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Hydrolysis of Letrozole Catalyzed by Macrocyclic Rhodium (I) Schiff-base Complexes

P. Muralidhar Reddy[1†], K. Shanker[2,†], V. Srinivas[2], E. Ravi Krishna[2], R. Rohini [2, 3], G. Srikanth[2], Anren Hu[4]* and V. Ravinder [2, *]

[1] *Department of Chemistry, Nizam College, Osmania University, Hyderabad, India*

[2] *Department of Chemistry, Kakatiya University, Warangal-506 009, A.P, India*

[3] *Department of Chemistry, National Dong Hwa University, Hualien-974, Taiwan*

[4] *Department of Laboratory Medicine and Biotechnology, Tzu Chi University, Hualien, Taiwan*

[†] *These authors contributed equally to this work.*

*** Authors to whom correspondence should be addressed**; E-Mails: ravichemku@rediffmail.com; anren@mail.tcu.edu.tw; Tel.: +886-3-8565301 (ext. 2334 or 2335); +91-9390100594; Fax: +886-3-8571917 (A.H.).

Abstract

Ten mononuclear Rhodium (I) complexes were synthesized by macrocyclic ligands having N_4 and N_2O_2 donor sites. Square planar geometry is assigned based on the analytical and spectral properties for all complexes. Rh(I) complexes were investigated as catalysts in hydrolysis of nitrile group containing pharmaceutical drug Letrozole. A comparative study showed that all the complexes are efficient in the catalysis. The percent yields of all the catalytic reaction products *viz.* drug impurities were determined by spectrophotometric procedures and characterized by spectral studies.

Keywords: rhodium (I) complexes, hydrolysis, Letrozole, spectrophotometry, spectral studies

1. Introduction

The macrocyclic metal complexes have attracted a great deal of attention because they can be used as models for more complex biological macrocyclic systems such as hemoglobin, myoglobin, cytochromes, chlorophylls, vitamin B12, valinomycin, and nonactin etc. These breakthroughs have created supramolecular chemistry and its tremendous diversity [1]. Generally, macrocycles can be synthesized by template and non-template methods [2-6]. Most of the synthetic routes of macrocycles involve templation, but the products are not easily scaled up. However, Schiff base condensation is preferred to overcome this problem [7-9]. Ortho-phthalaldehyde (OPA) serves as a good starting material for the synthesis of macrocycles [10]. Literature study discloses that a little bit of work was done to synthesize Schiff bases from OPA by either template or non-template methods [10-18]. In previous work, we have reported the non-template synthesis of N-, O-, donor macrocycles, benzimidazo/indolo [1,2-c] quinazolines[19-25] and their metal complexes [14-16, 26-30]. Still, the many of the existing OPA based macrocyclic metal compounds were synthesized by the direct treatment of OPA, diamine and metal salts [11, 12]. Since, macrocyclic Rhodium (I) complexes are not synthesized by the initial preparation of macrocycle followed by its treatment with $[Rh(COD)Cl]_2$.

In recent years, research towards the catalytic applications of macrocyclic metal complexes is rapidly increasing [26, 27]. It bids attractive chances for industry, which attempts to develop more environmentally benign manufacturing methods. Governing authorities are now giving critical attention on impurity profiling of active pharmaceutical ingredients (APIs) and demanding for the identification and quantization of impurities in APIs in order to protect the patient against the undesirable side effects [31-33]. Hence, International Conference on Harmonization (ICH) guideline [34] set a threshold of 0.1 percentage impurities in APIs, above

which the identification of the impurity is compulsory. Forced degradation (stress) studies [34, 35] are also to be executed to produce and detect these impurities and the recommended conditions include oxidation, hydrolysis at high and low pH, elevated temperature, photolysis of APIs. A number of recent reports have described a designed approach and guidance for isolating, detecting and synthesizing process related impurities [36, 37] and degradation products [38, 39]. Rhodium complexes are versatile catalysts and can be used for several organic reactions, like oxidation [40], reduction [41], carbonylation [42], addition [43], hydroformylation [44], hydroboration [45] etc. The Wilkinson catalyst, $RhCl(PPh_3)_3$ is the classic example of a homogeneous hydrogenation catalyst [46]. In the present study, we synthesized mononuclear macrocyclic Rh(I) complexes (Scheme 1) and utilized in the hydrolysis of Letrozole drug molecule to develop its impurities.

