AnnalsofClinicalandMedical Case Reports

ResearchArticle ISSN2639-8109Volume9

Synthesis,AnticancerAndCatalyticActivitiesOfNovelMonoNuclearCu^{2+},Co^{2+},AndZn^{2+} Complexes InvolvingBenzotriazol, Ethane-1, 2- DiamineAnd 4,4'- Diaminocyclohexyl-methane Ligands

QUmar,HYinandMLuo*

DepartmentofChemistryandChemicalEngineering,HefeiUniversityofTechnology,Hefei,23000,P.R.China

***Correspondingauthor:**

MLuo,
Department of Chemistry and Chemical Engineering, Hefei University of Technology, Hefei, 23000, P .R. China, E-mail: luomei@pku.edu.cn

Received: 12 Sep 2022
Accepted: 16 Oct 2022
Published:11Oct2022
JShort Name:ACMCR

Citation:

M Luo, Synthesis, Anticancer And Catalytic Activities OfNovelMonoNuclearCu^{2+},Co^{2+},AndZn^{2+}Complexesinvolving Benzotriazol,Ethane- 1,2-DiamineAnd 4,4'-Diaminocyclohexylmethane Ligands. AnnClinMedCaseRep.2022;V10(1):1-10

Keywords:

Coordinationcomplexes;Crystalstructures;Cytotoxic effects;Catalyticactivities

1. Abstract

Inthisstudy,servaleco-friendlynovelcomplexesweresynthe- sized and characterized having the general formula of [CoC_{46}H- Cl N O]**(I)**,[CuCHCl N O]**(II)**,[CuC HCl N O]**(III)** and[ClZn,CHN,HO]**(IV)**usingbenzotriazol,Ethane-1,2-Diamine,and4,4'-Diaminocyclohexylmethaneasligandsthrough one-pot method using anhydrous methanol or ethanol with different metal salt (2:1 eqv) metal to ligand stoichiometry. The crystal structures of these complexes were determined by X-ray diffraction and further characterized by elemental analysis, ESI-MS, IR, NMR and UV–Vis. Single-crystal XRD studies shows that the structural diversities are mainly affected and controlledbythetypesofcentralmetalions.Single-crystalXRDstudiesalso showsthatthecomplexesarecoordinatedwiththeligandsthrough N-metalandO-metalbonds,whichrevealedtheirmononuclear geometries.Theanticanceractivityofthesecomplexesshowedcytotoxiceffectsagainsthumantumourcell LinesA549.Amongthem the complex **(II)** showed the best activity with IC_{50} values 19.92. The synthesized complexes were also applied for use as organic reaction catalysis and good results were obtained.

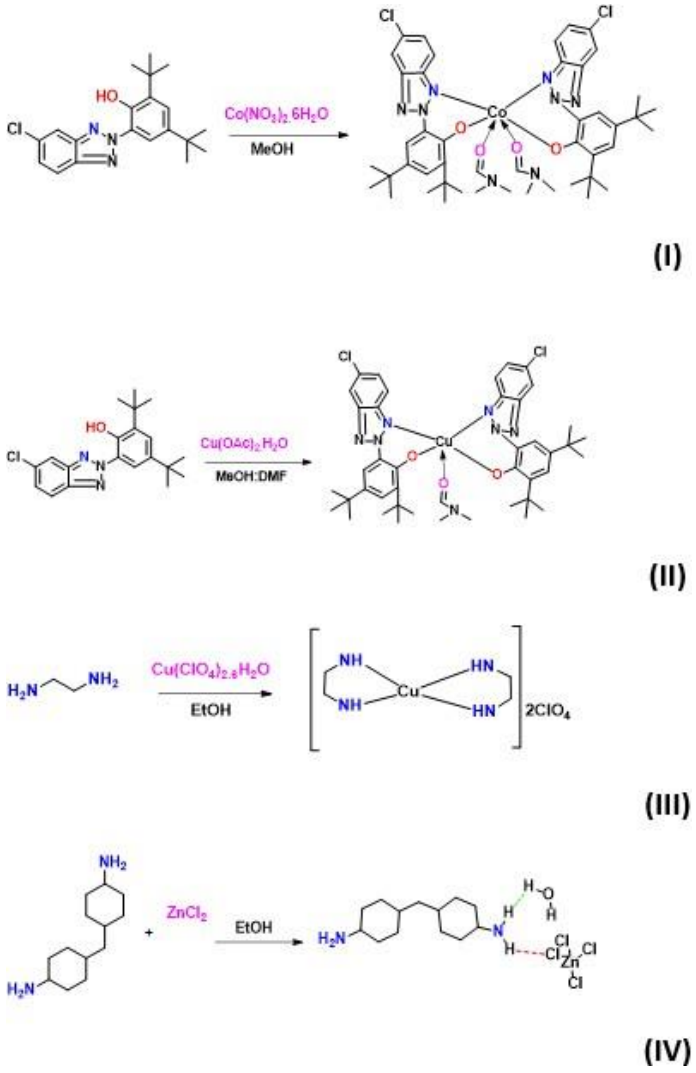
2. Introduction

Coordination complexes have many medicinal, industrial and other pharmacological applications, such as anti-cholesterol, anti-HIV,antibacterial,antifungal,analgesic,antitubercular,andanhistory. Soriano-García et al. (2007) synthesized 3β-(*p*-iodobenzoyloxy)-16α,17α-epoxypregn-4-En-6,20-dioneandusedintthe treatmentofandrogen-dependentdiseases[11].In2020,Hasijaet al.synthesized,characterizedandreportedonthescopeoffuran andnaptho-furanconsistingofmoleculesinelectronicdevices ticanceractivities.Thesereferences[1-10]providetheirsynthetic

and their pharmacological and biological activities [12]. Salama, Ahmed, and Hassan (2017) synthesized and characterized Co^{2+} complexes of amino acid Schiff bases from salicylaldehyde and three amino acids in basic medium and studied their biological activities[13].Iron-containingcomplexesareusefulinagriculture andotherbiologicalapplications.Arourietal.(2021)synthesized the$FeCl_4(C_5N_2H_6)(C_5N_2H_5)$complexandcharacterizeditbyX-ray, IR,UVmethodsand appliedit forvarioususes [14].Iyelabola,Akinkunmi,andAkinade(2020)synthesizedandcharacterizedmixed ligand complexes of Co^{+2}, Ni^{+2} and Cu^{+2} with 1,10-phenantroline and (±)-2-amino-3-(4-hydroxyphenyl)propionic acid as ligands and reported their biological activities [15]. Moriguchi, Kawata, and Jalli (2021) synthesized a new hydrogen-bonded cobalt(II) complex and used the title complex for therapeutic applications [16]. Nenwa et al. (2014) isolated an aqueous solution at room temperatureandobtainedanoveltrinuclearheterothalliccomplex of Cr^{+2} [17]. Fomuta et al. 2017 synthesized and characterized a new Ag^{+2} complex [18]. Similarly, Moriguchi, Kawata, and Jalli 2021synthesizedfourneweuropiumcomplexesandreportedphotoelectronic property applications in light-emitting devices [16]. Zincisessentialtoallformsoflife[19];althoughCu-Ncomplexes

arealsowellknownforcatalysingorganicreactions,ourresearch team successfully synthesized and characterized Cu^{+2}, Zn^{+2} and Co^{+2} complexes. Additionally, our synthesizing method is novel due to its fruitfulness, low toxicity compared to other synthetic methods, lack of fume production, low cost and environmental friendliness.Consideringthesesignificantfactors,ourproductwill be beneficial for anticancer activities as well as other medicinal applications and industrial applications. Although our product is air-stable, it could potentially be used for medicinal uses or other human development applications.

