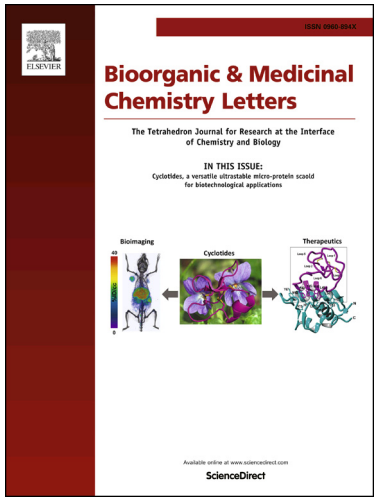

Agonists of the γ-Aminobutyric Acid Type B ($GABA_B$) Receptor Derived from β-Hydroxy and β-Amino Difluoromethyl Ketones

Munia F. Sowaileh, Amy E. Salyer, Kuldeep K. Roy, Jinu P. John, James R. Woods, Robert J. Doerksen, Gregory H. Hockerman, David A. Colby

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Graphical Abstract

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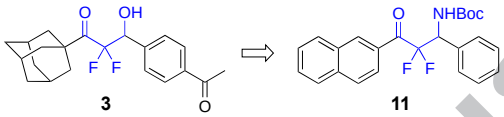

3

EC_{50} = 24.9 μM ($GABA_B$)
EC_{50} > 100 μM ($GABA_A$)

11

EC_{50} = 19.4 μM ($GABA_B$)
EC_{50} > 100 μM ($GABA_A$)

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Agonists of the γ-Aminobutyric Acid Type B ($GABA_B$) Receptor Derived from β-Hydroxy and β-Amino Difluoromethyl Ketones

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ABSTRACT

β-Hydroxy difluoromethyl ketones represent the newest class of agonists of the $GABA_B$ receptor, and they are structurally distinct from all other known agonists at this receptor because they do not display the carboxylic acid or amino group of γ-aminobutyric acid (GABA). In this report, the design, synthesis, and biological evaluation of additional analogues of β-hydroxy difluoromethyl ketones characterized the critical nature of the substituted aromatic group on the lead compound. The importance of these new data is interpreted by docking studies using the X-ray structure of the $GABA_B$ receptor. Moreover, we also report that the synthesis and biological evaluation of β-amino difluoromethyl ketones provided the most potent compound across these two series.

The inhibitory neurotransmitter, γ-aminobutyric acid (GABA), reduces the excitability of neurons and assists in the regulation of other neurotransmitters, especially in the central nervous system. The two major types of GABA receptors are $GABA_A$ and $GABA_B$ and both are validated targets for drug discovery.[1] The $GABA_A$ receptors are ion channels and can be controlled by three classes of pharmaceuticals, the barbiturates, the benzodiazepines, and the newer non-benzodiazepine sedatives, such as zaleplon and zopiclone.[2] The $GABA_B$ receptors are metabotropic G-protein-coupled receptors, and serve as the target of the muscle relaxant, baclofen.[3] Moreover, the $GABA_B$ receptors are the focus of drug discovery efforts in muscle spasticity disorders,[3] schizophrenia,[4] pain,[5] and gastroesophageal reflux disease (GERD).[6] Agonists,[7] antagonists,[8] positive allosteric modulators,[9,10] and negative allosteric modulators[11] of the $GABA_B$ receptor are known, and in 2013, the X-ray structures of this receptor in the ligand-free state and in the presence of agonists and antagonists were reported.[12]

Nearly all of the known agonists of the $GABA_B$ receptor display the structure of GABA, and, for example, baclofen is the 3-*para*-chlorophenyl analogue of GABA (Figure 1).[13] Although the pharmaceutical formulation of baclofen is a racemic mixture, the (*R*)-(–)-enantiomer is significantly more active. The 3-phenyl derivative is the agent, phenibut, and in a similar fashion, (*R*)-(–)-phenibut is the more active enantiomer.[14] Also, the 2-chlorothienyl group is a surrogate for the *para*-chlorophenyl group of baclofen and is displayed in $GABA_B$ agonist **1**.[15] Other key analogues of baclofen, which are also agonists of the $GABA_B$ receptor, are the pyridinyl methoxy derivative **2**,[16] (*R*)-(–)-GABOB,[17] and CGP44532.[18] The only known agonist of the $GABA_B$ receptor that does not display the backbone of GABA or baclofen is the difluoromethyl ketone **3**.[19]

