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A SIMPLIFIED TEMPLATE APPROACH TOWARDS THE SYNTHESIS OF A POTENT BETA-3 ADRENOCEPTOR AGONIST AT THE HUMAN RECEPTOR

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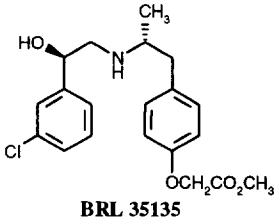
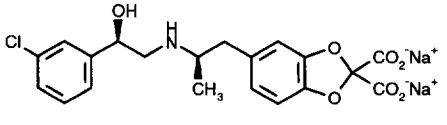
Abstract: *A simplified template approach was used to delineate the structural requirements for high potency and intrinsic activity of aryloxypropanolamines as agonists at the human beta-3 adrenoceptor. The information generated was used to prepare selective beta-3 adrenoceptor agonists.* © 1997, Elsevier Science Ltd. All rights reserved.

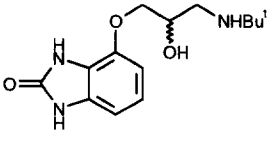
Selective beta-3 adrenoceptor agonists are potential drugs for the treatment of both non-insulin dependent diabetes and obesity. The mechanistic rationale is based upon cAMP mediated events in tissues expressing the beta-3 adrenoceptor[1]. Chronic dosing of beta-3 agonists leads to increased thermogenesis and improved insulin sensitivity. Since the first report[2] describing the existence of an "atypical" or beta-3 receptor several beta-3 agonists, such as the phenylethanolamines BRL 35135[3] and CL 316243[4], have been developed based on rodent assays.



BRL 35135
RR + SS Enantiomers



CL 316243



CGP 12177

However, it is now apparent that there is a significant difference between the pharmacology of the rodent and the human beta-3 adrenoceptor[5]. A major consequence of this pharmacological difference is that some beta-3

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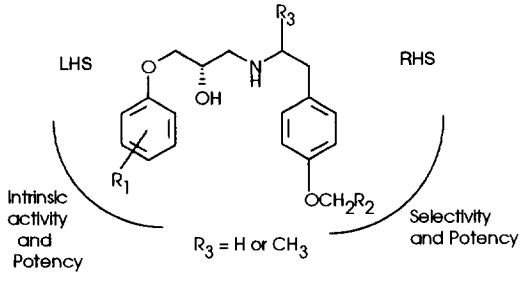
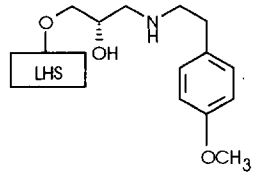
agonists have a lower intrinsic activity (relative to isoprenaline) at the human beta-3 receptor compared with the rodent receptor. In particular, phenylethanolamines such as BRL 35135 and CL 316243 are less active at the human receptor than would be predicted by their activity at the rodent receptor. Consequently, clinical trials with beta-3 adrenoceptor agonists have, so far, been disappointing.

In contrast, it is known that the aryloxypropanolamine CGP 12177 has greater intrinsic activity at the human beta-3 adrenoceptor than at the rodent receptor[5]. In addition aryloxypropanolamines generally exhibit antagonist activity at beta-1 and beta-2 receptors and therefore selectivity with respect to agonist activity should be easier to achieve. This prompted us to design aryloxypropanolamines as novel beta-3 adrenoceptor agonists. Our established SAR and receptor modeling studies, based on a bacteriorhodopsin template, suggested a catechol (R_1 = 3,4-dihydroxyphenyl) or an isosteric replacement on the left hand side (LHS) was necessary for high intrinsic activity, whilst an acidic group (R_2) on the right hand side (RHS) was required to enhance selectivity for the beta-3 over beta-1 and beta-2 adrenoceptors.