Inthispaper,wefirstdescribetheseveralnovelcomplexes, $[CoC_{46}H_{60}Cl_2N_8O_4]$**(I)**,$[CuC_{43}H_{53}Cl_2N_7O_3]$**(II)**,$[CuC_4H_{16}Cl_2N_4O_8]$ **(III)** and $[Cl_4Zn, C_{13}H_{28}N_2, H_2O]$ **(IV)**, prepared with the one-pot methodshowninScheme1andpresenttheircrystalstructures obtained by single-crystal X-ray diffraction and characterization byvariousspectroscopictechniques.Additionally,ourcomplexes have shown good cytotoxicity to lung cancer cells but negligible toxicity towards normal cells. The synthesized complexes were also applied for the catalysis of some important organic reactions and obtained good results.



Scheme1: Thesyntheticroutetocomplexes**(I)-(IV)**

3. Experimental

MaterialsandMethods

2,4-Di-tert-butyl-6-(5-chlorobenzotriazol-2-yl)phenol,ethane-1,2-diamineCo(NO).6HO,Cu(ClO).6HOandZnClwere purchasedfromAcros.[1]HNMRspectrawereobtainedusinga BrukerAM-300 spectrometer. ^1H and ^{13}C NMR spectra were re-cordedusingBrukerAM-500andBrukerAM-600spectrometers. Chemicalshiftsarereportedinppm(δ)withthesolventrelative to tetramethylsilane (TMS), which was employed as the internal standard (residual CHCl3, δH 7.26 ppm; $CDCl_3$, *c* 77 ppm). The followingabbreviationsareusedtodesignatemultiplicities:s= singlet,d=doublet,t=triplet,m=multiplet.Infraredspectrawere recordedonaMattsonGalaxySeriesFTIR3000spectrometer;the peaksarereportedincm^{-1}.Elementalanalyseswereperformed

onanElementalAnalyserAE-3000.Thecrystalstructureswere determined by a Gemini SUltra diffractometer.

CytotoxicityAssay

The human tumour cell line againstA549 (lung cancer) was used inthecytotoxicassay.Thesecelllineswereobtainedfrom ATCC (Manassas, VA, USA). Cells were cultured in RMPI-1640 or DMEM (Biological Industries, Kibbutz Beit Haemek, and Israel) supplemented with 10% foetal bovine serum (Biological Industries) at 37 °C in a humidified atmosphere with 5% CO2.The cytotoxicityassaywasevaluatedbyusingtheMTS(Promega,Mad- ison, WI, USA) assay. The cytotoxicity assay was evaluated by using the 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphe- nyl)-2-(4-sulfophenyl)-2H-tetrazolium,innersalt(MTS)(Promega,Madison,WI,USA)assay.Briefly,cellswereseededintoeach wellofa96-wellcellcultureplate.After12hofincubationat37 °C,atestcompound(100μM)wasadded.Afterincubationfor48 h, the cells were subjected to the MTS assay. Compounds with a growth inhibition rate of 50% were further evaluated at concentrations of 0.064, 0.32, 1.6, 8, 40 and 100 μM in triplicate with cisplatin and paclitaxel (Sigma, St. Louis, MO, USA) as positive controls.

General Experimental Details

All reactions were performed in flame-dried glassware under normal atmospheric pressure. Reagents were obtained from commercial sources. Nuclear magnetic resonance (NMR) spectrawere acquired on a 500 MHz Bruker Advance III spectrometer. Infrared spectra were recorded on a Mattson Galaxy Series FTIR 3000spectrometer;peaksarereportedincm^{-1}.Elementalanalysis wasperformedonaVARIOELIIIelementalanalyser.Thecrystal structuresweredeterminedbyusingaGeminiSUltradiffractom- eter. ^{1}H and ^{13}C NMR chemical shifts are reported in ppm and referencedtoCDCl3,7.26ppm;forDMSO-d_6,2.50ppm.Thefollowing abbreviations are used: s = singlet, d = doublet, t = triplet, q=quartet,m=multiplet.Meltingpointsweremeasuredbyusing aYanacoMicroMeltingPointSystemMP-J3andSANSYOMelt- ing Point Apparatus SMP-500 and are uncorrected.

GeneralProceduretheSynthesisofComplexes(I)-(IV)

Ligand and metal salts (molar ratio of 2:1) were heated and refluxedfor48h,thenfiltrationwasconductedimmediatelyafterthe reaction, and the filtrate was retained for slow volatilization. The metal-ligand complexes were successfully synthesized by reacting2,4-di-tert-butyl-6-(5-chlorobenzotriazol-2-yl)phenol,ethane-1,2-diamine and 4,4'-diaminocyclohexylmethane as ligands with $Cu(ClO4)_2.6H_2O$, $Co(NO_3)_2.6H_2O$ and $ZnCl_2$ respectively, andthe cultivated crystals were analysed and characterized by X-ray diffraction, IR, ^{1}HNMR, ^{12}CNMR, UV and E.A. The first key is to find the right ligands, and then the ligands and the corresponding metal salts were reacted. At the end of the reaction filtration wascarriedoutandasuitablesolventforcrystalprecipitationwas found.Theselectionbetweentheavailablesolventssuchasanhydrousmethanol,ethanol, chloroform,etc. isthe mostcritical step.