2. Experimental Section

2.1. Materials

The macrocyclic ligands (MLs) namely 7,8,17,18-tetrahydrodibenzo [f,n][1,4,9,12] tetraazacyclohexadecine[HBACHD] (**L1**), Tetrabenzo[b,f,j,n][1,4,9,12]tetraazacyclo hexadecane [BACHD] (**L2**),Dibenzo[f,n]dipyrido[2,3-b:3,2-j][1,4,9,12]-tetraazacyclohexadecine [BPACHD] (**L3**),Dibenzo[g,p]dinaphtho-[1,8-bc:1,8-kl][1,5,10,14]-tetraazacyclooctadecine[BNACOD](**L4**), 6,7-dihydrotribenzo-[e,i,m][1,4,7,12]-ioxadiazacyclotetradecine [HBOACTD] (**L5**), 13,14-dihydro-12H-tribenzo[b,f,j][1,12,4,9]dioxadiazacyclopentadecine[HBOACPD](**L6**),6,7-di hydro benzo [i]dipyrido[3,2-e:2,3-m][1,4,7,12]dioxadiazacyclotetradecine [HBPOACTD] (**L7**), 13,14-dihydro-12H-benzo-[f]-dipyrido-[3,2-b:2,3-j][1,12,4,9]-dioxadiazacyclopentadecine [HBPOAC PD](**L8**),21,22-dihydrobenzo[i]dinaphtho[2,3-e:2,3-m][1,4,7,12]dioxadiazacyclotetradecine [HB

NOACTD](**L9**) and 15,16-dihydro-14H-benzo[f]binaphthol[2,3-b:2,3-j] [1,12,4,9] dioxa diazacyclopentadecine [HBNOACPD] (**L10**) were synthesized according to literature procedures [10, 47]. $[Rh(COD)Cl]_2$ was obtained from Aldrich, USA, and all other compounds were analytical grade products from Merck. Aromatic amines, *o*-phthalaldehyde (OPA), and substituted aromatic amino alcohols were acquired from Aldrich, USA. The melting points of all the macrocyclic Rh(I) complexes were obtained on a Buchi- 510 melting point apparatus. The percentages of carbon, hydrogen, nitrogen were determined by using a Perkin-Elmer CHN analyzer at 240C. Rhodium was determined calorimetrically by treating with 2-mercapto-benzoxazole [48]. The IR spectra were recorded in KBr pellets on a Perkin Elmer-283 spectrophotometer. Brucker WH 300 (200 MHz) and Brucker WH 270 (67.93 MHz) spectrometers were used for ^{1}H NMR and ^{13}C NMR measurements. ESI and MALDI MS were used to obtain mass spectra. UV-Visible spectra were recorded with Shimadzu UV-160A double beam spectrophotometer with matched quartz cells of path length of 1 cm. Conductance measurements were done on 10^{-3} M solution of compounds in dichloromethane at room temperature using Digisun Digital conductivity meter model DL-909. Gouy balance calibrated with $Hg[Co(NCS)_4]$ was used for the determination of magnetic susceptibilities of complexes in solid state at room temperature. The solvents were dried by standard procedures, distilled and stored over molecular sieves. The purity of the compounds was checked by TLC using Merck 60F254 silica gel plates.

2.2. Typical procedure for preparation of macrocyclic Rh(I) complexes

A methanolic solution of $[Rh(COD)Cl]_2$ (1.47 g, 0.003 mol.) was added to the solution of ML component (0.003 mol.) in methanol and the solution was stirred magnetically for about 2h. The solution became thick in due course of the reaction. Then, solution volume was reduced to

half of its original volume and 15 ml diethyl ether was added drop-wise to initiate the crystallization of the product. It was filtered and washed with ether to give pure crystalline solid, which was dried under *vacuo*. Synthetic route of macrocyclic Rh(I) complexes are shown in Scheme 1

2.3. Drug solution and Reagents

Letrozole solution (200 µg/ml) was prepared by dissolving 20 mg of pure LTZ in 100 ml of double distilled water. 0.1 N NaOH solution (Merck) was prepared by dissolving 4 g in 1000 ml of double distilled water. Ferric chloride solution (Sd-Fine, 0.2 M) was prepared by dissolving 5.40 g in 0.1 M hydrochloric acid solution.

2.4. Hydrolysis of Letrozole

In a 100 ml round bottom (RB) flask, 3 ml of LTZ solution (200 µg/ml), 3 ml of NaOH and [Rh(HBACHD)]Cl (Comp.**1**, 0.02 mmol) were taken and refluxed for 15 min. The contents of RB flask were cooled for 10 min and transferred to 20 ml calibrated tubes. Now, 5 ml of ferric chloride was added to each tube and the total volumes were made up to 20 ml with double distilled water and kept aside for 5 min. The absorbance of the yellow colored solutions was measured at 380 nm against a similar reagent blank (Fig. S1). The amount of HLTZ was assayed from the calibration curve (Fig. S1). The procedure was repeated by changing the rhodium catalysts.

