Short Note

4-(2-Methyloxazol-4-Yl)benzenesulfonamide

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4-(2-Methyloxazol-4-yl)benzenesulfonamide

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Abstract: 4-(2-Methyloxazol-4-yl)benzenesulfonamide was synthesized by the reaction of 4-(2-bromoacetyl)benzenesulfonamide with an excess of acetamide. The obtained compound was evaluated as a potential inhibitor of human monoamine oxidase (MAO) A and B and was found to inhibit these enzymes with IC_{50} values of 3.47 μM for MAO-B and 43.3 μM for MAO-A. Thus, the new selective MAO-B inhibitor was identified, which may be used as the lead compound for development anti-Parkinson's disease agents.

Keywords: monoamine oxidase; inhibitors; 1,3-oxazole; benzenesulfonamide; drug research; Parkinson's disease; MAO

1. Introduction

Neurodegenerative diseases significantly affect the health of the human population and place a burden on economies of countries around the world. Among these diseases, Parkinson's disease (PD) is the second most common disorder and is associated with the death of dopaminergic motor neurons. At present, the disease is not curable, however, the motor symptoms of PD are effectively treated with levodopa, the metabolic precursor of dopamine. To enhance the therapeutic action of levodopa, this drug is frequently combined with monoamine oxidase (MAO) B inhibitors, compounds that reduce the central metabolism of dopamine [1]. While MAO-B inhibitors may allow for a reduction of the effective levodopa dosage, these compounds have also been studied as neuroprotective agents [2], candidates for reducing neuroinflammation [3], as well as compounds with potential value in the therapy of oncological diseases [4]. Possible mechanisms by which MAO-B inhibitors may exert neuroprotective effects include enhancement of the levels of brain-derived neurotrophic factor (BDNF) [5] and molecular adhesion of L1CAM (L1) nerve cells, which can also promote axonal regrowth and increase neuronal survival, synaptic plasticity and remyelination [6]. Thus, the development of a new generation of neuroprotective agents that act by inhibiting MAO might have relevance in the future treatment of neurodegenerative disorders.

Recently, benzenesulfonamide compounds have been identified as potent and isoform-specific inhibitors of MAO-B, with come compounds exhibiting potencies in the nanomolar range. Such compounds might represent promising candidates for the future treatment of PD [7,8]. Also, it has been established that 1,3-oxazole derivatives also exhibit potent and specific inhibition of the MAO-B isoform [9]. This work reports a successful attempt to combine both these structural features into a single molecule (Figure 1).

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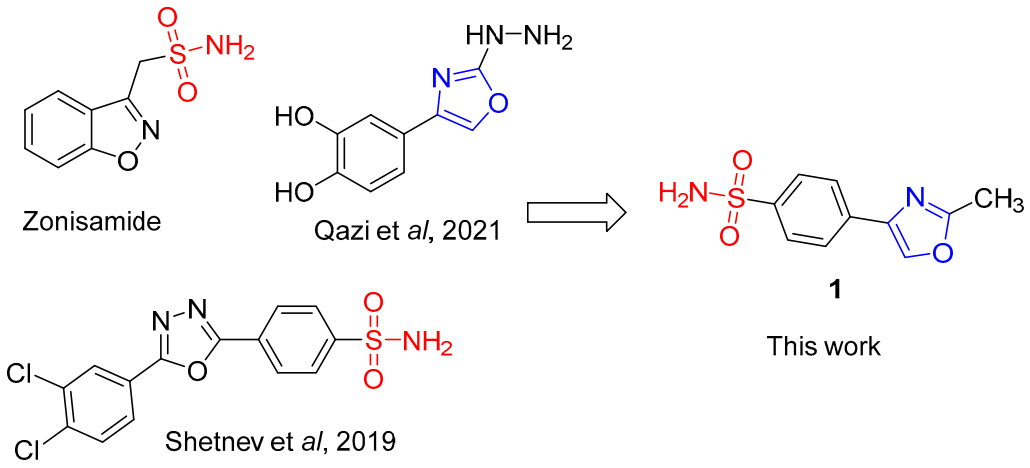


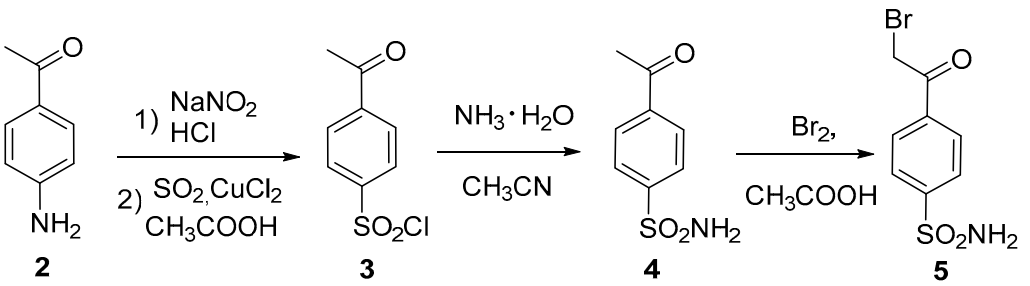
Figure 1. (**a**) Structures of MAO inhibitors containing and sulfonamide and 1,3-oxazole moieties.