3.4.1.SynthesisofComplex(I)

$Co(NO_3)_2.6H_2O$ (0.290 g, 0.001 mmol) dissolved in methanol (10 ml) was added dropwise to a hot solution of the ligand (0.7200 g, 0.0020mmol)inmethanol(30ml).Themixturewasrefluxedwith heatfor24hr.Afterhotfiltration,thefiltratewasretainedfornaturalevaporationatroomtemperature.Aftertwodays,theproduct was dissolved in methanol, and a small amount of DMF and the filtrate held for natural evaporation. After three days, bright red crystals appeared in the solution. These were suitable for X-ray single-crystal analysis resulting in a 85% yield, m.p. 118-120 °C, IRpeaksat(KBr;ν,cm^{-1})3397,2955,1651,1559,1478,1437, 1387,1360,1248,1202,1003,1048,937,845,834,805,752, 708,670,638,and587,^{1}HNMRresultsof(600MHz,cdcl3)δ 8.02–7.99(s,1H),3.54–3.51(s,2H),3.49–3.46(s,3H),3.44–3.41 (s,4H),3.36–3.33(s,2H),2.99–2.96(s,2H),2.94–2.91(s,4H), 2.90–2.87(s,5H),2.85–2.82(s,5H),2.82–2.79(s,5H),2.75–2.72 (s, 3H), 2.63–2.60 (s, 1H), and 1.31–1.28 (s, 1H).

SynthesisofComplex(II)

Complex**(II)**wassynthesizedfollowingthegeneralprocedureusingmetalsaltCu(OAc).H_2O(0.180g,0.001mmol)dissolvedin methanol (0.7200 g, 0.0020 mmol), which was added dropwise intoahotsolutionofliganddissolvedinmethanolandDMF(3:1) mL.Thesolutionwasrefluxwithheatfortwodays,andthefiltrate was retained for slow evaporation. After three days, bright blue crystals appeared in the solution. These were suitable for X-ray single-crystalanalysisresultingin80%yield,m.p.278-280°Cand IRpeaksat(KBr;ν,cm–1)2950,2865,1663,1568,1480,1443, 1388, 1238, 1050, 916, 801, 738, 715,687, 671, 580, and 544.

SynthesisofComplex (III)

Similarly, complex **(III)** was also synthesized following the general procedure using ethanediamine (0.710 g, 16.10 mmol) as a ligandand$Cu(ClO_4)_2.6H_2O$(2.964g,8.00mmol)asthemetalsalt (2:1). The reaction mixture was refluxed with heat for two days, filtered while hot and retained for natural evaporation. After one day, blue crystals that appeared at the bottom of the beaker that were suitable for X-ray single-crystal analysis resulting in 80.2% yield, m.p. 280–285 °C. IR peaks at (KBr; ν, cm–1): 3337, 3281, 2988,1590,1467,1321,1280,1108,1066,1021,919,884,701, and 620.The calculated compositions in % for [$C_4H_{16}Cl_2CuN_4O_8$] are: C, 12.56; H, 4.18; and N, 14.63 while the analysed compositions in % were: C, 12.98; H, 4.332; and N, 15.05.

SynthesisofComplex(IV)

For complex **(IV)**, using the general procedure, $ZnCl_2$ (1.14 g, 0.0052 mmol) metal salt was added dropwise to a hot solution of ligand (1.10 g, 0.00522 mmol) in methanol (30 ml).After hot filtration, the filtrate was retained for natural evaporation at room temperature.Aftertwodays,whitecrystalsappearedinthesolu-

tion. These were suitable for X-ray single-crystal analysis resulting in 90% yield, m.p. 320 °C. IR peaks at (KBr; ν, cm–1): 3366, 3124,2925,2860,1597,1574,1387,1503,1485,1452,1386, 1248,1200,1054,1045,1122,1021,999,971,932,897,669, 657, 603, and 570.The ^{1}H NMR results were (600 MHz, cdcl$_3$) δ 12.56–12.52(s,23H),9.14–9.09(m,3H),7.95–7.92(s,1H),and 6.45–6.33 (m, 1H).

3.4.5. X-ray Structure

X-raydiffractiondataforcomplexes**(I)-(IV)**werecollectedat roomtemperatureusinggraphite-monochromaticMoKαradiation (λ=0.71073Å)onanOxfordDiffractionGeminiSdiffractometer. Structure solutions and refinements for complexes 1-2 were carried out with the programs SHELXT [20] and SHELXL-2018/3 [21], respectively. MERCURY[22] was employed for molecular graphics and OLEX2 [23]. Nonhydrogen atoms in **(I)-(IV)** were refined anisotropically, while hydrogen atoms were treated by constrained isotropic refinement. Crystal data and refinement parameters for complexes **(I)-(IV)** are summarized in **Table 1**. The selectedbondlengthsandbondanglesareshowninTableS1,and hydrogen bonds of complexes I-IV are listed in **Table 2**.

Table1: Cellparametersandmeasurementsofthecrystallographicdataofcomplexes(**I)-(IV)**

Complex	I	II	III	IV
Empirical formula	$C_{46}H_{60}Cl_2CoN_8O_4$	$C_{43}H_{53}Cl_2CuN_7O_3$	$C_4H_{16}Cl_2CuN_4O_8$	$Cl_4Zn,C_{13}H_{28}N_2,H_2O$
Formula mass	918.85	850.36	382.65	437.56
Temp.(K)	293(2)	98(2)	296(2)	293(2)
Wavelength(Å)	1.34139	1.34139	0.71073	1.54184
Crystal system	Monoclinic	Triclinicc	Triclinic	monoclinic
Space group	P1 21/c 1	P-1	P-1	P1 21/c 1
a (Å)	14.6703(6)	10.9421(16)	5.7113(18)	7.57262(12)
b Å()	18.5175(8)	13.777(2)	7.804(2)	10.62573(18)
c (Å)	18.5323(8)	14.999(2)	7.963(3)	25.0728(5)
β (°)	79.154(5)	99.918(5)°	79.154(5)	96.2309(16)
Volume(Å$^{3)}$	4846.1(4)	2129.2(6)	332.31(18)	2005.55(6)
Z	4	2	1	4
D_{calcd} (g/cm^3)	1.259	1.326	1.912	0.335
μ(mm^{-1})	2.868	3.778	2.086	1.18
F (000)	1940	894	195	912
θραανγε(°)	2.722-57.525.	2.707-60.698.	2.62-26.467	7.094-146.048
Totalreflections	59170	47412	2393	7805
Unique reflections	9743	9750	1345	3893
R_1,wR_2[I> 2s(I)]	0.0429, 0.1217	0.0488, 0.1346	0.0272, 0.0831	0.0333, 0.0884
R_1,wR_2[alldata]	0.0478, 0.1261	0.0585, 0.1397	0.0283,0.0840	0.0347, 0.0897
Residuals(e.Å^3)	0.504, -0.830	1.296, -0.554	0.295, -0.402	

