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# Synthesis, molecular docking, and biological activity of 2-vinyl chromones: Toward selective butyrylcholinesterase inhibitors for potential Alzheimer's disease therapeutics

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ABSTRACT

We investigated the biological activity of a series of substituted chromeno[3,2-*c*]pyridines, including compounds previously synthesized by our group and novel compounds whose syntheses are reported here. Tandem transformation of their tetrahydropyridine ring under the action of activated alkynes yielding 2-vinylsubstituted chromones was used to prepare nitrogen-containing derivatives of a biologically active chromone system. The inhibitory activity of these chromone derivatives against acetylcholinesterase (AChE), butyrylcholinesterase (BChE) and carboxylesterase (CaE) was investigated using the methods of enzyme kinetics and molecular docking. Antioxidant (antiradical) activity of the compounds was assessed in the ABTS assay. The results demonstrated that a subset of the studied chromone derivatives selectively inhibit BChE but do not exhibit antiradical activity. In addition, the results of molecular docking effectively explained the observed features in the efficacy, selectivity, and mechanism of BChE inhibition by the chromone derivatives.

## 1. Introduction

Neurodegenerative diseases are characterized by progressive nervous system dysfunction and can be hereditary or sporadic. These disorders, often associated with atrophy of the affected central and/or peripheral structures of the nervous system, include Alzheimer's disease (AD), Parkinson's disease (PD), and other less prevalent conditions.

AD is a multifactorial and fatal neurodegenerative disorder characterized by a persistent decline in cognitive functions leading to complete degradation of personality.[1,2] The pathogenesis of AD involves degeneration of cholinergic neurons accompanied by diminished cholinergic transmission.[3]

Current treatment of AD consists of administering anticholinesterase drugs to compensate for the acetylcholine neurotransmitter deficiency.[4] These agents replenish the acetylcholine deficit in the brain by inhibiting cholinesterases, thereby attenuating acetylcholine hydrolysis. Consequently, cholinergic transmission is enhanced by the increased level and duration of neurotransmitter action on postsynaptic receptors.

In a normal brain, acetylcholine is predominantly (80%) hydrolyzed by AChE, whereas BChE plays a supplementary role. However, with progression of AD, the AChE activity decreases, whereas the activity of BChE gradually increases.[5,6] This phenomenon enhances the significance of BChE as an additional therapeutic target for reducing the cholinergic deficiency inherent in AD.[7–9]

To date, the number of approved drugs for AD is limited to only three cholinesterase inhibitors (rivastigmine, donepezil, and galantamine), and the *N*-methyl-D-aspartate (NMDA) receptor antagonist, memantine.[10,11] Among the three cholinesterase inhibitors, rivastigmine is known to inhibit both AChE and BChE.[8]

Oxidative stress – an imbalance between reactive oxygen or nitrogen species and the inability of the body to degrade them – is a significant factor in AD pathogenesis. Therefore, devising antioxidant

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strategies to retard or minimize potential biological damage is important,[12–14] and the development of cholinesterase inhibitors with ancillary antioxidant properties is an emerging trend in the design of new therapeutic agents for AD.[15–17]

Chromones have attracted interest in medicinal chemistry because of their remarkable pharmacological activities. The chromone moiety is an essential pharmacophore of a large number of bioactive molecules. For example, chromone derivatives have been found to exhibit the following medicinal properties: anticancer, antiviral (including anti-HIV), antimicrobial, antifungal, anti-inflammatory, antidiabetic, and antioxidant.[18,19]

Of particular interest in our present investigation is the fact that chromones and their derivatives (e.g., flavonoids) are known to play important roles as antioxidants and radical scavengers.[20] Moreover, the chromone moiety is recognized as a privileged scaffold and a useful template for the design of novel compounds with pharmaceutical potential, especially in the fields of neurodegenerative, inflammatory, and infectious diseases, as well as in diabetes and cancer.[18,21]

It has been discovered that some chromone derivatives display inhibitory activity against AChE and BChE.[22,23] A new family of tacrine-4-oxochromone hybrids has been synthesized and evaluated with respect to different types of AD targets. These hybrids have been found to present a dual-target mechanism toward human beta-site amyloid precursor protein cleaving enzyme 1 (BACE-1) and AChE as well as antioxidant and CNS-permeable properties.[24]

One of the promising synthetic pathways leading to chromone derivatives having a tetrahydropyridine ring in their structures is the previously described reaction of *N*-alkylpiperidones with substituted aromatic aldehydes yielding chromenopyridines.[25] This approach was used to synthesize a series of substituted chromeno[3,2-*c*]pyridines, including 2-benzyl-, 2-benzyl-8-bromo- and 2-benzyl-6-ethoxy-1,2,3,4-tetrahydro-10*H*-chromeno[3,2-*c*]pyridin-10-one (Fig. 1).

Transformations of different heterocyclic compounds containing a tetrahydropyridine ring under the action of activated alkynes was investigated earlier.[25–29] A convenient method for the transformation of 1,2,3,4-tetrahydro-10*H*-chromeno[3,2-*c*]pyridin-10-ones to vinyl-substituted chromones was also developed on this basis.[30] The products of the reaction depend on the nature of the alkynes that are used (Scheme 1), and this synthetic approach can be employed for the synthesis of 3-aminoacrylates **2**, enamines **3**, and aminomaleates **4** (Fig. 2; Table 1).