1

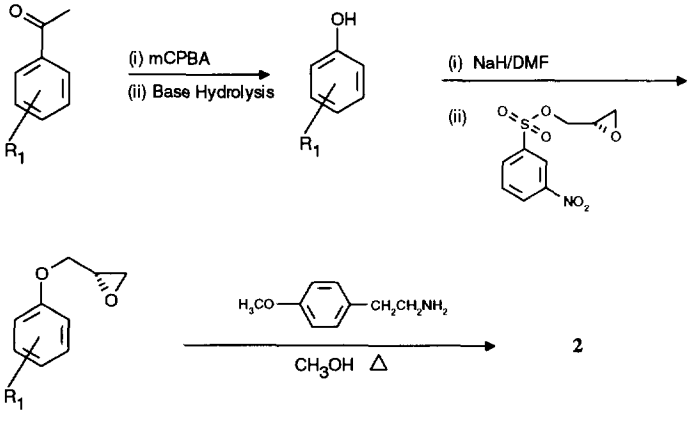


2

The convergent synthetic strategy used for the preparation of chiral aryloxypropanolamines **1** with an acidic RHS (e.g. R_2= CO_2H) is lengthy and inhibits rapid SAR generation. Therefore, in order to expedite the identification of the optimum catechol isostere, with respect to the beta-3 adrenoceptor, a simplified template **2** approach was conceived in which the 4-methoxyphenethyl group replaced the more complex acidic RHS. Such modifications impart sufficient beta-3 adrenoceptor potency to discriminate between different LHS, but do not afford very selective compounds. It was envisaged that leads generated by this simplified template approach could be optimised for beta-3 adrenoceptor selectivity by appropriate RHS substitution. This approach was thought to be particularly suitable for the design of agonists, as it is likely that within a given series agonists adopt similar conformation at the receptor and bind to the same key receptor amino acid residues.

The key LHS precursor phenols where not commercially available were generally prepared from substituted acetophenones or aromatic aldehydes via the Baeyer-Villiger reaction. The requisite phenols for **10**, **17**, **18**, **19** and **20** were prepared according to literature procedures[6,7,8]. Alkylation of the phenols with (2*S*)-(+)-glycidyl 3-nitrobenzenesulfonate and subsequent epoxide ring opening with 4-methoxyphenethylamine furnished analogues **2** in high enantiomeric purity and consistent with literature precedent[9] (*S*-enantiomer, see Scheme). For compounds **15** and **16** 2-amino-3-nitrophenol was initially *O*-alkylated with (2*S*)-(+)-glycidyl 3-nitrobenzenesulfonate and the bicyclic ring constructed[10,11] after epoxide ring opening with 4-methoxyphenylethylamine.

Scheme



Since the natural agonists adrenaline and noradrenaline are catechols it was anticipated that the analogue **3** should have good beta-3 potency. Our results (Table) show that **3** was a potent beta-3 agonist, compared with CGP 12177, and exhibited full intrinsic activity relative to isoprenaline. However, it is known that adrenaline has a short duration of action due to methylation[12] of the *meta*-hydroxy group to give the inactive ether and therefore **3** might be expected to behave similarly. Furthermore **3** exhibits chemical instability and is likely to undergo oxidative degradation in solution under aerobic conditions. The spatial arrangement of the two hydroxyl groups for interaction at the beta-3 receptor is clearly important as the isomeric 2,3-dihydroxyphenyl **4** was inactive. For the chemically stable monohydroxy analogues **5-7** the relative order of potency was 4-OH> 3-OH>>2-OH, although there was an indication that **6** has higher intrinsic activity. The sequential replacement of the 3- or 4-hydroxyl by fluorine, as in **8** and **9**, lowered intrinsic activity compared with **3** although the beta-3 potency for **9** was similar. With a combination of hydroxyl and methanesulfonylamino group, as in **10**, we were successful in achieving a potent and efficacious compound comparable to **3** with an improved activity

profile compared with CGP 12177. Presumably the sulfonamido N-H is able to mimic a hydroxyl whereas the 3-fluoro substituent in **8** is not a suitable replacement for a hydroxyl.

One effective replacement to catechols is the 3-hydroxymethyl-4-hydroxyphenyl moiety derived from beta-2 agonist work[13]. Inclusion of this moiety in **11** gave a less potent compound compared with **3** and the isomeric analogues **12** and **13** were inactive, again indicating a preference for 3,4 substitution pattern over other combinations. Surprisingly replacement of the 4-hydroxy by fluorine, as in **14** resulted in loss of activity whereas a similar substitution pattern as in **9**, retained activity.

