinones **11**, aniline **3** was coupled with sulfonyl chlorides **13–19** and deprotected with trifluoroacetic acid to yield the desired products [Scheme 1, eq 1)].[3d,5] For 2-alkyl-4-phenyl triazolones **8** [Scheme 1, eq 2)], formyl hydrazine **12** was added to 4-(chlorosulfonyl)phenylisocyanate followed by immediate treatment with aniline **3**. Cyclization was then effected with potassium hydroxide which, following deprotection, gave the desired products. Preparation of sulfonyl chlorides **13–19** is shown in Scheme 2, and generally involved treatment of the phenyl substituted heterocyclic rings with chlorosulfonic acid. Sulfonyl chlorides **14** and **15** could not be prepared by this method as the imidazolone ring was not stable to chlorosulfonylation conditions, and so amines **20** and **21** were prepared and added to 4-(chlorosulfonyl)phenylisocyanate [Scheme 2, eq 2)]. Subsequent addition of aqueous trifluoroacetic acid to the reaction effected deprotection and in situ cyclization.

Scheme 1. Synthesis of β_3 AR agonists **4–11** (see Table 1) containing cyclic ureidobenzenesulfonamides.



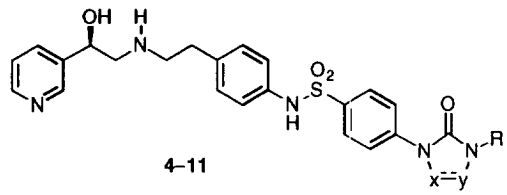
Scheme 2. Synthesis of sulfonyl chlorides **13–19**.



All the analogs were tested at the human β ARs; the in vitro results are shown in Table 1.[6,7] Derivatives **4–10** and **11b** were partial to full agonists of the β_3 receptor (44–100% activation). Hexyl triazolidinone **11a** did not activate the β_3 AR at 100 nM, and hence did not meet our criteria for titration to determine the EC_{50}. As with the pyridylethanolamine urea derivatives **2**, the longer octyl side chain generally gave significantly more potent compounds, although this did not necessarily result in a higher degree of selectivity over binding to the β_1 and β_2 ARs. The hexyl analogs showed no agonist activity at the β_1 and β_2 ARs at 10 μM. The octyl analogs were, however, weak partial agonists at the β_1 receptor (< 30% activation at 10 μM, data not shown).

Octyl imidazolidinone **4b** was the most potent 5-membered ring derivative prepared in the pyridylethanolamine series (β_3 EC_{50} = 2.2 nM), and although the hexyl derivative **4a** was more than eight-fold less potent, both compounds exhibited a similar degree of selectivity over binding to the β_1 and β_2 ARs (>125-fold selective). The unsaturated analogs, imidazolones **5a** and **5b**, showed a very similar trend in potency with the longer chain again resulting in a more potent compound. In this series, however, the hexyl derivative, L-

Table 1. Activity of derivatives **4–11** containing cyclic ureidobenzenesulfonamides at the cloned human β adrenergic receptors.



4–11

Compound	R[a]	x	y	nM β_3 EC_{50} (% act)[b]	β_1 binding IC_{50}[c] (nM)	β_2 binding IC_{50}[c] (nM)
4a	Hex	CH_2	CH_2	18 (62)	5000	2300
4b	Oct	CH_2	CH_2	2.2 (62)	580	380
5a	Hex	CH	CH	14 (56)	18000	12000
5b	Oct	CH	CH	3.4 (63)	5500	330
6a	Hex	CH	CMe	81 (100)	2000	7000
6b	Oct	CH	CMe	60 (100)	2000	7000
7a	Hex	N	CH	6 (56)	8500	4500
7b	Oct	N	CH	5.4 (68)	850	730
8a	Hex	CH	N	100 (44)	>10000	8500
8b	Oct	CH	N	15 (82)	2000	2000
9a	Hex	C=O	CH_2	130 (47)	>10000	>10000
9b	Oct	C=O	CH_2	16 (64)	5000	5000
10a	Hex	CH_2	C=O	13 (70)	7000	2000
10b	Oct	CH_2	C=O	4.9 (65)	2500	370
11a	Hex	N	C=O	(7)[d]	10000	10000
11b	Oct	N	C=O	100 (63)	10000	3000

[a]Hexyl and octyl chains were unbranched for all examples. [b]Adenylyl cyclase activation given as % of the maximal stimulation with isoproterenol. [c]Receptor binding assays were carried out with membranes prepared from CHO cells expressing the cloned human receptor in the presence of ^{125}I-iodocyanopindolol. [d]Single point data, % activation at 100 nM.

764,646 (**5a**), was over 850-fold selective for agonist activity at the β_3 AR over binding to and activation of the other β ARs. L-764,646 binds to the β_3 AR with an IC_{50} value of 81 nM and exhibited excellent selectivity (>100-fold) for agonist activity over a wide range of other receptors which were assayed.

Installation of a methyl substituent into the 4-position of the imidazolone ring resulted in the only compounds (**6a** and **6b**) which gave 100% activation of the β_3 AR. There was, however, a significant loss in potency (β_3 EC_{50} = 60–80 nM). Insertion of a nitrogen atom into the imidazolone ring gave triazolones **7** and **8**. The position of the hetero atom was important to maintain potency at the β_3 AR. Both 4-alkyl-2-phenyl-triazolone derivatives **7a** and **7b** were potent partial agonists of the β_3 AR. Hexyl derivative **7a** also showed excellent selectivity over binding at the β_1 and β_2 ARs (1400-fold and 750-fold, respectively). The alternate isomers **8a** and **8b** were significantly less potent β_3 agonists.

