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Synthesis and evaluation of potent and selective β_3 adrenergic receptor agonists containing heterobiaryl carboxylic acids

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Abstract—The design, synthesis, and SAR of a novel series of heterobiaryl phenethanolamine β_3 adrenergic receptor agonists are described. The furan analogue **49** was shown to elicit a significant dose-dependent lowering of plasma glucose in a rodent model of type 2 diabetes.

Activation of β_3 adrenergic receptors (AR) located on the surface of adipocytes induces lipolysis and stimulates the upregulation and activation of the mitochondrial uncoupling protein UCP1. This latter event mediates a proton conductance pathway that uncouples oxidative phosphorylation ultimately leading to thermogenesis and a net increase in energy expenditure.[1] The recognition of the role β_3 ARs play in the regulation of metabolic rate has led to significant efforts to identify potent and selective agonists of the β_3 AR for the treatment of diverse disease states including obesity and type 2 diabetes.[2] Several classes of β_3 AR agonists have been identified and optimized based upon their ability to activate rodent β_3 ARs. Compounds such as **1** (CL 316243),[3] **2** (BRL 37344),[4] and **3** (CGP 12177A)[5] were shown to elicit anti-obesity effects and exhibit potent anti-diabetic properties in relevant in vivo rodent models. These compounds were progressed into human clinical trials and while some indications of efficacy were observed, they ultimately failed due to a lack of potency or deleterious side effects such as tachycardia (β_1 AR effect) and muscle tremor (β_2 AR effect) arising from a lack of β adrenergic receptor selectivity.[6]

The eventual cloning and expression of the human, rat, and mouse β ARs revealed significant species variances in receptor homology.[7] Comparison of the β_3 AR activity of numerous agonists on the cloned human and rodent receptors showed significant interspecies differences.[8] This may, in part, explain the poor efficacy and side effect profiles observed with the early clinical candidates and emphasizes the importance of using cloned human receptor assays for the identification of selective and efficacious β_3 AR agonists. Recently, several selective β_3 agonists that are potent against the cloned human β_3 AR have been reported. Compounds such as **4** (BMS-194449),[9] **5** (L-755507),[10] and **6** (L-770644)[11] represent second generation β_3 AR agonists that have progressed into preclinical development (Fig. 1).

A series of phenethanolamines containing an anilino phenylacetic acid subunit, as exemplified by **7a**, has been disclosed.[12] Compound **7a** is a potent human β_3 AR full agonist ($pEC_{50} = 7.8$) that also exhibits activity against the human β_1 and β_2 ARs ($pEC_{50} = 7.1$ and $pEC_{50} = 7.3$, respectively). The homologated phenylpropionic analogue **7b** was also discovered to be a potent human β_3 AR agonist with slightly improved selectivity compared to **7a**. Recently, we disclosed a series of biarylaniline phenethanolamines as potent and selective β_3 agonists designed from the aniline

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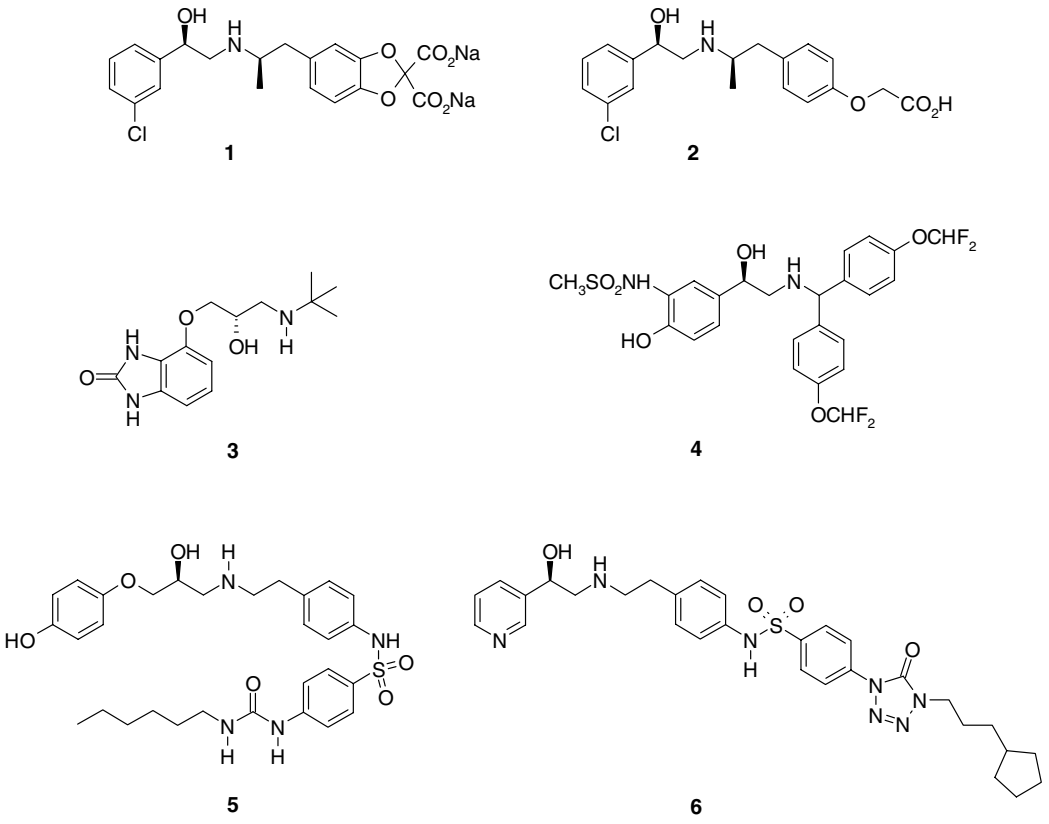


