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Preparation of a Series of 5-Methyl-3-(substituted)-[1,2,4]triazines

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Abstract

Procedures for the synthesis of thirty-six 5-methyl-3-(substituted)-[1,2,4]triazines have been described. These compounds were evaluated for antagonism at metabotropic glutamate receptor subtype 5. Two compounds, **5b** and **3c**, were determined to be low micromolar inhibitors of mGluR5.

Keywords

Triazine; mGluR5 Antagonist; Addiction; Heterocyclic synthesis

There are several studies that show that metabotropic glutamate receptor subtype 5 (mGluR5) plays a role in central nervous system disorders including addiction, pain, fragile X syndrome, and anxiety.^{1–5} In a previous study, we discovered that 3-(substituted phenylethynyl)-5-methyl-1,2,4-triazines (**1**) were potent antagonists of glutamate-mediated mobilization of internal calcium in an mGluR5 in vitro efficacy assay.⁶

In 2006, Buttelmann et al.⁷ reported that **2** had K_i of 1 nM in an mGluR5 binding assay and was active in an anxiolytic test after oral administration. We, therefore, considered it would be of interest to synthesize and evaluate triazine analogues of compound **2** (**3a–f** and **4a–f**) for antagonism at mGluR5. In addition, we prepared analogues **5a–f**, **6a–f**, **7a–f**, and **8a–f** where the oxygen atom was replaced by a sulfur or amino group.

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Supplementary Material

Experimental details including ¹H NMR, ¹³C NMR, MS, and elemental analysis data and calcium mobilization assay procedure are provided.

The phenoxy and benzyloxy substituted methyl-[1,2,4]triazines were synthesized from the corresponding phenols (**9a–f**) and benzyl alcohols (**10a–f**), which were first deprotonated with sodium hydride in THF and added to 5-methyl-3-sulfonyl[1,2,4]triazine (**11**) (Scheme 1). 5-Methyl-3-sulfonyl[1,2,4]triazine (**11**) was prepared as described previously.⁶ The products **3a–f** and **4a–f** were isolated in moderate yields after chromatographic separation.

The thio-linked compounds **5a–f** and **6a–f** were synthesized after deprotonation of the corresponding thiols (**12a–f**) and benzyl thiols (**13a–f**) with sodium hydride in THF followed by displacement of the methylsulfonyl group in **11** (Scheme 2).

Preparation of either aniline derivatives or benzyl amines did not require basic conditions to facilitate the displacement of the methylsulfonyl group in **11** (Scheme 3). Benzyl amines (**14a–f**) reacted rapidly in refluxing THF to provide the desired analogues (**7a–f**) in good yields. Reaction of various substituted anilines (**15a–f**) with **11** did not occur in refluxing THF but the desired products (**8a–f**) could be isolated by heating the reactants without solvent at 110 °C under N₂ blanket after chromatographic separation. The low yields (13 – 20%) were as a result of decomposition of **11** under heat.

Fluorimetric Ca²⁺/flux assay was used to evaluate the compounds for antagonism at mGluR5. Compounds were screened for *in vitro* efficacy using CHO-K1 cells stably transfected with the human mGluR5 cells. Through the screening process it was found that **5b**, **5f**, and **3c** were weakly to moderately active, producing >35% inhibition of calcium mobilization in CHO-K1-mGluR5 cells. Of these three compounds, the two compounds that showed higher levels of inhibition were reevaluated to determine the IC₅₀ values in a calcium efflux assay (Table 1). Compounds **5b** and **3c** were determined to be low micromolar inhibitors of mGluR5.

Supplementary Material

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Scheme 1.
Synthesis of substituted phenoxy and benzyloxy methyl[1,2,4]triazines

Scheme 2.

Synthesis of thiophenol and benzylthiol substituted methyl[1,2,4]triazines

Scheme 3.

Synthesis of aniline and benzylamine substituted methyl[1,2,4]triazines

Table 1

Selected Inhibition of Human mGluR5-Mediated Intracellular Calcium Mobilization for Heterocyclic-Linked Analogues

<div><div> 5b</div><div> 5f</div><div> 3c</div></div>			
Compound	5b	5f	3c
% inhibition at 10 μ M	44	35	51
IC ₅₀ (μ M)	13.4 $\pm$ 2.3	n.d.	15.2 $\pm$ 4.0