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Human β_3-Adrenergic Receptor Agonists Containing 1,2,3-Triazole-Substituted Benzenesulfonamides

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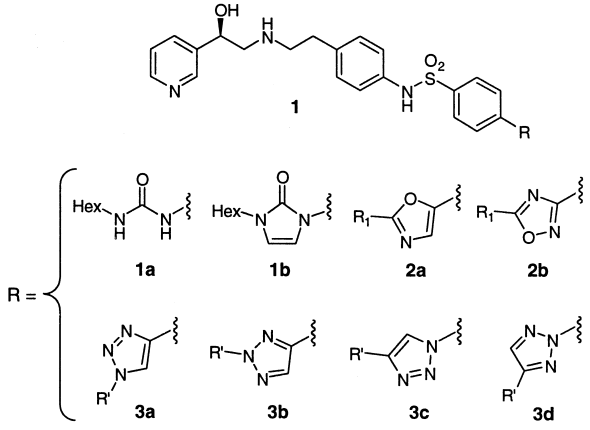
Abstract—Compounds containing a 1,2,3-triazole-substituted benzenesulfonamide were prepared and found to be potent and selective human β_3-adrenergic receptor agonists. The most interesting compound, trifluoromethylbenzyl analogue **12e** (β_3 $EC_{50} = 3.1$ nM with >1500-fold selectivity over binding to both β_1- and β_2 receptors), stimulates lipolysis in the rhesus monkey ($ED_{50} = 0.36$ mg/kg) and is 25% orally bioavailable in the dog.

Activation of the β_3-adrenergic receptor (β_3-AR), a discrete β-adrenoceptor subtype located on the plasma membranes of adipocytes, leads to an increase in metabolic rate. Consequently, selective β_3-AR agonists may prove to be practicable therapeutic agents for the treatment of obesity.[1] Work from these laboratories has shown that while aryl sulfonamides such as urea **1a** and imidazolone **1b** are potent and selective β_3-AR agonists (β_3 $EC_{50} = 6.3$ and 14 nM, respectively), both compounds suffer from poor oral bioavailability in the dog (%F = <1 and 7, respectively).[2] Recent publications from Merck describe the successful substitution of oxazole[3a] and oxadiazole[3b,c] functionalities for the urea moiety, resulting in compounds of general structure **2a** and **2b**. These series of compounds were found to be β_3-AR agonists with improved pharmacokinetic profiles.



Wishing to identify other suitable heterocyclic replacements for the urea functionality, we have targeted several series of 1,2,3-triazoles. A number of different substitution patterns about the triazole ring were explored as shown below. Analogues in which the benzenesulfonamide was linked to the triazole moiety at the 4-position (**3a** and **3b**) were moderately potent partial agonists of the β_3-AR (β_3 EC_{50}'s of 15–80 nM). These compounds, however, were nonselective for activation of the β_3 receptor over binding to the β_1- and β_2-ARs (data not shown) and as such, did not warrant further investigation. Significantly improved in vitro results were seen for analogues in which the point of attachment of the benzenesulfonamide was at either the 1- or the 2-position of the triazole functionality (**3c** and **3d**, respectively). Of these two series, it was found that, for maximal potency and selectivity, 2,4-disubstitution (**3d**) was preferred. Herein we report the synthesis and biological activity of analogues in this series. Recent work suggests that comparable β_3-AR agonist activity is observed when fluorinated aromatic rings are substituted for aliphatic

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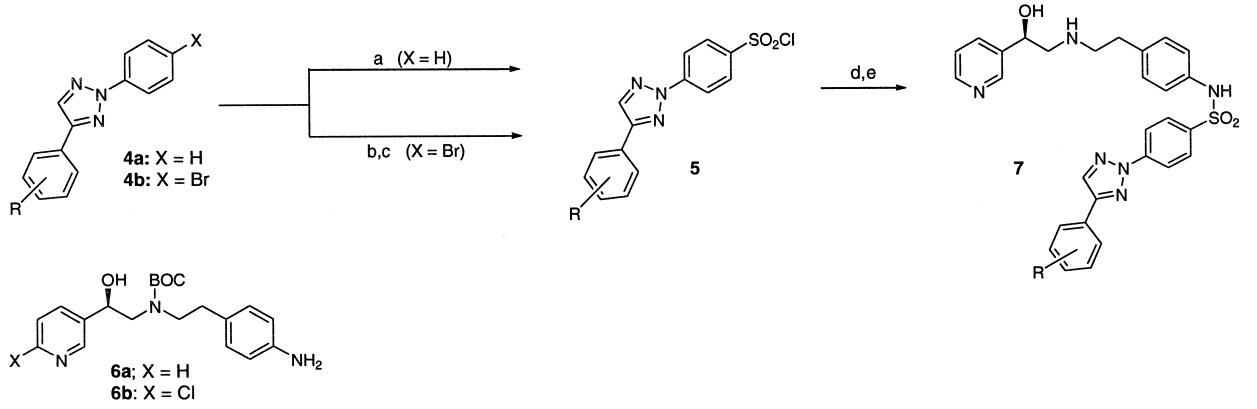
side chains.[3a,c] As these functionalities are less prone to oxidative metabolism than aliphatic groups, our efforts concentrated on the preparation of these derivatives.