Figure 1. Representative β_3 agonists.

phenethanolamines **7a** and **7b**.[13] In a continuing effort to develop this series as novel potent and selective human β_3 AR agonists, we targeted a series of heterobiaryl analogues based upon **7a** and **7b**.

Our general target design strategy is illustrated in Figure 2. The presence of a carboxylic acid or other negatively charged group has been demonstrated to play an important role in providing β_3 AR selectivity within certain phenethanolamine analogues.[14] Our target design involved replacing the linking group of the phenylacetic or phenylpropionic acid moieties with various heteroaryl rings to incorporate conformational restriction in the region of the carboxylic acid residue and investigate the influence of the spatial orientation of the carboxylic acid on β adrenergic receptor activity.

The synthesis of our β_3 AR agonist targets is depicted in Scheme 1. Treatment of the previously reported amino esters **9a** and **9b** with DIBAL provided aldehydes **10a** and **10b**, respectively,[12] which readily underwent reductive amination with a variety of synthetically prepared heterobiaryl anilines to yield the coupled products **23**–**36**. Deprotection of both the *N*-Boc carbamate and silyl ether protecting groups was achieved in a single step using 4 N HCl in dioxane and subsequent saponification of the ester functionality afforded the desired final targets **37**–**50**. The final targets are shown in Figure 3.

The syntheses of the novel heterobiaryl anilines utilized for the reductive amination with the key aldehyde intermediates **10a** and **10b** are described in Scheme 2. The synthesis of the 2-anilino-4-oxazolecarboxylic esters **11** and **12** entailed *N*-Cbz protection of 3-amino- and 4-aminobenzamide, respectively, followed by treatment with ethyl bromopyruvate in refluxing EtOH[15] and *N*-Cbz deprotection via hydrogenation. The analogous 2-anilino-4-thiazolecarboxylic esters **13** and **14** were prepared by converting the *N*-Cbz protected benzamides **51** and **52** to their corresponding thiobenzamides **53** and **54** with Lawesson's reagent in refluxing benzene and subsequent cyclization with ethyl bromopyruvate.[15] Removal of the *N*-Cbz protecting group under standard palladium catalyzed hydrogenation proved problematic but was readily achieved using 30% HBr in acetic acid to provide the desired anilino thiazoles **13** and **14**.

Cyclization of 3-nitro and 4-nitrophenacyl bromide with ethyl thiooxamate in refluxing EtOH[15] efficiently provides the nitroaryl-2-thiazolecarboxylic esters **55** and **56**. Tin (II) chloride mediated reduction of the nitro groups gave the desired 4-anilino-2-thiazolecarboxylic esters **15** and **16**.[16]

The synthesis of the 5-anilino-4-oxazolecarboxylic esters **17** and **18** was achieved by treating 3-nitro and 4-nitrobenzoyl chloride with a THF solution of ethyl isocyanoacetate in the presence of Et_3N for 72 h[17] followed by reduction of the nitro groups by palladium catalyzed hydrogenation.

