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Bioorganic & Medicinal Chemistry Letters 17 (2007) 4290–4296
Bioorganic & Medicinal Chemistry Letters

Arylpropanolamines: Selective β_3 agonists arising from strategies to mitigate phase I metabolic transformations

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Received 9 April 2007; revised 7 May 2007; accepted 9 May 2007
Available online 16 May 2007

Abstract—Utilization of N-substituted-4-hydroxy-3-methylsulfonanilidoethanolamines **1** as selective β_3 agonists is complicated by their propensity to undergo metabolic oxidative N-dealkylation, generating 0.01–2% of a very potent α_1 adrenergic agonist **2**. A summary of the SAR for this hepatic microsomal conversion precedes presentation of strategies to maintain the advantages of chemotype **1** while mitigating the consequences of N-dealkylation. This effort led to the identification of 4-hydroxy-3-methylsulfonanilidopropanolamines **15** for which the SAR for the unique stereochemical requirements for binding to the β adrenergic receptors culminated in the identification of the potent, selective β_3 agonist **15f**.

In prior papers we described the SAR of 4-hydroxy-3-methylsulfonoanilidoethanolamines **1** which yielded three selective β_3 adrenergic agonists as clinical candidates for treatment of diabetes and obesity.[1–3] Given the uncertainty as to whether adequate depots of brown adipose tissue were present in adult humans to elicit a thermogenic response,[4] we believed that full β_3 agonists represented the best chance for achieving Proof of Principle. The discovery that, out of 50 different catechol amine surrogates evaluated, only chemotype **1** were full β_3 agonists ensured our commitment to compounds possessing the 4-hydroxy-3-methyl-sulfonanilido moiety found in **1** despite the propensity for liberation of low levels of a potent α_1 adrenergic agonist **2**.[5] This paper, after delineating the SAR for metabolic conversion of **1**–**2**, focuses on our efforts to maintain the advantages of series **1** while mitigating the consequences of phase I metabolic N-dealkylation.

Cytochrome P-450 mediated N-dealkylation of **1** was not unexpected, given the facile cleavage of carbon–nitrogen bonds.[6] However, this transformation was a particularly serious problem for chemotype **1** since the N-substituent determined the adrenergic agonist profile. Although β_3 adrenergic agonists containing chemotype **1** have been reported by others, no mention of metabolite **2** exists.[7] Due to our concerns regarding release of **2**, the safety of compounds **1** was confirmed by iv administration of **1** at 10 mg/kg to mice, which are extremely sensitive to **2**,[8] prior to administration of **1** to *African green* monkeys (AGM). Our efforts to surmount the formidable challenge posed by 0.01 to ~2% in vivo metabolic conversions of **1**–**2** are described herein.

Incubation of representative examples of **1** with human, AGM, and rat hepatic microsomes suggested that the conversions of **1**–**2** were 3- and 10-fold greater, respectively, for AGM and rat than for human.[9] The 10,000-fold difference in amounts of **2** released by AGM hepatic microsomal oxidation illustrates the highly structure dependent nature of this metabolic pathway (Table 1).

Keywords: β_3 Agonists; Metabolic oxidative N-dealkylation; Arylpropanolamine; Drug metabolism.
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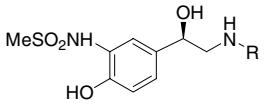
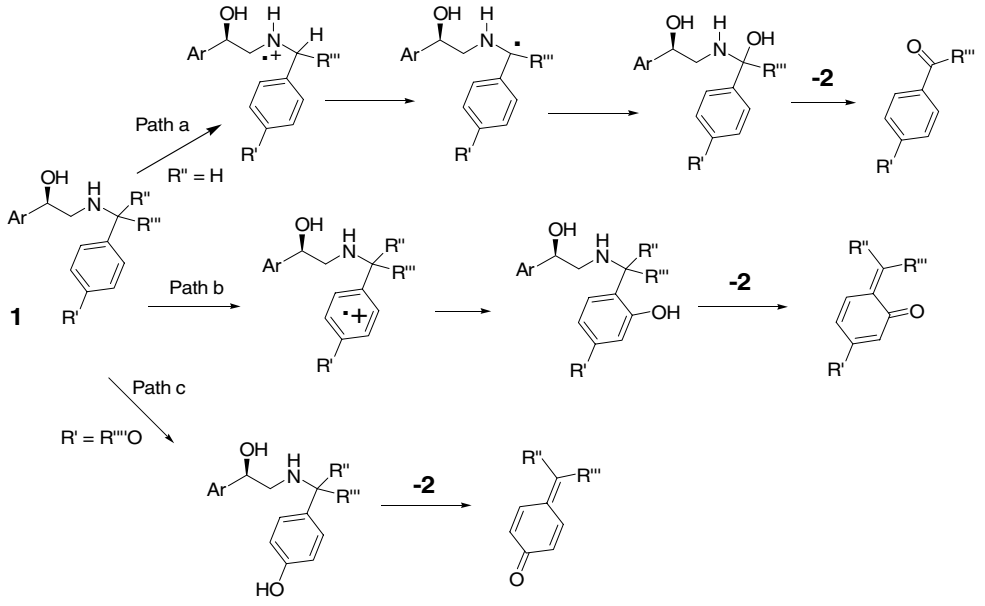
doi:10.1016/j.bmcl.2007.05.030

