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BMS-201620: a selective beta 3 agonist

W. N. Washburn,* C.-Q. Sun,* G. Bisacchi, G. Wu, P. T. Cheng, P. M. Sher, D. Ryono, A. V. Gavai, K. Poss, R. N. Girotra, P. J. McCann, A. B. Mikkilineni, T. C. Dejneka, T. C. Wang, Z. Merchant, M. Morella, C. M. Arbeeny, T. W. Harper, D. A. Slusarchyk, S. Skwish, A. D. Russell, G. T. Allen, B. Tesfamariam, B. H. Frohlich, B. E. Abboa-Offei, M. Cap, T. L. Waldron, R. J. George, D. Young, K. E. Dickinson and A. A. Seymour

Bristol-Myers Squibb Pharmaceutical Research Institute, PO Box 5400, Princeton, NJ 08543, USA

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Abstract—A series of N-(4-hydroxy-3-methylsulfonanilidoethanol)arylglycinamides were prepared and evaluated for their human β_3 adrenergic receptor agonist activity. SAR studies led to the identification of **BMS-201620** (**39**), a potent β_3 full agonist ($K_i = 93$ nM, 93% activation). Based on its favorable safety profile, **BMS-201620** was chosen for clinical evaluation.

The alarming increase in the incidence of obesity and noninsulin dependent diabetes mellitus is of great concern to health authorities of Western countries.[1] An attractive approach to treating these conditions entails increasing metabolic energy expenditure by selective activation of the β_3 adrenergic receptor.[2] As previously described,[3,4] our strategy has been to utilize full rather than partial β_3 agonists to enhance the probability of eliciting a thermogenic response from any brown adipose tissue (BAT) that may be present in man. Consequently, the high β_3 agonist intrinsic activity (IA) of 4-hydroxy-3-methylsulfonanilidoethanolamines ensured our continuing interest despite a poor prognosis for bioavailability.

Prior explorations of this chemotype had revealed that incorporation of benzyl amines containing a *para* hydrogen bonding acceptor (e.g., *p*-OMe, Table 1) enhanced β_3 affinity and selectivity, especially if a second aryl ring was attached to Cα via a 0 or 1 atom linker to reduce the conformational flexibility. We have presented SAR wherein the linker is a single bond (1,1-diarylmethylamines) or a methylene (1,2-diaryl-ethylamines) exemplified by **1** and **2**, respectively.[3,4] This paper focuses on the enhanced β_3 selectivity generated by a conformationally rigid carboxamide spacer joining the second aryl ring to Cα.

The promising selectivity obtained with compound **3** with *R*,*S* stereochemistry prompted further investigation. To establish the stereochemical preference, the *R*,*R* isomer **4** was also prepared. The 80-fold greater β_3 affinity and 15- to 40-fold greater selectivity for β_3 versus β_1 and β_2 of isomer **3** compared to isomer **4** established the preferred glycinamide stereochemical orientation to be *S*. This preference for the configuration of Cα to be *S* for the arylglycine series **3** and *R* for **2** reflects an identical spatial projection of the *p*-anisyl moiety into a common pocket of the β_3 receptor. The 162-fold binding selectivity of **3** versus β_2 was particularly striking, especially since the two series represented by compounds **1** and **2** rarely exhibited more than 13-fold β_2 selectivity.[3,4]

The initial SAR revealed tertiary anilides were not tolerated since N-methylation of **3** to generate **5** resulted in a 90-fold loss of β_3 affinity. Elongation of this spacer also proved unfavorable since homologation of **3** to generate benzyl amide **6** decreased β_3 affinity and β_2 selectivity 8- and 3-fold, respectively. It is essential that the planarity of the aniline ring be maintained. Upon replacement of the anilide moiety of **3** with a *t*-Bu amide (**9**) or a cyclohexyl amide (**10**), selectivity was maintained; but, β_3 affinity decreased 25- and 19-fold,

* Corresponding authors. Fax: +1-609-818-3550; e-mail addresses: william.washburn@bms.com; chongqing.sun@bms.com

