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3D QSAR models for α_{2a}-adrenoceptor agonists☆

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This paper is kindly dedicated to Professor Guy Quéguiner in honor of his 70th birthday.

Abstract

Three-dimensional structure–activity relationship studies of α_{2a}-adrenoceptor agonists were carried out by Distance Comparison (DISCOthech) and Comparative Molecular Field Analysis (CoMFA) methods to define the pharmacophore and a quantitative model, respectively, of this class of compounds. The statistical validation of the CoMFA model indicates its high predictive performance for binding affinities of new α_{2a}-adrenoceptor agonists.

Keywords: α_{2a}-Adrenergic receptor agonist; 3D-QSAR (3 dimensional quantitative structure activity relationship); DISCOtech (distance comparison); CoMFA (comparative molecular field analysis); Region focusing

1. Introduction

Adrenergic α_2-receptors are involved in a number of physiological and pathophysiological events. Their well-documented function is the control of adrenergic transmission due to presynaptic inhibition of norephinephrine release. α_2-Adrenoceptor has three highly homologous subtypes α_{2a}, α_{2b} and α_{2c} (Philipp and Hein, 2004). Non-selective α_2-adrenoceptor agonists have been widely applied in the therapy of various diseases, such as hypertension (Fenton et al., 2006; Blake et al., 2000), glaucoma (Savolainen et al., 2003), acute migraine (Kapoor et al., 2004), Parkinson's disease (Haapalinna et al., 2003; Archer and Frederiksson, 2003), analgesia, anesthesia and sedation (Romero-Sandoval and Eisenach, 2006; Tham et al., 2005; Schweimer et al., 2005) and drug and alcohol abuse (Lê et al., 2005; Georges et al., 2005; Francois and Gary, 2003). Moreover, the modulatory action on the cellular and humoral immunity (Elenkov et al., 2000) was described. Our focus on the field is due to the possible gastroprotective effect of such compounds (Fülöp et al., 2005; Jain et al., 2002; Müllner et al., 2002). Recent studies in knockout mice indicated that α_2-adrenoceptors might possess many roles under physiological and pathophysiological conditions. For instance, gene-targeted mouse models carrying deletions in these receptor genes (MacMillan et al., 1996; Link et al., 1996; Hein et al., 1999; Altman et al., 1999; Scheinin et al., 2001) allow to predict that prejunctionally α_{2a}-adrenoceptors are the main feedback regulators of release, although the α_{2b}- and α_{2c}-subtypes may also contribute to this

Abbreviations: (3D) QSAR, (3 dimensional) quantitative structure–activity relationship; AR, adrenergic receptors; CoMFA, comparative molecular field analysis; DISCOtech, distance comparison; *F*, Fisher value; LMO, leave-multiple-out; LOO, leave-one-out; *n*, optimum number of components; PLS, partial least square; q^2 (r_{cv}^2), crossvalidated r^2; r^2, conventional r^2; s, standard error of estimate; SDEP, standard error of prediction

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function. All three subtypes are present on the vascular smooth muscle postjunctionally, but the α_{2c} subtype may occur especially in venous smooth muscle (Dochtery, 1998). α_{2b}-Adrenoceptors were found to play an essential role for placental vascular development, whereas α_{2c}-adrenoceptors were found to be responsible for the control of catecholamine release from the adrenal gland.

Although these findings may have relevance for human physiology and pharmacology as well, similar expression patterns between human and mouse tissues do not guarantee similar functions. In order to reveal the functions of the individual subtypes further investigations of the differences in their molecular pharmacology are essential.