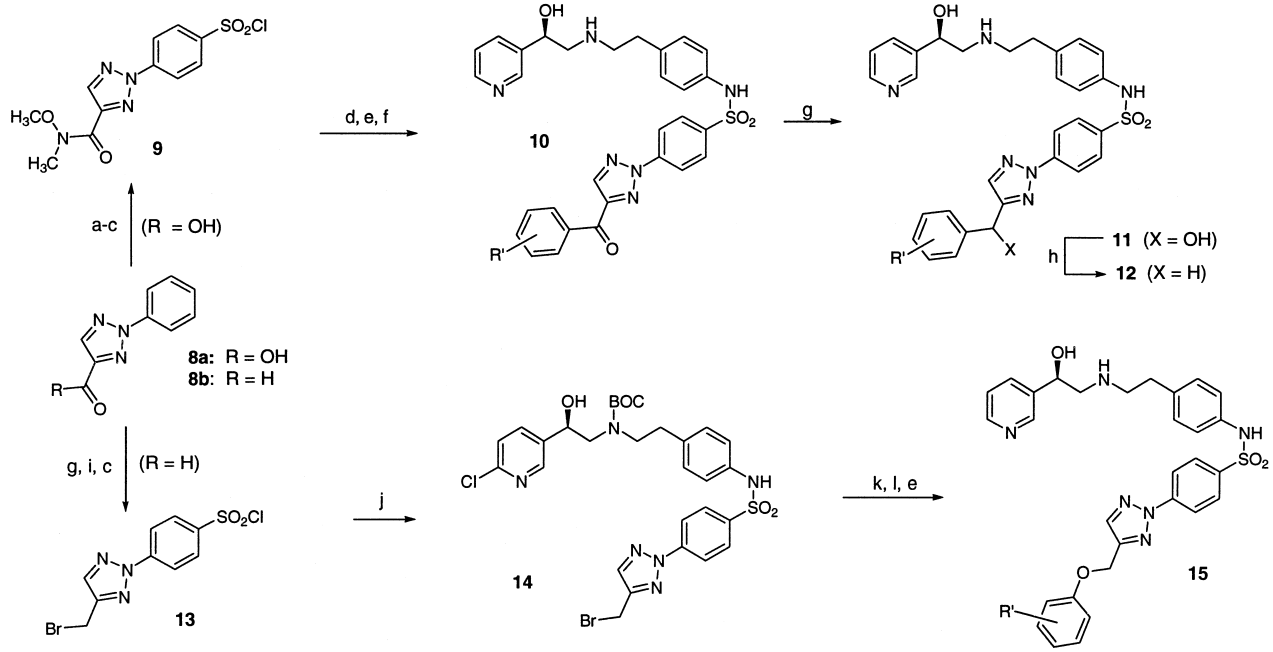
Chemistry

Treatment of arenes **4a**[4] (Scheme 1) with chlorosulfonic acid provided sulfonyl chlorides **5**, which were then coupled with aniline **6a**.[2a] Removal of the BOC protecting group with trifluoroacetic acid (TFA) furnished the desired diaryl-substituted products **7**. In an alternate route, aryl bromides **4b** were lithiated and converted to the corresponding sulfonyl chlorides via the sulfinic acid salt.[5]

