International Journal of Pharma and Bio Sciences V1(2)2010

NON-TEMPLATE SYNTHESIS AND ANTIMICROBIAL ACTIVITIES OF TETRAAZAMACROCYCLIC LIGANDS WITH VARIABLE RING SIZES

NIRDOSH PATIL*[1] AND RAMACHANDRA AKKASALI[2]

[1]Department of Chemistry, Appa Institute of Engg. & Technology, Gulbarga-585103. Karnataka, India
[2]Department of Chemistry, Kottureswara College, Kottur, Bellary-583134, Karnataka, India

Corresponding Author nirdosh68@yahoo.co.in

ABSTRACT

Three new macrocyclic ligands containing four aza groups have been prepared by the condensation reaction of 1-(2, 4-dihydroxyphenyl)-3-phynyl propane-1,3-dione with different diamines (1,2-diamino ethane, 1,3-diamino propane and 1,2-diamino benzene). The macrocycles prepared are "1,9-(2,4-dihydroxyphenyl)-1,2-diphenyl-1,5,8,12-tetraazacyclotetradeca-1,4,z8,11-tetraene", "4,10-di(2,4-dihydroxyphenyl)-2,12-diphenyl-1,5,9,13-tetraazacyclohexadeca - 1,4,9,12-tetraene" and dibenzo-[b,I]-4,9-di(2,4-dihydroxyphenyl)- 2, 11 -diphenyl - 1,5,8,12-tetraazacyclotetradeca-1,4,8,11-tetraene". All the macrocyclic ligands were characterized by elemental analysis and IR, UV, NMR and mass spectral investigations and have been screened *in vitro* for their possible antimicrobial activity.

KEYWORDS

Ligands, Macro cycles, Anti-microbial, Diketones

INTRODUCTION

Nature prefers macrocyclic derivatives for many fundamental biological processes such as photosynthesis, transfer of oxygen in mammalian and all respiratory systems[1]. Therefore, meaningful research in this direction might generate simple models for biologically occurring metalloenzymes[2]. Macrocycles with delocalised structures have also attracted attention as components of molecular electronic devices, as building blocks of electro active networks and for their molecular recognition properties[3]. Diverse macrocycles and hosts such as crown ether, cyclophanes, cryptands, molecular clefts, and like species are well known. The great majority of these macrocycles are organic molecules that are conformationally reasonably flexible and preferentially interact with cationic guests[4].Saturated macrocycles with different number of rings have

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been synthesized and interesting information concerning both the stabilities and structure of their metal complexes has been reported[5-6]. Early observations on complexes with 14-membered tetraaza macrocyclic ligands led to the suggestion that a constrictive effect might be responsible for their surprisingly large ligand field streangths[7,8]. Application of this phenomenon to macrocyclisation is attractive, since cyclisation of a large molecule by the usual synthetic methods employing kinetically controlled reaction is frequently a tedious and low yield process[9].

We report here the non-template synthesis of three new tetraaza macrocyclic compounds, which can be obtained by the condensation of diketone with ethylenediamine, o-phenylenediamine and diaminopropane and their characterization.

MATERIALS AND METHODS:

All the compounds are analytical grade products from Merks. The starting compound 7 was prepared following the procedures described elsewhere. The solvents were distilled and stored over molecular sieves. It is to be noted that other authors have criticized the elemental analysis of this type of compounds as an inappropriate criterion for purity in synthetic macrocyclic chemistry due to inclusion of solvent molecules. We have found the signals of solvent molecules in the 1H NMR spectra of a few macrocycles. Such compounds were stored for several days under vacuum after heating them in a vacuum drying using steam and then obtained analytical data that agree well with the theoretical values. Purity of the compounds was checked by the TLC using Merk $60F_{254}$ silica gel plates. IR spectra in KBr discs were recorded using a Perkin- Elmer-BX series FT-IR spectrophotometer. Mass spectra were recorded using Finnigan MAT-8230 and Varian MAT3111A/AMO massspectometer. The electronic spectra in methanol were recorded on Shimadzu 2401 PC spectrometer. Melting points (uncorrected) were determined in open capillary tubes using Cintex apparatus. The macrocycles were carried out using the Perkin-Elmer series II CHNS analyzer-2400 instrument.

1.Preparation of 4,9-di(2,4-dihydroxyphenyl) - 2, 11 – diphenyl - 1,5,8,12-tetraazacyclotetradeca-1,4,8,11-tetraene **10;** 4,10-di(2,4-dihydroxyphenyl)-2,12-diphenyl-1,5,9,13-tetraazacyclohexadeca-1,4,9,12-tetraene **11;** and Dibenzo-[b,I]-4,9-di(2,4-dihydroxyphenyl)-2,11-diphenyl-1,5,8,12-tetraazacyclotetradeca-1,4,8,11-tetraene **12**.

