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Short communication

Highly functionalized 2-amino-4*H*-pyrans as potent cholinesterase inhibitors

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ABSTRACT

Novel highly functionalized 2-amino-4*H*-pyrans were achieved in excellent yields under simple grinding at ambient temperature and were assessed for their potential for treating Alzheimer's disease (AD). The 2-amino-4*H*-pyran bearing nitro groups on both the aryl rings showed the highest activity, with an IC_{50} of 1.98 ± 0.09 μM against acetylcholinesterase (AChE) and 10.62 ± 0.21 μM against butyrylcholinesterase (BChE), the inhibition mechanisms on AChE and BChE receptors were revealed by means of molecular docking simulations.

1. Introduction

Most of the developed countries will experience a intense demographic shift toward an older population in the next 50 years, which is expected to significantly rise the occurrence of Alzheimer's disease (AD), the increase in the number of AD patients will place an excessive social and economic encumbrance on the developed world [1]. AD is an age-allied neurodegenerative disease categorized clinically by a progressive drop in memory and language [2] and pathologically by accumulation of senile plaques and neurofibrillary tangles in the brain [3]. AD is represented with characteristic symptoms, i.e. changes in levels of cholinesterase (ChEs), enhanced production and accumulation of β-amyloid peptide, formation of neurofibrillary tangles inside nerve cell bodies etc. In process of development of AD, the levels of ChEs are altered in different manner. In early stages of AD, the level of AChE is increased at a much higher rate than BChE while in later stages, level of AChE decreases and rapid increase in BChE level occurs in brain. In this stage, BChE substitutes the function of AChE – the hydrolysis of acetylcholine (ACh). Generally, the lower level of ACh during AD is obvious and therefore inhibition of ChEs represents one of the major pharmacological interventions for this disease [4] and hence ChE inhibitors are widely used to rectify cholinergic transmission in the treatment of AD.

As in the current scenario most of therapeutic treatments for AD has focused on the inhibition of ChEs [5], the discovery of new cholinesterase inhibitors that can become new drug candidates for the treatment of AD is still a goal for the scientific community and is the purpose of this work. It is pertinent to note that for the last few years, we have been involved in the discovery of novel organic molecules as ChE inhibitors [6–15]. Under this context, we would like to explore the possibility of functionalized pyran derivatives designed and synthesized by us as ChE inhibitors.

Pyran derivatives, the most honored heterocyclic frameworks occupy a significant place in the realm of natural and synthetic organic chemistry due to their simple structural complexity and important biological activities [16–22]. Among the pyrans, 4*H*-pyran-annulated heterocyclic frameworks are well distributed in naturally occurring compounds [23–25] and demonstrates a widespread array of biological activities such as antitumor, antibacterial, antiviral, spasmolytic, and anti-anaphylactic [26–29]. Compounds possessing 4*H*-pyran core structure have also been established in treating AD, schizophrenia, and Myoclonus disease [30]. It is worthy to mention that currently, a number of drug molecules bearing 4*H*-pyran moiety are in use in the treatment of various diseases [31–35]. Fig. 1 represents some of the pyran-annulated heterocyclic compounds exhibiting diverse kind of pharmaceutical applications [36–40]. In view of the biological significance of these functionalized pyrans in medicinal chemistry and also

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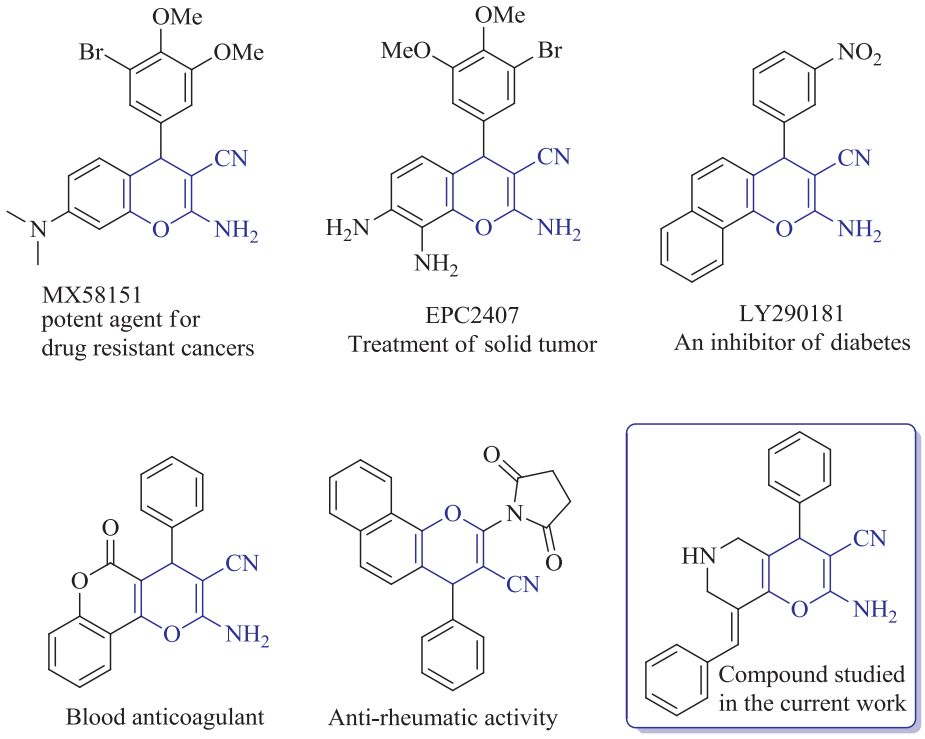