Moreover, the SAR suggested that, depending on 'R', N-dealkylation could occur via one of three different pathways (Scheme 1). Mechanistic studies suggested that N-dealkylation of amines such as **1a**–**1c** for which C_α is not quaternary proceeds via oxidative conversion to a carbinolamine with subsequent collapse. As outlined in path 'a', the carbinolamine arises via electron transfer to generate an amine radical cation and subsequent loss of a proton followed by oxygen rebound capture of the benzylic radical to generate a carbinolamine intermediate.[6a] If C_α is quaternary and an adequately stabilized aryl radical cation can be generated, we envisage a second route 'b' liberating **2** could become operative. This pathway entails electron transfer to generate an aryl radical cation that is subsequently hydroxylated to generate an *ortho* substituted phenol.[6b] Conversion of the latter to an *ortho* quinine methide would simultaneously release **2**. Formation of **2** by this pathway would predict a marked dependence on the α-aryl ring substituent(s), since the latter would modulate the oxidation potential. Detection of 10,000-fold more **2** generated from microsomal incubation of **1e** than from **1d** is consistent with this pathway, as is the 25-fold enhanced formation of **2** from **1f** versus **1b**. The finding that phenol **1g** spontaneously released **2** presumably via the non-enzyme mediated quinone methide route 'c' was particularly noteworthy since the amine substituent 'R' of **1** routinely contained a *para* phenolic ether attached to C_α to enhance β_3 selectivity. This latter pathway, necessitating P450 mediated oxidative O-dealkylation, would account for the inability to totally suppress release of **2** from compounds such as **1i** and **1j** and possibly **1h** for which the first two pathways would not be expected to be operative. Efforts to further modify 'R' to preclude any formation of **2** were not compatible with maintenance of high β_3 activity and selectivity.[10]

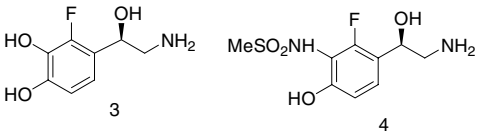
Table 1. % Conversion of **1a**–**1j** to **2** after 3-h incubation at 37 °C with AGM hepatic microsomes[9]



Compound[1–3]	R	% Conversion in vitro to 2
1a	(*S*)-CH(Ph-*p*-OMe)CONPh	0.05
1b	–CH(Ph-*p*-$OCHF_2$)$_2$	0.2
1c	(*R*)-CH(Ph-*p*-$OCHF_2$)CH_2Ph	1.1
1d	–CMe_2Ph	0.001
1e	–CMe_2-Ph-4-OMe	28
1f	–CH(Ph-*p*-OMe)$_2$	5
1g	(*R*)-CH(Ph-*p*-OH)CH_2(Ph-*p*-F)	2.2
1h	–CMe(Ph-*p*-$OCHF_2$)$_2$	0.1
1i	(*S*)-CMe(Ph-*p*-OMe)CONPh	0.57
1j	(*S*)-CMe(Ph-*p*-OMe) CONPh-4-PO(OEt)$_2$	0.49



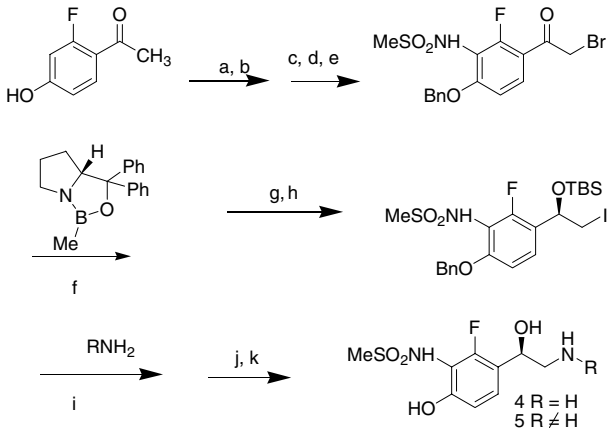
Scheme 1. Oxidative pathways leading to release of **2**.



