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Ethers of 3-hydroxyphenylacetic acid as selective gamma-hydroxybutyric acid receptor ligands

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Abstract—Gamma-hydroxybutyric acid (GHB) is a drug of abuse, a therapeutic, and purportedly a neurotransmitter with a complex mechanism of action in vivo due to direct actions at $GABA_B$ as well as GHB receptors and because of its metabolism to GABA. Herein, we describe 3-ethers of 3-hydroxyphenylacetic acid, which have relatively high affinity at GHB sites, no significant affinity at GABA receptors, and would not be expected to be rapidly metabolized to GABAergic ligands. The selectivity of these compounds (UMB108, UMB109, and UMB119) could prove to be useful for studying the biology of GHB receptors, free from GABAergic effects.

Gamma-hydroxybutyric acid (GHB) (**1**) (Fig. 1) is a drug of abuse, a therapeutic, and purportedly a neurotransmitter.[1] GHB interacts with GHB receptors with micromolar affinity, and is also an agonist at $GABA_B$ receptors and is rapidly metabolized to gamma-aminobutyric acid (GABA (**2**) Fig. 1),[2] resulting in GABAergic activity in vivo.[3–5] Thus, there is an urgent need for high affinity metabolically stable analogs of GHB that have little or no affinity for $GABA_B$ receptors.[6]

It has been shown that the hydrogen of the alcohol of GHB is not essential for affinity at GHB receptors, and that only a hydrogen bond accepting group is required (**3**) (Fig. 1) for affinity at GHB receptors.[7–9] As GHB is metabolized to **2** through oxidation of the alcohol of GHB followed by transamination,[10] we considered that its removal would slow this metabolic pathway, but recently showed that GHB-ethers (**4–6**) (Fig. 2) have lower affinity than GHB at GHB receptors.[11] One important finding was that 3-hydroxyphenylacetic acid (**7**) (Fig. 2) has greater affinity than GHB for GHB receptors and displaces [^{3}H]GABA by 44% from $GABA_A$ receptors at 1 mM (see Table 1).[11]

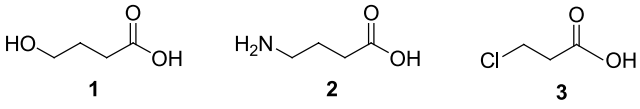
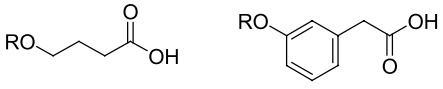


Figure 1. Structures of GHB, GABA, and 3-chloropropanoic acid.



1 R = H
4 R = $Ph(CH_2)_3$
5 R = $Ph(CH_2)_2$
6 R = $Ph(CH_2)$
8 R = Ph

7 R = H
9 R = $Ph(CH_2)_3$
10 R = $Ph(CH_2)_2$
11 R = $Ph(CH_2)$
12 R = Ph

Figure 2. Structures of the ethers of GHB and 3-hydroxyphenylacetic acid.

Thus, we investigated the introduction of ethers onto the 3-hydroxyl of **7** in order to compare the ethers of **7** with the 4-ethers of GHB, and to determine if the removal of the hydrogen bond donating hydroxyl group reduced the affinity at $GABA_A$ receptors.

The commercially available compounds (**8**, **12**) were purchased from Sigma–Aldrich, and the other ethers

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Table 1. IC_{50} values for GHB and its analog acids using [^{3}H]NCS-382 (16 nM) as a radioligand in rat cerebrocortical membranes, and inhibition of [^{3}H]GABA (10 nM) binding to $GABA_A$ and $GABA_B$ receptors in rat membranes from cerebral cortex and cerebellum, respectively, by the ligands at a concentration of 1 mM

Compound	[^{3}H]NCS-382 IC_{50} (μM)	Percent displacement of [^{3}H]GABA at 1 mM	
	GHB sites	$GABA_A$	$GABA_B$
1, GHB[a]	25.0 ± 1.8	35.5 ± 3.7	41.1 ± 3.1
7[a]	12.0 ± 5.5	44.2 ± 2.0	14.0 ± 4.0
8	210 ± 62	6.3 ± 1.7	6.5 ± 1.0
9, UMB109	4.5 ± 1.9	17.4 ± 13.2	6.0 ± 2.6
10, UMB108	8.3 ± 1.6	15.1 ± 7.5	−1.2 ± 7.3
11	46.0 ± 10	11.0 ± 6.2	−4.7 ± 4.7
12, UMB119	16.3 ± 0.8	2.7 ± 0.5	−5.5 ± 1.2

Each value is the mean ± SEM of at least three individual experiments performed in triplicate.
[a] Data from Ref. 11.

(**9–11**) (Fig. 2) were prepared through dialkylation of **7** with the relevant arylalkyl halide, followed by hydrolysis of the ester with NaOH. All five compounds were assayed in their acid forms.[12] Affinities were studied through [^{3}H]NCS-382 displacement assays as previously described,[6,11,13] and the results are presented in Table 1.

GHB (**1**) and 3-hydroxyphenylacetic acid (**7**) have affinity for GHB receptors and displace [^{3}H]NCS-382 binding with IC_{50}'s of 25 and 12 μM, respectively. Importantly, both compounds also have weak affinity for GABA receptors. The introduction of a phenyl ether into GHB to give **8** yielded a compound with an affinity of 210 μM at GHB receptors, consistent with the results obtained with other ethers of GHB, including the benzyl ether (**6**), phenethyl ether (**5**), and phenylpropyl ether (**4**), all of which have affinities at GHB sites an order of magnitude lower than GHB.[11] In contrast, when similar ethers were formed on **7** the marked decreases in GHB affinity were not observed and, in the case of phenylpropyl ether (**9**), GHB receptor affinity increased slightly, while displacement of [^{3}H]GABA from GABA receptors decreased. The phenethyl ether (**10**) and phenyl ether (**12**) were shown to have the same affinity as **7** at GHB receptors with decreased affinity at GABA receptors. The benzyl ether, **11**, had 4-fold lower affinity for GHB receptors than **7**, but also displaced GABA to a lower extent than **7**. The fact that the phenethyl ether (**10**, UMB108), phenylpropyl ether (**9**, UMB109), and phenyl ether (**12**, UMB119) had relatively high affinity at GHB receptors, and lower affinity at GABA receptors than **7**, suggests that the aromatic group in these ethers occupies a site which is favorable for affinity at GHB receptors and unfavorable for affinity at GABA receptors. UMB108 (**10**) was also shown to be selective (>100-fold) for GHB receptors over other sites, including the following: adenosine, adrenergic, dopamine, GABA, melatonin, muscarinic, opioid, serotonin, and sigma receptors, and calcium, potassium, sodium, and chloride channels.[14] Thus, UMB108, UMB109, and UMB119 could prove to be useful for studying GHB receptors, and the results of this study specifically suggest that the 3-hydroxyphenylacetic acid skeleton has the potential to facilitate the discovery of high affinity and selective ligands for GHB receptors.

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