The 2-anilino-3-furancarboxylic esters **19** and **20** were synthesized through the coupling of the

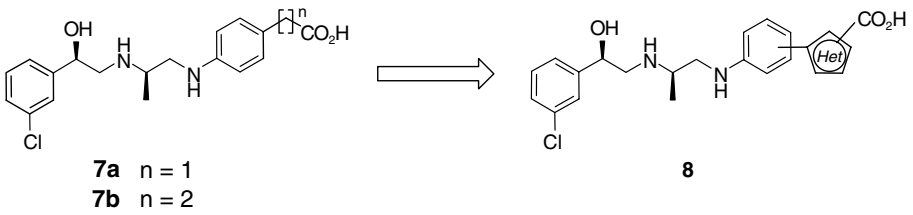
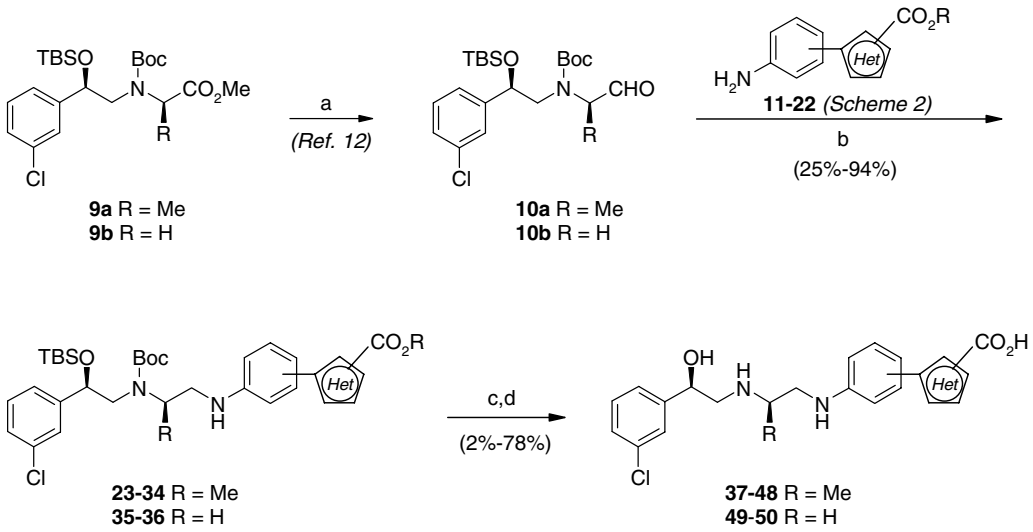


Figure 2. Heterobiaryl target design.



Scheme 1. Reagents and conditions: (a) DIBAL/toluene, Et_2O, −78 °C; (b) **11–22** (Scheme 2), $NaBH(OAc)_3$, AcOH (cat), CH_2Cl_2; (c) 4 N HCl/dioxane, rt; (d) LiOH, $MeOH/H_2O$.

nitrophenyldiazonium salt prepared from the appropriately substituted nitroaniline with 3-furancarboxylic acid[18] followed by esterification and reduction of the nitro groups by hydrogenation. The structurally related 2-anilino-3-thiophenecarboxylic esters **21** and **22** were synthesized in a similar manner.

The ability of these compounds to stimulate cAMP accumulation in vitro was measured in Chinese hamster ovary (CHO) cells expressing the cloned human β_3, β_2, or β_1 ARs.[19] For each analogue, potency (pEC_{50}) and efficacy (E_{Max}, the fitted maximal response to compound expressed as a percent of the maximal response to the nonselective full β AR agonist isoproterenol) were determined. These results are summarized in Table 1.

Lead compound **7b** was characterized in the above assays as a reference and profiled as a potent full human β_3 AR agonist (pEC_{50} = 7.6, E_{Max} = 104%). However, this compound also produces a response, albeit submaximal, at both the β_1 AR (pEC_{50} = 6.6, E_{Max} = 10%) and β_2 AR (pEC_{50} = 6.4, E_{Max} = 22%). The 2-(4-aminophenyl)oxazole-4-carboxylic acid analogue **37** exhibits enhanced potency at all three β ARs as compared to **7b**. Although potency at the β_3 AR improved insignificantly, overall selectivity decreased due to 4- and 20-fold elevations in β_2 and β_1 AR potencies, respectively. The isomeric analogue **38** in which the oxazole ring is *meta* to the aniline nitrogen gave comparable β_3 AR potency with increased intrinsic efficacy and 8- to 10-fold selectivity over both the β_1 and β_2 AR subtypes. Appreciable partial agonism was observed at the β_1 and β_2 ARs.

The 2-arylthiazole-4-carboxylic acid analogue **39** exhibited a slight increase in β_3 AR activity compared to the corresponding oxazole derivative **37**. A small decrease in β_1 AR potency was observed resulting in a minor improvement in β_1 selectivity. In contrast, transposition of the thiazole ring to the *meta* position of the aniline ring produced the full agonist **40** with subnanomolar potency at the β_3 AR (pEC_{50} = 9.1, E_{Max} = 97%) and significant improvement in selectivity. The measured selectivity of compound **40** for the β_3 AR versus the β_1 and β_2 AR subtypes was 100- and 200-fold, respectively.