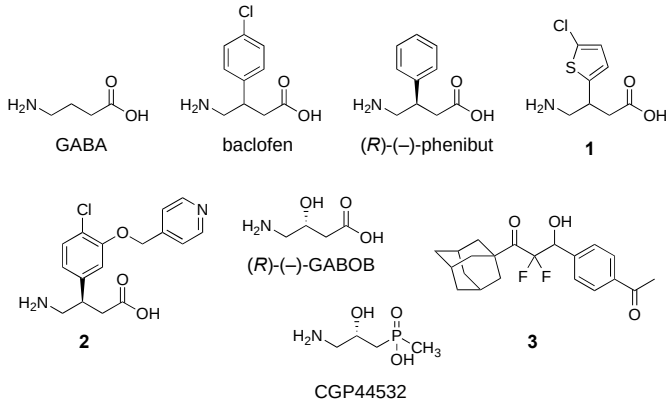
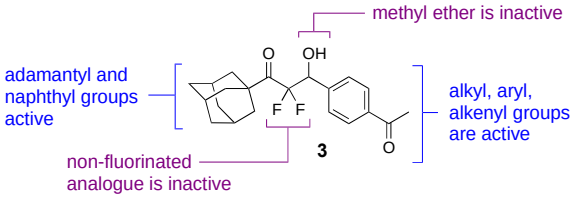


Figure 1. Structures of some known agonists of the $GABA_B$ receptor.

The β-hydroxy difluoromethyl ketones are a distinct group of ligands of the $GABA_B$ receptor and were first reported in 2013.[19] The structure–activity relationships for the lead compound **3** in this series are that the fluorines and the β-hydroxy substituent are

required for activity (Scheme 1).[19] Specifically, the non-fluorinated analogue of **3** is inactive and methyl ether derivative created from methylation of the β-hydroxy substituent of **3** is also inactive. The bulky, lipophilic adamantyl group or naphthyl group is common in other active derivatives. On the other hand, the *para*-acetyl phenyl group of **3** tolerates many other structures such as alkyl, alkenyl, and aryl groups. Although these data are insightful, the agent **3** presents additional opportunities to identify new structure-activity relationships for agonist activity for the $GABA_B$ receptor. In the present study, we have prepared new β-hydroxy difluoromethyl ketones and characterized the β-amino difluoromethyl ketones as another complementary scaffold.



Scheme 1. Structure–activity relationships for compd **3** and agonist activity at the $GABA_B$ receptor.

These unique compounds were discovered following the development of a new synthetic protocol that uses pentafluoro-*gem*-diols to produce difluoroenolates for aldol reactions[20,21] and was later extended to imino-aldol reactions.[22,23] The first objective was to define the role of substituents on the *para*-acetylphenyl group of **3**. Compounds **4**–**6** were synthesized,[24] and each displays a change to the *para*-acetyl group on the phenyl ring (Figure 2). Compound **7** was prepared to understand if a heteroaromatic group could replace the adamantyl group. The analogue **8** bears a larger isoindolinedione to replace the *para*-acetyl phenyl group. Next, the β-amino difluoromethyl ketones **10**–**14** were synthesized using the literature methods.[22,23] The naphthyl and adamantyl groups were conserved (i.e., **10**–**11** and **12**, respectively) and the *N*-phenylsulfonyl and *N*-*tert*-butylcarbamate groups were selected as substituents for the amine.