Table2. Hydrogenbondlengths(Å)andbondangles(°)forcomplexes**(I)-(IV)**

D–H···A(complexI)	**d(D–H)**	**d(H···A)**	**d(D···A)**	∠**D**HA
C(9)-H(9C)...O(1)	0.96	2.42	3.033(3)	121.8
C(10)-H(10A)...O(1)	0.96	2.37	2.998(3)	122.7
C(17)-H(17)...O(2)	0.93	2.46	3.102(2)	126.1
C(32)-H(32C)...O(2)	0.96	2.33	2.989(3)	125.2
C(33)-H(33A)...O(2)	0.96	2.27	2.928(3)	125.2
C(37)-H(37)...O(1)	0.93	2.38	3.117(2)	135.6
D–H···A(complex III)	**d(D–H)**	**d(H···A)**	**d(D···A)**	∠**D**HA
N1 H1C O1	0.89	2.34	3.144(4)	150.9
N2 H2C O2	0.89	2.36	3.179(3)	153.3
D–H···A(complexIV)	**d(D–H)**	**d(H···A)**	**d(D···A)**	∠**D**HA
N1H1ACl4	0.89	2.47	3.336(2)	165.7
N1 H1B O1	0.89	1.93	2.798(3)	163.9
N1 H1C Cl2	0.89	2.28	3.167(2)	171.2
N2H2ACl1	0.89	2.59	3.334(2)	141.6
N2 H2B Cl3	0.89	2.44	3.324(2)	173.3
O1H1DCl1	0.85	2.68	3.297(3)	130

4. ResultsandDiscussion

SynthesisMethod

Complexes **(I)-(IV)** were synthesized using the one-pot synthetic method. The synthetic route can be seen in **Scheme 1**.

(1): The syntheses of complexes **(I)-(IV)** were carried out under anhydrousmethanol/ethanolusing4-di-tert-butyl-6-(5-chlorobenzotriazol-2-yl) phenol, ethane-1,2-diamine, and 2,4'-diaminocyclohexylmethane as ligands with different metal salts, i.e., Co(NO$_3$)$_2$.6H$_2$OandCu(OAc)$_2$.H$_2$O,Cu(ClO$_4$)$_2$.6H$_2$OandZnCl$_2$, respectively(2:1eq).Themixturesweresrefluxedfor48h.After hotfiltration,crystalswereobtainedwhenthesolutionwasevaporatedslowlyintheair.Thecrystalswereconfirmedandcharacterizedbydifferentspectroscopictechniques,suchasUV,IR,andE.

A,ES-MSI aswell asXRD.

CrystalStructureAnalysis

(1): Thecrystalsizeofcomplex**(I)**is0.15x0.1x0.1mm^3.They havereddishcolourand,belongtothemonocliniccrystalsystem. AccordingtotheX-raydataoffourroundsinglecrystals,themolecularweightofthiscrystalis918.85,andthespacegroupisP1 21/c 1. The cell parameters are a = 14.6703(6) Å, b = 18.5175(8) Å,c=18.5323(8)Åandα=90°,β=105.7200(10)°,γ=90°,V= 4846.1(4)Å^3,Z=4,D=1.259Mg/m^3,andF(000)=1940.The bondlengthsandanglesforcomplexIIare[(Co1)-(N1) 2.1460(13) Å],[(Co1)-(N4)2.1816(14)Å],[(Co1)-(O1)1.9730(12)Å], [(Co1)-(O2) 1.9642(12) Å], [(Co1)-(O3) 2.1888(14) Å], and [(Co1)-(O4) 2.1792(13) Å].

(2): Complex**(II)**wascrystallizedundercertainexperimentalconditions, i.e., *P-1* shown in **Table 1**. For mono-nuclearmetalcomplex(I),thereisonemetalionandtwoligandspresentaswellasa DMF solvent molecule in the crystal structure.

The bluish crystals of complex (II) are composed of the central Cu ion and they adopt square-planar coordination by two ligands andoneDMFsolventmolecule.Thefivebondlengthsare$d_{Cu1\text{-}O1}$ =1.9055(15)Å,$d_{Cu1\text{-}O2}$=1.9115(15)Å,$d_{Cu1\text{-}N1}$=2.0446(18)Å, $d_{Cu1\text{-}N4}$ = 2.0686(18) Å and $d_{Cu1\text{-}O3}$= 2.1954(19). The angles around the Cu centre are [O(1)-Cu(1)-O(2) 178.96(6)], [O(1)-Cu(1)-N(1) 88.16(7)], [O(2)-Cu(1)-N(1) 91.05(7)], [O(1)-Cu(1)-N(4) 92.94(7)], [O(2)-Cu(1)-N(4) 88.10(7)], [N(1)-Cu(1)-N(4) 130.45(7)], [O(1)-Cu(1)-O(3) 90.64(7)], [O(2)-Cu(1)-O(3) 89.19(7)],[N(1)-Cu(1)-O(3)122.01(8)]and[N(4)-Cu(1)-O(3) 107.51(8)].

Thecrystalsizeofthecomplexis0.130x0.100x0.080mm^3,belonging to the monoclinic crystal system.According to the X-ray data of four round single crystals, the molecular weight of this crystal is 850.36, and the space group is P-1. The cell parame-ters are a = 104.587(6)° Å, b = 13.777(2) Å, c = 14.999(2) Å, α= 104.587(6)°,β=99.918(5)°,andγ=96.032(5)°.V=2129.2(6)Å3, D=1.326Mg/m3andZ=2.Thebondlengthsandanglesforcomplex(I)are:[(Cu1)-(O1)1.9055(15)Å],[(Cu1)-(O2)1.9115(15) Å],[(Cu1)-(O3)2.1954(19)Å],[(Cu1)-(N1)2.0446(18)Å]and [(Cu)-(N4)]2.0686(18)Å]and[O(1)-Cu(1)-O(2)]178.96(6), [O(1)-Cu(1)-N(1)]88.16(7),[O(2)-Cu(1)-N(1)]91.05(7),[O(1)-Cu(1)-N(4)] 92.94(7), [O(2)-Cu(1)-N(4)] 88.10(7), [N(1)-Cu(1)-N(4)]130.45(7),[O(1)-Cu(1)-O(3)]90.64(7),[O(2)-Cu(1)-O(3)]89.19(7),[N(1)-Cu(1)-O(3)]122.01(8)and[N(4)-Cu(1)-O(3)]107.51(8).Selectedbondlengths(Å)andangles(°) areshowninTableS2.Hydrogenbondsforthecomplexes[Åand °]areshownin**(Table2)**.

(3): Thecrystalsofcomplex**(III)**haveabluecolour.Accordingto the X-ray data of four round single crystals, the molecular weight ofthiscrystalis382.65,thesizeis0.12x0.1x0.1mm^3,thecrystalsystemistriclinic,andthespacegroupisP-1.Thecellparam- eters are: a = 5.7113(18) Å, b= 7.804(2) Å c = 7.963(3) Å and α= 75.313(4)°.β=79.154(5)°.andγ=77.952(4). V=332.31(18)Å^3, Z=1, D$_{calc}$=1.912 Mg/m^3, andF (000)=195.Allbond lengths and anglesforcomplex**(III)**are[(Cu1)-(N1)2.018(2)Å],[(Cu1)-(N1) 2.018(2) Å], [(Cu1)-(N2) 2.015(2) Å], and [(Cu1)-(N2) 2.015(2) Å].

