Bioorganic & Medicinal Chemistry 26 (2018) 3731–3762

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Developing hybrid molecule therapeutics for diverse enzyme inhibitory action: Active role of coumarin-based structural leads in drug discovery

Aliya Ibrar[a,*], Syeda Aaliya Shehzadi[b], Faiq Saeed[c], Imtiaz Khan[d,*]

[a] Department of Chemistry, Abbottabad University of Science and Technology, Havelian, Abbottabad, Pakistan
[b] Sulaiman Bin Abdullah Aba Al-Khail – Centre for Interdisciplinary Research in Basic Science (SA-CIRBS), Faculty of Basic and Applied Sciences, International Islamic University, Islamabad, Pakistan
[c] Tianjin Key Laboratory of Molecular Optoelectronic Science, Department of Chemistry, Tianjin University, 300072, PR China
[d] School of Chemistry, Cardiff University, Main Building, Park Place, Cardiff CF10 3AT, United Kingdom

ARTICLE INFO

Keywords:
Coumarin
Drug design
Enzyme inhibition
Hybrid heterocycles
Neurodegeneration
Molecular diversity

ABSTRACT

Hybrid drugs featuring two or more potentially bioactive pharmacophores have been recognized as advanced and superior chemical entities to simultaneously modulate multiple drug targets of multifactorial diseases, thus overcoming the severe side effects associated with a single drug molecule. The selection of these chemical moieties to produce hybrid structures with druggable properties is generally facilitated by the observed and/or anticipated synergistic pharmacological activities of the individual molecules. In this perspective, coumarin template has extensively been studied in pursuit of structurally diverse leads for drug development due to high affinity and specificity to different molecular targets. This review highlights the most commonly exploited approaches conceptualizing the design and construction of hybrid molecules by coupling two or more individual fragments with or without an appropriate linker. In addition to the design strategies, this review also summarizes and reflects on the therapeutic potential of these hybrid molecules for diverse enzyme inhibitory action as well as their observed structure-activity relationship (SAR). Several key features of the synthesized hybrid structures that assert a profound impact on the inhibitory function have also been discussed alongside computational investigations, inhibitor molecular diversity and selectivity toward multiple drug targets. Finally, these drug discovery and development efforts should serve as a handy reference aiming to provide a useful platform for the exploration of new coumarin-based compounds with enhanced enzyme inhibitory profile.

1. Introduction

New drugs with better efficacy and low toxicity are continually required to combat the unmet medical needs across diverse therapeutic areas and pharmaceutical industries are facing immense pressure to supply these drugs to the market. For the delivery of new drugs, molecular complexity is becoming a crucial concept in drug discovery due to its close association with target selectivity and success in progressing into clinical development [1,2].

Coumarin (benzopyran-2-one) has attained a central position as a privileged structure in the design and discovery of novel drug molecules possessing high affinity and specificity to different molecular targets [3]. The presence of several key features such as planar aromatic ring fused with lactone functionality, a readily available group for hydrogen bonding as well as for protein-ligand interaction, makes this heterocycle a unique pharmacophore in medicinal chemistry arena [4]. Recognizing the presence of these features within coumarin template, this nucleus has extensively been studied in pursuit of structurally diverse leads for drug development [5,6]. Several research groups have documented the comprehensive account of therapeutic potential of coumarins against various molecular targets [7–16]. However, the development of hybrid multifunctional molecules still remains an active area of research. The target structures thus obtained may have better inhibitory actions, improved selectivity profiles, different or dual modes of action and/or reduced undesired side effects. Over the last few years, several research groups have designed and accessed coumarin-hybrid compounds which display different pharmacological properties. These molecules incorporate coumarin and other heterocyclic and non-heterocyclic scaffolds [17–23]. The increasing number of publications reflects the importance and research intensity in this field thus opening up new avenues for the discovery of active and potent structural leads for drug development in medicinal chemistry. The discussion in the previous reviews was focused mainly on the non-enzymatic properties of coumarin nucleus itself or their hybrid derivatives [15,16]. However,

* Corresponding authors.
E-mail addresses: jadoonquaidian@gmail.com (A. Ibrar), kimtiaz@hotmail.co.uk (I. Khan).

https://doi.org/10.1016/j.bmc.2018.05.042
Received 22 December 2017; Received in revised form 8 May 2018; Accepted 23 May 2018
Available online 26 May 2018
0968-0896/ © 2018 Elsevier Ltd. All rights reserved.