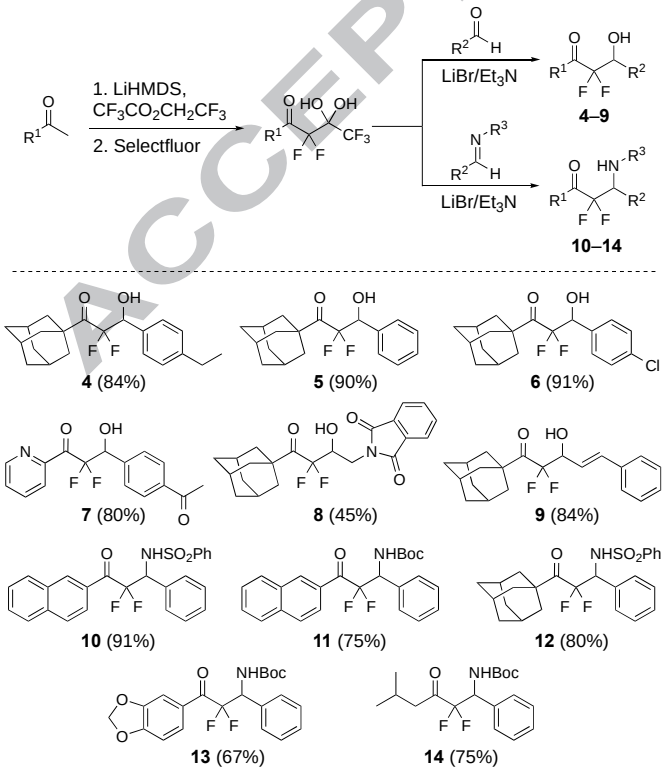


Figure 2. Preparation of β-hydroxy difluoromethyl ketones **4**–**9** and β-amino difluoromethyl ketones **10**–**14**. Isolated yields for the aldol and imino-aldol reactions are given in parenthesis.

In 2018, we reported a procedure in which unactivated imines bearing *N*-benzyl, aryl, or alkyl group reacted with difluoroenolates generated from pentafluoro-*gem*-diols in the presence of magnesium salts.[25] This process enables the creation of additional β-amino difluoromethyl ketones displaying a *N*-benzyl group to complement those bearing *N*-phenylsulfonyl and *N*-*tert*-butylcarbamate group (Figure 3). The naphthyl derivative **15** completes the series from **10** and **11**, and compound **16** and **17** were prepared to obtained additional structure-activity data.[25]

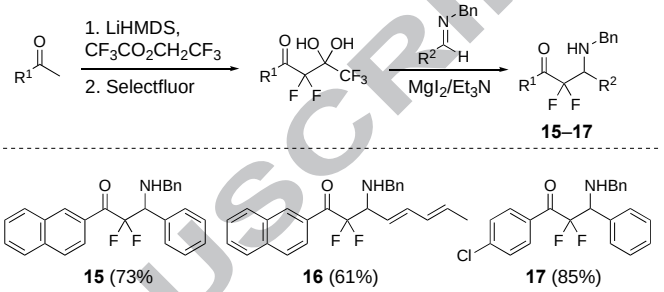


Figure 3. Synthesis of β-amino difluoromethyl ketones **15**, **16**, and **17**. Isolated yields for the imino-aldol reactions are given in parenthesis. See ref. 25.

Compounds **4**–**17** were tested for agonist activity at the $GABA_A$ and $GABA_B$ receptors according to the previously reported procedures.[19] The screen for agonist activity at the $GABA_B$ receptor is conducted in a HEK293/Cre-luc cell line expressing both subunits of the human $GABA_B$ receptor. Activation of the $GABA_B$ receptor accesses an endogenous signaling pathway and results in the inhibition of cAMP production. In this assay, forskolin is applied to stimulate cAMP production, and inhibition of the forskolin-stimulated cAMP production is measured (assays are performed in triplicate). All of the compounds that display activity at the $GABA_B$ receptor are also screened for agonist activity at the $GABA_A$ receptor using a whole-cell voltage-clamp method with HEK293 cells transfected with the $\alpha_1\beta_2\gamma_2$ subunits of the rat $GABA_A$ receptor. The pharmaceutical, baclofen, is a racemic mixture and selective agonist for the $GABA_B$ receptor; however, most of its pharmacological activity results from the (–)-baclofen enantiomer.[19] In a similar fashion, the lead compound **3** also has more agonist activity from a single enantiomer (i.e., the (+)-**3**-enantiomer); however, an absolute stereochemical assignment of secondary alcohol was not reported.[19] The fluorinated compounds **4**–**17** were all tested as racemic mixtures. The β-hydroxy difluoromethyl ketones **4**–**8** do not display any observable activity, even at concentrations up to 100 μM. These results demonstrate the low tolerance for changes to the *para*-acetyl phenyl group, especially as the replacement of the acetyl with an ethyl group produces an inactive compound (i.e., compound **4**). On the other hand, some structural variation is allowed because our prior studies validated that the styrene **9** displays activity of 40 μM compared to the lead compound **3** at 24.9 μM at the $GABA_B$ receptor.[19] The β-amino difluoromethyl ketone **11** was characterized as the most active agent across the entire difluoromethyl ketone series. The β-amino difluoromethyl ketone **11** displays EC_{50} = 19.4 μM, and, notably, when the *N*-Boc group in **11** is replaced with *N*-SO_2Ph in **10** or with *N*-Bn in **15**, agonist activity decreases to EC_{50} = 32.7 μM or EC_{50} = 91 μM, respectively. All three of these molecules display no activity at the $GABA_A$ receptor, which correlates well with the β-hydroxy difluoromethyl ketones, which also preferential for the $GABA_B$

receptor (over the $GABA_A$ receptor). The other β-amino analogues **12**–**14** and **16** were inactive at the $GABA_B$ receptor. The para-chlorophenyl derivative **17** displays moderate activity at the $GABA_B$ receptor.