Prior investigators had reported that the *ortho* fluorine of **3** virtually eliminated the α adrenergic activity of noradrenaline and adrenaline while maintaining β_1 and β_2 activity.[11] The abolition of α activity was attributed to the conformational constraints imposed on the ethanolamine side chain due to hydrogen bonding of the benzylic hydroxyl to the aryl fluoride.[12] In our in vitro assays, the β_3 agonist profile of **3** was similar to that of noradrenaline: β_3 affinity of **3** (8100 nM) was twice that of noradrenaline (18,000 nM); moreover, the β_3 intrinsic activities (IA) were 75% and 91%, respectively, for **3** and noradrenaline. Both compounds exhibited similar binding selectivities of 0.05 and 0.3 versus β_1 and β_2, respectively, where selectivity is defined as the ratio of β_1 K_i or β_2 K_i to β_3 K_i.

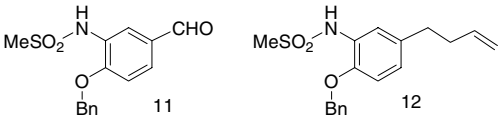
Accordingly, **4**, the *o*-fluoro counterpart of **2**, was prepared (Scheme 2). As expected, **4** was devoid of α agonist activity; however, **4** was a β_3 antagonist exhibiting 10-fold diminished β_3 affinity relative to **2**, although the β_1 and β_2 affinities of **2** and **4** were comparable. In hopes of enhancing β_3 agonist activity, a series of N-substituted analogs of **4** were prepared. The 10-fold or greater diminution in β_3 affinity of these fluorinated compounds **5a**–**5d** when compared to a corresponding set of des-fluoro β_3 agonists **1a**, **1c**, **1e**, and **1f** was disappointing (Table 2). In addition, these fluorinated compounds tended to be partial β_3 agonists.

An alternative approach entailing elongation of the spacer between the catechol surrogate and the ethanolamine moiety was prompted by the report of Beeley et al. of aryloxypropanolamines exhibiting β_3 agonist activity.[17] Our finding that **6**, the 4-hydroxy-3-methylsulfonoamidophenoxypropanolamine counterpart of **2**, exhibited little α adrenergic activity was sufficiently promising to warrant the synthesis of analogs **7a**–**7c**. The key synthetic step was a Baeyer–Villiger oxidation of a SEM protected 4-hydroxy-3-nitrobenzaldehyde to generate the prerequisite phenol **8** necessary for subsequent transformation to the enantiomerically pure chiral epoxide **9** (Scheme 3). Heating of **9** with an appropriate amine generated **7a**–**7c**. Unlike the aryl ethanolamine counterparts **1c** and **1k**, N-substitution with (*R*)-1,2-diarylethyl moieties generated high affinity albeit partial β_3 agonists such as **7b** and **7c** (Tables 2 and 3). However, once the susceptibility of **7a**–**7c** to air oxidation became apparent, SAR delineation ceased for this series.[18]



Scheme 2. Reagents and conditions: (a) HNO_3, AcOH, 50 °C, 25%; (b) NaH, BnBr, DMF, 90%; (c) $SnCl_2$, EtOH, 89%; (d) MsCl, Pyr, 94%; (e) Br_2, dioxane, 60 °C, 86%; (f) $BH_3{\cdot}Me_2S$, THF, 96% (98.2% ee); (g) NaI, acetone, 65 °C, 96%; (h) TBSCl, DMAP, ImH, DMF, 100%; (i) $EtN(i\text{-}Pr)_2$, heat, 120 °C, 50–75%; (j) KF, THF; (k) H_2, MeOH, 85% (2 steps).

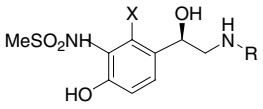
The oxidatively more robust arylbutanolamine counterparts **10a**–**10c** were briefly examined. Synthesis of arylbutanolamines **10a**–**10c** entailed conversion of 4-hydroxybenzaldehyde to **11**.[19] Sequential treatment of **11** with allyl magnesium Grignard, mesylation, and $LiAlH_4$ reduction generated 4-(4-benzyloxy-3-methylsulfonamido-phenyl)-1-butene **12** which after epoxidation with MCPBA, condensation with the appropriate amine, and debenzylation yielded compounds **10a**–**10c**. However, their markedly inferior β_3 affinity and intrinsic activity relative to chemotype **1** discouraged sustained efforts.