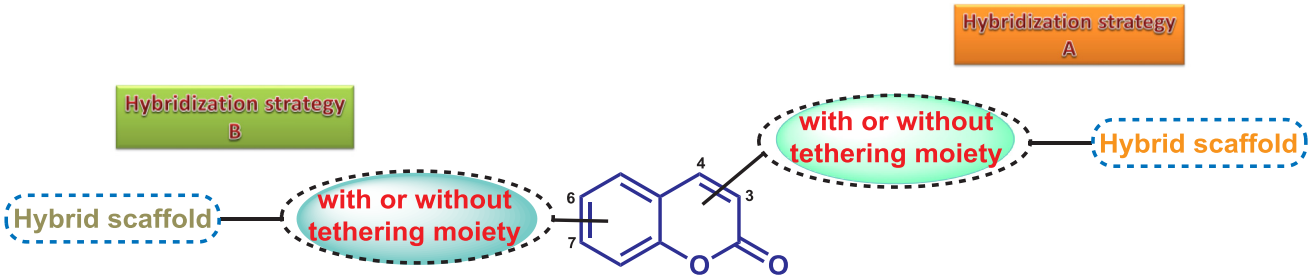


Fig. 1. Illustrative strategic model for the design and synthesis of coumarin-hybrid scaffolds.

the inhibition of diverse enzymes for the better management of numerous disorders has not comprehensively been considered. This review article combines recently published data (2014–2017) on the coumarin-hybrid compounds that showed inhibition toward several enzymatic targets with author's research on this particular topic. We aimed to review the developments in this field from the perspective of enzyme inhibitory activities, rationalizing their biological results with the aid of molecular docking investigations. In addition, an overview of the most relevant and potent structures is provided that are obtained *via* one or both of the following hybridization strategies (Fig. 1).

a) Substitution of heterocyclic or non-heterocyclic fragment at 3- & 4-position of α-pyrone ring.
b) Substitution of the hybrid moiety at the aryl ring of coumarin.

In this way, a number of coumarin-hybrid pharmacophores were readily accessed and presented herein. Whenever possible, a general structure-activity relationship overview is discussed, summarizing the key findings and future prospects within each class. Compounds obtained through these strategies were closely associated with the generation of novel leads with enhanced enzyme inhibitory properties. We believe that this review will surely provide a new platform to the drug hunters and medicinal chemists for the exploration of new coumarin-based compounds contributing remarkably toward the drug discovery programs.

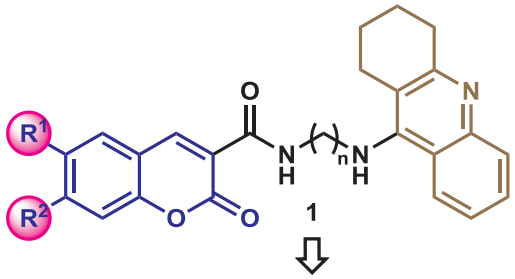
2. Coumarin-hybrids as enzyme inhibitors

2.1. Coumarin-hybrids as cholinesterase inhibitors

Cholinesterase enzymes comprising of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) are major biological players in Alzheimer's disease, a progressive neurodegenerative disorder of the brain. Acetylcholinesterase is found primarily in the blood and is involved in the hydrolysis of the neurotransmitter acetylcholine. Based on the cholinergic hypothesis, a deficiency of cholinergic neurotransmitters in the basal forebrains is predominantly involved in Alzheimer's disease. Therefore, supplementing brain cholinergic neurotransmission is a propitious strategy in the treatment of Alzheimer's disease, and it is an imperative methodology for the inhibition of acetylcholinesterase based on the cholinergic hypothesis. Therefore, using cholinesterase inhibitors is among the best recognized approach toward the treatment of Alzheimer's disease by increasing cholinergic neurotransmitters by impeding the degradation of acetylcholine [24–28].