Encouraged by the improvement in selectivity observed for 2-arylthiazole-4-carboxylic acid analogue **40**, we prepared and evaluated isomeric 4-arylthiazole-2 carboxylic acid analogues. Placement of the thiazole ring *para* to the aniline nitrogen as in analogue **41** provided a compound with slightly increased potency at the β_3 and β_1 ARs compared to the isomeric thiazole derivative **39** resulting in an overall enhanced selectivity profile. The *meta* positional isomer **42** displayed an improved selectivity profile relative to compound **41**, but was much less selective than thiazole analogue **40**. In addition, both of the isomeric 4-arylthiazole-2-carboxylic acid analogues possess increased agonism of the β_2 AR.

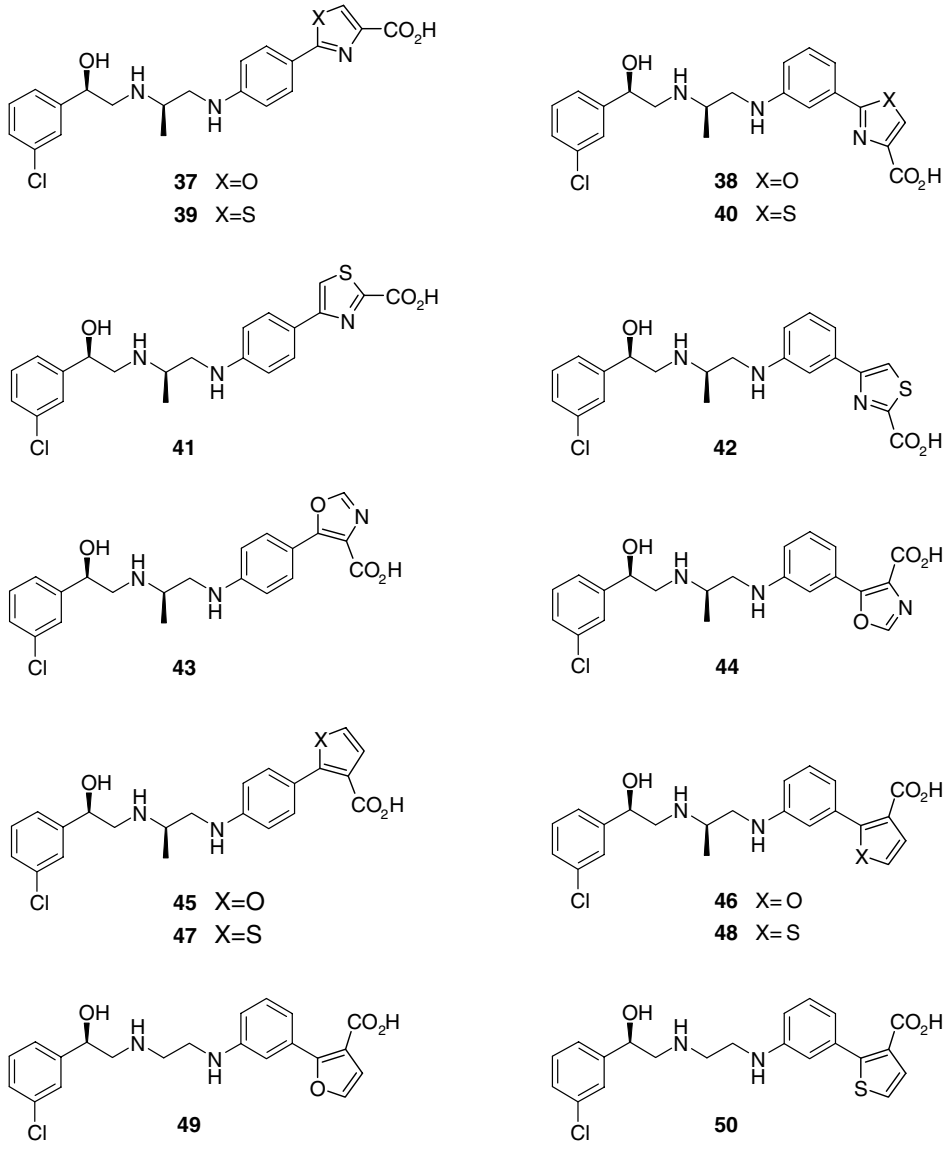


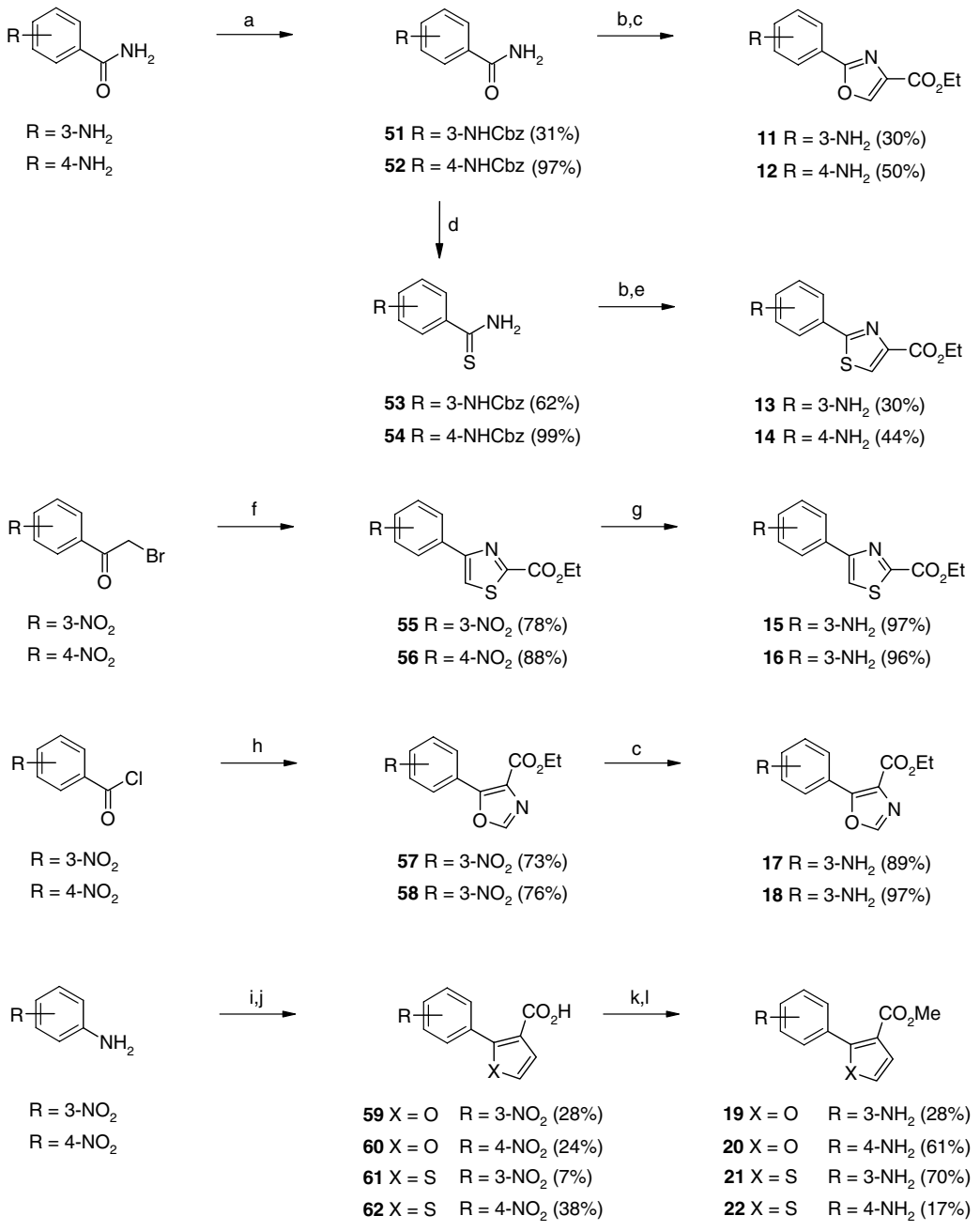
Figure 3. Synthesized heterobiaryl carboxylic acid analogues.

All of the aforementioned analogues position the carboxylic acid in an orientation that extends away from the core structure. In an effort to examine the effect of positioning the carboxylic acid in a spatial orientation in closer proximity to the aniline ring, we synthesized and evaluated a series of heterobiaryl analogues wherein the aniline ring and the carboxylic acid group were incorporated adjacent to each other on the heterocyclic ring system.

The 5-(4-aminophenyl)oxazole-4-carboxylic acid analogue **43** is a potent and selective full β_3 AR agonist ($pEC_{50} = 8.9$, $E_{Max} = 90\%$). Oxazole **43** is highly selective versus the β_2 AR (320-fold) and modestly selective versus the β_1 AR (20-fold). Notably, this agonist is an order of magnitude more potent against the β_3 AR with diminished potency at the β_1 and β_2 ARs than the oxazole isomer **37** with the extended carboxylic acid. Furthermore, the selectivity of **43** is markedly higher than **37** showing a 20- and 50-fold increase in β_3 selectivity over the β_1 and β_2 ARs, respectively. The structurally related *meta* substituted compound **44** is also a potent and selective full β_3 AR agonist. Interestingly, the selectivity profile for compound **44** is reversed compared to **43** with greater β_3 selectivity being observed versus the β_1 AR than the β_2 AR. Both isomers **43** and **44** display significant partial agonist activity at the β_2 AR.

