BILE ACID-BASED RECEPTORS FOR RECOGNITION OF ANIONS AND ADENINE DERIVATIVES

By

VIJAY KUMAR KHATRI

Department of Chemistry

Submitted

in fulfillment of the requirements of the degree of

Doctor of Philosophy

to the

INDIAN INSTITUTE OF TECHNOLOGY, DELHI

May, 2007

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Dedicated to my family,

whose support and guidance has helped me throughout...

CERTIFICATE

This is to certify that the thesis entitled, **"Bile acid-based receptors for recognition of anions and adenine derivatives"**, being submitted by Mr. Vijay Kumar Khatri, to the Indian Institute of Technology, Delhi, for the award of the degree of 'Doctor of Philosophy in Chemistry', is a record of bonafide research work carried out by him. Mr. Vijay Kumar Khatri has worked under my guidance and supervision and has fulfilled all the requirements for the submission of this thesis, which to my knowledge has reached the requisite standard. The results embodied in this thesis have not been submitted in part or in full, to any other University or Institute for award of any degree or diploma.

(Pramod S. Pandey)

Thesis Supervisor

Associate Professor

Department of Chemistry

Indian Institute of Technology, Delhi

New Delhi-110016

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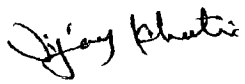
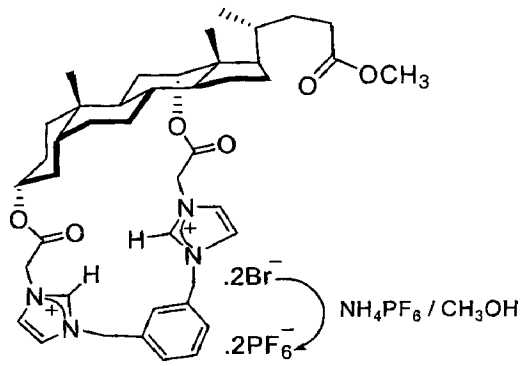


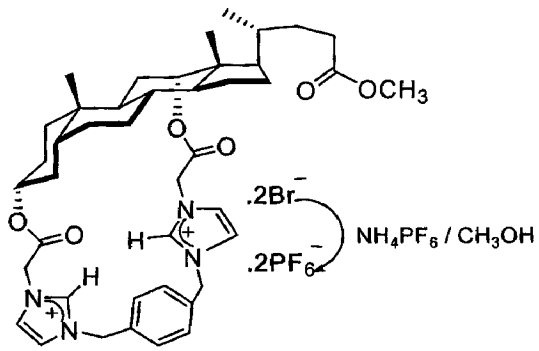
Vijay Kumar Khatri

ABSTRACT

There has been considerable interest in recent years towards design and synthesis of artificial receptors for molecular recognition. In particular, anion recognition has attracted much attention due to the biological, medical and environmental significance of anions. Recognition of nucleobases has also received considerable interest as the hydrogen bonding motif prevalent in DNA and RNA can be used to assemble elegant supramolecular structures to design useful materials. Present thesis deals with the design, synthesis and study of bile acid-based receptors for recognition of anionic species and nucleobases such as adenine derivatives. The thesis has been divided into four chapters. **Chapter 1** describes a brief literature survey on the recent developments in design of neutral and positively charged receptors containing amide, urea, pyrrole, guanidinium and 1,3-disubstituted imidazolium groups for recognition of anions. **Chapter 2** deals with the synthesis and study of cholic and deoxycholic acid-based receptors containing imidazolium and benzimidazolium groups for anion recognition. Recently, 1,3-disubstituted imidazolium groups have been introduced to bind anions by forming (C-H)$^{+}$--X^{-} polar hydrogen bonds between C(2)-H of imidazolium rings and the anion.