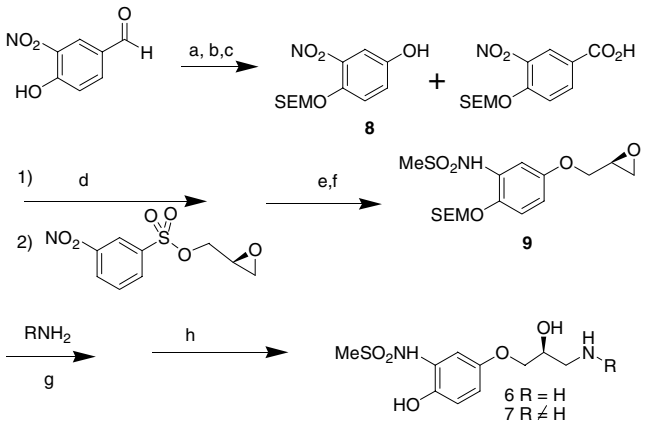
The finding that insertion of a two-atom spacer between the ethanolamine moiety and the catechol surrogate abolished α agonist activity of **6** prompted homologation of **2** to generate the corresponding 3-arylpropan-2-ol-1-amine **13**. Diazotization of chiral 3-nitrotyrosine in aq H_2SO_4 proceeded with retention to generate chiral α-hydroxy acid **14**. Conversion of **14** to the primary amine **13** and selected analogs **15** by solution chemistry entailed condensation with an appropriate amine, followed by borane reduction (Scheme 4). However, most N-substituted analogs **15** were prepared combinatorially via solid state synthesis.[20]

Encouraged by the finding that **13** was devoid of α adrenergic activity, the SAR of this chemotype was further elucidated. All three β receptors exhibited an atypical stereochemical preference for ligands containing homobenzylic alcohols with *S* chirality, which is opposite to the projection of the hydroxyl preferred for arylethanolamines or aryloxypropanol-amines.[21] In particular, the affinity of the β_3 receptor was 10-fold greater for the *S* configured homobenzylic alcohols **15b** and **15d** than the corresponding *R* isomers **15a** and **15c** (Table 4).

Table 2. β_3 Affinity and intrinsic activity for 2-fluoro4-hydroxy-3-methyl-sulfonoanilidoethanolamines **4** and **5** relative to **1** and **2**[13]



R	X = H[16]			X = F[16]		
	Compound	β_3 K_i (nM)	β_3 IA	Compound	β_3 K_i (nM)	β_3 IA
H	**2**	17,000	93	**4**	120,000	0
(*S*)-CH(Ph-*p*-OMe)CONPh	**1a**	77	119	**5a**		58
(*R*)-CH(Ph-4-$OCHF_2$)-CH_2Ph	**1c**	21	107	**5b**	270	77
–CMe_2Ph-4-OMe	**1e**	7	86	**5c**	200	88
–CH(Ph-4-$OMe)_2$	**1f**	81	100	**5d**	1700	24
(*R*)-CHPh-3,4-$(OMe)_2$-CH_2Ph	**1k**	11	110			

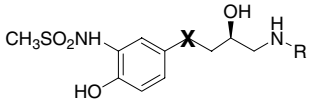


Scheme 3. Reagents and conditions: (a) SEMCl, EtN(*i*-Pr)$_2$, CH_2Cl_2, 82%; (b) MCPBA, CH_2Cl_2; (c) NaOH/H_2O/MeOH, 19% (2 steps); (d) NaH, DMF, 94%; (e) H_2, EtOAc, PtO_2; (f) Ms_2O, CH_2Cl_2, 95% (2 steps); (g) excess RNH_2, 100 °C, 65%; (h) TFA, EtOH, 40–70%.

A more complete SAR pattern emerged following characterization of the four diastereomers **15e**–**15h**. β_3 affinity was enhanced by >5-fold if the chirality of the homobenzylic alcohol was *S* (compare K_i β_3 of **15f** and **15g** to that of **15e** or **15h**). The *S*,*R* diastereomer **15f** was not only the most potent β_3 agonist of these four diastereomers but also was the only full β_3 agonist.[23] Both β_1 and β_2 affinities were greatest for **15g**, the *S*,*S* diastereomer. In addition, β_1 IA was somewhat reduced for **15f** versus for **15g**; whereas, β_2 IA remained an invariant 100% for both of these diastereomers.[24] These fortuitous divergences in the stereochemical preferences for the three β receptors offered additional means to enhance β_3 in vivo selectivity. These findings also underscore the divergence in IA sensitivity to the ligand/receptor interactions, β_1 being the most sensitive, β_2 the least.