Insert Scheme 1

3. Results and Discussion

In the present investigations, ten new tetra coordinated Schiff base macrocyclic Rh(I) complexes were synthesized by treating $[Rh(COD)Cl]_2$ with the ten MLs separately (see Scheme

1). The percentages of carbon, hydrogen and nitrogen were determined experimentally using CHN analyzer. The percentage of rhodium in these macrocyclic Rh(I) complexes were determined by literature method [49]. The physical and analytical data (Table 1) for the newly synthesized macrocyclic Rh(I) complexes is in good agreement with the proposed molecular formulae viz. [Rh(I)(L)]Cl (where L= tetra dentate macrocyclic ligand).

Insert Table 1

3.1. Infrared spectral analysis

The infrared spectra of the MLs are compared with the macrocyclic Rh(I) complexes to elucidate the binding mode of the MLs to Rh(I) ion. In the IR spectra of the MLs, a medium intensity $\upsilon_{C=N}$ band was observed in the range of 1630-1608 cm^{-1} [10]. This band was shifted towards lower side about 19-38 cm^{-1} which was in the range of 1601-1573 cm^{-1} [15, 16] in case of macrocyclic Rh(I) complexes. This supports the fact that the MLs coordinate to the metal ions through the nitrogen of the C=N group in all the macrocyclic Rh(I) complexes. This fact is further proved by the presence of a medium intensity band in the region of 502-537 cm^{-1} assignable to υ_{M-N} vibration [15, 16]. On the other hand, in MLs, υ_{C-O-C} band was observed in the range of 1208-1141 cm^{-1}[10, 47], which was shifted towards lower side about 19-43 cm^{-1} and found in the range of 1187-1116 cm^{-1} [16] for corresponding macrocyclic Rh(I) complexes. This supports the fact that the MLs coordinate to the metal ions through an oxygen of the C-O-C group in addition to the nitrogens of the C=N group in these complexes. This is further confirmed by the appearance of a medium intensity band in the region of 432-408 cm^{-1} assignable to υ_{M-O} vibration [15, 16]. The characteristic bands due to pyridine $\upsilon_{C=N}$ and aromatic stretching vibrations in the spectra of respective macrocyclic Rh(I) complexes were remain almost upshifted (Table 2).

Insert Table 2

3.2. ^{1}H NMR spectral analysis

^{1}H NMR spectral comparison between MLs and Rh(I) complexes was made to confirm the binding nature of MLs to Rh(I) ion. The integral intensities of each signal in the ^{1}H NMR spectra of ligands/Rh(I) complexes were found to agree with the number of different types of protons present. In all the MLs signals corresponding to CH=N protons were observed in the range of 8.02-8.83 δ [10, 47] and in the spectra of Rh(I) complexes these signals were observed slightly in the down field regions of 8.15-8.98 δ confirming the coordination of nitrogen atom of this group to Rh(I) ion. In the spectra of MLs (**L5**-**10)**, a signal is appeared in the range of 3.90-4.37 δ corresponding to O-CH_2 protons. However, in the spectra of the corresponding Rh(I) complex this signal was observed with a little down field in the range of 3.97-4.42 δ. The above fact supports the coordination of these MLs through an oxygen atom of O-CH_2 group in addition to the nitrogen atom of CH=N group. There is no major change in the peak positions corresponding to aromatic protons.

3.3. ^{13C} NMR spectral analysis

The ^{13}C NMR spectra of all the MLs contain signals in the range of 150.4-179.0 δ due to the presence of carbon which is doubly bonded to nitrogen [10]. Though, in the spectra of Rh(I) complexes, an up field shift in peak position was observed in the range of 156.3-178.6 δ. This fact confirms that all the MLs coordinate by the nitrogen atoms. However, the MLs **L5**-**10** contain peaks in the range of 60.0-67.4 δ corresponding to carbon atoms adjacent to oxygens. This range was shifted to up field region to 61.8-72.1 δ in the Rh(I) complexes, representing the coordination of the oxygen atoms of O-CH_2 group to Rh(I) ion in addition to the two nitrogen atoms of CH=N group[14, 26, 27]. Significant changes in peak positions were not observed with

respect to aryl carbons and carbons adjacent to ring nitrogen atom [28]. The specific ^{1}H peak positions of selected protons and ^{13}C peak positions of carbon atoms of all the macrocyclic Rh(I) complexes are given in Table 3.

