NOVEL BILE ACID AND DIPYRROMETHANE BASED RECEPTORS FOR ION AND FLAVIN RECOGNITION

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by

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Department of Chemistry

Submitted

in fulfillment of the requirements of the degree of

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to the

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This thesis is dedicated to Sai Baba and my parents

CERTIFICATE

This is to certify that the thesis entitled, **"Novel Bile Acid and Dipyrromethane Based Receptors for Ion and Flavin Recognition"**, being submitted by Mr. Pradeep Kumar Muwal, 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. Pradeep Kumar Muwal 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.

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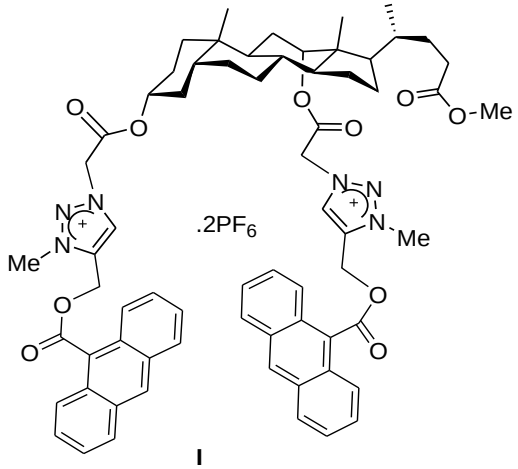
Pradeep Kumar Muwal

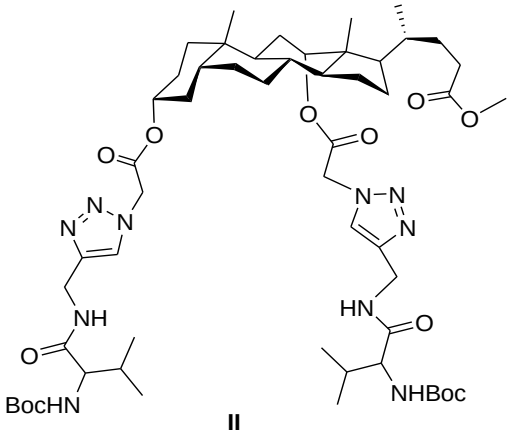
ABSTRACT

The present thesis deals with the synthesis of steroidal and non-steroidal receptors and studies of their binding properties towards ions and a flavin derivative. It also focuses on the design and synthesis of a dipyrromethane-based receptor and studies of its ion recognition properties. The thesis has been divided into five chapters.

The first chapter presents a brief literature survey on ion recognition based on bile acids and dipyrromethane scaffolds and on 2,4-diaminopyridine-based flavin receptors. The second chapter describes the synthesis and ion recognition properties of steroidal and non-steroidal receptors. Deoxycholic acid-based 1,2,3-triazolium acyclic receptor **I** and 1,2,3-triazole receptor **II** were synthesized and their anion recognition property has been studied.



I

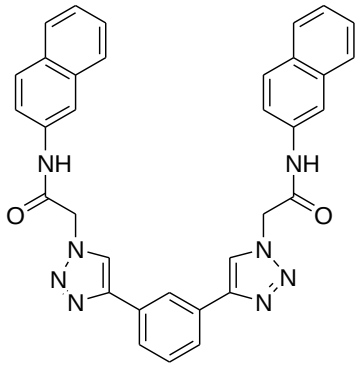


II

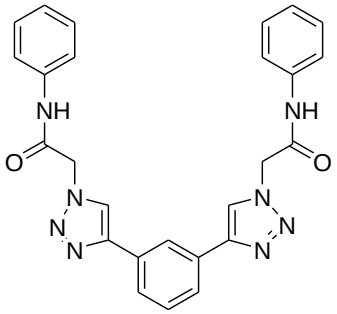
The anion binding property of the bile acid-based receptors **I** and **II** was examined in chloroform by ^{1}H NMR titration. Both receptors showed the highest affinity for acetate ion with an association constant of about 1500 M^{-1} and 1480 M^{-2} respectively. The observed selectivity trend was $CH_3COO^- > Cl^- > Br^- > F^- > HSO_4^- > I^-$. Receptor **I** also showed precipitation behavior with $H_2PO_4^-$ ion in acetonitrile.

The synthesis and anion binding behavior of non-steroidal receptors **III** and **IV**, containing 1,2,3-triazole as well as amide moieties have also been described . Receptors **III** and **IV** showed high selectivity for dihydrogen phosphate ion with a binding constant of 400 M^{-1} and