The remaining triazole analogues were synthesized by the routes shown in Scheme 2. Conversion of carboxylic acid **8a**[6] to the Weinreb amide followed by chlorosulfonylation provided sulfonyl chloride **9**. Condensation with aniline **6a** and removal of the BOC protecting group was followed by treatment with a large excess of an appropriately substituted Grignard reagent to give ketones **10**. Reduction of the ketone with sodium borohydride provided the corresponding alcohols **11**, which were then treated with triethylsilane and TFA giving the desired benzylic compounds **12**. Reduction of aldehyde **8b**[6] followed by bromination of the resultant alcohol and chlorosulfonylation provided the sulfonyl chloride **13**. As this compound contained a reactive benzylic bromide, use of the less nucleophilic aniline **6b** was necessary to provide sulfonamides **14** in good yield. Displacement of the bromide by appropriately substituted phenoxides, followed by removal of the chlorine atom and the BOC protecting group provided the desired phenoxymethyl analogues **15**.

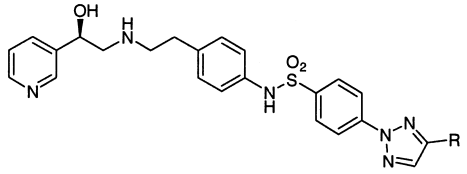


Scheme 1. Reagents: (a) $HOSO_2Cl$, NaCl, 50 °C; (b) *n*BuLi, THF, −78 °C, then SO_2; (c) *N*-chlorosuccinimide, CH_2Cl_2, 25 °C; (d) aniline **6a**, pyridine, CH_2Cl_2, 25 °C; (e) TFA, CH_2Cl_2, 25 °C.



Scheme 2. Reagents: (a) ClCOCOCl, CH_2Cl_2, cat. DMF, 25 °C; (b) $H_3CONHCH_3HCl$, Et_3N, CH_2Cl_2, 25 °C; (c) $HOSO_2Cl$, 50 °C; (d) aniline **6a**, pyridine, CH_2Cl_2, 25 °C; (e) TFA, CH_2Cl_2, 25 °C; (f) 10–20 equiv R′PhMgX, THF, 50 °C; (g) $NaBH_4$, MeOH, 25 °C; (h) Et_3SiH, TFA, CH_2Cl_2, 25 °C; (i) CBr_4, PPh_3, Et_2O, 25 °C; (j) aniline **6b**, pyridine, CH_2Cl_2, 25 °C; (k) R′PhO$^-$Na$^+$, DMF, 25 °C; (l) H_2, $Pd(OH)_2$, MeOH, 25 °C.

Table 1. Comparison of β_3-AR agonist activity and β_1- and β_2-AR binding affinities[8]



Compound	R	β_3 EC_{50} (nM) (% act)[a]	β_1 Binding IC_{50}[b] (nM)	β_2 Binding IC_{50}[b] (nM)
7a	3-F-Ph	52 (89)	8700	8800
7b	4-F-Ph	24 (91)	40,000	9300
7c	3,4-Difluoro-Ph	14 (82)	2600	1300
7d	3-F, 4-OCH_3-Ph	22 (80)	5600	2500
7e	4-CF_3-Ph	14 (90)	21,000	21,000
7f	4-OCF_3-Ph	18 (84)	1300	1600
12a	3-F-PhCH_2–	6.4 (87)	3000	380
12b	4-F-PhCH_2–	14 (75)	2500	780
12c	2,6-Difluoro-PhCH_2–	24 (84)	28,000	5000
12d	3,4-Difluoro-PhCH_2–	7.2 (86)	2000	1000
12e	4-CF_3-PhCH_2–	3.1 (85)	20,000	4700
12f	4-OCF_3-PhCH_2–	4.1 (91)	2600	860
12g	2,4,6-Trifluoro-PhCH_2–	48 (83)	10,000	8800
15a	3,4-Difluoro-PhOCH_2–	10 (63)	930	690
15b	4-CF_3-PhOCH_2–	11 (72)	920	730
15c	4-OCF_3-PhOCH_2–	14 (75)	6200	620

[a]Adenylyl cyclase activation given as % of the maximal stimulation with isoproterenol.
[b]Receptor binding assays were carried out with membranes prepared from CHO cells expressing the cloned human adrenoceptor in the presence of ^{125}I-iodocyanopindolol.