In this section, we will focus on coumarin-hybrid compounds that have been identified as potent inhibitors of cholinesterases. The representative coupling entities include tacrine, urea, thiourea, piperidine, piperazine, acridine and benzyl pyridinium unit.

In 2014, Yang and co-workers have designed and synthesized a series of novel tacrine-coumarin hybrids to investigate the comparative and improved inhibitory potency of the synthesized scaffolds compared to tacrine as an individual entity [29]. These hybrids were accessed by reacting 5,6-substituted coumarin-3-carboxylic acid with the tacrine moiety in the presence of a catalyst or a coupling agent such as benzotriazole-1-yl-oxytripyrrolidinophosphoniumhexafluorophosphate (PyBOP) to improve the reaction yields. A chain of the methylene linker has been employed to tether the reacting moieties. All the synthesized derivatives were tested for their human AChE and BuChE inhibition by using tacrine and galanthamine as reference inhibitors. Good anti-AChE and BuChE potential in the nanomolar range was observed. Among them, **1** displayed the highest AChE inhibition (K_i = 16.7 nM), being 2-fold more potent than tacrine (K_i = 35.7 nM) and 3.5-fold stronger inhibitor compared to galanthamine (K_i = 61.9 nM) respectively, while the lead BuChE inhibitor showed comparable inhibition (K_i = 8.1 nM) to the reference tacrine (K_i = 8.7 nM). The investigated SAR of the synthesized hybrids revealed that inhibition potential can be greatly influenced by two factors; (i) methylene spacer tethering the coumarin and tacrine unit, (ii) substitution at 6- and 7-position on the benzene ring of coumarin moiety. All the synthesized scaffolds were categorized into three groups based on the methylene number as 5, 6, and 7 methylene linker. It was observed that the 6-methylene spacer appeared to be best suited for hAChE inhibition while the compounds with 5-methylene and 7-methylene spacers showed the diminished activity. Substitution influence can be observed by analyzing the compounds with electron-donating groups (OCH_3 and OCF_3) at the 6-position of coumarin with reduced potential. The diminished inhibition was also observed in compounds with electron-donating (OCH_3) groups at 7-position and it can be attributed to the steric hindrance of the substituents.



Maximum hAChE inhibition observed when n = 6 & coumarin nucleus is unsubstituted
K_i = 16.7 nM (tacrine, K_i = 35.7 nM)

These correlations between the inhibition potential and variable chain length of spacer were further validated by molecular docking and molecular dynamic simulations. Several key interactions including hydrogen bonding and π-π stacking were part of stabilization of the inhibitor in the active pocket of the enzymes. The network of hydrogen bonding between the amide oxygen of coumarin and related amino acid residues was determined as a key factor inducing the difference in the inhibition potential by varying the spacer length (Fig. 2).

Soon after, Kuca and co-workers have developed another series of tacrine derivatives and tacrine-coumarin hybrids to investigate their human cholinesterase (hChE) inhibitory potential [30]. A wide variety of tethering agents like alkylenediamine spacers of variable lengths and the spacer with thiosemicarbazides and thiazolidinone heterocycle were used to connect the tacrine and coumarin fragments. The simultaneous interactions could be permitted between these heteroaromatic fragments and both catalytic

Download English Version:

https://daneshyari.com/en/article/7772564

Download Persian Version:

https://daneshyari.com/article/7772564

Daneshyari.com