(4): The crystal size of complex **(IV)** is 0.22 x 0.1 x 0.1 mm3, their colour is white, and they belong to the monoclinic crystal system.AccordingtotheX-raydataoffourroundsinglecrystals, themolecularweightofthiscrystalis437.56,andthespacegroup is P 1 21/c 1. The cell parameters are: a = 7.57262(12) Å, b = 10.62573(18)Å,c=25.0728(5)Å,α=90°,β=96.2309(16)°,γ= 90°,V=2005.55(6)Å3,Z=4,Dcalc=0.3351.259Mg/m3,andF (000) = 912. The bond lengths and angles for complex (IV) are [(Zn1)-(Cl2)2.2739(6)Å],[(Zn1)-(Cl4)2.2648(6)Å],[(Zn1)-(Cl3)2.2563(6)Å],[(Zn1)-(Cl1)2.2889(6)Å],[(Cl2)-(Zn1)-(Cl1) 110.38(3)Å],[(Cl4)-(Zn1)-(Cl2)106.87(2)Å],[(Cl4)-(Zn1)–(Cl1) 111.52(3)Å],[(Cl3)-(Zn1)-(Cl2)110.25(2)Å],[(Cl3)-(Zn1)-(Cl4) 110.69(3)Å],and[(Cl3)-(Zn1)-Cl1)107.17(2)Å].

IRspectroscopyofcomplexes(I)-(IV)

The IR analyses show several peaks that can be found in all IR spectra (shown in **Fig. 1**).These include all C-H stretching vibrations between 3000 and 2800 cm^{-1}, C=C stretching vibrations at approximately11600cm^{-1},andC-Ovibrationsat1280/1090cm^{-1} [24]. The 3100 to 3000 cm^{-1} peak of the aromatic C-H stretching vibration combines stronger absorption at 1600 cm^{-1},' which can be referred to as aromatic C-C double bonds, and aliphatic C-H stretching vibrations in the range between 3000 and 2800 cm^{-1}. The determination of aromatic structures has been supported by the presence of the spectral region between 1500-1630 cm^{-1}; the absorbancebandsat1300cm^{-1}to1400cm^{-1}canbeassignedtothe bending vibrations of the CH_3 group, and broad absorption in the regionbetween1050and1150cm−1isdominatedbyC-Ostretch- ing vibrations [25]. Stretching vibration peaks appeared at 600- 650 cm^{-1} and 500-600 cm^{-1} for metal-nitrogen and metal-oxygen bonds,respectively,andapeakappearedat650-700cm^{-1}forC-Cl.

UV-visiblespectroscopyforcomplexesI-IV

The absorption spectra of the complexes and raw materials were recorded in methanol. The broad peaks at 230 nm, 250 nm, 311-344nmand359nmareduetoσ-σ*andn-σ*,π-π*andn-π*transitions[21,22,23,24].TheUVspectraofthecomplexesarepresented in **Figure 2**.

Thecrystalstructuresofcomplexes**(I-IV)**areshowninFigure1.

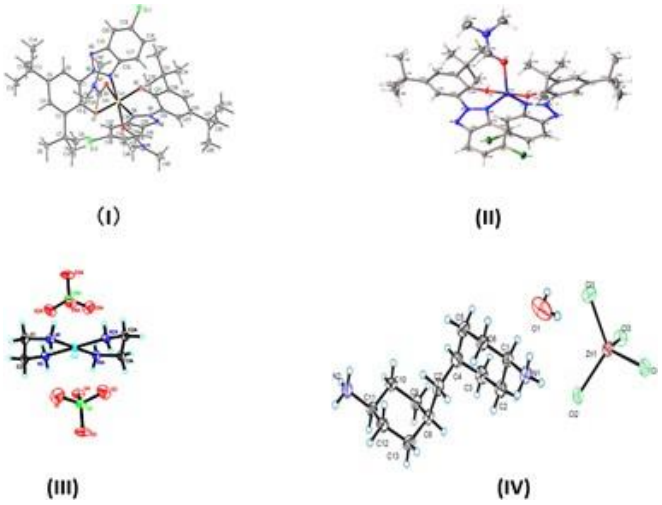
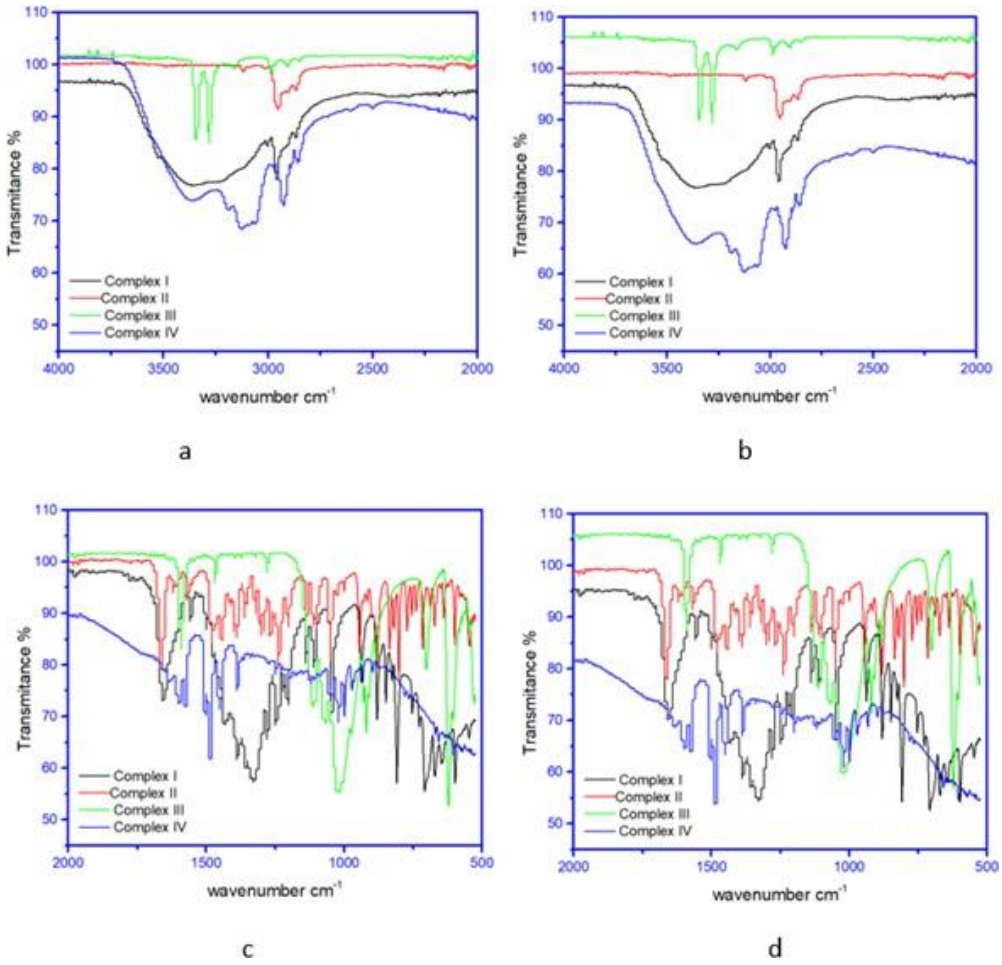