Insert Table 3

3.4. Molar conductance, magnetic properties, electronic and thermal data

The molar conductance values for all the Rh(I) complexes (10^{-3} M) were determined in DCM. These values were found between 36.2-52.7 $ohm^{-1}cm^{2}mol^{-1}$ signifying 1:1 electrolytic nature (see Table 1). The electrolytic nature of the complexes is owing to the presence of one chloride ion outside the coordination sphere [50]. This was confirmed by the addition of $AgNO_3$ reagent leading to the formation of a white precipitate [26]. The magnetic susceptibility measurements have been carried out by a Gouy balance for Rh(I) complexes and were found to be diamagnetic and hence, Rh(I) ion is in the low spin configuration. The diamagnetic nature of complexes was further confirmed by the sharp, well-defined signals in the ^{1}H NMR spectra. The electronic spectra recorded for all the Rh(I) complexes in acetone exhibited mainly two bands of comparable intensity in the range of 520-240 nm (see Table 1). The bands in the visible region may be assigned to metal-ligand charge-transfer transaction [51]. Whereas the bands observed in the UV region are assigned to intra-ligand transitions. No d-d transitions were detected. The Rh(I) species are a strong reducing in character that their d-d transitions are usually obscured by charge-transfer transitions. The thermograms of TGA and DTA of Rh(I) complexes with all the MLs exhibit decomposition in only one stages around 250 ^{o}C, corresponding to the loss of organic moiety, demonstrating that, there are no water molecules of both types (lattice held/coordinated) in all the complexes[26]. The nonexistence of water molecules in the Rh(I) complexes were further evidenced by their DTA curves which contain only one exothermic peak

in the temperature range around 250 ^{o}C corresponding to the loss of organic moiety. Above 540 ^{o}C, the organic moieties in Rh(I) complexes were decomposed leading to the formation of their oxide.

3.5. Mass spectral analysis

The molecular ion peaks of Rh(I) complexes shows different m/z values with different intensities. The mass spectra contain molecular ion peaks at *m/z* 454 (M^+, Comp.**1**), 573 (M^++Na, Comp. **2**), 552 (M^+, Comp.**3**), 650 (M^+, Comp.**4**), 503 (M^++Na, Comp.**5**), 494 (M^+, Comp.**6**), 482 (M^+, Comp.**7**), 496 (M^+, Comp.**8**), 580 (M^+, Comp.**9**), and 594 (M^+, Comp.**10**). This data is in good agreement with the corresponding molecular formulae.

4. Drug catalysis

Letrozole (LTZ), chemically known as 4-[(4-cyanophenyl)-(1,2,4-triazol-1-yl)methyl] benzonitrile is an oral non-steroidal aromatase inhibitor that has been introduced for the adjuvant treatment of hormonally-responsive breast cancer [52]. It contains two Nitrile groups and able to produce carboxylic acid derivative by hydrolysis.

4.1. Hydrolysis of Letrozole

Hydrolysis of Nitrile compounds is an area of great synthetic significance for the preparation of amides and carboxylic acids in view of the industrial applications and pharmacological interest of both the classes of these compounds. However, amides can be obtained by the selective hydrolysis of Nitrile compounds. Nitrile groups vary greatly in their ease of hydrolysis depending on the substrates and conditions. Hence, in order to activate Nitrile groups, strong inorganic acid or base and high temperatures are normally needed. Base catalyzed

reactions are generally preferred because these reactions are faster than the acid catalyzed reactions and the application of strong acidic solutions requires a careful control of the temperature due to the exothermic behavior. Pombeiro et. al. reviewed metal mediated and metal catalyzed hydrolysis of nitriles [53]. Wang reported the enantioselective biotransformations of nitriles in organic synthesis [54]. One of the main goal of the present studies is the hydrolysis of Nitrile group containing Letrozole by Rh (I) catalysts to prepare its hydrolysis derivatives, which can be considered as a potential impurity of LTZ. The percent yield of hydrolyzed Letrozole (HLTZ) was determined spectrophotometrically [55] using acidified ferric chloride reagent.

4.2. Optimum conditions

The hydrolysis of LTZ was investigated by using [Rh(HBACHD)]Cl (Comp.**1**) by optimizing the volume of sodium hydroxide. Three mL of sodium hydroxide was found to be adequate for the hydrolysis of LTZ, below which the percent yield of HLTZ was low and above it was constant. To investigate the optimum heating time for hydrolysis of LTZ, 3 ml of LTZ solution was mixed with 3 mL of sodium hydroxide in the presence of rhodium catalyst and heated in an interval of 5-120 min in a water bath at 70 °C. HLTZ was treated with acidified ferric chloride. Maximum color intensity was obtained at 15 min heating time and remained constant on further heating. Therefore, 15 min of heating time was maintained throughout the experiment. 0.02 mmol of rhodium catalyst was found to be sufficient for the reaction. The highest absorbance was obtained with 5 ml of acidified ferric chloride, which remain unchanged with higher volume. The λ_{max} value of the colored product was found to be 380 nm and was up to 30 min at room temperature (Figure S1). Similar tendencies were observed with the remaining nine Rh(I) complexes.