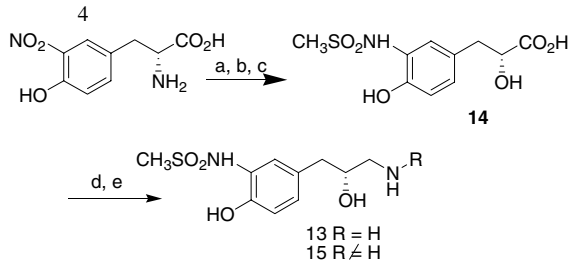
Proper orientation of this ligand in the β_3 receptor appeared dependent on the α-aryl ring being 3,4-disubstituted with oxygen substituents. The diminished affinity and β_3 IA of **15b** or **15d** relative to **15f** underscore the importance of both methoxyls on the α-aryl ring to elicit a strong β_3 agonist response; whereas, only the 4-methoxyl is essential for the corresponding arylethanolamine series **1**.[1] The effect was not steric in origin, since selectivity was ablated upon replacement of both methoxyls with chlorine (**15i**). Reduction in the acceptor hydrogen bonding potential of the phenolic oxygen appendages correlated with loss of selectivity; compare **15f** or **15j**–**15k**.

Table 3. β_3 AR agonist activity and selectivity versus β_1 and β_2 for 4-hydroxy-3-methylsulfonoamidophenoxypropanolamines **6** and **7a**–**7c**, and 4-hydroxy-3-methylsulfonoamidophenoxybutanolamines **10a**–**10c**[13]



R[16]	Compound	β_3 K_i (nM)	β_3 IA (% act)	Selectivity[a] versus	
				β_1	β_2
	X = O				
H	**6**	15,000	47	0.08	0.04
–CH_2Ph-4-OMe	**7a**	360	46	3	0.4
(*R*)-CH(Ph-4-$OCHF_2$)-CH_2Ph	**7b**	5	48	66	7
(*R*)-CHPh-3,4-$(OMe)_2$-CH_2Ph	**7c**	3	67	120	15
	X=CH_2				
–CH_2Ph-4-OMe	**10a**	3700	42	1	1
(*R*)-CH(Ph-4-$OCHF_2$)-CH_2Ph	**10b**	880	40	38	7
(*R*)-CHPh-3,4-$(OMe)_2$-CH_2Ph	**10c**	160	60	112	27

[a] Selectivity is defined as the ratio of β_1 K_i or β_2 K_i to β_3 K_i.

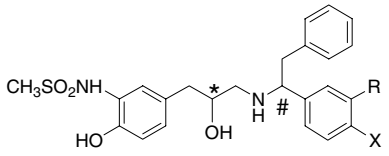


Scheme 4. Reagents and conditions: (a) $NaNO_2$, aq H_2SO_4, 0 °C 71%; (b) H_2, 10% Pd/C, MeOH, 95%; (c) MesCl, py 63% (2 steps); (d) RNH_2, EDC, HOAt, DMF, 20 °C; (e) BH_3, THF).

Further modifications of the N-substituent are shown in Table 5. Chlorination of the β-aryl ring to generate **15l**–**15n** was not beneficial, since β_3 IA decreased compared to **15f**. Deletion of either the β-aryl ring (**15o**) or α-aryl ring (**15p**) severely reduced β_3 affinity and essentially eliminated any selectivity for β_3. Incorporation of the two aryl rings in a symmetrical amine substituent was not encouraging; both the 1,1-diarylmethyl substituent **15q** and the 1,3-diaryl-2-propyl moiety **15r** produced a 50-fold decrease in β_3 affinity and loss of selectivity versus β_1 and β_2 receptors.

However, the β adrenergic profile of **16a**, arising from homologation of **15f**, encouraged further SAR elucidation (Table 6). The high β_3 affinity of **16a** was dependent on both methoxyls just as was the case for **15f**. The interaction between the *para* methoxyl and the β_3 receptor appears the more important; compare the 5-fold reduced β_3 selectivity and affinity of **16b** to the 40-fold reduction in β_3 affinity of **16c**. Replacement of the methoxyls with difluoromethoxy (**16d**) reduced β_3 affinity and increased β_1 and β_2 affinity. Substitution of the γ-aryl ring was not promising: an *ortho* (**16e**) or *meta* (**16f**) chlorine enhanced β_1 and β_2 affinity while decreasing that of β_3, whereas a *para* chlorine (**16g**) produced little effect on β_3 selectivity or affinity.