Results and Discussion

Compounds **7**, **12**, and **15** were tested in vitro for their ability to stimulate increases in cAMP in CHO cells expressing the cloned human β-ARs.[7,8] The in vitro results are presented in Table 1. In general, all of these analogues activated the β_3 receptor to a high degree (63–91% activation) with no significant efficacy at the β_1- and β_2-ARs (< 50% activation at 10 μM, data not shown). As a rule, potencies were good to moderate with β_3 EC_{50}'s ranging from 3.1 to 52 nM. In both the phenyl and benzyl series, the 4-trifluoromethyl analogues **7e** and **12e** were the most potent analogues with β_3 EC_{50}'s of 14 and 3.1 nM, respectively. These derivatives were also significantly more selective than all other analogues, none of which showed such impressive selectivity (>1500-fold) for activation of the β_3-AR over binding to both the β_1- and the β_2-ARs. Interestingly, this trend did not translate to the phenoxymethyl series, as in this case the 4-trifluoromethyl analogue showed poor selectivity over binding at the β_1- and β_2-ARs (84- and 66-fold, respectively). Within the benzyl series, bis *ortho*-substitution appeared to be detrimental, as compounds **12c** and **12g** were 2- to 8-fold less potent than the other analogues shown.

The advanced intermediate ketones and alcohols (compounds **10** and **11**, respectively) were also submitted for screening in the β_3 assay (data not shown). Analogues **10b** and **11b** (R′ = 4-F) were the most potent derivatives in these series with β_3 EC_{50}'s of 6.4 nM and 3.3 nM, respectively. These analogues also exhibited excellent selectivities of >2500-fold for activation of the β_3 receptor over binding to both the β_1- and β_2-ARs. However, preliminary pharmacokinetic studies in the dog showed that not only was the ketone **10b** metabolized to the corresponding alcohol **11b**, but also that the alcohol itself had a low AUC after oral administration. Thus, due to the metabolic lability and inadequate pharmacokinetic properties of these compounds, further investigation of these analogues was not pursued.

The pharmacokinetic properties of select analogues were studied in dogs (3 mg/kg iv, and 10 mg/kg po) and found to be far superior to the oral bioavailabilities of the acyclic and cyclic urea leads **1a** and **1b**. Compounds **12d** and **12e** were 38% and 25% orally bioavailable with half-lives of 4 and 6 h, respectively. Analogue **7e** had an oral bioavailability of 18% with an excellent half-life of 15 h.

The efficacy of the most potent and selective derivative (**12e**) was examined in a rising dose infusion study in anesthetized rhesus monkeys.[8b] This compound elicited hyperglycerolemia (ED_{50} = 0.36 mg/kg) and produced a maximum response equivalent to 95% of that of the full agonist isoproterenol. This compound displayed excellent separation between lipolytic potency and tachycardia, as heart rate effects were minimal (< 5%) even at the highest dose of 10 mg/kg.

Conclusion

We have identified a new series of human β_3-adrenergic receptor agonists containing 1,2,3-triazoles as heterocyclic urea replacements which show markedly improved oral bioavailabilities while maintaining potency, selec-

tivity, and in vivo efficacy. In particular, 4-trifluoromethylbenzyl analogue **12e** is an exceptionally selective human β_3 agonist (β_3 $EC_{50} = 3.1$ nM; with 6500- and 1500-fold selectivity over binding to β_1- and β_2 receptors, respectively). When administered intravenously to rhesus monkeys, **12e** elicits a lipolytic response at low dose with minimal effects on heart rate. The 25% oral bioavailability of this compound in dogs is a marked improvement over the low bioavailability of acyclic and cyclic urea leads **1a** and **1b**.

Acknowledgements

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References and Notes

1. For recent reviews see: (a) Weyer, C.; Gautier, J. F.; Danforth, E. Jr., *Diab. Metab.* **1999**, *25*, 1; (b) Weber, A. E. *Annu. Rep. Med. Chem.* **1998**, *33*, 193; (c) Dow, R. L. *Exp. Opin. Invest. Drugs*, **1997**, *6*, 1811; (d) Lowell, B. B.; Flier, J. S. *Annu. Rev. Med.* **1997**, *48*, 307; (e) Arch, J. R. S.; Wilson, S. *Int. J. Obesity* **1996**, *20*, 191.

