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Research paper

Chroman-4-one and chromone based somatostatin β-turn mimetics

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ABSTRACT

A scaffold approach has been used to develop somatostatin β-turn mimetics based on chroman-4-one and chromone ring systems. Such derivatives could adopt conformations resembling type II or type II′ β-turns. Side chain equivalents of the crucial Trp8 and Lys9 in somatostatin were introduced in the 2- and 8-positions of the scaffolds using efficient reactions. Interestingly, this proof-of-concept study shows that **4** and **9** have K_i-values in the low μM range when evaluated for their affinity for the sst2 and sst4 receptors.

1. Introduction

The use of peptides as drugs is limited due to their low bioavailability which is mainly related to poor absorption and rapid elimination following efficient enzymatic degradation *in vivo*. One way to overcome these issues is to develop peptidomimetics. Peptidomimetics are non-peptidic compounds containing the amino acid side chains (or equivalents) required to obtain optimal interactions with the peptide receptor and thereby the same pharmacological effect as the parent peptide [1–3]. These types of structures can be expected to show improved absorption properties and higher metabolic stability compared to natural peptides. We have had a long term interest in the synthesis and use of chromones and chroman-4-ones as peptidomimetics [4–6]. In this study we focus on chroman-4-one/chromone based β-turn mimetics. The β-turn represents one of the major secondary structures of peptides and proteins and often constitutes the bioactive conformation of the peptide [7]. It functions as the site of recognition and binding to the target receptor. Hence the β-turn structure is considered a useful template when developing mimetics [8]. The four amino acids constituting the β-turn in a peptide (*i*–*i*+*3*) are represented by the substituents in the 3-, 2-, 8- and 6-positions in the chromone ring system, respectively (Fig. 1).

The inhibitory peptide hormone somatostatin adopts a type II′ β-turn [9,10] as the bioactive conformation where the β-turn comprises the tetrapeptide Phe7-Trp8-Lys9-Thr10 (the numbering refers to the somatostatin sequence) [11]. The hormone was chosen as the model for designing substituted chroman-4-one and chromone derivatives as potential β-turn mimetics. The Trp8 and Lys9 side chains are considered particularly important for activity [10–14]. Somatostatin is expressed in the CNS, the GI tract and in the endocrine tissues and inhibits the release of e.g. growth hormone, glucagon and insulin [15–18]. There are five different somatostatin receptor subtypes (sst1–sst5) that belong to the G-protein coupled receptor superfamily (GPCRs) [19]. The fact that somatostatin shows low metabolic stability when given orally makes the peptide an attractive target for development of stabilized mimetics. An extensive number of peptidic analogues of somatostatin has received considerable attention over the years [20]. Of special interest for the present study have been the scaffold

Abbreviations: Boc, *tert*-butyloxycarbonyl; BSA, bovine serum albumin; CNS, central nervous system; DMF, dimethylformamide; DMSO, dimethyl sulfoxide; ESI-MS, electrospray ionization mass spectrometry; FT-ICR-MS, Fourier transform ion cyclotron resonance mass spectrometry; GI, Gastrointestinal; GPCR, G-protein coupled receptor; HEPES, 4-(2-hydroxyethyl)piperazine-1-ethanesulfonic acid; HPLC, high-performance liquid chromatography; HRMS, high resolution mass spectrometry; MW, microwave; NMR, nuclear magnetic resonance; PEI, polyethylenimine; RMSD, root mean square deviation; sst, somatostatin receptor; THF, tetrahydrofuran.

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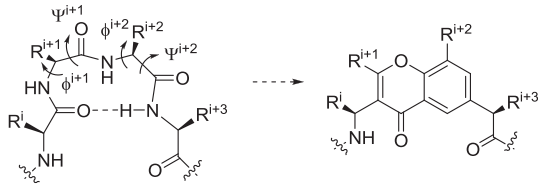


Fig. 1. 2,3,6,8-Tetrasubstituted chromone derivatives as potential β-turn mimetics.

mimetics based on β-D-glucose (**A**) [21], catechol (**B**) [22], and pyrrolinone (**C**) [23] (Chart 1). Also benzodiazepines [24], β-peptides [25,26] and peptoid analogs are of interest [27]. These mimetics show affinity for the human somatostatin receptors (hsst) with K_i or IC_{50}-values in the low μM range.

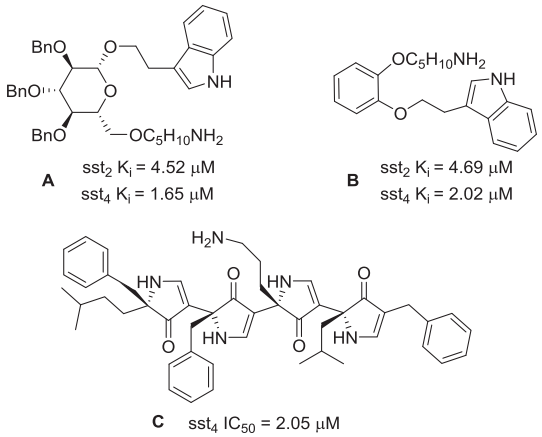


Chart 1. Examples of known non-peptidic somatostatin receptor agonists.