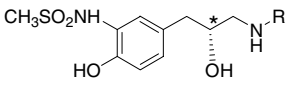
Table 4. SAR for agonist activity for β_3 AR compared to β_1 and β_2 AR for 4-hydroxy-3-methylsulfonoamidophenylpropanolamines **15a**–**15k**[13]



Compound[16]	R	X	Chirality		β_3 K_i[a] (% β_3 IA)	β_1 K_i[a] (% β_1 IA)[24]	β_2 K_i[a]
			*	#			
15a	OMe	H	*R*	*R*	1100 (27)	>10,000 (0)	2700
15b	OMe	H	*S*	*R*	110 (44)	3600	350
15c	H	OMe	*R*	*R*	460 (30)	>10,000 (0)	3100
15d	H	OMe	*S*	*R*	53 (65)	6000	510
15e	OMe	OMe	*R*	*R*	25 (43)	>10,000 (0)	1500
15f	OMe	OMe	*S*	*R*	6 (86)	2600 (60)	66
15g	OMe	OMe	*S*	*S*	9 (62)	560 (75)	24
15h	OMe	OMe	*R*	*S*	150 (70)	47,000 (48)	820
15i	Cl	Cl	*S*	*R*	133 (70)	1500	38
15j	OH	OMe	*S*	*R*	8 (70)	3200	1070
15k	$OCHF_2$	$OCHF_2$	*S*	*R*	19 (60)	690 (0)	102

[a] Expressed in nM.

Table 5. β_3 AR agonist activity and selectivity versus β_1 and β_2 for 4-hydroxy-3-methylsulfonoamidophenylpropanolamines **15l**–**15r**[13]

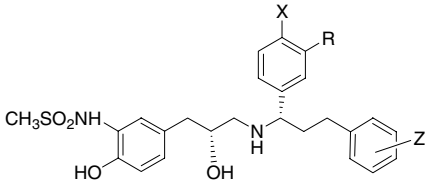


Compound[16]	R	*	β_3 K_i[a] (% IA)	Selectivity[b]	
				β_1	β_2
15l	(*R*)-CH(Ph-3,4-$(OMe)_2$)CH_2Ph-2-Cl	*S*	7 (65)	58	13
15m	(*R*)-CH(Ph-3,4-$(OMe)_2$)CH_2Ph-3-Cl	*S*	6 (68)	52	13
15n	(*R*)-CH(Ph-3,4-$(OMe)_2$)CH_2Ph-4-Cl	*S*	24 (68)	24	6
15o	CH_2Ph-4-OMe	Rac	1100(50)	2	0.3
15p	CH_2CH_2Ph-3,4-$(OMe)_2$	Rac	7300(35)	0.6	0.1
15q	CH(Ph-4-$OCHF_2)_2$	*S*	340 (60)	3	0.6
15r	CH(CH_2Ph-3,4-$(OMe)_2)_2$	*S*	170 (75)	3	0.2

[a] Expressed in nM.

[b] Selectivity is defined as the ratio of β_1 K_i or β_2 K_i to β_3 K_i.

Table 6. SAR for agonist activity for β_3 AR compared to β_1 and β_2 AR for 4-hydroxy-3-methylsulfonoamidophenylpropanolamines **16a**–**16g**[13]



Compound[16]	R	X	Z	β_3 K_i[a] (% β_3 IA)	β_1 K_i[a] (β_3 Sel)[b]	β_2 K_i[a] (β_3 Sel)[b]
16a	OMe	OMe	H	9 (84)	1000 (111)	390 (43)
16b	H	OMe	H	31 (93)	730 (24)	280 (9)
16c	OMe	H	H	390 (44)	570 (1)	200 (0.5)
16d	$OCHF_2$	$OCHF_2$	H	59 (86)	490 (8)	71 (1)
16e	OMe	OMe	2-Cl	7 (73)	270 (39)	57 (8)
16f	OMe	OMe	3-Cl	29 (57)	420 (14)	26 (1)
16g	OMe	OMe	4-Cl	12 (89)	1050 (88)	120 (10)

[a] Expressed in nM.
[b] Selectivity is defined as the ratio of β_1 K_i or β_2 K_i to β_3 K_i.

Table 7. In vivo response of *African Green* Monkeys

Compound	AGM response to 0.1 mg/kg iv dose		
	Δ HR	Δ K^+	Δ FFA
1c	+26*	+0.08	1.05*
5d[a]	+4	−0.49	+0.39
15f	+24	−0.08	1.06*
15m	6	−0.55*	0.92*
16a	+29*	−0.25*	0.95*
16g	32*	−0.32*	0.87*

[a] Administered iv at 0.5 mg/kg.
* $P < 0.05$.

Table 8. Dose–response of *African Green* Monkeys (iv administration)

Compound	Lipolysis ED_{50} (mg/kg)	β_1 margin before onset of tachycardia[a]	β_2 margin before decrease in serum K^+[a]
15f	0.009	>3 < 11	>55
1b (194449)	0.08	>6 < 12	>60
1c (196085)	0.03	>3 < 5	>25
1j (201620)	0.1	>25	>25

[a]The margin of separation was the ratio of the dose that produced the onset (statistically significant) of a β_1 or β_2 event to the ED_{50} for lipolysis.