4.3. Product analysis

The IR spectrum of LTZ shows a peak around 2200 cm^{-1} due to the stretching of C≡N group. It does not show any signals around 1700 cm^{-1} corresponding to the carbonyl stretching vibrations of acid group. The disappearance of a peak around 2200 cm^{-1} and the appearance of a new peak at 1724 cm^{-1} in HLTZ are indicating the hydrolysis of a Cyano group of LTZ to the carboxylic acid group (Figure S2). The ^{1}H NMR spectrum of LTZ doesn't contain any peak above 9.0δ. But in the spectrum of HLTZ a peak is appears at 10.07 (corresponding to the –COOH proton confirming the hydrolysis of a Nitrile group of LTZ to its acid derivative (Figure S3). The^{13}C-NMR spectrum of LTZ shows a peak at 118 (corresponding to the carbon belonging to Nitrile group. But, in the spectrum of HLTZ, this peak was not appeared. Instead of this, a new peak appeared at 176.3 δ belonging to carboxylic acid carbon indicating the conversion of -CN group to COOH group (Figure S4). The mass spectrum of HLTZ was shown molecular ion peak at a m/z value of 324.5 (M^{+}).

4.4. Mechanism of catalytic cycle

A probable mechanism has been proposed for Rh(I) catalyzed hydrolysis of LTZ (Scheme S1) in the presence of sodium hydroxide. Initially, two hydroxyl ions attack the two Nitrile carbons of LTZ, which in turn hydrolyses to produce carboxylic acid groups with the release of two ammonia gas molecules. Now, two hydroxyl ions from two water molecule attacks the two catalyst molecules, replace two chlorine atoms which in turn combine with two sodium ions and forms two sodium chloride molecules. The regeneration of Rh(I) catalyst takes places finally by the addition of two hydrochloric acid.

Insert Scheme 2 and 3

4.5. Chemistry of colored species

The Nitrile groups in LTZ are hydrolyzed with Rh(I) catalysts leading to the formation of carboxylic acid groups. These groups react with ferric chloride and form a yellow colored product (Scheme S2). The percent yields of HLTZ with all the ten macrocyclic Rh(I) complexes were determined spectrophotometrically (Table 4).

Insert Table 4

5. Conclusions

Macrocyclic Rh(I) complexes were synthesized by treating $[Rh(COD)Cl]_2$ precursor with the ten MLs separately. In all Rh(I) complexes the MLs **L1-L4** coordinate through four nitrogen atoms of C=N group, and the MLs **L5-L10** coordinates through two nitrogen atoms of C=N group and two oxygen atoms of O-CH_2 group to Rh(I) ion. These compounds were found to have mono-electrolytic nature. Square-planar structures were assigned to these complexes based on elemental and spectral data. All these Rh(I) catalysts were applied for the catalytic hydrolysis of LTZ. The catalytic procedure involves mild reaction condition and easy to work-up. The spectrophotometric determination method is simple and the chemistry involved in this is familiar. Hence, this approach can be effectively used for the hydrolysis of APIs containing Nitrile group to produce their impurities with carboxylic acid groups.

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Electronic supporting information is available