Molecular modeling has become a useful tool for the characterization of structure–function relationships for a receptor, and for the identification of structural motives of both ligands and receptors, which may play important roles in the binding processes. Such information, if it were available for α_2-adrenoceptor subtypes, may also facilitate the design of new subtype-selective ligands. Principally, there are two efficient modeling procedures used for designing and/or selecting new potentially bioactive (having affinity toward the target receptor/enzyme) molecules. In *de novo* design, the molecules are constructed based on the receptor model, and subsequently the docking process provides the binding energy value. This procedure utilizes the homology modeling method if the receptor structure is not available. The other designing procedure is a retrospective analysis in its nature; the most important structural motives of a set of ligands with experimentally determined biological data are extracted by QSAR methods. It could result in semiquantitative (pharmacophore) or quantitative models. Both *de novo* and QSAR methods have their own limitations, therefore, for efficient ligand-designing protocols, both procedures are generally employed.

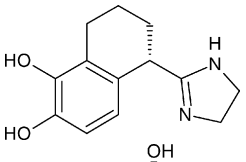
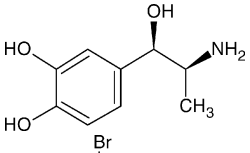
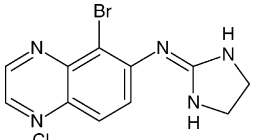
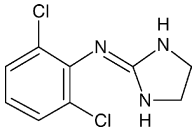
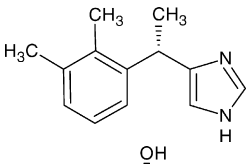
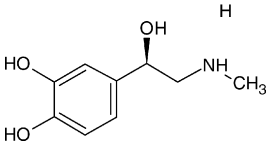
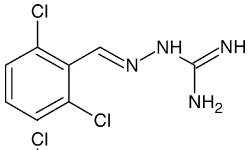
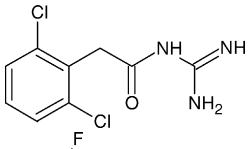
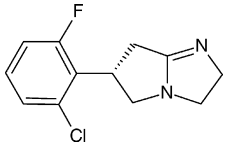
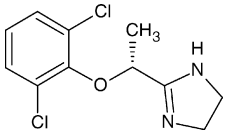
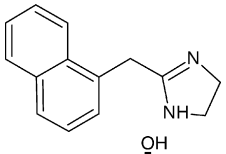
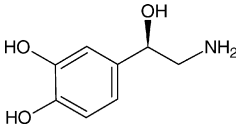
We recently developed an atomic resolution model for α_{2a}-adrenoceptors, and then docked a series of known ligands into the receptors. The binding free energy (ΔG_b) values were also estimated and an excellent correlation was obtained for 14 compounds (N) ($r^2 = 0.90$; $r^2_{cv} = 0.84$; $F = 48.62$; $s^2 = 0.19$; $N = 14$) (Balogh et al., 2007). As a continuation of this work, we now describe 3D QSAR studies on agonists of α_{2a}-adrenoceptors to define pharmacophore and Comparative Molecular Field Analysis (CoMFA) models for quantitative prediction of binding affinities of agonists toward this adrenoceptor subtype.

2. Methods

2.1. The α_{2a}-agonists selected for the study

Twenty known agonists of α_{2a}-adrenoceptors were selected from the literature with their binding affinities (Table 1) (Jasper et al., 1998). These compounds represent a fairly structurally diverse set of α_2-AR agonists, including: (i) catecholamines (*adrenaline*, *noradrenaline*, *α-methylnoradrenaline*); (ii) structures containing an imidazoline ring (*A-54741*, *brimonidine*, *clonidine*, *dexmedetomidinide*, *ICI 106270*, *levlofexidine*, *naphazoline*, *oxymetazoline*, *para-aminoclonidine*, *ST-91*, *tramazoline*, *xylometazoline*); (iii)

Table 1
The chemical structures of α_{2a} agonists

Name	Structure	pK_i
A-54741		6.61
α-Methilnoradrenaline		5.44
Brimonidine (UK-14304)		6.67
Clonidine		7.21
Dexmedetomidinide		7.88
Epinephrine (adrenaline)		5.83
Guanabenz		7.66
Guanfacine		7.03
ICI 106270		8.10
Levlofexidine		7.84
Naphazoline		7.68
Noradrenaline (norepinephrine)		5.70