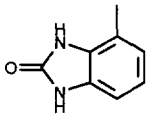
Table: Simplified Template Derivatives

COMPOUND	Structure 2 (LHS)	Beta-3 EC_{50} μM^a	Intrinsic Activity^b
Isoprenaline		1.0	1.0
CGP 12177		2.0	0.7
3	3,4-dihydroxyphenyl	0.82	1.0
4	2,3-dihydroxyphenyl	inactive	
5	2-hydroxyphenyl	inactive	
6	3-hydroxyphenyl	2.0	0.4
7	4-hydroxyphenyl	1.0	0.16
8	3-fluoro-4-hydroxyphenyl	7.9	0.23
9	3-hydroxy-4-fluorophenyl	1.1	0.33
10	3-methanesulfonylamino-4-hydroxyphenyl	0.40	0.9
11	3-hydroxymethyl-4-hydroxyphenyl	4.7	0.5
12	2-hydroxymethyl-4-hydroxyphenyl	inactive	
13	3-hydroxymethyl-5-hydroxyphenyl	inactive	
14	3-hydroxymethyl-4-fluorophenyl	inactive	

a Adenylate Cyclase assay (reference 14) performed on chinese hamster ovary cells transfected with the human beta-3 adrenoceptor, n= 2 or 3. *b* intrinsic activity (IA) measured relative to isoprenaline = 1

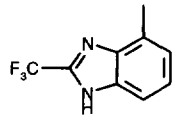
Of the heterocyclic LHS the benzimidazolone **15** had comparable potency with CGP 12177, whereas replacement of the benzimidazolone carbonyl by a trifluoromethyl group **16** gave an inactive compound. The carbostyril derivatives **18** and **19** derived from carteolol, which has been reported to be thermogenic in mice[15], were inactive. However, introduction of a hydroxyl group as in **20** conferred high potency and intrinsic activity. The hydroxyl group is clearly important as the related benzoxazine analogue **17** was inactive.

A general trend from the results presented here indicates that with aryloxypropanolamines 3,4-substitution of the phenyl ring with hydrogen bonding capability is a necessary feature for beta-3 activity. The exception to this trend is analogue **15** which is a potent beta-3 agonist containing a 2,3-substituted phenyl. Interestingly, a 3,4- arrangement of the benzimidazolone ring system gave an inactive compound[16].

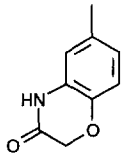


15

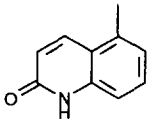
Beta-3 EC_{50} 2.2μM, IA 1.0



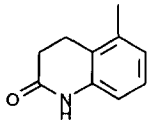
16



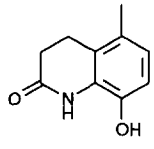
17



18



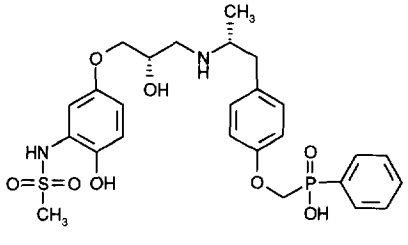
19



20

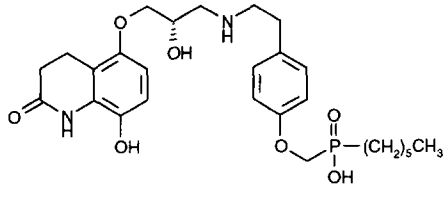
Beta-3 EC_{50} 0.56μM, IA 0.8

In this manner we have devised an effective simplified template approach towards identification of catechol isosteres. Using this approach we have identified the methanesulfonylamino analogue **10** and the carbostyril **20** as important leads in identifying potent beta-3 adrenoceptor agonists. As expected these simplified template analogues were not selective for the beta-3 over beta-1 and beta-2 adrenoceptors.



21

Beta-3 EC_{50} 0.12μM, IA 1.29



22

Beta-3 EC_{50} 0.29μM, IA 0.84

To gain selectivity the neutral 4-methoxyphenyl group was replaced with phenylphosphinic, or *n*-hexylphosphinic acid moieties to afford compounds **21**[17] and **22**[18] respectively. Both compounds showed high potency and intrinsic activity compared to CGP 12177. Compound **21** in particular exhibited low affinity

for the beta-1 and beta-2 adrenoceptor suggesting good selectivity for the beta-3 adrenoceptors. Further exploitation of the leads obtained by this simplified template approach will be reported in due course.

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