Figure1: TheORTEPmolecularstructuresofcomplexes**(I)**to**(IV)**shownas30%thermalellipsoid probabilities



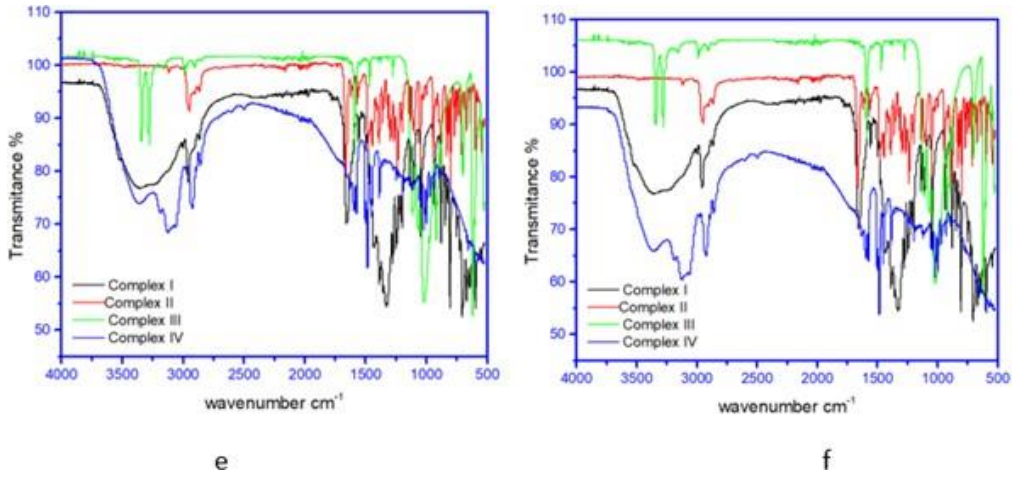


Figure1.IRspectraofcomplexes**(I)-(IV)**

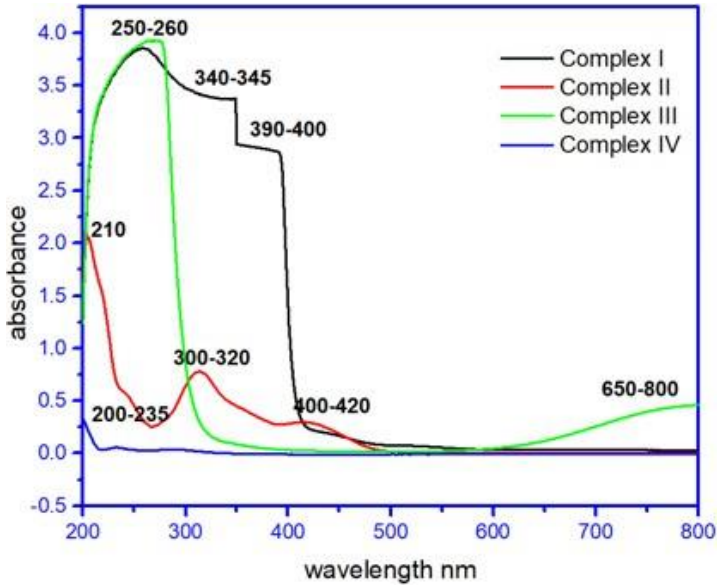


Figure2.UV–visiblespectraofcomplexes**(I)-(IV)**

CytotoxicityAssay

The human tumour cell line SMMC-7721(Liver cancer)wasusedinthecytotoxicassays.Thesecelllineswereobtainedfrom ATCC(Manassas,VA,USA).CellswereculturedinRMPI-1640 or DMEM (Biological Industries, Kibbutz Beit Haemek, Israel) supplemented with 10% foetal bovine serum, (Biological Industries) at 37 °C in a humidifiedatmosphere with 5% CO_2.The cytotoxicityassayswereevaluatedbytheMTS(Promega,Madison, WI, USA) assay method. The cytotoxicity assays were evaluated bythe3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt (MTS) (Promega, Madison,WI,USA)assaymethod[12].Briefly,cellswereseeded intothewellsofa96-wellcellcultureplate.After12hofincuba- tion at 37 °C, the 100 µM of the appropriate test compound was added to each well.After incubation for 48 h, the cells were subjectedtotheMTSassay.Compoundswithagrowthinhibitionrate of50%,orhigher,werefurtherevaluatedatamountsoff0.16,0.8, 4.0,20and100µMintriplicatewithcisplatinandpaclitaxel (Sigma,St.Louis,MO,USA)aspositivecontrols.TheIC50valuesof eachcompoundwerecalculatedwithReedandMuench'smethod [13]. The results are presented in Table 3.

By comparing the activity of complexes **(I)–(IV)**, complex (II) showedthebestcytotoxiceffectsagainstthelungcancercellLine A549,withanIC50valueof19.92µM.Cisplatinisalsoshownfor the sake of comparison, as shown Table 3.

T**able3.**Cytotoxicityofcomplexes**(I-IV)**againsthumantumourcell LinesA549,with cisplatinusedasanexperimental control.

	IC_{50}(mM)[a]
Complex	A549
I	>100
II	19.92
III	31.57±1.59
IV	N/A
cisplatin	24.37±0.13

[a]Cytotoxicity as IC_{50}values for each cell line, the concentration of complex that caused 50% reduction relative to untreated cells determined by the SRB assay. Cisplatin was used as the control.

4.6 Catalytic application

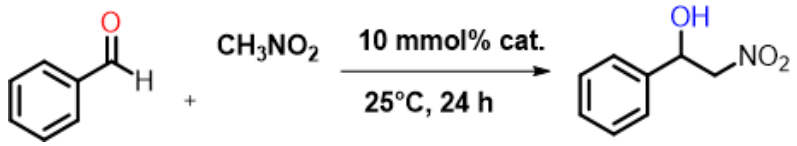
CatalysisofHenryreaction,shownin**scheme2**,wasachievedusing10mmol%complexes**(I)**to**(IV)**withoutanyadditives.Using complexes **(I)** to **(IV)** (0.10 mmol), benzaldehyde (0.10 mL), and nitromethane(0.50mL)weresuccessivelyaddedtogetherin2mL anhydrous methanol at room temperature for 24 h [30-38].

