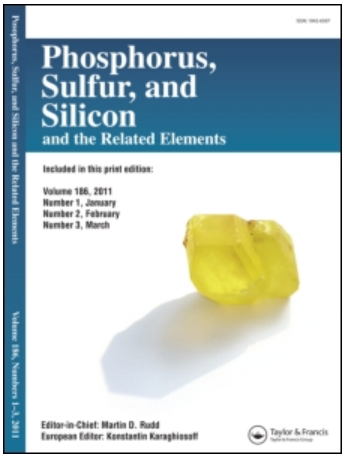

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Synthetic Adrenaline Receptors Based on Bisphosphonates

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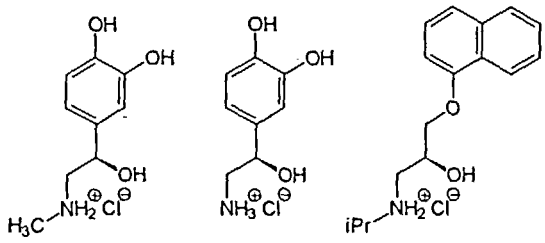
Synthetic models of the natural adrenergic receptors are presented, and their binding properties to several biologically important amines and amino alcohols in dimethylsulfoxide and methanol are discussed. NMR titrations have been carried out to determine their binding constants.

Keywords: signal transduction; amino alcohols; molecular recognition; adrenergic receptors; bisphosphonates; macrocycles

INTRODUCTION

The hormone adrenaline (1) is set free in the adrenal gland when the human body suddenly needs large amounts of energy to react adequately upon a critical situation. Because the adrenergic receptors have a very complex structure and are difficult to isolate, it is useful to build synthetic models which can help to better understand the natural prototype, and which may even allow to predict the effect of a given substrate upon the natural receptor.[1]

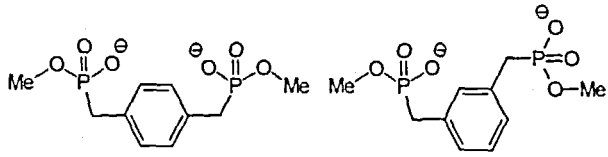


1 2 5

FIGURE 1. Adrenaline, noradrenaline and propranolol

XYLYLENE BISPHOSPHONATES

Force-field calculations suggest that adrenaline and its derivative noradrenaline (2) should exert strong electrostatic and hydrogen bond interactions with the xylylene bisphosphonates 3 and 4 in a chelate-type binding mode.[2]



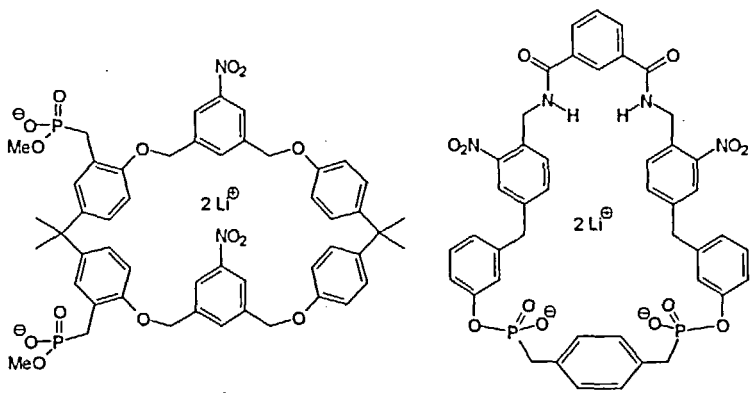
3 4

FIGURE 2. *p*- and *m*-xylylene bisphosphonate receptors

NMR titrations of various amines and amino alcohols in dimethylsulfoxide gave association constants of up to 66,000 M^{-1} for the complex of the β-blocker propranolol (5) with 4.[3] As predicted by the force-field calculations, the hydroxyl group of amino alcohols is included in the molecular recognition.[4] Unfortunately, the catecholamines adrenaline and noradrenaline were bound less strongly because of competing interactions between the aromatic hydroxyl groups and the phosphonate anions.[5]

MACROCYCLIC BIS(BENZYLPHOSPHONATE) 6

The simplest model of a selective three-dimensional binding site is a macrocyclic molecule. We have prepared the macrocycle 6 in a convergent and modular 10-step synthesis. This molecule contains a hydrophobic cavity with electron-deficient arenes for the recognition of the catechol moiety, and two phosphonate groups in the periphery of the ring.[6]



6 7

FIGURE 3. Macrocyclic bisphosphonates

Force-field calculations suggest that the amino alcohol moiety of noradrenaline is bound to the bisphosphonate group by electrostatic and hydrogen bonding interactions, and that the catechol ring is inserted into the hydrophobic cavity. NMR titrations in dimethylsulfoxide resulted in nearly the same association constants for noradrenaline (2) and propranolol (5) of about 20,000 M^{-1}. This proves, that the catechol hydroxyls do not longer compete with the complexation of the amino alcohol moiety and indicates, that they are inserted into the shielding hydrophobic cavity.[7] In methanol, the association constant with noradrenaline reaches 1,000 M^{-1}. This 20-fold decrease in binding strength upon solvent change from DMSO to methanol is distinctly lower than the 100-fold decrease which we

observed with the simple xylylene bisphosphonates. It provides further evidence of hydrophobic interactions, which are stronger in methanol than in DMSO. Non-aromatic amino alcohols are bound 2-fold less strongly than their aromatic counterparts, a fact which also agrees with the influence of hydrophobic interactions within the cavity.

MACROCYCLIC XYLYLENE BISPHOSPHONATE 7

For a more selective complexation we have synthesized the macrocycle 7 in a convergent and modular 17-step synthesis. Force field calculations suggested that 7 does not only interact with the amino alcohol moiety of noradrenaline (2) like the simple xylylene bisphosphonates, but also recognizes the catechol group by hydrophobic, π-stacking and hydrogen bond interactions.[8] First NMR titrations of noradrenaline (2) showed a low association constant in DMSO, but a high one in methanol.

ACKNOWLEGDEMENTS

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