Table 1. $GABA_A$ and $GABA_B$ assay data for baclofen and compds **3**–**17.**

compd	$GABA_B$ EC_{50} (μM)[a]	$GABA_A$ EC_{50} (μM)[a]
GABA[c]	0.53 ± 0.33	2.30 ± 0.59
(±)-baclofen[c]	1.7 ± 0.10	>100
(±)-**3**[b]	24.9 ± 1.30	>100
(–)-**3**[b]	37.8 ± 0.78	nd[c]
(+)-**3**[b]	15.9 ± 1.84	nd
4	>100[d]	nd
5	>100[d]	nd
6	>100[d]	nd
7	>100	nd
8	>100	nd
9[c]	40 ± 3.59	>100
10	32.7 ± 1.44	>100
11	19.4 ± 7.69	>100
12	>100	nd
13	>100	nd
14	>100	nd
15	91 ± 5.7	>100
16	>100	nd
17	57.4 ± 2.2	>100

[a] Values are given with the standard error.

[b] Ref 19.

[c] nd is not determined..

[d] Cytotoxic in assay at 50 μM and 100 μM doses.

Additional biological characterizations of compounds **3** and **11** were performed using a radio-ligand binding assay screen with cloned neurotransmitter receptors and transporters (Table 2).[26] Difluoromethyl ketones are known in the literature to display activity at many targets,[27,28] so these screens provide an important perspective on the relative role of these ligand for the $GABA_B$ receptor over other neurotransmitter receptors. Adrenoreceptors and biogenic amine, dopamine, opioid, histamine, muscarinic, serotonin, and sigma receptors were examined, and interestingly, both **3** and **11** display less than 30% inhibition and are considered inactive in all of these assays. These data strengthen the knowledge of the preference of this class of compounds (i.e., β-hydroxy difluoromethyl ketone and β-amino difluoromethyl ketone) for the $GABA_B$ receptor.

Table 2. Radio-ligand binding assay screen for compds **3** and **11** in cloned receptors and transporters. Both **3** and **11** are inactive in all assays.

Adrenoreceptors	α_{1A}, α_{1B}, α_{1A}, α_{2A}, β_1, β_2, β_3
Biogenic amine transporters	DAT, NET, SERT
Dopamine receptors	D_1, D_2, D_3, D_4, D_5
Opioid receptors	DOR, KOR, MOR
Histamine receptors	H_1, H_2, H_3, H_4
Muscarinic receptors	M_1, M_2, M_3, M_4, MS
Serotonin receptors	5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_3, 5-HT_{5A}, 5-HT_6, 5-HT_7
Sigma receptors	$rSigma_1$, $rSigma_2$

In order to integrate the new structure–activity relationships with the prior data, both enantiomers of the lead compound **3** were docked into the (*R*)-baclofen-bound $GABA_B$ receptor complex (PDB ID: 4MS4),[12] using the Induced Fit Docking protocol of the Schrödinger small molecule drug discovery suite.[24] The difluoromethyl ketone **3** is hydrated in the model, because difluoromethyl ketones are known to exist in the hydrated (*gem*-diol) form at physiological pH.[19] The respective *gem*-diol, in turn, occupies a similar site as the carboxylate of baclofen. Hydrogen-bonding is conserved with Ser130 and Gly171 (as observed with GABA-bound X-ray structure, PDB-ID:4MS3) and the *gem*-diol maintains a close proximity to the Ser153 (Figure 4). The β-hydroxy substituent in both the (*R*)-**3** and (*S*)-**3** alcohols cannot occupy the same site as the amino group of baclofen due to the shorter intramolecular distance from the difluoromethyl ketone group. However, the *para*-acetylphenyl group of both the (*R*)-**3** and (*S*)-**3** compounds employs a similar site as the *para*-chlorophenyl group of baclofen and maintains key interactions with the Trp278 residue. Lastly, docking studies present potential docking poses for **3** that accommodate the bulky adamantyl group within the ligand binding site of the $GABA_B$ receptor.