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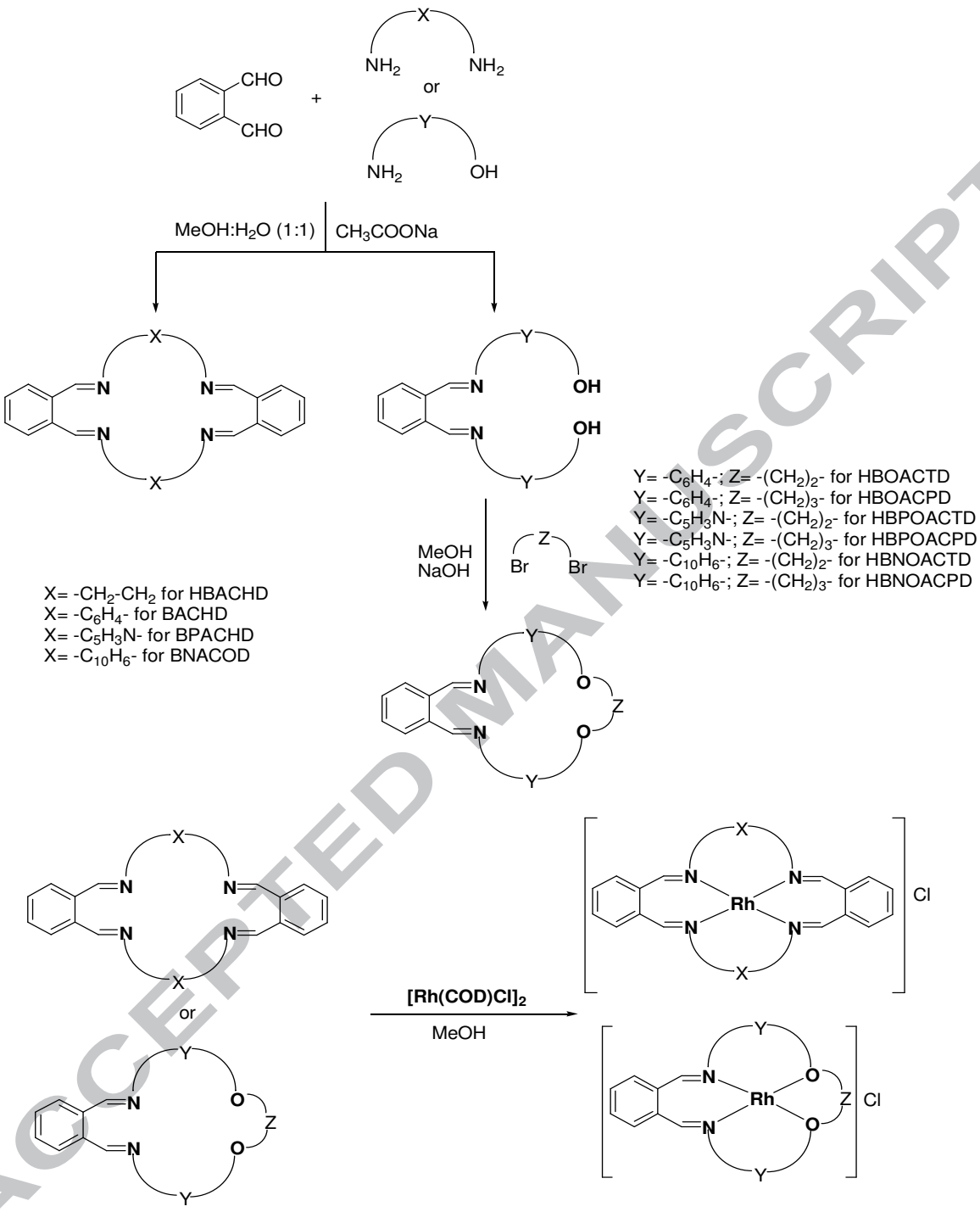


Scheme 1. Synthetic route of N_4 and N_2O_2 donor macrocyclic ligands and their Rh(I) metal complexes

Table1

Analytical and electronic spectral data of macrocyclic Rh(I) complexes

Comp. No.	Mac. Rh(I) complex/ Molecular formula	λ_{max} (nm)	Λ_M	Analyses (%) Found (Calculated)			
				C	H	N	Rh
1.	[Rh(HBACHD)]Cl $C_{20}H_{20}ClN_4Rh$	512, 254	51.0	52.47 (52.82)	4.51 (4.43)	12.40 (12.32)	22.67 (22.63)
2.	[Rh(BACHD)]Cl $C_{28}H_{20}ClN_4Rh$	510, 240	48.5	60.96 (61.05)	3.72 (3.66)	10.12 (10.17)	18.73 (18.68)
3.	[Rh(BPACHD)]Cl $C_{26}H_{18}ClN_6Rh$	520, 290	43.6	56.23 (56.49)	3.37 (3.28)	15.29 (15.20)	18.53 (18.61)
4.	[Rh(BNACOD)]Cl $C_{36}H_{24}ClN_4$ Rh	483, 269	50.1	66.59 (66.42)	3.61 (3.72)	8.78 (8.61)	15.92 (15.81)
5.	[Rh(HBOACTD)]Cl $C_{22}H_{18}ClN_2O_2$ Rh	512, 282	38.8	55.07 (54.96)	3.81 (3.77)	5.70 (5.83)	21.38 (21.41)
6.	[Rh(HBOACPD)]Cl $C_{23}H_{20}ClN_2O_2$ Rh	490, 247	47.3	55.89 (55.83)	3.98 (4.07)	5.60 (5.66)	20.92 (20.80)
7.	[Rh(HBPOACTD)]Cl $C_{20}H_{16}ClN_4O_2$ Rh	517, 280	39.1	49.83 (49.76)	3.21 (3.34)	11.77 (11.61)	21.20 (21.32)
8.	[Rh(HBPOACPD)]Cl $C_{21}H_{18}ClN_4O_2$ Rh	491, 260	52.7	50.87 (50.77)	3.72 (3.65)	11.12 (11.28)	20.64 (20.72)
9.	[Rh(HBNOACTD)]Cl $C_{30}H_{22}ClN_2O_2$ Rh	504, 272	36.2	61.93 (62.03)	3.74 (3.82)	4.97 (4.82)	17.83 (17.72)
10.	[Rh(HBNOACPD)]Cl $C_{31}H_{24}ClN_2O_2$ Rh	482, 265	45.9	62.62 (62.59)	3.94 (4.07)	4.83 (4.71)	17.52 (17.30)