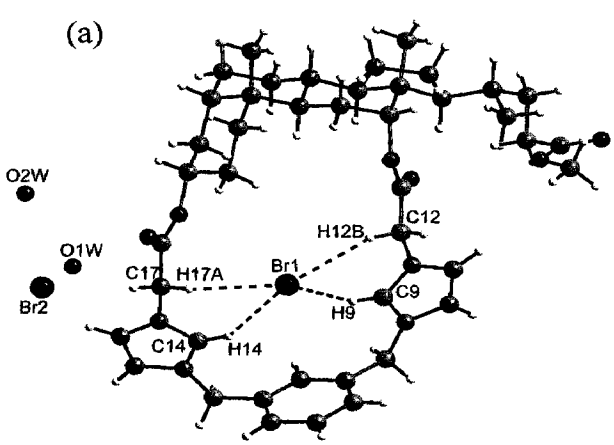


I

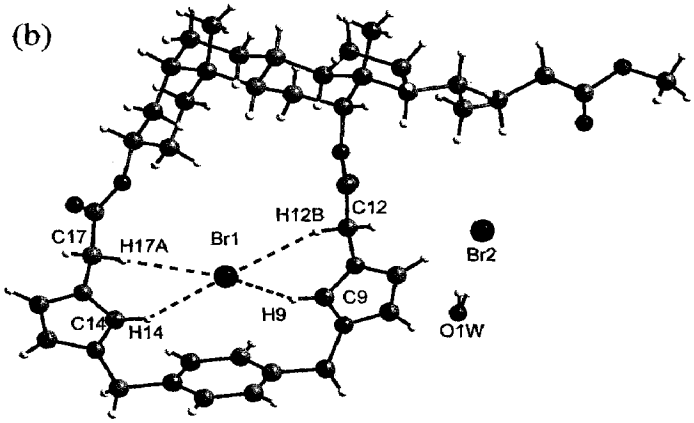


II

Deoxycholic acid-based cyclic receptors **I**-$(PF_6)_2$ and **II**-$(PF_6)_2$ with different cavity sizes have been synthesized and anion binding properties of these receptors were studied by ^1H NMR titration experiment and data were analyzed using WinEQNMR software program. Upon addition of anions as their tetrabutylammonium salts, large downfield shifts were observed for the C(2) proton of each imidazolium moiety in **I**-$(PF_6)_2$ and **II**-$(PF_6)_2$ due to the complexation of anions through $(C\text{-}H)^+\text{--}X^-$ hydrogen bonds. The exact mode of binding was confirmed by the single-crystal X-ray structures of **I**-$(Br)_2$ and **II**-$(Br)_2$. The crystal



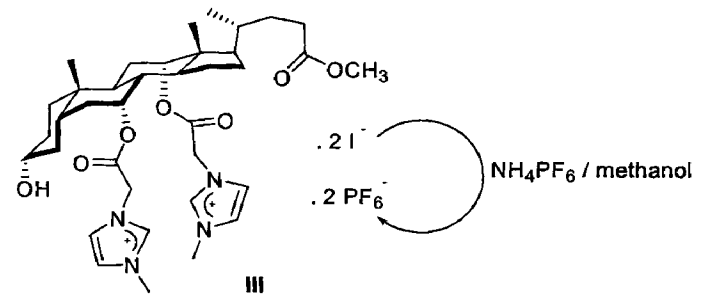
I-$(Br)_2 \cdot 2CHCl_3 \cdot 2H_2O$



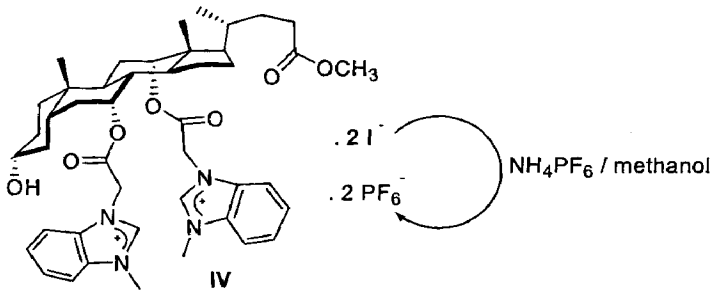
II-$(Br)_2 \cdot 1.5H_2O$

structures showed bromide bound within the molecular cavity in a four fold array of strong hydrogen bonds to C(2)-H atom of each imidazolium ring and inwardly directed methylene protons of both the acetyl units. Receptor **I**-$(PF_6)_2$ with *m*-xylene as spacer shows a moderate selectivity for fluoride ion with an association constant of 2400 M^{-1} whereas receptor **II**-$(PF_6)_2$ with *p*-xylene as spacer exhibits high affinity and selectivity toward chloride ion with an association constant of 12000 M^{-1}.