Method: To an ethanolic solution (30ml) of 1-(2,4-dihydroxyphenyl)-3-phenylpropane-1,3-dione(0.02mol) **7**, ethanolic solution of diamines, such as ethylenediamine **8**, diaminopropane **9** and o-phenelynediamine **10** were added. To the mixture add few drops of HCl. The resultant solution was refluxed for15-20 hours. The resultant compounds were stored for several days under vacuum after heating them in a vacuum drying using steam and were kept in desiccators for 18-20 days. The products were recrystallised from methanol until pure by TLC, the yield of the products were very less. The analytical data and spectral data are given below.

1.2. Macrocycle 11: Brown crystalline, yield 1.5gm. (55%) mp.278-280^{0}C. UV λ_{max} (nm) ($10^3\varepsilon_{max}$)210 (5.160), 255(3.040), 320(0,530); IR,3530,1620,1550,cm^{-1};^{1}H NMR spectrum (δ) 12.03, (4H,m,HC=N azomethine protons) 2.95 (8H, m, N-CH_2); mass spectrum m/z 560(0.8%,M^+), 429(90%), 298(25%), 149(17%), 109(15%),

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80(20%); C H N Calcd. For $C_{34}N_4H_{34}O_4$; C,72.85;H,5.71;N,10.00;found.C,72.89;H,5.75;N,10.10;

2.1.2. Macrocycle 12: brown crystalline, yield 1.3gm.(57%); mp.255-257^{0}C.UV λ_{max} (nm) ($10^3\varepsilon_{max}$)215(5.28),250(2.97),315(0.520);IR3550,1625,1560cm^{-1};^{1}H NMR spectrum(δ) 12.15, (4H,br,phenolic protons), 7.15-7.40 (16H, m, aromatic-SH); 8.35(4H, m,HC=N, azomethine protons) 2.85(8H, m, N-CH_2); mass spectrum m/z 588(0.7%,M^+), 443(85%), 312(30%), 163(18%), 135(25%), 109(40%); 80(15%), C H N Calcd. For $C_{36}H_{36}N_4O_4$; C,73.00,H,6.12,N,9.52; found.C,73.09, H,6.29, N,9.60;

2.1.3. Macrocycle 13: brown crystalline, yield 1.6gm.(60%); mp.275-277^{0}C.UV λ_{max} (nm) ($10^3\varepsilon_{max}$)218(5.35),257(3.05),310(0.510),IR,3520,1610,1550cm^{-1}, ^{1}H NMR spectrum(δ) 12.10, (4H,br,phenolic protons), 7.12-7.50 (24H, m, aromatic-HS); 8.45(4H, m, HC=N, azomethine protons); mass spectrum m/z, 658(0.5%,M^+), 464(60%), 347(100%), 136(25%), 94(15%), 65(20%); C H N Calcd. for $C_{42}H_{34}N_4O_4$; C,76.59,H,5.16,N,8.51; found.C,76.61, H,5.19, N,8.55;

The antimicrobial activity of the macrocycles **11, 12** and **13** were determined by agar cup-plate method. The antibacterial activity against *Escherichia coli* and *Pseudomonas aeroginosa* and antifungal activity against *Aspergillus niger* and *Candida albicans*, were screened by the macrocycles. The medium was prepared as per the instructions of the manufacturer of dry Mueller Hinton agar powder (Hi-Media). The test macrocycles were dissolved in dimethylsulphoxide (DMSO) at a concentration of 100µg/ml. Ciproflaxacin (100µg/ml) in DMSO was used as reference standard for antibacterial and flucanozole (100µg/ml) in DMSO was used as reference standard for antifungal activity. The solvent control (only DMSO) was also maintained throughout the experiment. The zones of inhibition are reported in Table-1.

Table 1
Antibacterial and antifungal activity data of macrocycles (Zone of inhibition in mm*)

Macro cycles	Antibacterial		Antifungal	
	E.coli	*P.aeroginosa*	*A.niger*	*C.albicans*
11	13	16	12	10
12	14	17	13	11
13	15	18	14	12
Ciproflaxacin	27	30	__	__
Flucanozole	__	__	24	23
DMSO	00	00	00	00

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RESULTS AND DISCUSSIONS:

The starting compound required for the synthesis of macrocycles is 1-(2,4-dihydroxy phenol)-3-phenyl propane-dione, which can be obtained by the resorcinol **1** is treated with acetic acid in presence of zinc chloride, resulted as acetophenone **2** which was a dark pink coloured compound, is treated with benzoyl chloride **3** in presence of 10%sodium hydroxide **4** resulted as aroyloxyacetophenone **5.** The yield of the compound **5** is very high, it was crystallized from 95% ethanol and it was undergoes the Baker-Venkataraman rearrangement reaction with potassium hydroxide **6** in pyridine resulted as1-(2,4-dihydroxy phenyl)-3-phenyl-propane –1,3-dione **7** (diketone), which was a yellow solid and crystallized from ethanol.

The reaction between the compound **7** and diamines such as ethylenediamine **8** diaminopropane **9** and o-phenylenediamine **10** in presence of few drops of hydrochloric acid, the resultant compound were kept in desiccators for 10-20 days, the solid separated are tetraaza macrocycles **11-13**. The tetraaza macrocycles obtained in the reactions are of 14-, 16- and 14-membered ring with four aza nitrogen atoms **(11-13)**. The isolation of tetraaza macrocycles with such a range of ring sizes is interesting, for the choice of reaction conditions and solvents that allow the separation of free macrocyclic ligands to separate from solution even in the absence of any catalyst[10]. There have been very limited reports [11] of successful ring closure reactions to give metal free 14- and 16-membered 'N_4` macrocycles.