Replacement of the oxazole nitrogen present in compounds **43** and **44** with carbon provides the furan derivatives **45** and **46**. Both of these targets are potent and selective β_3 AR agonists with subnanomolar activity. Both furan analogues also exhibit greater β_3 selectivity over the β_2 AR than the β_1 AR with the *meta* substituted analogue **46** displaying the highest levels of selectivity. Each furan, however, still exhibits significant partial agonist activity at the β_2 AR.

Thiophene compounds **47** and **48** are direct analogues of agonists **45** and **46** whereby the furan oxygen has been replaced with sulfur. Both thiophene compounds are highly potent agonists with excellent selectivity profiles.



Scheme 2. Reagents and conditions: (a) $PhCH_2OCOCl$, Na_2CO_3, THF, H_2O, 0 °C to rt; (b) $BrCH_2COCO_2Et$, EtOH, reflux; (c) H_2, 10% Pd/C, EtOH; (d) Lawesson's reagent, benzene, reflux; (e) 30% HBr/HOAc, CH_2Cl_2, rt; (f) H_2NCSCO_2Et, EtOH, reflux; (g) $SnCl_2$, EtOH, reflux; (h) $NCCH_2CO_2Et$, Et_3N, THF, rt; (i) $NaNO_2$, concd HCl, H_2O, 0 °C; (j) 3-furancarboxylic acid or 3-thiophenecarboxylic acid, $CuCl_2$, acetone, H_2O; (k) H_2SO_4, MeOH, reflux; (l) H_2, 10% Pd/C, MeOH.

The *para* substituted analogue **47** exhibits subnanomolar activity at the β_3 AR receptor ($pEC_{50} = 9.4$, $E_{Max} = 96\%$) with high selectivity over both the β_1 and β_2 AR subtypes (250- and 1600-fold, respectively). The *meta* substituted thiophene analogue **48** is an extremely potent β_3 AR agonist ($pEC_{50} = 10.2$, $E_{Max} = 85\%$) with remarkable selectivity over both the β_1 and β_2 ARs (>20,000- and 13,000-fold, respectively). Compound **48** represents the most potent and selective β_3 AR agonist in this series.

Encouraged by the potencies and selectivities observed for compounds **45**–**48**, we synthesized and evaluated the des-methyl furan and thiophene analogues **49** and **50**. The removal of the methyl substituent adjacent to the phenethylamine serves to eliminate one of the stereogenic centers, potentially simplifying the development of this class of β_3 agonists if acceptable potency, selectivity, and drug properties are retained. While it is documented that the inclusion of the methyl substituent adjacent to the nitrogen with the appropriate stereochemical integrity can influence both β_3 AR potency and selectivity, it is not essential for β AR activity.[20] For example, Merck has disclosed a series of potent and selective des-methyl arylethanolamines bearing a variety of right hand side phenyl substituents.[21]

Table 1. Stimulation of cAMP accumulation in CHO cells expressing human β_3, β_2, and β_1 ARs[a]

Compound	pEC_{50}[a], (E_{max}, %)[b]			Selectivity[c]	
	β_3	β_2	β_1	β_2/β_3	β_1/β_3
ISO	8.5 (112)	9.8 (116)	9.0 (109)	0.1	0.3
7a	7.8 (117)	7.3 (90)	7.1 (24)	3	5
7b	7.6 (104)	6.4 (22)	6.6 (10)	16	10
37	7.8 (92)	7.0 (53)	7.9 (23)	6	0.8
38	7.8 (115)	6.9 (39)	6.8 (30)	8	10
39	8.2[d] (100)	7.3[d] (41)	7.7[d] (21)	8	3
40	9.1 (97)	6.8[d] (48)	7.1 (21)	200	100
41	8.8 (100)	7.3 (63)	7.92 (19)	32	8
42	8.7 (97)	7.0 (76)	7.0 (20)	50	50
43	8.9 (90)	6.4 (55)	7.6 (24)	320	20
44	8.4 (102)	6.5 (49)	6.4 (14)	79	100
45	9.5 (85)	7.1 (36)	7.7 (18)	250	63
46	9.6 (87)	6.9 (38)	7.0 (14)	500	400
47	9.4 (96)	6.2 (19)	7.0 (14)	1600	250
48	10.2 (85)	6.1 (9)	5.9[e] (<7)	13,000	20,000
49	8.1 (91)	5.6[e] (<5)	5.3 (<5)	320	630
50	8.9 (103)	5.3 (<5)	5.4[e] (<2)	4000	3200

[a] Human β_1, β_2, and β_3 receptors expressed in CHO cells. EC_{50}, compound concentration which produces a cAMP response equal to 50% of its maximal response. Values had a standard deviation of $\leqslant$10% ($n \geqslant 3$ unless noted).