The catalytic activities of the novel complexes in the Henry reactionarepresentedin**Table4**.Thistableshowsthattheconversion efficiencyofthesethreeofthecomplexeswasmorethan85%,and thattheyaregoodcatalystsfortheHenryreaction.Themechanism that can be proposed is that the complexes could greatly activate theC=Obond,andthenthereisanucleophilicadditionreactionof CH NO_2^-onto the carbonyl group:

Table4. Henryreactionofbenzaldehydecatalysedby**(I)-(IV)***

Complex	Yield, %
1	>**99**
2	>**99**
3	**57**
4	>**99**

*Conv.% was determined by ^{1}HNMR; reactions were carried out with 0.1 mL PhCHO and 0.5 mL CH_3NO_2 in 2 ml anhydrous methanol using 0.10 mmol of catalyst at room temperature for 24 h.



Scheme2. Henry reaction

5. Conclusions

In addition to describing their synthesis, and characterization this paper also presents the anticancer and catalytic activities of mononuclearCu^{2+},Co^{2+}andZn^{2+}complexesinvolving2,4-di-tert-bu- tyl-6-(5-chlorobenzotriazol-2-yl) phenol and ethane-1,2-diamine ligands and 2,4'-diaminocyclohexylmethane ligands. The synthesizedcomplexeswereconfirmedandcharacterizedusingtechniques such as FTIR, NMR, UV–visible and E. A, as well as by single-crystal X-ray diffraction. Our synthesized complexes can be used in medicinal as well catalytic applications. Additionally, they showed cytotoxic activity against A549 cells. Among them, complex **(II)** exhibited the best bioactivity against A549 cells compared to other complexes, with an IC_{50} value of 19.92 μM. Theresultsclearlyshowthattheanticanceractivityofthesecomplexes depends on the type of metal ion and cell line, as well as the geometries of the corresponding compounds.These useful results provide motivation for the design and development of new therapeuticdrug-likemolecules.Thesynthesizedcomplexeswere tested in some catalytic reactions obtaining excellent results.

6. Acknowledgements

This work was supported by the Hefei University of Technology andStateKeyLaboratoryofPhotochemistryandPlantResources in West China.

Reference

1. VKA Kalalbandi and J Seetharamappa, "Synthesis, Characterization, Crystal Studies of (E)-3-(3-(4-Fluorophenyl)-1-isopropyl-1H-indol-2-yl) Acrylaldehyde," Cryst. Struct. Theory Appl, 2013; 02(04): 148-154.
2. SM Kumar, BC Manjunath, GS Lingaraju, MMM Abdoh, MP Sadashiva, et.al "A Hirshfeld Surface Analysis and Crystal Structure of," Cryst. Struct. Theory Appl. 2013; 2013: 124-131.
3. A Okamoto, A Nagasawa, Siqingaowa, and N Yonezawa, "Crystal Structure Study on Non-Coplanarly Organized Accumulating AromaticRingsMolecules:SpatialOrganizationofC,C,N-TriarylSubstitutedImines,"Cryst.Struct.TheoryAppl,2013;02(04):139-147.
4. DDBibelayi,KilungaPI,Lundemba.A.S,BokoloM.K,MpianaP.T, etal.,"InteractionofIron(III)-5,10,15,20-Tetrakis(4-Sulfonatophenyl) Porphyrin with Chloroquine, Quinine and Quinidine," Cryst. Struct. Theory Appl, 2017; 6(3): 25–38.
5. KellyA, "非対称側鎖を有するオリゴチオフェンの結晶構造 Crystal Structure of,"Acta Chem. Scand., 2019; 19(7) 2019.
6. LVela,MContel,LPalomera,GAzaceta,andIMarzo,"Iminophosphorane-organogold(III)complexesinducecelldeaththroughmitochondrial ROS production," J. Inorg. Biochem, 2011;105(10)1306-13.
7. LGlans, EhnbomA, de Kock C, MartínezA, Estrada J, et.al., "Ruthenium(ii)arenecomplexeswithchelatingchloroquineanalogueligands:Synthesis,characterizationandinvitroantimalarialactivity," Dalton Trans., 2012; 41(9) 2764-73.
8. CSAllardyceandPJDyson."Metal-baseddrugsthatbreakthe rules,"DaltonTrans,2016;45(8):3201-09.