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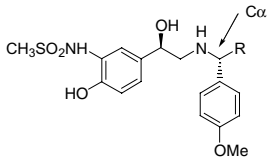
Table 1. Comparison of β adrenergic profiles of compounds **1**–**11**[5]

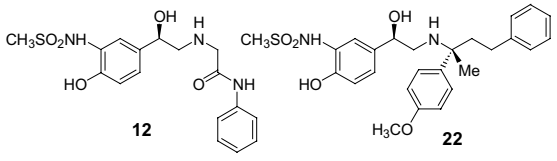


Compound	R	β_3 K_i (nM)	β_3 IA (% act)	Selectivity[b] versus	
				β_1	β_2
1[a]	Ph-4-OMe	81	100	17	22
2	(*R*)-CH_2Ph	44	99	60	8
3	(*S*)-CONHPh	370	90	60	162
4	(*R*)-CONHPh	30,000	45	4	4
5	(*S*)-CON(Me)Ph	33,000	78	4	3
6	(*S*)-$CONHCH_2Ph$	3100	105	39	55
7	(*S*)-$CONH_2$	2910	92	46	31
8	(*R*)-$CONH_2$	14,100	29	4	3.5
9	(*S*)-CONH-*t*-Bu	9600	80	>100	>100
10	(*S*)-CONH-*c*-hexyl	7000	95	>14	>100
11	(*S*)-CO-piperidine	10,000	99	15	10

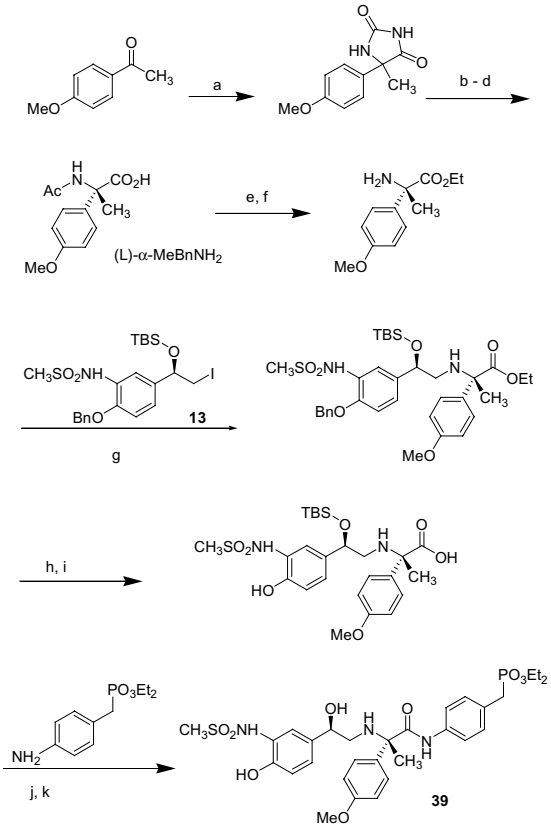
[a] Racemate.
[b] Selectivity is defined as the ratio of β_1 K_i or β_2 K_i to β_3 K_i.

respectively. The weak affinity and diminished selectivity of the piperidinyl amide **11** is consistent with the need for planar secondary amides. The contribution of each aryl ring to β_3 selectivity and affinity of **3** was ascertained. Upon deletion of the α-anisyl ring (**12**), β_3 affinity diminished 22-fold (β_3 K_i = 8200 nM) relative to that of **3**; selectivity versus β_1 and β_2 was abolished. In contrast, β_3 affinity of **7**, the primary amide counterpart of **3**, was reduced 8-fold relative to that of **3**, with no change in β_1 and 5-fold diminution in β_2 selectivity.