The in vivo β_3 activity of the more promising compounds was ascertained following iv administration to ketamine sedated *African green* monkeys (AGM) by monitoring the β_3 induced increase in free fatty acid levels (FFA). A dose–response was determined for those compounds which produced a statistically significant elevation in free fatty acid (Δ FFA) unaccompanied by β_2 mediated decrease in serum K^+ concentrations[26] (Δ K^+) or β_1 or β_2 induced tachycardia (HR). The fluorinated hydroxysulfonanilides **5** produced weak responses consistent with partial β_3 agonist activity (Table 7). For example, 0.5 mg/kg of **5d** induced an increase in FFA levels less than that induced by **1c** (**BMS-196085**) at 0.1 mg/kg. The lack of separation between the β_3 and β_2 mediated responses for compounds **15m**, **16g**, and particularly **16a** was disappointing.

Only **15f** offered any promise as a selective thermogenic agent; however the margins between the ED_{50} dose for lipolysis and the doses inducing the onset of significant β_1 or β_2 mediated events were not superior to that previously determined for the three clinical candidates (Table 8).

Efforts to continue to progress either **15f** or alternatively to identify a superior analog ceased once the inability of **BMS-196085** to induce a persistent thermogenic response in the clinic became apparent.[2]

Acknowledgments

We acknowledge the contributions of members of the Bristol-Myers Squibb analytical chemistry department, D. Kirk for a sample of **3**, and D. Strosberg for transfected CHO cells.

References and notes

1. Washburn, W. N.; Sher, P. M.; Poss, K.; Girotra, R. N.; McCann, P. J.; Gavai, A. V.; Mikkilineni, A. B.; Mathur, A.; Cheng, P.; Dejneka, T. C.; Sun, C. Q.; Wang, T. C.; Harper, T. W.; Russell, A. D.; Slusarchyk, D. A.; Skwish, S.; Allen, G. T.; Hillyer, D. E.; Frohlich, B. H.; Abboa-Offei, B. E.; Cap, M.; Waldron, T. L.; George, R. J.; Tesfamariam, B.; Ciosek, C. P.; Young, D. A.; Dickinson, K. E.; Seymour, A. A.; Arbeeny, C. M.; Gregg, R. E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 3035.
2. Gavai, A. V.; Sher, P. M.; Mikkilineni, A. B.; Poss, K. M.; McCann, P. J.; Girotra, R. N.; Fisher, L. G.; Wu, G.; Bednarz, M. S.; Mathur, A.; Wang, T. C.; Sun, C. Q.; Slusarchyk, D. A.; Young, D. A.; Dickinson, K. E.; Seymour, A. A.; Arbeeny, C. M.; Washburn, W. N. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 3041.
3. Washburn, W. N.; Sun, C. Q.; Bisacchi, G.; Wu, G.; Cheng, P.; Sher, P. M.; Ryono, D.; Gavai, A. V.; Poss, K.; Girotra, R. N.; McCann, P. J.; Mikkilineni, A. B.;

Dejneka, T. C.; Wang, T. C.; Merchant, Z.; Morella, M.; Arbeeny, C. M.; Harper, T. W.; Slusarchyk, D. A.; Skwish, S.; Russell, A. D.; Allen, G. T.; Tesfamariam, B.; Frohlich, B. H.; Abboa-Offei, B. E.; Cap, M.; Waldron, T. L.; George, R. J.; Young, D.; Dickinson, K. E.; Seymour, A. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3525.