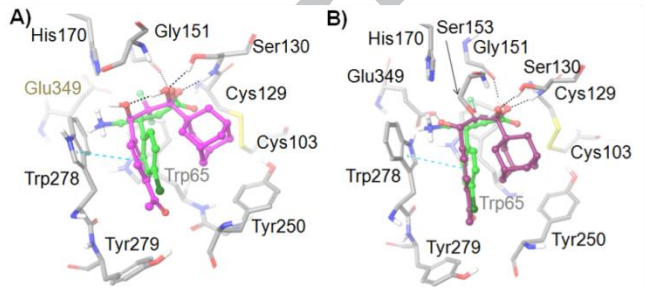


Figure 4. Active site residues (gray) of the $GABA_B$ receptor from docking studies with: A) (*R*)-**3** (GlideScore = –10.080) (magenta) and B) (*S*)-**3** (GlideScore = –9.606) (purple). (*R*)-Baclofen (GlideScore = –11.063) is also shown in each image (green). Amino acids are depicted as tubes and ligands are represented as ball-and-stick. H-bonds and aromatic π–π stacking are shown as black and cyan dashed lines, respectively.

We attempted to dock both enantiomers of **10** and **11** into the $GABA_B$ receptor using both SP and XP Induced Fit Docking, and the methods gave similar results, so we report the XP ones. The sulfonamide group of (*S*)-**10** is engaged in hydrogen-bonding with Ser130 whereas the *gem*-diol of (*S*)-**11** is hydrogen-bonded to the Ser130 and Gly151, and both these functional groups lie in close proximity to Ser153 (Figure 5). The phenyl group attached to the stereogenic carbon in (*S*)-**10** occupies the same site as the amino group of baclofen. By contrast, the naphthalene ring of (*S*)-**11** occupies this site. Moreover, the naphthyl group of (*S*)-**10** is in the site occupied by the *para*-chlorophenyl group of baclofen, whereas for (*S*)-**11** this site is occupied by its phenyl group (Figure 5). (*R*)-**10** failed to dock into the binding site in several trials with different grid settings. The docked pose of (*R*)-**11** (GlideScore = −8.500) is provided in the supplementary information. Hence, we predict that the (*S*)-enantiomers are the more active for **10** and **11**.

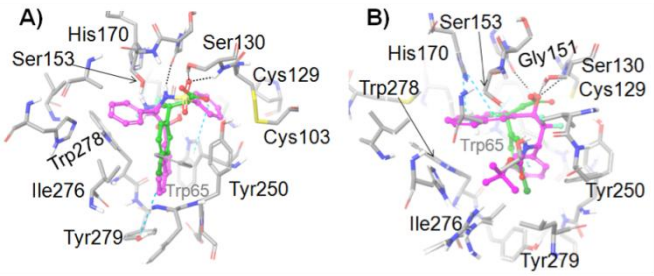


Figure 5. Active site residues (gray) of the $GABA_B$ receptor from docking studies with: A) (*S*)-**10** (GlideScore = −11.037) (magenta) and B) (*S*)-**11** (GlideScore = −10.592) (magenta). (*R*)-Baclofen is also shown in each image (green). Amino acids are depicted as tubes and ligands are represented as

ball-and-stick. H-bonds and aromatic π–π stacking are shown as black and cyan dashed lines, respectively.

The difluoromethyl ketones represent the newest class of agonists of the $GABA_B$ receptor, and further investigations through synthesis, biological evaluation, and computational analysis have not only revealed that enhancements in potency are possible but also that the structure–activity relationships are distinct from other classes of agonists that display the structure of GABA. The critical nature of the substituent on the aromatic group of the β-hydroxy difluoromethyl ketone was characterized. Also, the identification of the β-amino difluoromethyl ketones as potent agonists of the $GABA_B$ receptor is another significant advance.

Acknowledgments

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Supplementary Material

Experimental procedures; molecular modeling procedures and supporting results; and ^{1}H, ^{19}F, and ^{13}C NMR spectra. Supplementary data associated with this article can be found in the online version.

Highlights

- β-Hydroxy difluoromethyl ketones have distinct SAR data at the $GABA_B$ receptor
- β-Amino difluoromethyl ketones are now characterized as $GABA_B$ agonists
- Docking studies at the $GABA_B$ receptor suggest similar binding modes to baclofen