Compounds **3**–**11** were prepared from the appropriate arylglycine.[8] Following sequential Cbz protection, EDC or EEDQ mediated amide formation, and hydrogenolysis over $Pd(OH)_2$, the resulting arylglycinamide was condensed at 110 °C in THF/EtN(*i*-Pr)$_2$ with iodide **13**.[9] Sequential deprotection mediated by NH_4F and then H_2/Pd/MeOH yielded **3**–**11**. During the condensation with **13**, partial epimerization of the arylglycinamide typically occurred thereby necessitating preparative HPLC purification of the final product.[10]

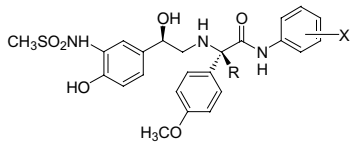


Prior to embarking on an extensive SAR study, the consequence of quarternization of the α-carbon of **3** to preclude epimerization was ascertained, and the *p*-hydrogen bonding acceptor of the α-aryl ring optimized. All of the α-methylated arylglycinamides were prepared as shown in Scheme 1.[10] Comparison of **3**, **14**, and **15** to their respective α-methylated counterparts **16**, **17**, and **18** (Table 2) revealed methylation increased β_3 affinity ~5- to 10-fold and maintained full β_3 agonist activity. However, β_1 and β_2 affinity was enhanced even more; consequently, selectivity versus β_1 and β_2 diminished as much as 5-fold. With respect to α-aryl ring



Scheme 1. Reagents and conditions: (a) $(NH_4)_2CO_3$, NaCN, DMF, 76%; (b) $NaOH/H_2O$, 95%; (c) Ac_2O, 100%; (d) (L)-α-methylbenzylamine, EtOH, 50%; (e) concd HCl/H_2O; (f) EtOH, HCl, 84% (two steps); (g) diisopropylethylamine, diglyme, 145 °C, 65%; (h) LiOH/MeOH/THF/H_2O; (i) H_2, Pd/C, MeOH, 90% (two steps); (j) EDC, HOAt, 5:1 DCE/DMF, 20 °C; (k) NH_4F, MeOH/HOAc, 64% (two steps).

Table 2. Comparison of β_3 AR agonist activity and selectivity versus β_1 and β_2 as a consequence of α-methylation[5]



Compound	R	X	β_3 K_i (nM)	β_3 IA (% act)	Selectivity[a] versus	
					β_1	β_2
3	H	H	370	90	60	162
14	H	3,4-OCH_2O–	280	85	15	89
15	H	4-Cl	89	101	32	573
16	Me	H	77	119	11	81
17	Me	3,4-OCH_2O–	33	97	9	38
18	Me	4-Cl	8.8	117	15	100

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

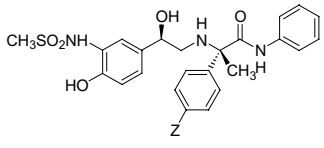
substitution, **16** was found to be superior to **19**, **20**, and **21** (Table 3), presumably reflecting the superior hydrogen bonding capability and better accommodation of the steric demands of the *para* methoxyl substituent.

The importance of the conformation restriction imposed by the carboxamide moiety is readily apparent upon comparison of **16** with **22** for which the carboxamide linkage was replaced with a flexible ethano tether. Although **22** exhibited similar β_3 affinity (59 nM) to that of **16**, the 1000-fold increase in β_1 (0.8 nM) and β_2 (1.1 nM) affinity abolished both β_1 and β_2 selectivity.

The salient β_3 agonist SAR for analogs of **16** arising from modification of the anilide moiety is illustrated in Table 4. The effect of substituent position is readily apparent from the regioisomeric dependence of β_3 K_i upon methylation, methoxylation, and chlorination of **16** to generate sets **23**–**25**, **29**–**31**, and **18**, **26**–**27**, respectively. *para* Substitution was more favorable than *meta*, which in turn was strongly preferred to *ortho*. In every instance, *ortho* substitution was deleterious; even *ortho* fluorination of **18** to form **28** decreased β_3 affinity 3-fold. Affinity relative to hydrogen was increased by lipophilic *meta* substituents such as Me (**24**) or Cl (**27**) or Br (**34**) whereas the unfavorable interactions of a more hydrophilic *meta* phenolic ethers such as methoxy (**30**) or PhO (**32**) progressively diminished affinity as steric demands increased. In contrast, any nonpolar *para* substituent, even OPh (**33**), bound to β_3 with ~5-fold higher affinity than the unsubstituted parent **16**. *meta*–*para* Annelation to generate bicyclic entities (**17**) and (**37**) was favorable. The β_3 binding pocket also accommodated *para* polar groups such as OH (**36**), CONHPr (**38**), or $CH_2PO(OEt)_2$ (**39**); whereas, β_3 affinity was diminished 5-fold for *meta* polar moieties such as OH (**35**). *meta* or *para* Substitution with either cationic (**40**, **41**, **42**) or anionic (**43**, **44**, **45**) substituents was unfavorable, particularly if the charge was in close proximity to the anilide ring as in the case of **43**.