180 M^{-1}, respectively. The observed selectivity trend in both cases was $H_2PO_4^-$ > CH_3COO^- > F^- > Cl^- > Br^-.

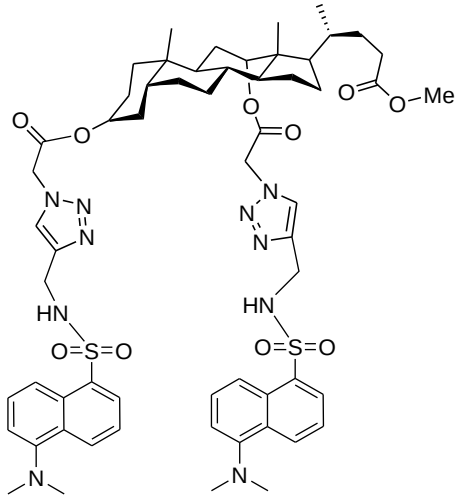


III

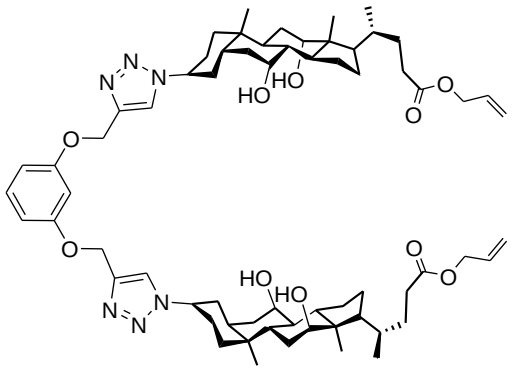


IV

This chapter also deals with the synthesis of bile acid-based 1,2,3-triazole receptors **V** and **VI** for the recognition of metal ions. The binding behavior of the receptor **V** towards metal ions was studied in $CHCl_3$:MeOH (7:3, v/v) by molecular fluorescence and UV-Vis titration. Receptor **V** showed very high selectivity for Hg^{2+} ion with a binding constant of 3.3×10^4 M^{-1}. However, compound **VI** was found to be selective for Cu^{2+} metal ion. Receptor **VI** also showed precipitate formation with Hg^{2+} ion in $CHCl_3$:MeOH (7:3, v/v).



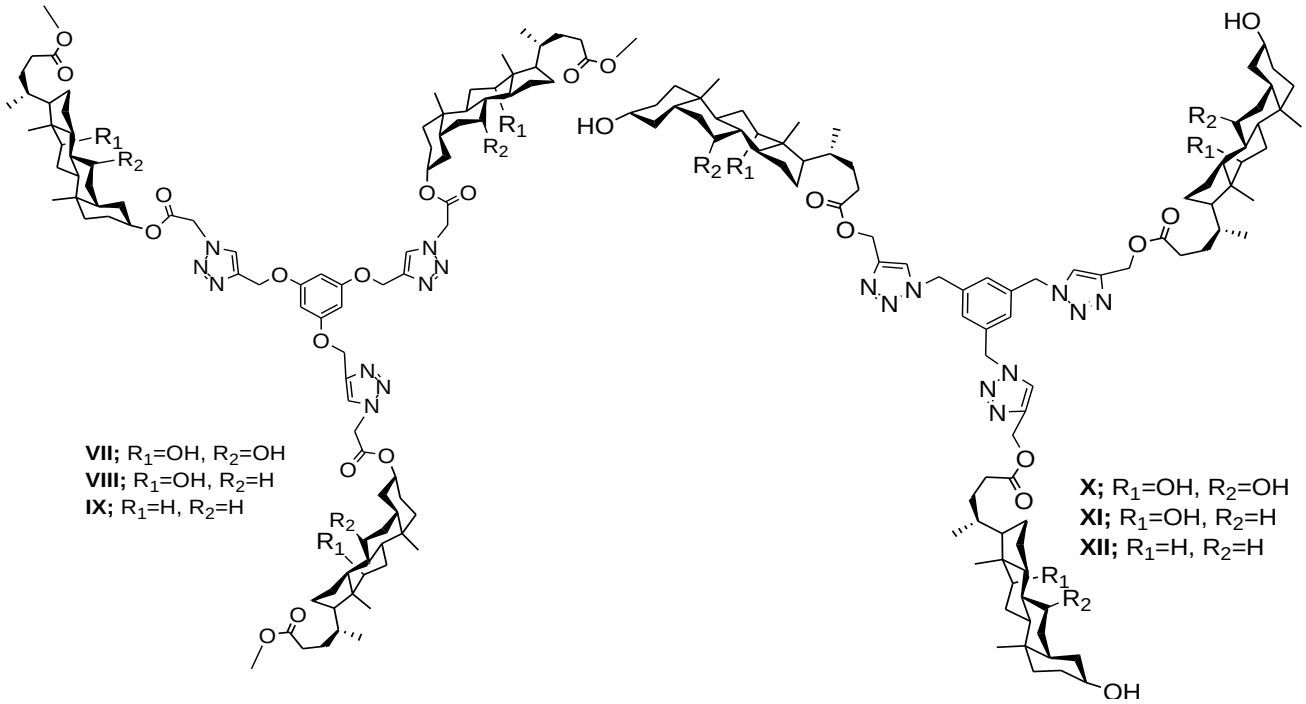
V



VI

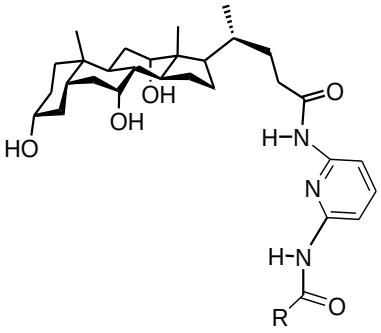
The third chapter deals with the synthesis of 1,2,3-triazole containing tripodal receptors **VII-XII**, their application in stabilization of silver nanoparticles and their ion-sensing properties. An efficient method for the synthesis of silver nanoparticles has been developed through the