2. (a) Naylor, E. M.; Colandrea, V. J.; Candelore, M. R.; Cascieri, M. A.; Colwell, L. F., Jr.; Deng, L.; Feeney, W. P.; Forrest, M. J.; Hom, G. J.; MacIntyre, D. E.; Strader, C. D.; Tota, L.; Wang, P.-R.; Wyvratt, M. J.; Fisher, M. H.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3087. (b) Parmee, E. R.; Naylor, E. M.; Perkins, L.; Colandrea, V. J.; Ok, H. O.; Candelore, M. R.; Cascieri, M. A.; Deng, L.; Feeney, W. P.; Forrest, M. J.; Hom, G. J.; MacIntyre, D. E.; Miller, R. R.; Stearns, R. A.; Strader, C. D.; Tota, L.; Wyvratt, M. J.; Fisher, M. H.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 749.

3. (a) Ok, H. O.; Reigle, L. B.; Candelore, M. R.; Cascieri, M. A.; Colwell, L. F.; Deng, L.; Feeney, W. P.; Forrest, M. J.; Hom, G. J.; MacIntyre, D. E.; Strader, C. D.; Tota, L.; Wang, P.; Wyvratt, M. J.; Fisher, M. H.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1531. (b) Feng, D. D.; Biftu, T.; Candelore, M. R.; Cascieri, M. A.; Colwell, L. F., Jr.; Deng, L.; Feeney, W. P.; Forrest, M. J.; Hom, G. J.; MacIntyre, D. E.; Miller, R. R.; Stearns, R. A.; Strader, C. D.; Tota, L.; Wyvratt, M. J.; Fisher, M. H.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1427. (c) Biftu, T.; Feng, D. D.; Liang, G.-B.; Kuo, H.; Qian, X.; Naylor, E. M.; Colandrea, V. J.; Candelore, M. R.; Cascieri, M. A.; Colwell, L. F., Jr.; Forrest, M. J.; Hom, G. J.; MacIntyre, D. E.; Stearns, R. A.; Strader, C. D.; Wyvratt, M. J.; Fisher, M. H.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1431.

4. For the synthesis of 2,4-diaryl-1,2,3-triazoles (**4a**,**b**) from substituted phenylglyoxals see El Khadem, H.; El-Sadik, M. M.; Meshreki, M. H. *J. Chem. Soc.* **1968**, 2097. The requisite phenylglyoxals were prepared by selenium dioxide oxidation of appropriately substituted acetophenones according to Joshi, K. C.; Dubey, K.; Dandia, A. *Heterocycles* **1981**, *16*, 1545.

5. Graham, S. L.; Hoffman, J. M.; Gautheron, P.; Michelson, S. R.; Scholz, T. H.; Schwam, H.; Shepard, K. L.; Smith, A. M.; Smith, R. L.; Sondey, J. M.; Sugrue, M. F. *J. Med. Chem.* **1990**, *33*, 749.

6. For the synthesis of 2-phenyl-1,2,3-triazole-4-carboxylic acid (**8a**) and the corresponding carboxaldehyde (**8b**) from fructose see Riebsomer, J. L.; Sumrell, G. *J. Org. Chem.* **1948**, *13*, 807.

7. The human β_3-AR was obtained from Professor J. Grannemann (Wayne State University), Grannemann, 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.; Lefkowitz, 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).

8. (a) The activity of an agonist at the β_3-AR is best described by its ability to stimulate adenylyl cyclase in a functional assay (EC_{50}), since this method measures affinity for the high-affinity, G-protein coupled state of the receptor. This assay accurately predicts the lipolytic potential of compounds in native adipocytes.[8b] The β_3-AR IC_{50} values are a measure of the compound's binding affinity for both the high and low affinity states of the β_3-AR, thus are lower than the respective EC_{50} values. The triazoles exhibited low efficacy at the β_1- and β_2-ARs ($< 50\%$ 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. (b) For experimental details see Fisher, M. H.; Amend, A. M.; Bach, T. J.; Barker, J. M.; Brady, E. J.; Candelore, M. R.; Carroll, D.; Cascieri, M. A.; Chiu, S.-H. L.: Deng, L.; Forrest, M. J.; Hegarty-Friscino, B.; Guan, X.-M.; Hom, G. H.; Hutchins, J. E.; Kelly, L. J.; Mathvink, R. J.; Metzger, J. M.; Miller, R. R.; Ok, H. O.; Parmee, E. R.; Saperstein, R.; Strader, C. D.; Stearns, R. A.; Thompson, G. M.; Tota, L.; Vicario, P. P.; Weber, A. E.; Woods, J. W.; Wyvratt, M. J.; Zafian, P. T.; MacIntyre, D. E. *J. Clin. Invest.* **1998**, *101*, 2387.