The position of the carbonyl group was also found to be important when the two series of hydantoins **9** and **10** were tested. When the substitution was made in the 4-position (**10a** and **10b**) there was very little difference in potency or selectivity between these two derivatives and the imidazolidinones **4** and imidazolones **5**; octyl derivative **10b** was the most potent (β_3 EC_{50} = 4.9 nM), however, the hexyl analog **10a** was more selective (β_3 EC_{50} = 13 nM, > 160-fold selective over binding at the β_1 and β_2 ARs). The isomeric hydantoins **9a** and **9b** were several times less potent at the β_3 AR than the unsubstituted ring systems, although the octyl analog **9b** did show > 330-fold selectivity over binding to the β_1 and β_2 ARs. Triazolidinones **11** contained both the nitrogen atom and the carbonyl group in the position which led to the most potent triazolone **7** and hydantoin **10**. The effect was not additive as the hexyl analog did not activate the β_3 AR at 100 nM and the longer chain derivative was of modest potency.

Three derivatives (**4a, 4b, and 5a**) were administered intravenously in a rising dose study to anesthetized rhesus monkeys.[8] Hexyl and octyl imidazolidinones **4a** and **4b** show an eight-fold difference in in vitro potency (β_3 EC_{50} = 18 and 2.2 nM, respectively); however, both compounds exhibited a nearly full lipolytic response in vivo with a maximum response 80% of that of isoproterenol and similar ED_{50} values for glycerolemia (0.2 and 0.1 mg/kg, respectively). Minimal heart rate increases were seen at 10 mg/kg (≤15%). L-764,646 (**5a**) had a maximum response which was 60% of that of isoproterenol with an ED_{50} value for glycerolemia of 0.1 mg/kg. This compound showed enhanced selectivity as significant heart rate effects were not seen until a dose of 30 mg/kg was administered.

To establish if these less polar cyclic compounds would have improved absorption, the oral bioavailabilities of two representative compounds, L-760,087 (**4a**) and L-764,646 (**5a**), were determined in dogs (3 mg/kg iv, 10 mg/kg po). Both L-760,087 and L-764,646 had oral bioavailabilities of 7% (PEG/EtOH/saline vehicle) with excellent half-lives (20 and 17 h, respectively). While the bioavailabilities were still relatively low, radiolabelling experiments suggested that removing the highly polar urea had, as hoped, greatly improved absorption. Thus, administration of [^{3}H]-L-760,087 to bile duct cannulated dogs at a dose of 10 mg/kg led to an overall absorption of radioactivity of 29% (12% recovered in the bile and 17% recovered in the urine).[9]

In conclusion, we have identified several new series of human β_3 adrenergic receptor agonists which have good potency and selectivity but do not contain the highly polar urea moiety. L-764,646 (**5a**), in particular, is an exceptionally selective human β_3 agonist (β_3 EC_{50} = 14 nM), with >850-fold selectivity over binding to or activation of the β_1 and β_2 receptors and >100-fold selectivity over all other receptors assayed. When administered intravenously to rhesus monkeys, imidazolone L-764,646, and members of the imidazolidinone series evoke lipolysis at low doses with minimal effects on heart rate. The oral bioavailability of L-760,087 (**4a**) and L-764,646 (**5a**), though still modest, is a marked improvement over the negligible absorption of parent urea L-757,793 (**2a**). It was subsequently found that slight modification both to the side-chain and cyclic ureidobenzenesulfonamide led to human β_3 AR agonists with dramatically improved bioavailabilities. These alterations will be the subject of future publications.

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5. (a) All compounds were characterized by ^{1}H NMR, mass spectrometry, and HPLC analysis prior to submission for biological evaluation. For experimental details see: Fisher, M. H.; Mathvink, R. J.; Ok, H.O.; Parmee, E. R.; Weber, A. E. U. S. Patent 5 451 677, 1995; *Chem. Abstr.* **1996**, *124*, 116877 and Fisher, M. H.; Naylor, E. M.; Weber, A. E. U. S. Patent 5 541 197, 1996; *Chem. Abstr.* **1996**, *125*, 221588. (b) The 3-pyridylethanolamines **4–11** were prepared as the optically active *(R)*-enantiomers from aniline **3** (90% ee).[3d] 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.

6. The human β_3 AR was obtained from Professor J. Grannemann (Wayne State Universtiy), Granneman, J. G.; Lahners, K. N.; Rao, D. D. *Mol. Pharmacol.* **1992**, *42*, 964. The human β_1 and β_2 ARs were cloned as described in Frielle, T.; Collins, S.; Daniel, K. W.; Caron, M. G.; Lefkowitz, R. J.; Kobilka, B. K. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 7920 and Kobilka, B. K.; Dixon, R. A.; Frielle, T.; Dohlman, H. G.; Bolanoski, M. A.; Sigal, I. S.; Yan-Feng, T. L.; Francke, U.; Caron, M. G.; Lefkowsitz, R. J. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 46. The receptors were expressed in CHO cells at receptor densities of 46–88 fmol/mg (β_3 receptors) or 300–500 fmol/mg (β_1 and β_2 ARs). Agonist activity and binding affinity were assessed by measurement of cellular cAMP levels relative to isoproterenol and inhibition of ^{125}I-cyanopindolol binding, repectively.

7. Compounds were assayed for their ability to stimulate increases in cAMP in 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 accurately predicts the lipolytic potential of compounds in native adipocytes.[4] 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. These derivatives 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.

8. All in vivo experiments were performed as described in ref 4.

9. [^{3}H]-L-760,087 was prepared from aniline **3** as described in ref 3c.