4. Himms-Hagen, J.; Ricquier, D. In *Handbook of Obesity*; Bray, G. A., Bouchard, C., James, W. P. T., Eds.; Marcel Dekher: New York, 1998; p 415.
5. Larsen, A. A.; Gould, W. A.; Roth, H. R.; Comer, W. T.; Uloth, R. H. *J. Med. Chem.* **1967**, *10*, 462.
6. (a) Guengerich, F. P.; Yun, C. H.; Macdonald, T. L. *J. Biol. Chem* **1996**, *271*, 27321; (b) Guengerich, F. P. *Chem. Res. Toxicol.* **2001**, *14*, 611.
7. Hu, B.; Ellingboe, J.; Han, S.; Largis, E.; Mulvey, R.; Oliphant, A.; Sum, F.-W.; Tillet, J. *J. Med. Chem.* **2001**, *44*, 1456.
8. LD_{100} for mice was 57 μg/kg of **2** administered iv; iv doses of 0.5–5.7 μg/kg produced progressively more pronounced piloerection; 0.05 μg/kg was a no effect dose. This dose dependent response suggested that piloerection following iv administration of 10 mg/kg of **1** during the murine safety screen was indicative of 0.01–0.1% of the dose being converted to **2**. A few compounds, such as **1f**, were lethal at 10 mg/kg but not at 1 mg/kg implying that metabolic conversion to **2** was ~0.1–1%.
9. Typically, a 100 μM solution of compounds of structure **1** was incubated for 3 h in pH 7.4 phosphate buffer (0.1 M) containing *African green* monkey hepatic microsomes (3 mg/mL protein) and 3 mM NADPH whereupon the protein was precipitated by addition of 2 volumes MeCN prior to determination of the conversion to **2** by LC/MS. Since control studies entailing incubation of compounds of structure **1** as described above in the absence of NADPH generated minuscule amounts of **2**, solvolytic release of **2** due to chemical instability of **1** after protonation was of minimal importance.
10. Subsequently during clinical studies with **BMS-196085** (**1c**), **BMS-194449** (**1b**), and **BMS-201620** (**1j**) dose dependent incidences of sweaty palms, flushing, and piloerection, all classic manifestations of an α adrenergic agonist, as well as detection of trace levels of **2** validated these concerns regarding metabolic liberation of **2**.
11. (a) Kirk, K. L.; Cantacuzene, D.; Creveling, C. R. *Biomed. Aspects Fluorine Chem.* **1982**, 75; (b) Brasili, L.; Cantalamessa, F.; Picchio, M. T.; Quaglia, W. *Eur. J. Pharm.* **1987**, *144*, 141.
12. Hieble, J. P.; Hehr, A.; Li, Y.; Ruffolo, R. R. *Proc. Western Pharmacol. Soc.* **1998**, *41*, 225.
13. Receptor binding assays were run in triplicate with membranes prepared from CHO cells expressing the three cloned human β receptors in the presence of ^{125}I-iodocyanopindolol.[14] β_3 AR agonist activity was assessed by measurement of cAMP accumulation levels in CHO membranes expressing human β_3 AR.[15] IA is given as a percentage of the maximal stimulation with isoproterenol.
14. All compounds were evaluated using the truncated human β_3 adrenergic receptor reported by Emorine, L. T.; Marullo, S.; Briend-Sutren, M. M.; Patey, G.; Tate, K.; Delavier-Klutchko, C.; Strosberg, A. D. *Science* **1989**, *245*, 1118.
15. Sher, P. M.; Fisher, L. G.; Skwish, S.; Michel, I. M.; Seiler, S. M.; Washburn, W. N.; Dickinson, K. E. *J. Med. Chem. Res.* **1997**, *7*, 109.
16. Spectral data were fully consistent with structures.
17. Beeley, L. J.; Berge, J. M.; Chapman, H.; Dean, D. K.; Kelly, J.; Lowden, K.; Kotecha, N. R.; Morgan, H. K. A.; Rami, H. K.; Thompson, M.; Vong, A. K. K.; Ward, R. W. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 219.
18. In 95% EtOH at 20 °C, $t_{1/2}$ was ~40 min to presumably generate quinones.
19. Larson, A. A.; Gould, W. A. US Patent 1,171,477.
20. Wu, G.; Cai, Z. W.; Bednarz, M. S.; Kocy, O.; Gavai, A. V.; Godfrey, J. D.; Washburn, W. N.; Sher, P. M. *J. Comb. Chem.* **2005**, *7*, 99.
21. Stereochemical preferences had not previously been addressed in the few reports concerning arylpropanolamine as adrenergic ligands.[22]
22. (a) Fuhrer, W.; Ostermayer, F.; Zimmermann, M.; Meier, M.; Müller, H. *J. Med. Chem.* **1984**, *27*, 831; (b) Lövgren, K.; Hedberg, H.; Nilsson, J. L. G. *J. Med. Chem.* **1981**, *24*, 451; (c) Alderová, E.; Trčka, V.; Šmejkal, V.; Protiva, M. *Collect. Czech. Chem. Commun.* **1969**, *34*, 479; (d) WO 2000/012462; (e) WO 1999/051564.
23. Absolute stereochemistry of **15f** assigned by X-ray crystallography.
24. β_1 IA was determined by measuring the acceleration in contraction of spontaneously beating guinea pig atria relative to that induced by isoproterenol.[25] β_2 IA was determined by measuring relaxation of guinea pig trachea rings submaximally contracted with carbacol relative to that induced by isoproterenol.
25. Tesfamariam, B.; Allen, G. T. *Br. J. Pharmacol.* **1994**, *112*, 55.
26. Lipworth, B. J.; McFarlane, L. C.; Coutie, W. J.; McDevitt, D. *Eur. J. Clin. Pharmacol.* **1989**, *37*, 297.