2. Results and discussion

2.1. Design and synthesis

Molecular mechanics calculations were used for energy minimization of five types of β-turn structures (I, I′, II, II′, and VIII) of Ac-Ala-Ala-NHMe using the MMFFx force field [28] as implemented in the MOE software (version 2013.08) [29]. Conformational constraints were introduced to keep the desired peptide turn structure during the energy minimization procedure. The energy minimized conformations were manually superimposed with different low energy conformations identified in conformational analyses of 2,3,6,8-tetramethyl substituted chromone and the four different stereoisomers of the chroman-4-one scaffolds. Of the energy minimized peptide structures the type II and II′ β-turns gave good alignments with the global minimum conformations of both scaffolds (data not shown). As the same β-turns have been identified in previous studies of other bicyclic systems used as potential β-turn mimetics of somatostatin [30] these results prompted us to synthesize 2,8-disubstituted chroman-4-one and chromone derivatives and test them for affinity at the sst2 and sst4 somatostatin receptors.

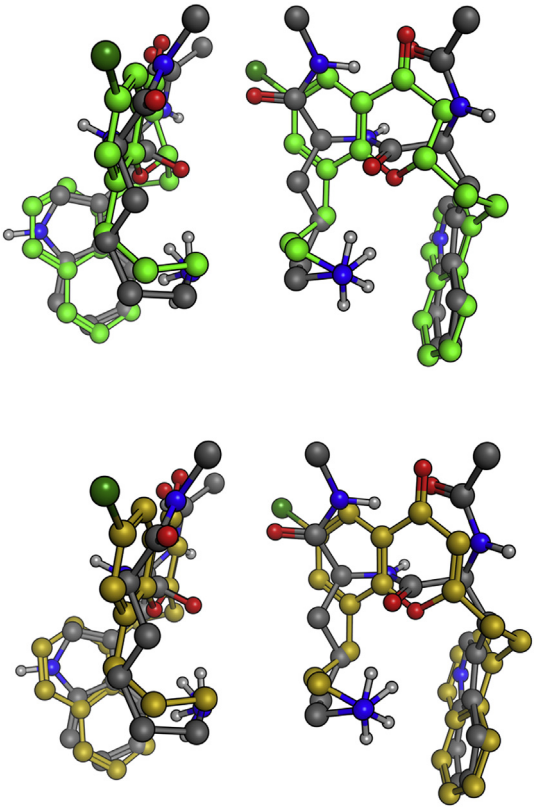
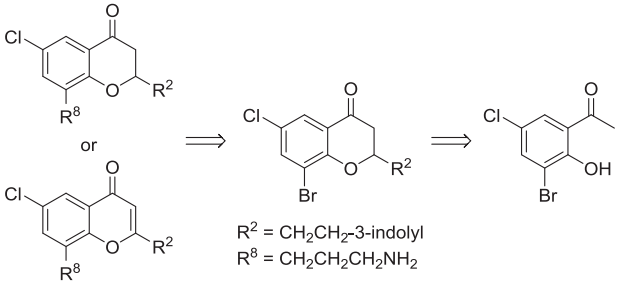


Fig. 2. Two orthogonal views of aligned AcGlyTrpLysGlyNHMe β-turn type II′ (grey) and the best hit of the chroman-4-one 4S (green) together with two views of the same conformation of peptide together with the best hit of the chromone 9 (yellow). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The retrosynthetic analysis of the desired 2,8-disubstituted chromone and chroman-4-one β-turn mimetics is shown in Scheme 1. The chroman-4-one framework with the desired R^2-substituent can be efficiently synthesized via an aldol condensation of a 3′-bromo-2′-hydroxyacetophenone and an appropriate aldehyde as described previously [31]. Subsequently, the alkylamine-containing substituent in the 8-position can be introduced via a Sonogashira reaction using the corresponding alkyne.

3′-Bromo-5′-chloro-2′-hydroxyacetophenone seemed to a convenient starting material as it is commercially available and generally gives the chroman-4-one derivatives via our reported method in the highest yields. Initially, 3′-bromo-5′-chloro-2′-hydroxyacetophenone and 3-(3-indolyl)propionaldehyde were successfully reacted in a base catalyzed aldol reaction using *i*-Pr_2NH in EtOH under microwave heating (1 h, 170 °C) to afford the 2-[(3-indolyl)ethyl]chroman-4-one derivative in good yield as described earlier by our group [31]. Attempts to introduce *N*-Boc-propargylamine in the 8-position via the envisioned Sonogashira cross coupling reaction did however not result in the desired product. Also the use of chroman-4-ones as starting material with an *N*-benzyl or *N*-tosyl protected indole moiety did not facilitate product formation.



Scheme 1. Retrosynthetic analysis for the formation of substituted chroman-4-ones and chromones. The R^2-and R^8-position should mimic Trp8 and Lys9 representing the essential amino acids of the β-turn of somatostatin.