The impact of anilide substitution on selectivity is more complex. In general, β_1 and β_2 affinities were not altered by *ortho* or *meta* substitution. Consequently, selectivity, being solely dependent on β_3 affinity, varied accordingly. Only modest selectivity perturbations were observed upon *para* substitution since affinity to all three receptors tended to be commensurately enhanced. Our criteria for in vivo evaluation were high β_3 binding selectivity and reduced potency and/or partial agonist activity in a β_1 functional assay measured using spontaneously beating guinea pig atria.[11] Diminished β_1 IA of <20% were determined for lipophilic agonists, such as dichlorides **46** and **47** or trichloride **48**, suggesting that there was an apparent inverse correlation of β_1 IA with ACD log*P* values ($r^2 = 0.62$, $P < 0.0001$, $n = 28$). The β_1

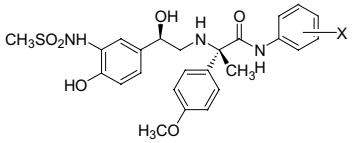
Table 3. Comparison of β_3 AR agonist activity and selectivity versus β_1 and β_2 as a consequence of substitution of the α-aryl ring[5]



Compound	Z	β_3 K_i (nM)	β_3 IA (% act)	Selectivity[a] versus	
				β_1	β_2
16	OMe	77	119	11	81
19	Br	950	69	6	13
20	$CONH_2$	400	77	40	150
21	$OCHF_2$	190	105	17	75

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

Table 4. SAR for anilide substitution for β_3 AR agonist activity and selectivity versus β_1 and β_2[5]



Compound	X	β_3 K_i (nM)	Selectivity[a] versus		EC_{50} β_1 (% IA)[b]	ACD log *P*
			β_1	β_2		
16	H	77	11	80	1200 (95)	2.36
17	3,4-OCH_2O–	33	9	38	950 (93)	2.56
23	2-CH_3	2200	1	3	4500 (83)	2.82
24	3-CH_3	61	17	74	5300 (73)	2.82
25	4-CH_3	28	19	39	1100 (90)	2.82
26	2-Cl	380	4	12		2.55
27	3-Cl	17	27	59	1700 (50)	3.08
18	4-Cl	15	9	67	4300 (62)	3.32
28	2-F-4-Cl	47	32	79	56,000 (43)	3.38
29	2-OCH_3	3100	2	4	15,000 (60)	2.25
30	3-OCH_3	142	14	46	500 (85)	2.53
31	4-OCH_3	17	8	65	140 (85)	2.37
32	3-OPh	490	5	23		4.49
33	4-OPh	14	3	17		3.93
34	3-Br	19	54	116	13,700 (50)	2.85
35	3-OH	340	6	32	750 (96)	2.00
36	4-OH	23	11	139	300 (90)	1.61
37	3,4-NC(Me)S–	11	66	173	1700 (70)	2.55
38	4-CONHPr	20	7	11		2.49
39	4-$CH_2PO_3Et_2$	93	51	194	2400 (55)	2.2
40	3-CH_2NH_2	115	63	209	12,000 (91)	1.23
41	3-$O(CH_2)_2NMe_2$	520	10	23	23,600 (85)	2.38
42	4-$O(CH_2)_2NMe_2$	260	3	1	1600 (92)	2.23
43	3-CO_2H	1800	10	38		−0.67
44	3-OCH_2CO_2H	450	30	138	4600 (87)	1.73
45	4-OCH_2CO_2H	370	4	65	3200 (100)	1.58
46	3,4-Cl_2	24	36	32	48,000 (8)	3.92
47	3,5-Cl_2	71	21	16	16,000 (13)	3.82
48	3,4,5-Cl_3	51	51	13	34,000 (15)	4.53
49	3,4-$(OCH_3)_2$	46	35	313	2100 (89)	2.44
50	3,4,5-$(OCH_3)_3$	370	79	281	23,000 (66)	2.40