[b] E_{max} is the fitted maximal value of the concentration-response expressed as a percent of the maximal response to **R**-(−)-isoproterenol (ISO).

[c] Defined as the ratio of the pEC_{50} of β_1 or pEC_{50} of β_2 to the pEC_{50} of β_3.

[d] Value calculated with $n = 2$ experiments.

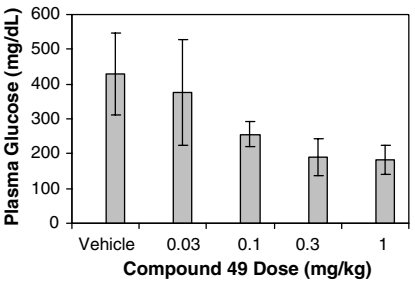
[e] Response was too weak in two of the three trials to fit a curve. This value is the average of the maximal observed response rather than the fitted response.

The des-methyl furan and thiophene analogues **49** and **50** proved to be potent and highly selective full β_3 AR agonists. The absence of the methyl substituent resulted in an overall decrease in β AR potency, most notably on the β_1 and β_2 ARs. Although the observed decrease in β_3 AR potency for the des-methyl furan **49** ($pEC_{50} = 8.1$) and the des-methyl thiophene **50** ($pEC_{50} = 8.9$) was 20- to 30-fold, this loss in potency is readily acceptable given the subnanomolar potencies of the parent methylated compounds **46** and **48**. The des-methyl furan and thiophene analogues **49** and **50** both failed to exhibit appreciable activation of the β_1 or β_2 ARs and represent promising potent and selective β_3 AR agonists.

The in vitro screening data for these compounds offer some insights into the SAR of this class of β_3 AR agonists. For a given heterobiaryl ring system, *meta* substitution of the right hand side aniline ring generally led to a decrease in activity at the β_1 and β_2 ARs while maintaining or improving β_3 AR potency. As a result, the *meta* substituted heterobiaryl analogues generally provided the better selectivity profile compared to their structurally related *para* substituted derivatives. Selectivity was also influenced by the structural features of the incorporated heterocyclic ring. Replacement of a heterocyclic oxygen atom with sulfur results in an overall selectivity profile enhancement as evidenced by comparing the structurally related thiazoles **39** and **40** with oxazoles **37** and **38** and the thiophenes **47** and **48** with furans **45** and **46**. Those analogues in which the linking heterocyclic ring was substituted with the carboxylic acid and aniline ring adjacent to each other were the most potent and selective β_3 AR agonists. This indicates that the spatial orientation of the carboxylic acid group is important for β_3 AR activity and selectivity. It should be noted that the majority of the analogues in this series possess modest to significant activity at the human β_2 AR (E_{Max} = 19–76%). Finally, removal of the methyl substituent from the amino chain resulted in an overall decrease in β AR potency. Potent β_3 AR activity, however, is retained while preserving high β_3 selectivity.

The pharmacokinetic properties of the more selective compounds **40**, **43**–**46**, and **48**–**50** were evaluated in dogs to determine if their progression into in vivo studies was appropriate. Each compound was administered intravenously at 0.2 mg/kg and plasma drug levels were determined by LC–MS/MS. Compounds **40**, **43**–**46**, and **48** had modest clearances (5.3–16.5 ml/min/kg) with extremely short half-lives ($\leqslant$1 h). The des-methyl thiophene **50**, however, displayed low clearance (1.5 ml/min/kg) and an improved half-life (1.6 h). More significantly, the des-methyl furan **49** exhibited low clearance (0.65 ml/min/kg) with an extended half-life of 6.1 h. Further studies with furan **49** determined good systemic exposure via oral administration (F = 60%) could be achieved when dosed as a suspension. It is worth noting that the compounds lacking the methyl group on the amino chain exhibit lower clearances and longer half-lives than their corresponding methylated analogues.

Based on its potent and selective β_3 AR activity and promising pharmacokinetic profile, the des-methyl furan compound **49**[22] was selected for in vivo evaluation in a rodent model of type 2 diabetes. A dose–response study was performed in 8-week-old male db/db mice.[23] Compound **49** was administered twice daily (BID) for 14 days by oral gavage and the effects on plasma glucose were measured. The results are summarized in Figure 4. Efficacious lowering of serum glucose occurred in a dose-dependent manner with effects on glucose observed at doses as low as 0.03 mg/kg. The maximal effective dose of 0.3 mg/kg reduced plasma glucose levels from 428 ± 118 mg/dL in vehicle treated mice to 191 ± 53 mg/dL. Thus, chronic dosing of compound **49** produced effective lowering of plasma glucose in a