9. NFarrell.“MetalComplexesasDrugsandChemotherapeutic Agents,” Comp Coord. Chem. II, 2004; 9: 809-40.
10. VSShivankar,RBVaidya,SRDharwadkarandNVThakkar.“Synthesis, Characterization, and Biological Activity of Mixed Ligand Co(II) Complexes of 8-Hydroxyquinoline and SomeAminoAcids,” Synth. React. Inorg. Met. Chem. 2003; 33(9) 1597-1622.
11. M Soriano-García, E Ramírez, E Bratoeff and M Cabeza, “Crystal structure and synthesis of 16β-methyl-17α-propionyloxypregna-4,6-diene-3,20-dione,” Anal. Sci. X-ray Struct. Anal. Online. 2007; 23(6) 39-47.
12. A Hasija, V Prakash, MS Prakash, Vasu, G Krishnasamy and D Chopra, “Crystal and Molecular Structure Analysis in Knoevenagel Condensation Product of Substituted Napthofuran-2-Carbaldehydes,” Cryst. Struct. Theory Appl. 2020; 09(03) 49-62.
13. MMSalama,SGAhmed,andSSHassan,“Synthesis,Characterizations, Biological, and Molecular Docking Studies of SomeAmino Acid Schiff Bases with Their Cobalt(II) Complexes,” Adv. Biol. Chem. 2017;07(05): 182-94.
14. Arouri A, R Dridi, R Kefi and MF Zid, “Structural Study, Vibrational, Optical,Thermal Properties and Hirshfeld SurfaceAnalysis of a New Iron (III) Complex: FeCl4(C5N2H6) (C5N2H5)” Cryst. Struct. Theory Appl. 2021; 10(01): 14-26.
15. TOAiyelabola, EOAkinkunmi and RAkinade. “Syntheses of Coordination Compounds of (±)-2-Amino-3-(4-Hydroxyphenyl)PropionicAcid,MixedLigandComplexesandTheirBiological Activities,” Adv. Biol. Chem. 2020; 10(02): 25-42. doi: 10.4236/abc.2020.102003.
16. T Moriguchi, H Kawata and V Jalli, “Design, Synthesis, Crystal Structure and Photoluminescence Properties of Four New Europium (III) Complexes with Fluorinated β-Diketone Ligand,” Cryst. Struct. Theory Appl. 2021; 10(01): 1-13.
17. J Nenwa, I Kaboré, YAMbiangué, PL Djonwouo and PT Ndifon, “A Chiral Three Dimensional Potassium(I)/Strontium(II)/Chromium(III)Oxalato-BridgedCoordinationPolymerSynthesis,CharacterizationandThermalAnalysis,”Cryst.Struct.TheoryAppl.2014; 03(04) 67-75.
18. TR Fomuta, G Djimassingar, J Ngoune, NO Ngnabeuye, JJ Anguile, and J Nenwa, “Synthesis, Structural Characterization and DFT Studies of Silver(I) Complex Salt of Bis(4,5-dihydro-1-benzo[g]indazole),” Cryst. Struct. TheoryAppl. 2017; 06(02): 11-24.
19. VAOnline,“3-Amino-1-propanolandN-methylaminoethanol:coordinationtozinc(ii)vs.decompositiontoammonia†”.2020;8-13, doi: 10.1039/c9nj05005a.
20. AAAmer,“SynthesisofSomeNewPolyfunctionalizedPyridines,” J. Heterocycl. Chem. 2018; 55(1) 297-301.
21. DyachenkoIV,VDDyachenko,PVDorovatovsky,VNKhrustalev andVGNenajdenko,“One-PotSynthesisofThieno[2,3-b]pyridine andPyrido[3′,2′:4,5]thieno[3,2-d]pyrimidineDerivatives,”Russ.J. Org. Chem. 2020; 56(6): 974-82.
22. MPurushothaman,KThanigaimani,SArshad,S.Silambarasan,IA Razak, and KMS Ali, “2,6-Diamino-4-(4-chlorophenyl)-1-methyl-1,4-dihydropyridine-3,5-dicarbonitrile,”ActaCrystallogr. Sect. E Struct. Reports Online. 2014; 70. doi: 10.1107/S1600536814014354.
23. EL Little, WJ Middleton, DD Coffman, VA Engelhardt, and GN Sausen, “Cyanocarbon Chemistry. X. Pyridines from Tetracyanopropenes,” J. Am. Chem. Soc. 1958; 80(11): 2832-2838. doi: 10.1021/ja01544a060.
24. Ramaswamy K and R Venkatachalapathy, “Infrared Spectroscopic Study of Neyveli Lignite Samples from Mine Cut-I and II,” Spectrosc. 1991; 24(6) 759-78.
25. VCepus,MBorthandMSeitz,“IRSpectroscopicCharacterization of Lignite as a Tool to Predict the Product Range of Catalytic Decomposition,” Int. J. Clean Coal Energy. 2016; 05(01): 13-22.
26. CZhang,XHan,GVKorshin,AMKuznetsov,andM.Yan,“Interpretation of the differential UV–visible absorbance spectra of metal-NOMcomplexesbasedonthequantumchemicalsimulationsfor themodelcompoundesculetin,”Chemosphere.2021;276:130043.
27. TAReenaandMRPKurup,“Copper(II)complexesderivedfromdi- 2-pyridyl ketone-N4-phenyl-3-semicarbazone: Synthesis and spectral studies,” Spectrochim. Acta - Part A Mol. Biomol. Spectrosc. 2010; 76(3–4): 322-7.
28. X Ran, L Wang, D Cao, Y Lin, and J Hao, “Synthesis, characterization and in vitro biological activity of cobalt(II), copper(II) and zinc(II) Schiff base complexes derived from salicylaldehyde and D,L-selenomethionine,”Appl.Organomet.Chem.2011;25(1): 9-15.
29. JCostamagna,GLEstiú,AHJubertandJVargasc,“UV-visiblespectroscopyintheinterpretationofthetautomeric,”1996:367:97-110.
30. VA Larionov, Yashkina LV, Medvedev MG, Smol’yakov AF, PeregudovASetal.,“HenryReactionRevisited.CrucialRoleofWater in anAsymmetric Henry Reaction Catalyzed by Chiral NNO-Type Copper(II) Complexes,” Inorg. Chem. 2019; 58(16) 11051-65.
31. W Jin, X Li and B Wan, “A highly diastereo-and enantioselective copper(I)-catalyzed henry reaction using a bis(sulfonamide)-diamine ligand,” J. Org. Chem. 2011; 76(2) 484-91.
32. TArai,MWatanabeandAYanagisawa,“Practicalasymmetrichenryreactioncatalyzedbyachiraldiamine-Cu(OAc)2complex,”Org. Lett. 2007; 9(18): 3595-97.
33. JD White and S Shaw, “A new catalyst for the asymmetric Henry reaction:Synthesisofβ-nitroethanolsinhighenantiomericexcess,” Org. Lett. 2012; 14(24): 6270-73.
34. NooleA,KLippur,AMetsala,MLopp,andTKanger,“Enantioselective Henry reaction catalyzed by CuII salt and bipiperidine,” J. Org. Chem. 2010; 75(4): 1313-16.
35. KK Bania, GVKarunakar, K Goutham, and RC Deka, “Enantioselective henry reaction catalyzed by ‘ship in a bottle’ complexes,” Inorg. Chem. 2013; 52(14) 8017-29.
36. BMChoudary,MLKantam,KKRao,FFigueras,andAAEinstein, “Henry reactions catalysed by modified Mg – Al hydrotalcite: an efficient reusable solid base for selective synthesis of no. August. 1999; 4: 187-90.
37. JMConcello,PLBernad,CConcello,DQuiandOV“AConvenient

Samarium-PromotedSynthesisofAliphatic(E)-Nitroalkenesun- der Mild conditions. J Org Chem, 2007; 72(14): 5421-3

38. RG Soengas andAMS Silva. “Indium-catalyzed henry-type reaction of aldehydes with bromonitro-alkanes,” Synlett. 2012; 23(6): 873-876. doi: 10.1055/s-0031-1290617.
39. NAnanthiandSVelmathi,“AsymmetricHenryreactioncatalysed by transition metal complexes:Ashort review,” Indian J. Chem. - Sect. B Org. Med. Chem. 2013; 52(1): 87-108.
40. AToussaintandA.Pfaltz,“AsymmetricHenryreactionscatalyzed by metal complexes of chiral boron-bridged bisoxazoline (bora- box) ligands,” European J. Org. Chem. 2008; 27: 4591-4597. doi: 10.1002/ejoc.200800570.
41. MJAm.“AsymmetricHenryReactionCatalyzedbyC2-Symmet- ricTridentate Bis (oxazoline) and Bis (thiazoline) Complexes: Metal-ControlledReversalofEnantioselectivityHenryreactionof R - keto esters with nitromethane in the presence of readily available c. 2005; 3712-3715.