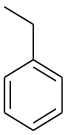
stabilization of nanoparticles with tripodal compounds **VII-XII** under visible light. These nanoparticles have been used for the colorimetric sensing of transition metal ions and anions. All of these nanopaticles showed remarkably selective colorimetric sensing for Hg^{2+} ion. As for the anion sensing, silver nanoparticles stabilized with **VIII** and **IX** showed the colorimetric response for both $H_2PO_4^-$ and NO_3^- ions. However, silver nanoparticles stabilized with compounds **XI** and **XII** were found to be sensitive only for $H_2PO_4^-$ ion.

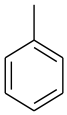


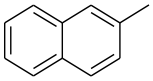
The fourth chapter describes the synthesis of bile acid-based receptors **XIII-XVI** containing 2,6-diaminopyridine unit and their binding studies with a flavin analogue. Flavoproteins containing flavin cofactors FAD (flavin adenine dinucleotide) or FMN (flavin mononucleotide) catalyze a variety of biological redox transformations. 2,6-Diaminopyridine derivatives have been found to bind flavin derivatives through three hydrogen bonds. The binding properties of the bile acid-based receptors **XIII-XVI** with *N*(10)-hexylflavin were examined in chloroform by ^{1}H NMR titration. It was observed that there was significant aromatic π-stacking interaction between the flavin ring and the aromatic unit of these

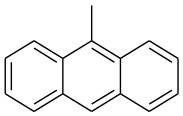
receptors along with the hydrogen bonding interaction with amide protons. The binding constants for **XIII**, **XIV** and **XV** were found to be 3500, 2000 and 1000 M^{-1}, respectively. In the case of **XVI**, very little change in the chemical shift of amide and other protons was observed. The unexpected decrease in the binding of **XVI**, may be due to the steric hindrance arising from the anthracene ring preventing the N-H--X hydrogen bond interaction.



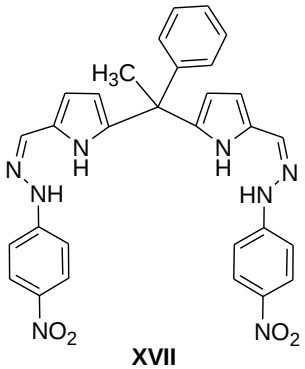
XIII; R = 

XIV; R = 

XV; R = 

XVI; R = 

The fifth chapter deals with the synthesis of a dipyrromethane-based receptor **XVII** and its ion recognition properties. The binding behavior of receptor **XVII** towards metal ions was studied in acetonitrile by UV-Vis titration. It showed very high selectivity for fluoride and copper ions with binding constants of 6.02×10^3 and 9.82×10^3 M^{-1}, respectively. It also showed the colorimetric change with fluoride and copper ions.



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Glossary of symbols and Abbreviations

%	percentage
δ	chemical shift
°C	degree centigrade
Ar	aryl
bs	broad singlet
$CDCl_3$	deuterated chloroform
CD_3OD	deuterated methanol
$Cu(SO_4)_2$	copper sulphate
d	doublet
DMF	*N,N′*-dimethylformamide
DMSO-d_6	deuterated dimethyl sulfoxide
g	gram
mp	melting point
h	hour
min.	minute
IR	infrared
J	coupling constant
m	multiplet
mg	milligram
K_a	association constant
MHz	megahertz

Hz	hertz
mmol	millimole
Soln	solution
M	molar
NMR	nuclear magnetic resonance
rt	room temperature
s	singlet
TLC	thin layer chromatography
TMS	tetramethylsilane
t	triplet
m/z	mass/charge
HRMS	high resolution mass spectrum
ESI	electrospray ionization
TEM	transmission electron microscopy
SEM	scanning electron microscopy
AgNP	silver nanoparticle

NOTES

1. All the melting points reported in the thesis were taken on an electrical melting point apparatus.
2. All the solvents were purified by routine methods and were distilled before use.
3. TLC was performed on silica gel plates using iodine for visualizing spots.
4. Purification of the compounds was done by flash chromatography using Spectrochem silica gel 60-120 mesh.
5. IR spectra were recorded on a Nicolet Protégé 460 FTIR Spectrometer, using potassium bromide pellets.
6. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Spectrospin DPX 300. Tetramethylsilane was used as internal reference and the chemical shifts are expressed as displacement (δ) in ppm downfield from tetramethylsilane.
7. High resolution mass spectra (ES) were recorded on a Bruker MicroTOF-Q II.
8. Absorption spectra were recorded on Perkin Elmer Lambda bio-20 double-beam spectrophotometer.
9. Fluorescence spectra were recorded on Horiba scientific fluoromax-4
10. SEM images were recorded on Carl Zesis EVO 50 WDS electron microscope.
11. TEM images were recorded on Tecnai G^2 20 electron microscope operated at 200 kV.