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

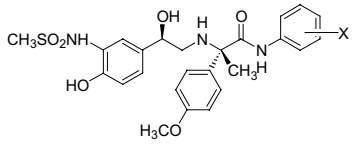
[b] β_1 IA determined using spontaneously beating guinea pig atria by measuring contraction acceleration relative to isoproterenol response.[11]

blocker activity exhibited by **46** during in vivo characterization summarized in Table 5 was in accord with this finding.

Upon iv administration to ketamine anesthetized African green monkeys (AGM), the in vitro/in vivo correlation in this series was particularly poor since most of the compounds were devoid of in vivo activity (Table 5). Serum stability was acceptable; whereas, both intestinal and hepatic first pass glucuronidation were rapid. A dose response was determined for those compounds which produced a statistically significant elevation in free fatty acid (FFA) unaccompanied by β_2 mediated decrease in serum K^+ concentrations[12] or β_1 or β_2 induced tachycardia (HR). Efforts to exploit the diminution of β_1 IA to minimize onset of tachycardia were frustrated by weak in vivo β_3 activity of lipophilic agonists such as **46**.

Table 6 summarizes the in vivo potency and the functional margin of separation between β_3 mediated effects

Table 5. In vivo response in African green monkeys (iv)



Compd	R	β_3 K_i (nM)	AGM response to 0.1 mg/kg iv dose		
			ΔHR	ΔK^+	ΔFFA
27	3-Cl	17	+2	−0.14	+0.9*
34	3-Br	19	+11	+0.1	+0.37
18	4-Cl	15	+2	+0.5	+0.88*
38	4-CONHPr	20	+23	+0.1	+0.7
39	4-$CH_2PO(OEt)_2$	93	+11	−0.24	+0.7*
46	3,4-Cl_2	24	−11	+0.19	+0.39
17	3,4-OCH_2O–	33	+16	+0.33	+0.73*
37	3,4-NC(Me)S–	11	+3	+0.06	+0.4

* $p < 0.05$.

Table 6. Dose response of African green monkeys (iv administration)

Compd	Lipolysis ED_{50} (mg/kg)	β_1 Margin[a] before onset of tachycardia	β_2 Margin[a] before decrease serum K^+
17	0.08	>1<6	>6
18	0.07	>7	>7
39	0.1	>25	>25
196085	0.03	>3<5	>25
194449	0.08	>6<12	>60

[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.

and β_1 or β_2 dependent events in ketamine anesthetized African green monkeys. Compound **39** was unique among all the arylglycinamides with respect to the safety margin magnitude. This margin was superior to that of the other two BMS β_3 agonists, 1,1-diarylmethylamine **BMS-194449**[3] and 1,2-diarylethyl-amine **BMS-196085**,[4] that entered clinical trials.

The unfavorable biophysical and PK profile of **39** did not differ from that of other arylglycinamides. Rat and AGM oral bioavailability of less than 1–2% were consistent with Caco-2 permeability of 6–20 nm/sec. Following iv administration a low V_{ss} of ~2.5 L/kg and high clearance of 68 mL/min/kg combined to produce a $t_{1/2}$ of 1 h in AGM. Despite these inauspicious values, we continued to pursue **39** in hopes that the large safety margin, full β_3 IA and good β_3 affinity would produce a definitive indication whether β_3 agonists could elicit a sustained robust thermogenic response in man.

Intravenous administration of **39** to six volunteers produced no separation between the onset of lipolysis and prolongation of QT interval.[13] Further studies with **39** (**BMS-201620**) were terminated.

Acknowledgements

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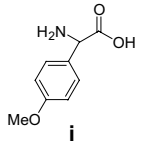

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9. Preparation of **13** analogous to **25** of Ref. 3.
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