For comparative studies, acyclic systems, cholapod **III** and **IV** containing imidazolium and benzimidazolium groups at 7α- and 12α-positions



III

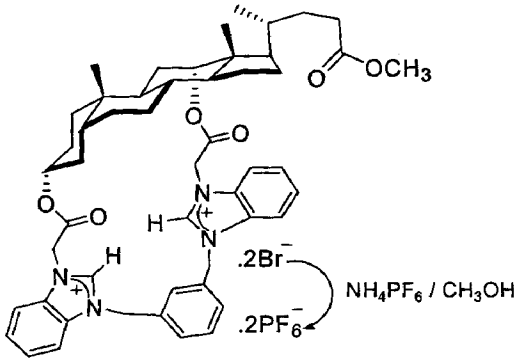


IV

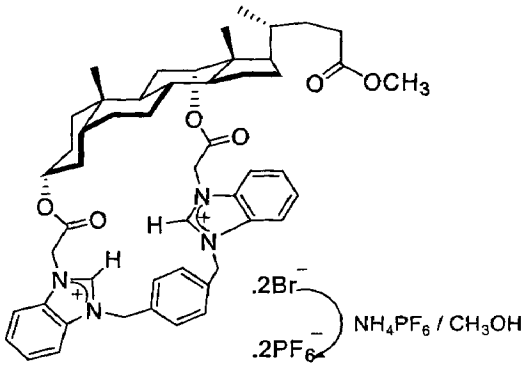
of methyl cholate were synthesized from methyl cholate. Receptor **III**-$(PF_6)_2$ showed slightly higher selectivity for hydrogensulphate and acetate ions as compared to spherical ions (halide ions). Among halogen ions, a moderate selectivity for fluoride ion was observed. Cholapod **IV**-$(PF_6)_2$ containing benzimidazolium groups showed higher affinity for spherical anions as compared to cholapod **III**-$(PF_6)_2$ containing imidazolium groups with highest selectivity for fluoride ion.

Since cholic acid-based bisbenzimidazolium receptor has shown increase in binding affinity for anions as compared to their bisimidazolium analogue, deoxycholic acid-based cyclic receptors **V**-$(PF_6)_2$ and **VI**-$(PF_6)_2$ containing benzimidazolium groups have also

been synthesized. These receptors showed the enhanced binding affinity for anions



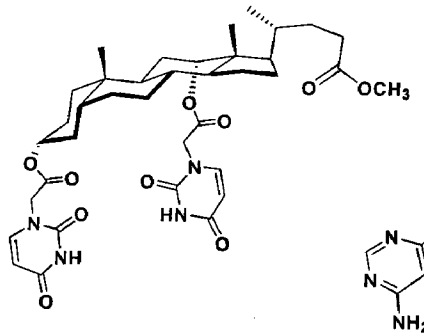
V



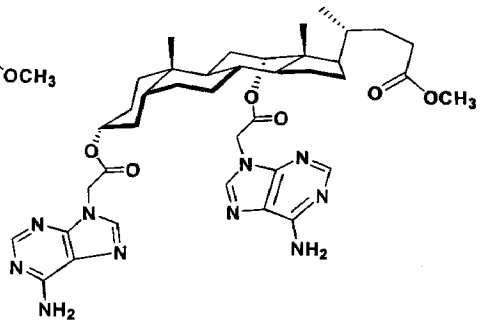
VI

as compared to that shown by their imidazolium analogues **I**-$(PF_6)_2$ and **II**-$(PF_6)_2$. The receptor **V**-$(PF_6)_2$ shows a preferential binding for fluoride ion with an association constant of 3500 M^{-1} while receptor **VI**-$(PF_6)_2$ has the highest affinity and selectivity for chloride ion with an association constant of 20500 M^{-1}. The comparison of these values with that of imidazolium receptors reveals that the selectivity order remains the same for imidazolium and benzimidazolum analogues as the same spacers have been used for the cyclization and hence the cavity size remains the same.