Recently our research group reported a variety of new lead compounds for the development of isoform specific MAO-B inhibitors such as 2.1-benzisoxazoles [10], indazoles [11,12] and pyrazolo[1,5-*a*]quinoxalin-4-ones [13]. Continuing the search of novel MAO inhibitors, in this work we used a simple convergent approach to synthesize a new 1,3-isoxazole compound substituted with a primary benzene sulfonamide functionality.

2. Results

2.1. Chemistry

We examined the possibility of synthesizing the target oxazole **1** by the reaction of sulfonamide-containing phenacyl bromide **5** with acetamide or ammonium acetate.



Scheme 1. Synthesis of 4-(2-bromoacetyl)benzenesulfonamide (**5**).

The starting material, phenacyl bromide **5**, was obtained according to a well-known three-step procedure using 4-acetylaniline (**2**) as key reagent [14]. The best yield (63%) of the target oxazole **1** was obtained by fusing phenacyl bromide **5** with excess acetamide at 150 °C. When using ammonium acetate in acetic acid [15], the target oxazole **1** was obtained in much lower yield (24%).

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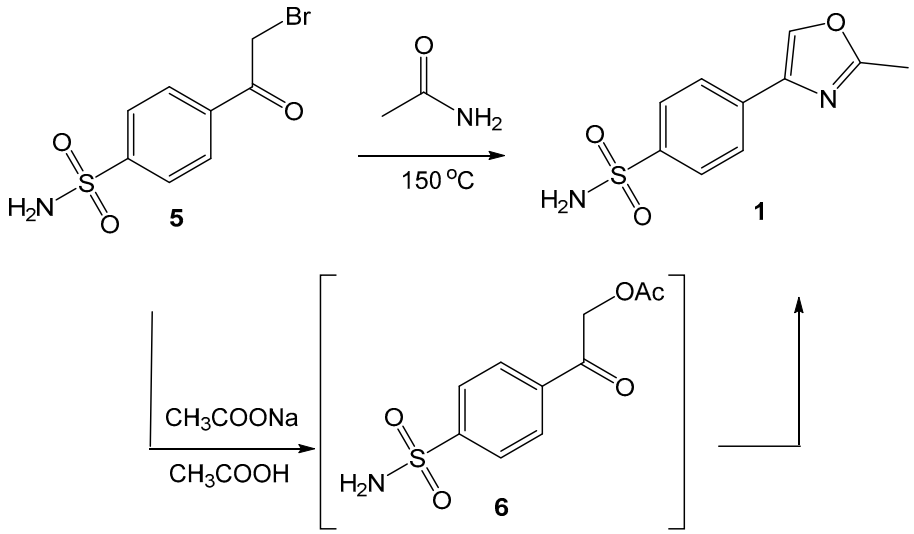
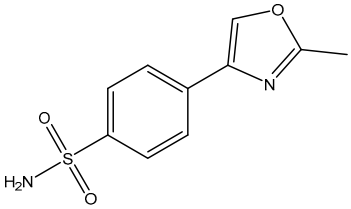


Scheme 1. Synthesis of 4-(2-methyloxazol-4-yl)benzenesulfonamide (**1**).

2.2. MAO inhibition

The MAO inhibition potency of 4-(2-methyloxazol-4-yl)benzenesulfonamide (**1**) was evaluated using recombinant human MAO-A and MAO-B, following the protocol described in literature [15]. The results of the MAO inhibition studies are presented in table 1. Compound **1** inhibited MAO-B with an IC_{50} value of 3.47 μM, whereas weak inhibition of the MAO-A isoform was recorded.

Table 1. The inhibition of human MAO-A and MAO-B by 4-(2-methyloxazol-4-yl)benzenesulfonamide (**1**).

Structure	IC_{50} (μM ± SD)[1]	
	MAO-A	**MAO-B**
	43.3 ± 7.12	3.47 ± 0.31
Curcumin[2]	5.02 ± 0.45	2.56 ± 0.21
Toloxatone [13][2]	3.92	-

[1] The IC_{50} values are presented as the means ± standard deviation (SD) of triplicate measurements. [2] Reference inhibitors.

