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

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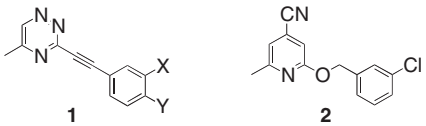
ABSTRACT

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 (mGluR5). Two compounds, **5b** and **3c**, were determined to be low micromolar inhibitors of mGluR5.

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-methy[1,2,4]triazines (**1**) were potent antagonists of glutamate-mediated mobilization of internal calcium in an mGluR5 in vitro efficacy assay.[6]

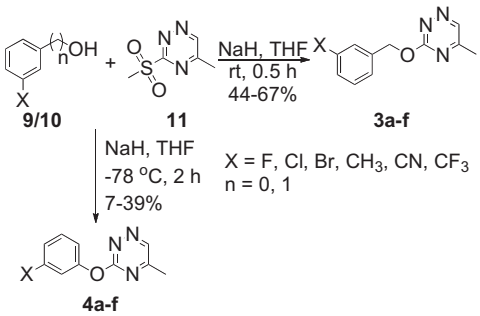


In 2006, Buttelmann et al.[7] reported that **2** had K_i of 1 nM in an mGluR5 binding assay and was active in an anxiolytic test after oral administration. We, therefore, considered it would be of interest to synthesize and evaluate triazine analogues of compound **2** (**3a–f** and **4a–f**) for antagonism 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.

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 N_2 blanket after chromatographic separation. The low yields (13–20%) were a result of decomposition of **11** under heat.



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

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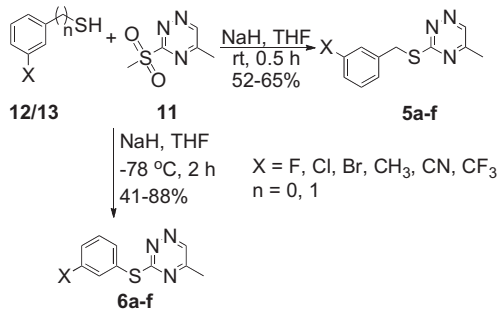
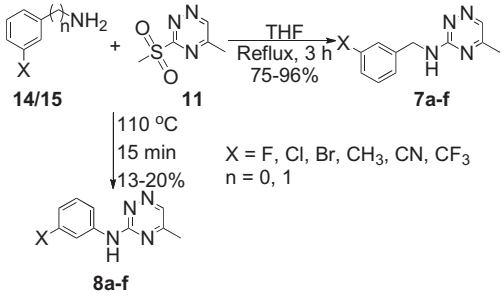


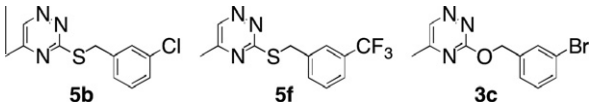
Scheme 2. Synthesis of thiophenol and benzylthiol substituted methyl[1,2,4]-triazines.



Scheme 3. Synthesis of aniline and benzylamine substituted methyl[1,2,4]triazines.

Fluorimetric Ca^{2+} 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. Through the screening process it was found that **5b**, **5f**, and **3c** were weakly to moderately active, producing >35% inhibition of calcium mobilization in CHOK1-mGluR5 cells. Of these three compounds, the two compounds that showed higher levels of inhibition were reevaluated to determine the IC_{50} values in a calcium efflux assay (Table 1). Compounds **5b** and **3c** were determined to be low micromolar inhibitors of mGluR5.

Table 1
Selected inhibition of human mGluR5-mediated intracellular calcium mobilization for heterocyclic-linked analogues



Compound	5b	5f	3c
% Inhibition at 10 μM	44	35	51
IC_{50} (μM)	13.4 ± 2.3	n.d.	15.2 ± 4.0

Acknowledgment

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Supplementary data

Supplementary data (experimental details including ^{1}H NMR, ^{13}C NMR, MS, and elemental analysis data and calcium mobilization assay procedure are provided) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.04.075.

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