The present work had four aims. (1) To extend the pool of potential biologically active chromone derivatives by the synthesis of new compounds with systematically varied substituents on the nitrogen atom and positions 6 and 8 of the chromone core. (2) To investigate the inhibitory properties of the synthesized chromenopyridines and chromones against the key enzymes of the cholinergic nervous system, AChE and BChE, using both kinetic and computational molecular modeling methods; (3) To assess the ability of the compounds to scavenge free radicals using the 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) assay. (4) To determine the inhibitory activity of the synthesized compounds toward carboxylesterase (CaE, EC 3.1.1.1), a serine hydrolase structurally related to cholinesterases that catalyzes the hydrolysis of many therapeutically important agents bearing ester and other hydrolyzable groups.[31,32] We included aim (4) because the ability of anticholinesterase compounds used for AD therapy to inhibit CaE could lead to undesirable drug-drug interactions.[33]

## 2. Results and discussion

### 2.1. Synthesis of chromone derivatives

Previously, we described a convenient method for synthesis of vinyl-substituted chromones **2a-c, 3a, 4a,c** in high yields by the reactions of 2-benzyl-1,2,3,4-tetrahydro-10*H*-chromeno[3,2-*c*]pyridin-10-one and its substituted analogues **1a-c**[30] with methyl propiolate, acetyl acetylene or dimethyl acetylenedicarboxylate (DMAD) in methanol at room temperature (Scheme 1). This tandem reaction proceeds through two steps: (1) formation of an intermediate ammonium salt via addition of the nitrogen atom of the tetrahydropyridine fragment to the triple bond of the alkyne; and (2) Hofmann degradation of the salt under the action of methoxide anion.

Our further work toward potentially active substituted compounds has produced compounds **3b-c** and **4b** from *N*-benzylchromeno[3,2-*c*]pyridines **1b-c**, and **2d-f** from *N*-methylchromeno[3,2-*c*]pyridines **1d-f** by the same method. Another reaction of compounds **1a-c** with DMAD takes place in the presence of formic acid, which deactivates methoxide anion, to yield debenzylation products **5a-c**.

Structures of individual compounds of general formulae **1**–**5** are listed in Table 1.

### 2.2. Inhibition of AChE, BChE, and CaE; Structure-activity relationships

For all derivatives **1**–**5**, we have determined their esterase profiles, i.e., the relative ability to inhibit several esterases; in this instance, AChE, BChE, and CaE. This approach enables one to estimate both primary pharmacological effects of the tested compounds and their possible adverse effects.[34–40] AChE from human erythrocytes was used along with two enzymes of non-human origin: equine serum BChE and porcine liver CaE. These sources of BChE and CaE were used because of their relatively low cost, high sequence identity to human enzymes,[35,37] and the exploratory character of this work.

The inhibitory potency against the esterases was characterized as the percent inhibition relative to control activity at 20 μM or as the $IC_{50}$ value, i.e., the inhibitor concentration required to decrease the enzyme activity by 50%. Tacrine, an effective AChE and BChE inhibitor, and bis-4-nitrophenyl phosphate (BNPP), a selective CaE inhibitor, were used as positive controls in the study of enzyme inhibition. The results of the inhibitory activity of 5 groups of chromone derivatives against AChE, BChE, and CaE, representing the esterase profiles of the compounds, are presented in Table 1.

The data given in Table 1 indicate that, in general, the tested compounds have low inhibitory activity against AChE and CaE, and, in contrast, some groups of the compounds have rather high activity against BChE.

Compounds of the first group, chromeno[3,2-*c*]pyridines **1a-f**, proved to be only very slight inhibitors of the cholinesterases.

It is noteworthy that *N*-benzyl-substituted chromones **2a–2c** containing the *N*-vinylmethoxycarbonyl group are effective and selective inhibitors of BChE. The introduction of a bromine substituent at position 6 of the chromone fragment increases anti-BChE activity (compound **2b**, $IC_{50}$ = 2.27 ± 0.18 μM), while the introduction of the ethoxy group at position 8 (compound **2c**) significantly decreases the inhibitory activity against BChE, which is only 16.3 ± 1.7% at a concentration of 20 μM.

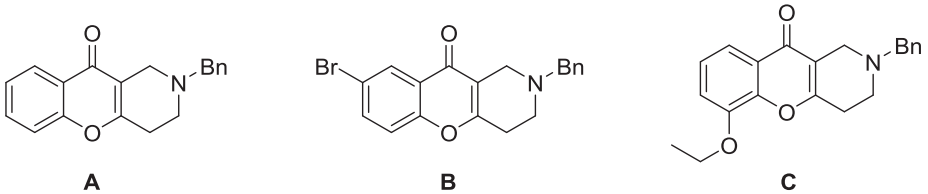


**Fig. 1.** Structures of substituted chromeno[3,2-*c*]pyridines. (A) 2-benzyl-; (B) 2-benzyl-8-bromo-; and (C) 2-benzyl-6-ethooxy-1,2,3,4-tetrahydro-10*H*-chromeno[3,2-*c*]pyridin-10-one.

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