3. Discussion

This study reports the MAO inhibition potency of 4-(2-methyloxazol-4-yl)benzenesulfonamide (**1**). This compound inhibited MAO-B with an IC_{50} value of 3.47 μM while the MAO-A isoform was inhibited with an IC_{50} value of 43.3 μM. The discovery of this active MAO-B inhibitor paves the way for the future discovery of MAO-B inhibitors among 1,3-isoxazole derivatives substituted with a primary benzene sulfonamide. Such compounds may find application in the treatment of neurodegenerative disorders such as PD.

4. Materials and Methods

4.1. General

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All reagents and solvents were obtained from commercial sources (Aldrich, Merck, Aladdin) and were used without purification. Reactions were monitored by analytical thin layer chromatography (TLC) using Merck TLC sheets. Visualization of the developed sheets was performed by fluorescence quenching at 254 nm. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 400 Unity Plus instrument (400 MHz for ^{1}H and 100 MHz for ^{13}C, respectively). Chemical shifts (δ) are given in parts per million (ppm) and were referenced to the solvent signal for DMSO-*d*6 (2.50 ppm for proton and 39.52 ppm for carbon), while the coupling constants (J) are reported in hertz (Hz). Multiplicities are abbreviated as follows: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet. Melting points were determined on an Electrothermal IA 9300 series digital melting point apparatus. Mass spectra were recorded on a microTOF spectrometer (ESI ionization).

4.2. Procedure for the preparation of 4-(2-bromoacetyl)benzenesulfonamide (5)

4-Acetylbenzenesulfonamide (**4**) (1g, 4.5 mmol, 1 equiv.) was dissolved in acetic acid (22 ml), while bromine (0.752 g, 4.7 mmol, 1.05 equiv) was mixed separately with acetic acid (5 ml). The first portion of bromine was added to the reaction mixture and the solution became colorless. The remaining bromine solution was subsequently added dropwise. The reaction mixture was stirred at 40 °C for 1 h, cooled to room temperature and the solvent was evaporated under reduced pressure. The resulting oil was diluted with cold water (25 ml) and the precipitate that formed was collected by filtration, washed with water (15 ml) and air-dried at 25 °C. 4-(2-Bromoacetyl)benzenesulfonamide (**5**) 1.22 g (98%) isolated as the beige crystalline solid. m.p. 154-155 °C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.17 (d, J = 8.2 Hz, 2H), 7.96 (d, J = 8.2 Hz, 2H), 7.57 (s, 2H), 4.98 (s, 2H) (*Scobie et al, 2018*).

4.3. Synthesis and characterization of 4-(2-methyloxazol-4-yl)benzenesulfonamide (1)

Acetamide (0,12 g, 0.002 mol, 3 equiv.) and 4-(2-bromoacetyl)benzenesulfonamide (**5**; 0,19 g, 0.00068 mol, 1 equiv.) were mixed together. The reaction mixture was melted, stirred at 150 °C for 20 min and subsequently diluted with cold water (30 ml). The resulting precipitate was collected by filtration, washed with water (10 ml) and air-dried at 50 °C. Yield 0.101 g, 63%, beige solid, mp 237-239 °C; ^{1}H NMR (400 MHz, DMSO-*d6*) *δ* 8.61 (s, 1H), 7.93 (d, *J* = 8.4 Hz, 2H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.38 (s, 2H), 2.48 (s, 3H); ^{13}C NMR (101 MHz, DMSO) *δ* 162.58, 143.67, 139.18, 136.95, 134.91, 126.93, 125.92, 14.21; MS (ESI^{+}): *m/z* [M+H]$^{+}$. Anal. Calcd for $C_{10}H_{10}N_2O_3$: 239.0485. Found: 239.0489.

4.6. MAO inhibition studies

The measurement of IC_{50} values for the inhibition of human MAO-A and MAO-B was carried out according to a previously reported protocol [8, 16]. Recombinant human MAO-A and MAO-B were obtained from Sigma-Aldrich and fluorescence measurements were recorded with a SpectraMax iD3 multi-mode microplate reader (Molecular Devices). The measurement of MAO activity was based on the fluorescence signal generated when the substrate, kynuramine, is oxidized by the MAOs to yield 4-hydroxyquinoline.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org. Copies of ^{1}H and ^{13}C NMR spectra.

Author Contributions: Conceptualization of the study was done by Anton Shetnev; formal analysis and investigation - Julia Efimova and Anél Petzer; writing—original draft preparation was done by Anton Shetnev; writing—review and editing was done by Mikhail Korsakov and Jacobus P. Petzer. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: Not applicable.

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Conflicts of Interest: The authors declare no competing interests.

Appendix A

Not applicable

Appendix B

Not applicable

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