Table 2

Infrared spectral data of macrocyclic Rh(I) complexes

Comp. No.	Mac. Rh(I) complexes	Selected IR bands (cm^{-1})			
		$\upsilon_{C=N}$	υ_{C-O-C}	υ_{Rh-N}	υ_{Rh-O}
1.	[Rh(HBACHD)]Cl	1586	-	523	-
2.	[Rh(BACHD)]Cl	1591	-	510	-
3.	[Rh(BPACHD)]Cl	1600	-	537	-
4.	[Rh(BNACOD)]Cl	1578	-	529	-
5.	[Rh(HBOACTD)]Cl	1593	1116	502	414
6.	[Rh(HBOACPD)]Cl	1582	1152	525	408
7.	[Rh(HBPOACTD)]Cl	1593	1163	518	427
8.	[Rh(HBPOACPD)]Cl	1601	1181	509	432
9.	[Rh(HBNOACTD)]Cl	1573	1139	518	418
10.	[Rh(HBNOACPD)]Cl	1589	1187	532	430

Table 3

^{1}H NMR and ^{13}C NMR spectral data of Rh(I) complexes

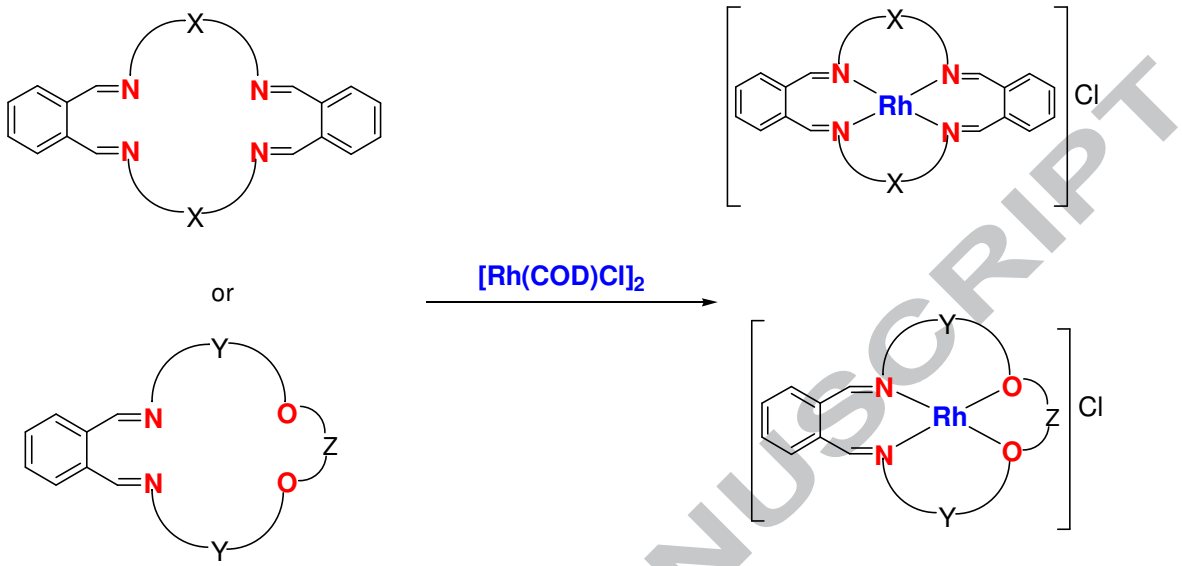
Comp. No.	Mac. Rh(I) complex	^{1}H NMR peak position (δ ppm)	^{13}C NMR peak position (δ ppm)
1.	[Rh(HBACHD)]Cl	3.74 (8H, s, CH_2-CH_2), 6.91-7.53 (8H, m, Ar-H), 8.15 (4H, s, CH=N)	52.5 (4C, CH_2-CH_2), 129.0, 134.3, 136.6 (12C, Ar-C), 167.5 (4C, CH=N)
2.	[Rh(BACHD)]Cl	6.78-7.49 (16H, m, Ar-H), 8.51 (4H, s, CH=N)	123.4, 128.0, 132.0, 133.4, 137.0, 142.1 (24C, Ar-C), 160.4 (4C, CH=N)
3.	[Rh(BPACHD)]Cl	6.32-7.52 (12H, m, Ar-H), 8.22 (2H, s, CH=N in pyridine), 8.84 (4H, s, CH=N)	119.3, 131.7, 133.1, 133.5, 137.8, 137.9, 145.4, 155.4 (20C, Ar-C) 170.6 (2H, Ar-CH=N), 171.1 (4C, CH=N)
4.	[Rh(BNACOD)]Cl	7.00-8.03 (20H, m. Ar-H), 8.98 (4H, s, CH=N)	121.5, 129.3, 130.2, 132.0, 133.4, 135.3, 137.4, 137.9 (32C, Ar-C), 162.1 (4C, CH=N)
5.	[Rh(HBOACTD)]Cl	4.29 (4H, s, O–CH_2), 6.60-7.83 (12H, m, Ar-H), 8.64 (2H, s, CH=N)	69.8 (2C, O-CH_2-CH_2-O), 110.3, 128.2, 129.4, 133.0, 138.1, 153.6 (18C, Ar-C), 175.0 (2C, CH=N)
6.	[Rh(HBOACPD)]Cl	2.31-2.52 (2H, m, C–CH_2–C), 3.97 (4H, t, O–CH_2), 6.78-7.82 (12H, m, Ar-H), 8.64 (2H, s, CH=N)	30.4 (1C, C-CH_2-C), 72.1 (2C, O-CH_2), 127.2, 128.0, 129.5, 138.8, 151.7 (18C, Ar-C), 158.0 (2C, CH=N)