Fig. 1. Some of the biologically and pharmacologically active 4*H*-pyrans.

due to the fact that there have been less reports for 2-amino-4*H*-pyran derivatives as cholinesterase inhibitors [41], herein we aimed to explore our preliminary findings on the green synthesis and anticholinesterase activity of functionalized 4*H*-pyran derivatives.

2. Results and discussion

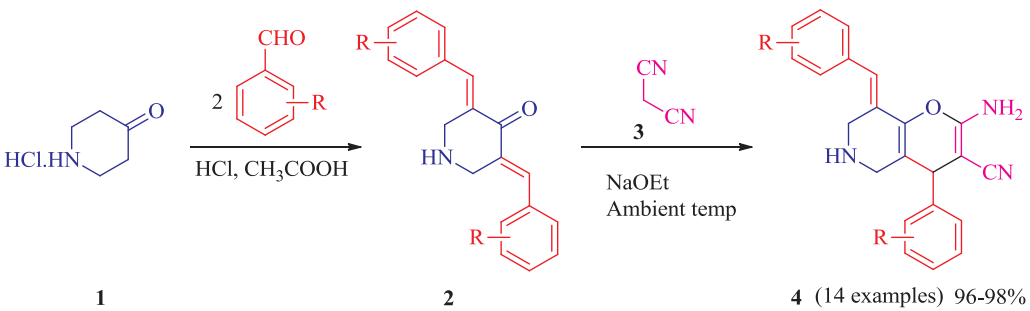
2.1. Chemistry

Schematic representation for the synthesis of desired 2-amino-4*H*-pyran derivatives **4(a-n)** is demonstrated in Scheme 1. The starting precursors *viz*, 3,5-bis[(*E*)-*arylmethylidene*]tetrahydro-4(1*H*)-pyridinones **2(a-n)** were synthesized following the method reported by dimmock et al. [42]. With a small library of these bisarylidenepyridinone derivatives in hand, we then performed the reaction of **2** with malononitrile (**3**). In a representative experiment, an equimolar mixture of **2i**, **3** and solid sodium ethoxide at ambient temperature was milled thoroughly for 2–3 min. Completion of the reaction was designated by the fading color of the reaction mixture, which became colorless at the end of the reaction, thus avoiding TLC monitoring. It is pertinent to note that the product **4i** was obtained in excellent yield (96%). As this reaction affords solely 2-amino-4*H*-pyrans **4(a–n)** without any impurities, purification of the products involving either crystallization or column chromatography is not required. All of the 2-amino-*4*H-pyran derivatives **4(a–n)** were obtained in quantitative yields, except for the slight loss during workup. All the fourteen 2-amino-4*H*-pyran derivatives synthesized are new and their structures are in good agreement with their spectroscopic data. Scaling up of the reaction does not envisage any drop in either the yield or purity of the product, as the reaction requires only a thorough mixing of the reactants at ambient temperature, which can be readily confirmed by suitable grinds. The easy availability of starting precursors, short reaction time and high yield of the products renders this method more attractive.

The structure of **4** was elucidated using FT-IR, NMR spectroscopic and Mass spectrometry studies considering **4i** as a representative case (vide supplementary data).

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.bioorg.2018.08.009.

The mechanism depicted in Scheme 2 envisages an initial Michael addition of the active methylene compound malanonitrile (**3**) to α,β-unsaturated moiety of **2** to afford the Michael adduct **5** which upon tautomerisation affords compound **6**. Cyclisation of **6** leads to the



Scheme 1. Synthesis of highly functionalized 2-amino-4*H*-pyrans **(4a-n)**.