The physical characteristics and the analytical data of the compounds are presented in section 2. The infrared spectra of the compounds **11-13** do not show the characteristic absorption of the $–NH_2$ group and C=O group that are found in the compounds **8-10** and compound 7. This is further confirmed by the absence of a signal around 4.0-5.0 ppm corresponds to the NH_2 protons, the ^1H NMR spectra of compound **7** show a signal around 2.5 ppm assignable to $OC-CH_2-CO$ protons, this signal is observed in the slight down field around 2.8 ppm and the high intensity signal of azomethine protons are observed around 8.8-9.3 ppm. The IR spectra of the compound **7** shows the absorption bands in the region 1730-1750cm^{-1} are due to C=O group, these absorption bands are not observed in the compound **11-13** because the condensation reaction between C=O group of compound **7** and amine group of compounds **8-10**.Therefore the compounds **11-13** show the absorption bands around 1600-1610cm^{-1} are due to the stretching frequency of C=N group. This indicates the cyclisation through condensation by the loss of H_2O.

All three compounds **11-13** exhibit molecular ion peaks in the mass spectra and the fragmentation patterns confirm the formation of the products as shown in scheme.

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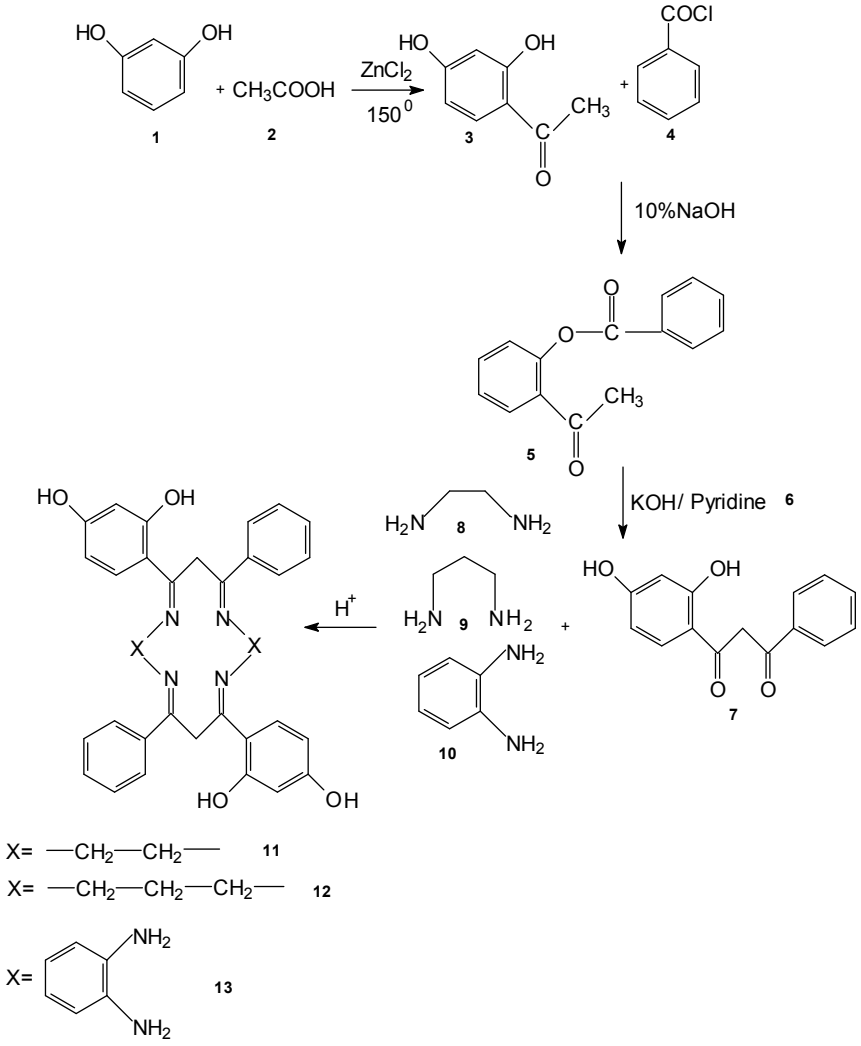

From the Table-1, it is clear that all the macrocycles **11, 12** and **13** show moderate activity against all the antibacterial and antifungal microorganisms[12]. Even though the test compounds are less active with reference to the standards drug *ciproflaxacin* and *flucanozole*, the data reported in this article may be a helpful guide for the medicinal chemists who are working in the area.

ACKNOWLEDGEMENT

The authors are thankful to Prof. V H Kulkarni and S D Angadi for helpful suggestions. Our thanks are also due to Poojya, Dr. Sharanabasvappa Appa, President, Appa Institute of Engg. and Tech. Gulbarga and Prof. Mruttyunjaya Swamy, Chairman, Department of Chemistry, Gulbarga University, for providing the facility.

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