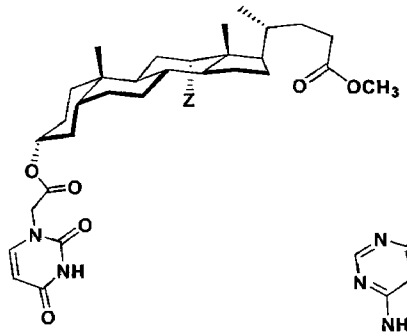
Chapter 3 describes the synthesis of deoxycholic and lithocholic acid-based uracil and adenine derivatives. The complexation behaviour of steroidal uracil derivatives towards steroidal adenine derivatives has been investigated by monitoring the change in the chemical shifts of the imide protons of uracil units in ^1H NMR titration experiment and data were analysed using WinEQNMR software program. The results indicated that two



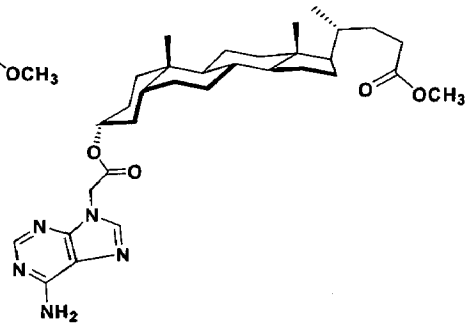
VII



VIII

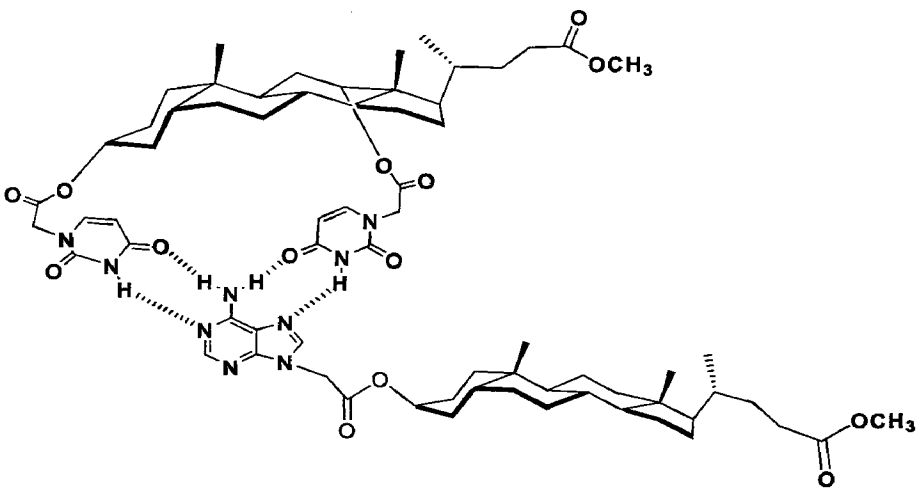


IX; Z = H
X; Z = OH



XI

uracil units in receptor **VII** binds steroidal adenine derivatives through simultaneous Watson-Crick and Hoogsteen base pairing. However, receptor **IX** and **X,** interact with



1:1 complex formation between **VII** and **XI**

steroidal adenine derivative through only Watson-Crick base pairing, the bulky steroidal moiety in **IX** and **X** may presumably restrict the intermolecular Hoogsteen base pairing. Self-association of steroidal adenine and uracil derivatives has also been determined by dilution experiment which shows no significant self-association of these steroidal adenine and uracil derivatives.

Chapter 4 describes the experimental procedures and physical and spectroscopic characterization data for compounds synthesized in chapter 2 and chapter 3.

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