7.	[Rh(HBPOACTD)]Cl	4.15 (4H, s, O–CH_2), 6.02-7.04 (8H, m, Ar-H), 7.78 (2H, s, CH=N in pyridine), 8.88 (2H, s, CH=N)	67.3 (2C, O-CH_2), 119.7, 121.2, 133.0, 136.6, 142.0, 143.2 (16C, Ar-C), 151.5 (2C, Ar-CH=N), 176.4 (2C, CH=N)
8.	[Rh(HBPOACPD)]Cl	2.20-2.31 (2H, m, C–CH_2–C), 3.98 (4H, t, O–CH_2), 7.81 (2H, s, CH=N in pyridine), 6.42-7.41 (8H, m, Ar-H), 8.74 (2H, s, CH=N)	30.4 (1C, C-CH_2-C), 62.3 (2C, O-CH_2), 122.5, 123.4, 133.8, 142.2(16C, Ar-C), 155.7 (2C, Ar-CH=N), 178.6 (2C, CH=N)
9.	[Rh(HBNOACTD)]Cl	4.42 (4H, s, O–CH_2), 7.01-7.54 (16H, m, Ar-H), 8.54 (2H, s, CH=N)	68.2 (2C, O-CH_2), 109.5, 124.1, 125.7, 126.2, 127.0, 133.3, 134.0, 140.5, 150.1 (26C, Ar-C), 174.8 (2C, CH=N)
10.	[Rh(HBNOACPD)]Cl	2.30-2.41 (2H, m, C–CH_2–C), 3.99 (4H, t, O–CH_2), 7.21-7.92 (16H, m Ar-H), 8.58 (2H, s, CH=N)	30.5 (1C, C-CH_2-C), 61.8 (2C, O-CH_2), 125.7, 126.0, 126.0, 126.7, 133.6, 148.1 (26C, Ar-C), 156.3 (2C, CH=N)

Table-4

Percent yields of HLTZ formed with macrocyclic Rh(I) complexes

Comp. No.	Macrocyclic Rh(I) Complex	Yield(%)
1.	[Rh(HBACHD)]Cl	96.66
2.	[Rh(BACHD)]Cl	89.24
3.	[Rh(BPACHD)]Cl	91.00
4.	[Rh(BNACOD)]Cl	90.37
5.	[Rh(HBOACTD)]Cl	97.43
6.	[Rh(HBOACPD)]Cl	88.50
7.	[Rh(HBPOACTD)]Cl	89.31
8.	[Rh(HBPOACPD)]Cl	92.22
9.	[Rh(HBNOACTD)]Cl	94.06
10.	[Rh(HBNOACPD)]Cl	93.98

Graphical Abstract



Highlights

- Mononuclear Rhodium (I) complexes with macrocyclic ligands having N_4 and N_2O_2 donor sites were reported
- Investigated as effective catalysts in hydrolysis of Nitrile group containing pharmaceutical drug Letrozole
- Catalytic procedure involves mild reaction condition and easy to work-up
- This approach can be effectively used for the hydrolysis of Nitrile group containing APIs.