Dose (mg/kg)	Glucose (mg/dL)
Vehicle	428±118
0.03	376±153
0.1	255±36
0.3	191±53
1	183±42

Figure 4. Glucose lowering effect of compound **49** in db/db Mice after 14 days of treatment. Data are shown as means ± SD (n = 10/group).

rodent model of diabetes consistent with the anti-diabetic properties of β_3 agonists.[24]

In summary, we have identified a novel series of heterobiaryl carboxylic acid analogues that are potent and selective full agonists of the human β_3 adrenergic receptor. These compounds were designed to explore the effect of the spatial orientation of the carboxylic acid on β AR activity by replacing the carbon tether between the aniline ring and carboxylic acid of the previously disclosed β_3 AR agonists **7a** and **7b** with various five-membered heterocyclic ring systems as rigidifying linkers. The in vitro screening results revealed that both the structural features of the heterocyclic ring and the spatial orientation of the carboxylic acid influence potency and selectivity. In addition, removal of the methyl substituent from the amino chain afforded interesting results. The des-methyl compounds exhibited an overall decrease in β AR potency while maintaining high β_3 selectivity. Furthermore, the des-methyl compounds showed improved pharmacokinetic properties. These results suggest that removal of the methyl substituent from the amino chain is permissible when working with very potent and β_3 selective agonists. The results from these studies are consistent with data previously observed with our biarylaniline phenethanolamine series.[13]

From this work, heterobiaryl analogue **49** was shown to elicit a potent and efficacious reduction of plasma glucose in a rodent model of diabetes. This result in combination with the excellent in vitro profiles against cloned human β adrenergic receptors suggests that this novel class of β_3 selective agonists may have relevant utility for the treatment of type 2 diabetes mellitus in man. The further development of these compounds will be reported in due course.

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22. Synthesis of compound **49**: Reductive amination of aldehyde **10b**[12b] (1.17 g, 2.73 mmol) and methyl

2-(3-aminophenyl)furan-3-carboxylate **19** (742 mg, 3.42 mmol) with $Na(OAc)_3BH$ (1.20 g, 5.66 mmol) and HOAc (2 drops) in CH_2Cl_2 (10 mL) afforded, after work up and silica gel chromatography eluting with 1:8 EtOAc in hexane followed by 1:5 EtOAc in hexane, 1.15 g (67%) of amine **35** as a colorless oil. MS (ES) *m*/*z* 629 (MH^+). Intermediate **35** was treated with 4 N HCl/dioxane (10 mL) and stirred at ambient temperature for 2 h during which time a white precipitate formed. This mixture was diluted with diethyl ether (40 mL), stirred for 10 min, and then the precipitate was collected by suction filtration to afford, after drying in vacuo, 613 mg (92%) of methyl 2-{3-[(2-{[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]amino}ethyl)-amin]phenyl}-3-furoate dihydrochloride. Saponification of the isolated ester (613 mg, 1.35 mmol) with $LiOH{\cdot}H_2O$ (304 mg, 7.25 mmol) in 3:1 $MeOH/H_2O$ (12 mL) followed by silica gel chromatography eluting with 60:30:1 $CHCl_3$/$MeOH/NH_4OH$ afforded 317 mg (59%) of acid **49** as a white solid. 400 MHz ^1H NMR (DMSO-d_6) δ 2.60–2.90 (4H, m), 3.16 (2H, br s), 4.74 (1H, d, J = 9.5 Hz), 5.72 (1H, br s), 6.58 (1H, d, J = 7.2 Hz), 6.72 (1H, s), 7.04 (1H, d, J = 7.5 Hz), 7.09 (1H, t, J = 7.9), 7.26–7.32 (4H, m), 7.39 (1H, s), 7.67 (1H, s). Anal. ($C_{21}H_{21}N_2O_4Cl$) C, H, N.

23. Compound **49** was administered twice daily (BID) by oral gavage to male db/db mice (10 mice/group; 60 days of age at onset of dosing) for 14 days. The reconstitution vehicle for the in vivo studies was 0.025 M methanesulfonic acid. Dosing solutions were prepared fresh daily. Prior to the start of dosing, 10 mice were anesthetized and exsanguinated by cardiac puncture for baseline measurements (Day 0 predose values) of postprandial glucose, glycosylated hemoglobin, and insulin. Subsequently, on days 7 and 14 of dosing, mice from each dose group were sacrificed and blood samples for glucose measurements were obtained. Body weights were measured throughout the study and there were no significant effects of any of the compounds on body weight gain in these studies. All serum biochemical measurements were made using an ILAB600 automated chemistry Analyzer (Instrumentation Laboratories).
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