Synthesis of Modafinil Analogue 2-(Benzylsulfinyl)Acetamide and Two Parallel Series of Novel Derivatives: A Family of Potential Dopamine Transporter Inhibitors

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Introduction:
Dopamine is a crucial neurotransmitter which, when released into the synapse, regulates cognition and promotes reinforcing behaviors.\(^5\) The dopamine transporter (DAT) is an essential protein responsible for the movement of dopamine back into neurons and is thus responsible for regulating dopamine levels within the brain.\(^5\) Dysfunctions in dopamine levels are associated with conditions such as Parkinson’s disease, schizophrenia, and drug addiction.\(^5\) Dopamine transporter inhibitors prevent DATs from regulating dopamine levels and prevent termination of neurotransmission.\(^5\) DAT inhibitors are a target of interest in the field of biomedical research including pharmaceutical treatments for addiction, as well as psychiatric and neurodegenerative diseases.\(^4,5\) Modafinil (Figure 1), a known DAT inhibitor,\(^3\) is a cognitive enhancer and wake-promoting agent approved by the U.S. Food and Drug Administration (FDA) for treating narcolepsy, shift work sleep disorder (SWSD), and obstructive sleep apnea/hypopnea syndrome (OSAHS).\(^1,5\)

Based on the structure of modafinil, 2-(benzylsulfinyl)acetamide (Figure 2) is a molecule that has been recently synthesized to potentially serve as a novel dopamine transporter inhibitor. The structure of this molecule is nearly identical to the structure of modafinil, with one less benzene ring. Ten derivatives of this parent compound have also been recently synthesized: 3-chloro-, 3-bromo-, 3-methoxy-, 3-nitro-, 3-methyl-, 4-chloro-, 4-methoxy-, 4-methyl-, and 4-nitro-2-(benzylsulfinyl)acetamide

Target Molecules:

![Figure 1. Modafinil](Image 1)

![Figure 2. 2-(benzylosulfinyl)acetamide](Image 2)

![Figure 3. Series of Meta Derivatives](Image 3)

![Figure 4. Series of Para Derivatives](Image 4)

Chemical Synthesis:

![Figure 5. Scheme 1: Synthesis of 2-(benzylosulfinyl)acetamide and its derivatives](Image 5)

Results:

![Figure 6. 1H NMR Spectrum of 3-chloro-2-(benzyloxy)acetic acid](Image 6)

![Figure 7. 1H NMR Spectrum of 3-chloro-2-(benzyloxy)acetic acid](Image 7)

![Figure 8. 1H NMR Spectrum of 3-chloro-2-(benzyloxy)acetic acid](Image 8)

Conclusions:
The syntheses of the parent compound, 2-(benzylosulfinyl)-acetamide, and its ten derivatives have been completed. It was previously assumed that procedures would be fairly identical to the synthesis of Modafinil, due to structural similarities. However, the first step of the synthesis of these new analogues required a forced S\(^{2}\) substitution reaction, which differs from the S\(^{2}\) reaction in the published synthesis of Modafinil. Once the S-C bond was made under nucleophilic basic conditions, the acid was converted to the amide, and the sulfide was selectively oxidized to the sulfone. The cyclodehydration oxidation state is confirmed by the presence of diastereotopic proton splitting in the 1H NMR spectra of the final compounds.

Future Directions:
(Benzylosulfinyl)acetamide and its series of ten derivatives have been purified and will be tested by means of pharmacological assays for possible biological activity, including affinities for DAT and other receptors, and efficacy in inhibiting dopamine transport.

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References: