Fe_3O_4 Nanoparticle: An Efficient Recyclable Catalyst for the Friedel-Crafts Reaction of Indoles with Isoquinoline-1,3,4-trione in Water

M.Sc. Thesis

By

NAMRATA KHADSANG

DISCIPLINE OF CHEMISTRY

INDIAN INSTITUTE OF TECHNOLOGY, INDORE

JUNE 2016

Fe_3O_4 Nanoparticle: An Efficient Recyclable Catalyst for the Friedel-Crafts Reaction of Indoles with Isoquinoline-1,3,4-trione in Water

A THESIS

Submitted in partial fulfillment of the
requirements for the award of the degree

of

Master of Science

by

NAMRATA KHADSANG

DISCIPLINE OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY INDORE
JUNE 2016

INDIAN INSTITUTE OF TECHNOLOGY INDORE

CANDIDATE’S DECLARATION

I hereby certify that the work which is being presented in the thesis entitled **“Fe_3O_4 Nanoparticle: An Efficient Recyclable Catalyst for the Friedel-Crafts Reaction of Indoles with Isoquinoline-1,3,4-trione in Water”**in the partial fulfillment of the requirements for the award of the degree of **MASTER OF SCIENCE** and submitted in the **DISCIPLINE OF CHEMISTRY, Indian Institute of Technology Indore**, is an authentic record of my own work carried out during the time period from July 2014 to June 2016 under the supervision of Dr Sampak Samanta, Associate Professor, Discipline of Chemistry, Indian Institute of Technology, Indore.

The matter presented in this thesis has not been submitted by me for the award of any other degree of this or any other institute.

Namrata Khadsang

This is to certify that the above statement made by the candidate is correct to the best of my/our knowledge.

(Dr. Sampak Samanta)

Namrata Khadsang has successfully given her M.Sc. Oral Examination held on 5 July 2016.

Signature of Supervisor of MSc thesis	Convener, DPGC
Date:	Date:
Signature of PSPC Member	Signature of PSPC Member
Date:	Date:

ACKNOWLEDGEMENTS

I feel extremely fortunate to place on the record my sincere gratitude and indebtedness to my supervisor **Dr. Sampak Samanta**, Associate Professor, Discipline of chemistry, IIT Indore for his whole hearted co-operation, moral and inspiring guidance, constructive criticism & valuable suggestions for carrying out this work.

I wish to express my sincere thanks to Head of the Department, for providing infra –structure facilities to carry out the project work.

I wish to express my sincere thanks to my lab mates and friends for their valuable co-operation in the completion of the project

Last but not least I would like to pay sincere gratitude to my loving parents for their continuous help and moral support throughout my project work.

List of Abbreviations

Ac	acetyl
AIBN	2,2’-azobisisobutyronitrile
Ala	alanine
Ar	aryl
Boc	tert-butoxycarbonyl
br	broad (spectral)
CCl_4	carbon tetrachloride
C_6D_6	deuterated benzene
$CDCl_3$	deuterated chloroform
$(CD_3)_2CO$	deuterated acetone
$(CD_3)_2SO$	deuterated dimethyl sulphoxide
Cl	chloride
CN	cyanide
delta	chemical shift in parts per million downfield from TMS
d	doublet (spectral)
1D	one-dimensional (in NMR)
2D	two-dimensional (in NMR)
DCC	N,N-dicyclohexylcarbodiimide
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
ES	electrospray (in mass spectroscopy)
ESI-MS	electrospray ionization (in mass spectroscopy)
Et	ethyl
EtOAc	ethyl acetate
EtOH	ethanol
HCl	hydrochloric acid
HRMS	high-resolution mass spectroscopy

Hz	hertz
IR	infrared
J	coupling constant (in NMR)
μ	micro
m	multiplet (spectral)
M	moles per litre
Me	methyl
MeOH	methanol
MHz	megahertz
Min	minutes
Mol	mole(s)
Mp	melting point
MS	mass spectrometery
m/z	mass to charge ratio (in mass spectrometery)
NaCl	sodium chloride
$NaHCO_3$	sodium bicharbonate
NBS	N-bromosuccinimide
NH_4Cl	ammonium chloride
NMR	nuclear magnetic resonance
Pd/C	palladium on carbon catalyst
ppm	parts per million (in NMR)
Q	quartet
R_f	retention factor (in chromatography)
RT	room temperature
s	singlet
$S_N{}^2$	bimolecular nucleophilic substitution
t	triplet
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography

I DEDICATE MY
THESIS WORK
TO MY LOVING
PARENTS

Abstract

A green, convenient and efficient procedure has been developed for the synthesis of hydroxyindole derivatives. Magnetically separable and recyclable nanoparticles are used as a heterogeneous catalyst for the synthesis of indoles via the one-pot Friedel–Crafts reaction with isoquinoline -1,3,4-trione . Interestingly, indole derivatives are regioselectively acylated in the 3-position under mild conditions, short reaction times high yields with the green aspects by avoiding toxic catalysts. The catalyst could be easily separated from the reaction mixture by using an external magnet and recycled. These operational simple procedures furnish good to high yields of corresponding synthetically as well as biologically interesting functionalized 4-hydroxy-4-indolylisoquinoline-1,3(2H,4H)- diones.

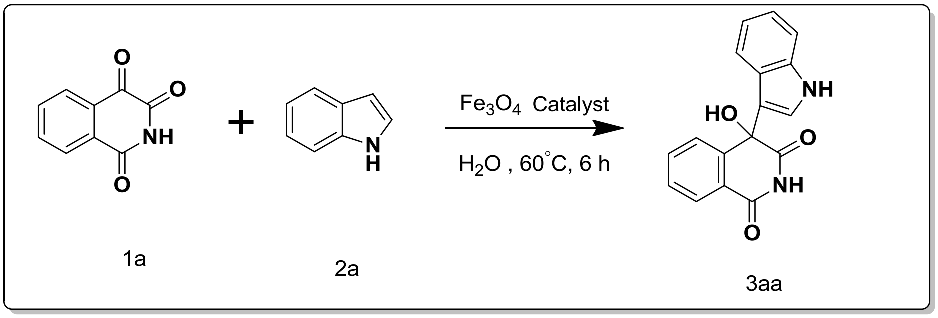


Table of Contents

LIST OF FIGURES

CHAPTER 1

Introduction

1.1 General Introduction and literature background

1.1.1 Biological Importance of Indole framework

Indole based heterocyclic moiety has been a crucial research field. A vast number of natural and synthetic indole derivatives have been found a venerable value in pharmaceutical and medical applications since they are able to bind with high affinity to many receptors.[1] Literature studies showed that several practical and efficient methods are reported for the syntheses of functionalized hydroxy indolyl and bisindolyl methane scaffolds through Friedel-Crafts reactions of indoles with a variety of aldehydes or activated ketones involving several metals or metal-free based homogeneous and heterogeneous Lewis/Brønsted acids or Brønsted base catalysts.[2] Indole frameworks are found in variety of fine or special chemicals such as natural products, drugs, materials and synthetic biologically active molecules etc.[3-4].The marketed antiviral drugs delavirdine **1**, arbidol **2** and methisazone **3** are indole derivatives.[5] Many naturally occurring spiro-indoles exhibit biological activity for example; mitraphylline **4** (from Ucaria tomentosa) exhibits antiproliferative activity against brain carcinoma cell lines, neuroblastoma SKN-BE(2), and malignant glioma GAMG.[6] Spirotryprostatins A **5** and B **6** (from the fermentation broth of Aspergillus Fumigates) inhibit the G2/M progression cell division in mammalian tsFT210 cells.[7-8], 5-lipoxygenase (5-LOX) [9](Fig.**1**).

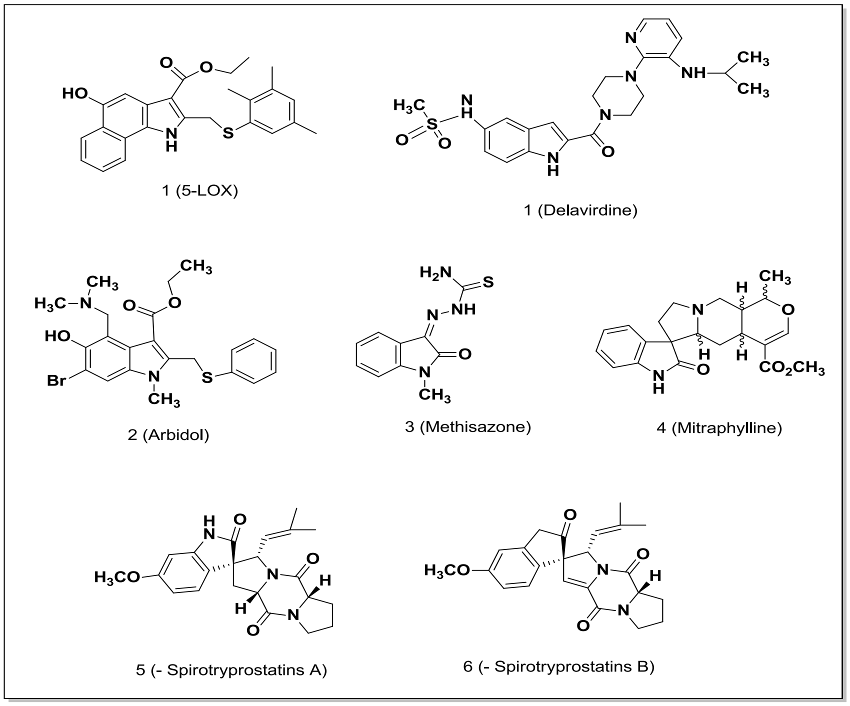


Figure 1: Some biologically active natural products

1.1.2 Activation of Friedel-Crafts Alkylation

The Friedel–Crafts reaction promoted by Lewis acid or Brønsted acid is one of the most efficient methods for the construction of carbon–carbon bonds to aromatics and hetroaromatics.[10] And that Friedel–Crafts type reaction of isoquinoline-1,3,4-triones with indole has arisen increasing attention.[11] It has been well reported that the C-2/3 position of indole is susceptible to nucleophilic attack and Friedel–Crafts type reaction is readily performed. Based on these chem-information, we speculated that the reaction between isoquinoline-1,3,4-triones and highly nucleophilic reagents indoles may be able to proceed smoothly under certain mild conditions leading to 4-hydroxy-4-indolylisoquinoline-1,3(2H,4H)-diones. However, through carefully researching literature, we found the reported, the direct condensation of indole with various substituted 4-hydroxy-4-indolylisoquinoline-1,3(2H,4H)-diones.

1.1.3 Fe_3O_4 Nanoparticle

In addition, there had been Fe_3O_4 nanoparticle as a catalytic processes And that magnetic nanoparticle catalysts have attracted much attention because they show good dispersibility and increasing interest in their properties including a large surface to volume ratio, low toxicity, biocompatibility, super paramagnetism, and potential applications in several fields[12, 13.] And that magnetic nanoparticles (MNPs) allow facile separation from the reaction mixture through an external magnet that not only eliminates the necessity of cumbersome filtration and centrifugation procedures but also reduces energy consumption, catalyst loss and saves time in achieving catalyst recovery.

1.1.4 Application of Fe_3O_4 Nanaoparticle

It has many applications such as magnetic bioseparations [14], drug delivery[15], magnetic resonance imaging (MRI) contrast agents[16], treatment of cancer [17] and catalysis[18], sorbents, pigments, flocculants, coatings, gas sensors, ion exchangers and for lubrication.[19] So by using these nano catalysts has been widely by supported . Magnetically separable catalysts are very attractive heterogeneous catalysts owing to their facile recycling process.[20]

1.1.5 Proposed of the Research work

In this thesis, we are interested to perform the FC alkylation reaction of indole with isoquinoline-1,3,4-trione in water by using Fe_3O_4 nanoparticle as an powerful heterogeneous catalyst in an cost-effective and environmental-friendly[21]. And also Friedel–Crafts alkylation using Fe_3O_4 nanoparticle as catalyst will be investigated. How to work and recover catalyst in the reaction as shown in **fig.2**

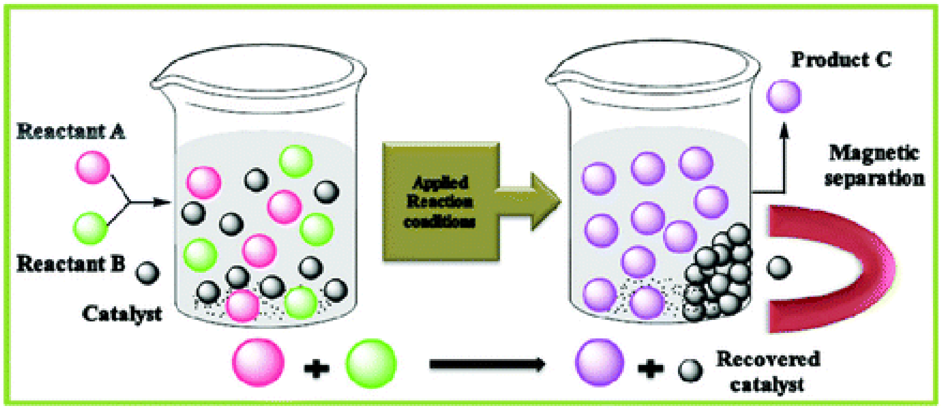


Figure 2: Friedel-Craft type reaction by using Fe_3O_4 nanoparticle

1.1.6 Scope in the area

Isoquinoline-1,3,4-triones and its derivatives are most important in biologically and Pharmaceuticals. Because they are selective, irreversible, slow-binding, pan-caspase inhibitors.[22] Furthermore, these inhibitors attenuated apoptosis induced by β-amyloid(25–35) in PC12 cells and primary neuronal cells.Most interesting and important in research area is that , the resurgence or scientist have much interest in caspases (Csp) as therapeutic targets for the treatment of neurodegenerative diseases[23] and caspase-3 is a caspase protein which is a programmed cell death protease involved in neuronal apoptosis during physiological development and under pathological conditions. By reporting literature, isoquinoline-1,3,4-trione and its derivatives inhibit caspase-3.[24]

CHAPTER 2

Experimental section

2.1 Experimental procedure

2.1.1 Synthesis of Fe_3O_4 Nanoparticle:

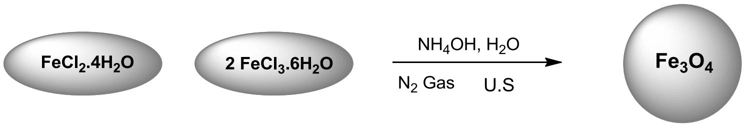


Figure 3: Synthesis of Fe_3O_4 nanoparticle

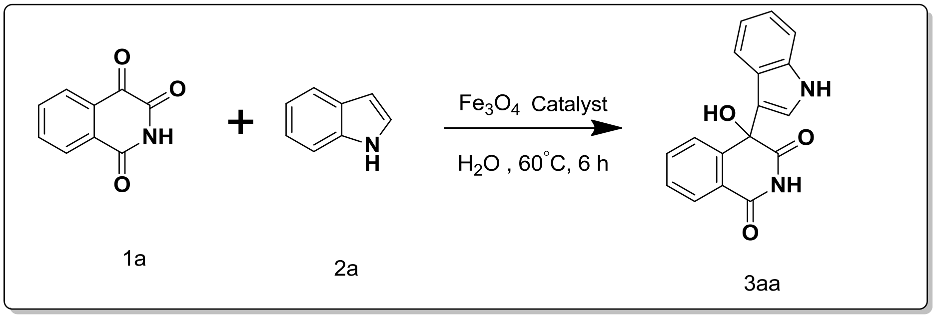
Nowadays, functional nanoparticles are of industrial and scientific importance.[25] And occur in a great variation of surroundings from geological to nanoscale technological applications. Several techniques have been used to developeding to synthesis of Fe_3O_4 nanoparticle such as co-precipiation[26], sol-gel[27], hydrolyzation[28], micro-emulsion[29], surfactant mediated, microwave-assisted hydrothermal technique, hydrothermal[30], ultra radiation[31] etc.And we have to use one of them method, co-precipitation. Co-precipitation is a preferred choice for most researchers because the reaction could be performed under a mild condition by using water as solvent because of its simplicity and productivity.[32] The Fe_3O_4 NPs were prepared by using the published method[33] with modification. Ferric chloride and ferrous chloride were mixed in 2:1 molar ratio under the presence of N_2 gas. $FeCl_3$(20 mmol) and $FeCl_2$(10 mmol) were dissolve into 4 ml of deoxygenated distilled water under nitrogen atmosphere with ultrasound irradiation for 15 min at 60°C, chemical precipitation was achieved by adding of ammonium hydroxide (15 mL, 28 wt%). The solution was immediately turned black. The reaction was kept at 60°C for 20 min under ultrasound irradiation. These black colour of particles were then separated from the solution by using external magnet and then were washed many times with distilled water. The resulting Fe_3O_4 nanoparticles were dried for 12 h at room temperature under vacuum and characterized by XRD, FTIR.

2.1.2 Synthesis of Isoquinoline-1,3,4-trione

In the 1st step, 1.47 g of phthalimide were mixed with 35-40 ml acetonitrile thoroughly, resulting mixture was poured into 100 ml flask followed by adding 2.8 g of potassium carbonate and 1.1 ml of chloroacetone, and heated with 82°C (a reflux condensing tube was needed to be equipped on the flask, and the system was protected by argon). After the reaction was conducted for 24 h, excess of chloroacetone was removed under a reduced pressure by vaccum, then filtered with buchner's filter, resulting pour compound was evaporated, and dried under vaccum to obtain 1H-Isoindole-1,3(2H)-dione,2-(2-oxopropyl)-. In the 2nd step, To a reflux condensing tube, take 10 ml methnol was added in two-necked bottle, followed by adding 0.350 g of metallic sodium (or directly adding 10 mmol of sodium methoxide). After the metallic sodium was dissolved entirely , the solution was heated and refluxed and then solid compound 1H-Isoindole-1,3(2H)-dione,2-(2-oxopropyl)- was added in methanol (5 ml of CH_3OH and 1 g of compound) in one portion. After addition, the reaction was heated at reflux for 2h and then the system was processed as following: the system was cooled with ice bath and then neutralized with 1 M HCl. The resulting suspension was stirred for 15-20 min in ice water bath after which a large amount of solid emerged and then filtered under reduced pressure by vaccum, washed with a small amount of ethyl acetate and dried under vaccum to obtain 1(2*H*)-Isoquinolinone, 3-acetyl-4-hydroxy- And then for 3rd step, In a small flask , taking mixture of 1.5 ml of conc. sulfuric acid and 0.5 ml conc. Nitric acid under a ice bath for stirring 5 min and then add 250 mg 1(2*H*)-Isoquinolinone, 3-acetyl-4-hydroxy- solid compound. After the completion of reaction, doing the workup and the resulting pour compound was evaporated to obtain isoquinoline-1,3,4-trione and characterized by ^{1}HNMR ,MS and FT-IR.

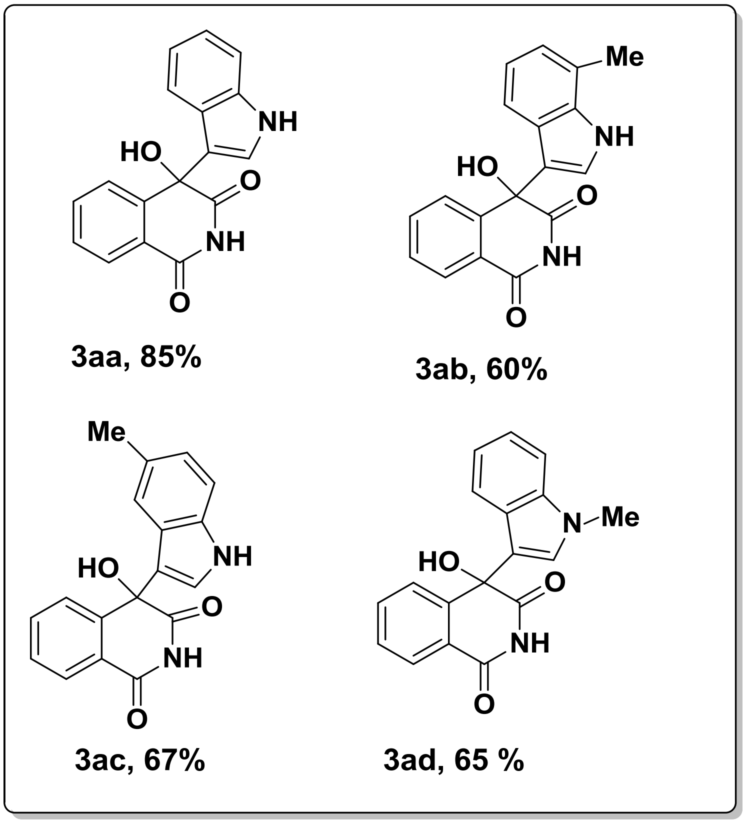
2.1.3 Synthesis of 4-hydroxy-4-(1H-indol-3-yl)isoquinoline-1,3 (2H,4H) -dione

At the beginning, Friedel–Crafts hydroxyalkylation of indole (2a) with isoquinoline-1,3,4-trione (1a) and Fe_3O_4 (20% mmol) as catalyst was investigated in water at room temperature. But after 48h reaction not happened at room temperature. Afterwards it was tried to be heating at 60°C. And it was happened in only 6 h (monitored by TLC). After that, Fe_3O_4 nanoparticles were separated from this reaction mixture by external magnetic bar. Then the reaction mixture was concentrated under reduce pressure to leave a crude residue which was purified by column chromatography over silica gel using ethyl acetate\hexane. And evaporated the reduce pressure to give a greenish colour of pure solid which is 4-hydroxy-4-(1H-indol-3-yl)isoquinoline-1,3(2H,4H)-dione (3aa). That was gives 85% yield. By this procedure, Fe_3O_4 can be recycled several times without losing its catalytic activity by external magnetic bar. The Friedel–Crafts products were fully characterized by their spectroscopic data (^{1}H NMR, ^{13}C NMR, FT-IR and HRMS data).



Scheme 1:. Synthesis of 4-hydroxy-4-(1H-indol-3-yl)isoquinoline-1,3(2H,4H) -dione

With these experimental results in hand, next, we tested the general trend of this Friedel-Crafts hydroxyalkylation reaction by using a wide range of structurally diverse steric and stereoelectronic environments of indole moieties with functionalized isoquinoline-1,3,4-trione scaffolds in our optimized reaction conditions. All the obtained results are systematically collected in the following substrates.



3aa, 85%

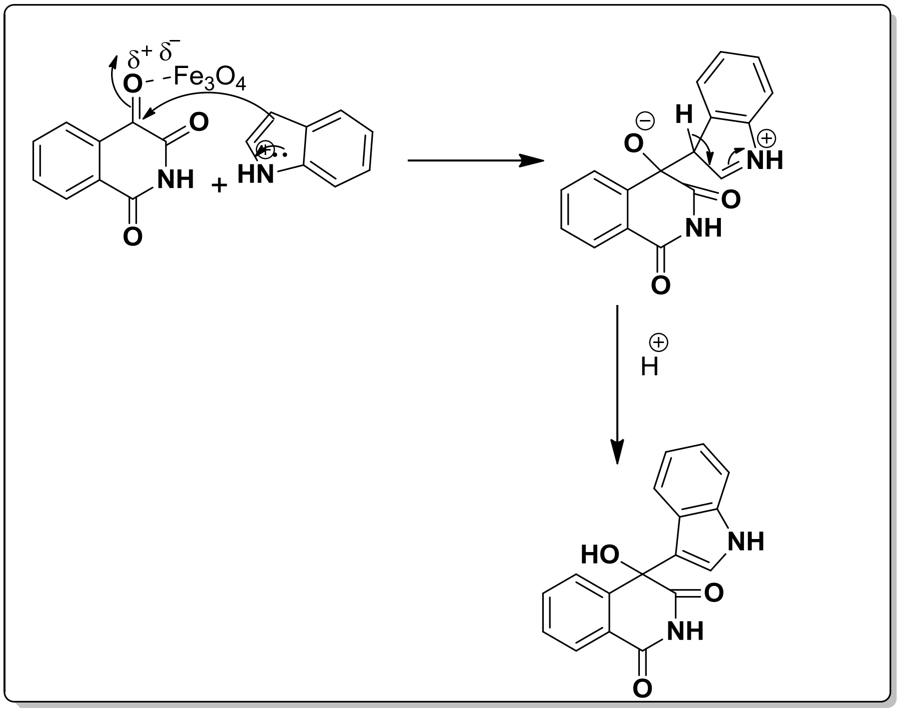
3ab, 60%

3ac, 67%

3ad, 65 %

Figure 4: Structure of Indole Substrates

2.1.3. (a) Mechanism proposed of 4-hydroxy-4-(1H-indol-3-yl)isoquinoline-1,3(2H,4H)-dione



Scheme 2: Mechanism of 4-hydroxy-4-(1H-indol-3-yl)isoquinoline-1,3(2H,4H)-dione

All reactions were carried out at 60 °C and monitored by TLC using Merck 60 F254 pre coated silica gel plates (0.25 mm thickness) and the products were visualized by UV detection. Flash chromatography was carried out with silica gel (200–300 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance (III) 400 MHz spectrometer. Data for 1 H NMR are reported as a chemical shift (dppm), multiplicity (s ¼singlet, d ¼doublet, q¼quartet, m¼multiplet), coupling constant J (Hz), integration, and assignment, data for ^{13}C are reported as a chemical shift. High resolutions mass spectral analyses (HRMS) were carried out using ESI-TOF-MS. All the starting materials were either synthesized by literature procedure or purchased from commercial sources.

CHAPTER 3

Results and Discussion

3.1.1 Characterization of Fe_3O_4 nanoparticle

The product X-ray diffraction pattern contained the five characteristic reflections at 33^0(220), 35^0(311), 39^0(222), 54^0(111), 62^0(220) which is intensity matching with reference data and also FT–IR spectrum contained an absorption band at 552 cm^{-1}, characteristic of Fe–O vibration.

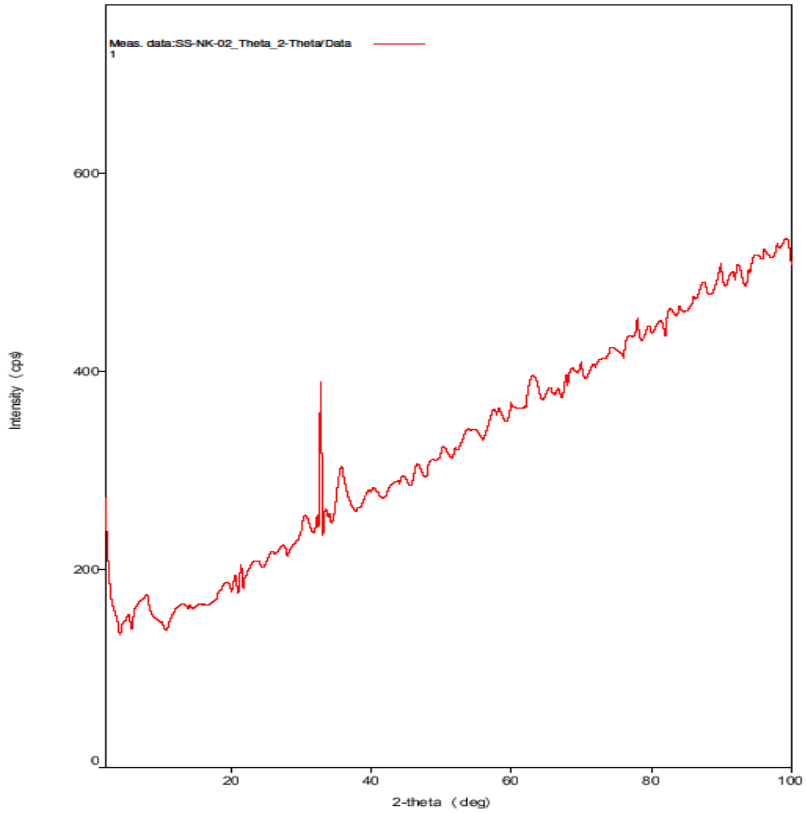


Figure 5: Characterized of Fe_3O_4 nanoparticle by **P-XRD**

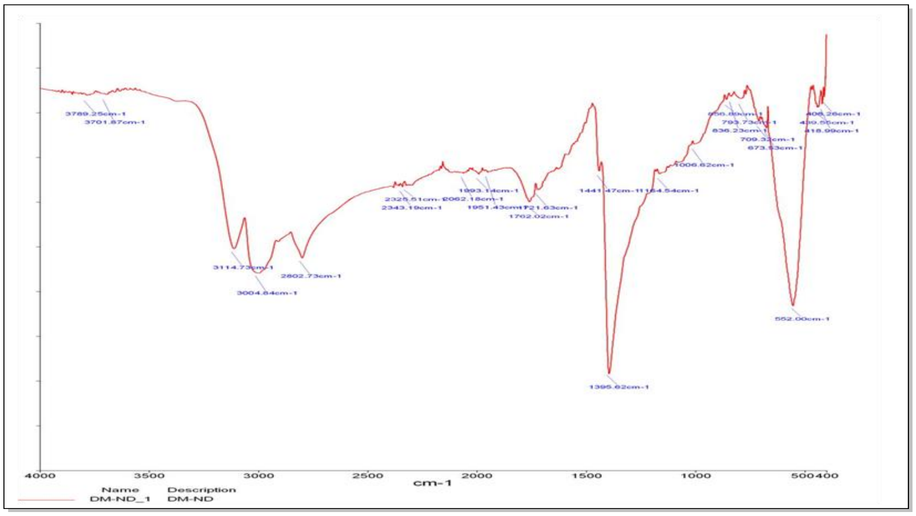
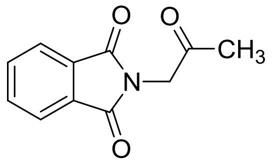


Fig.5: Characterized of Fe_3O_4 nanoparticle by **FT-IR**

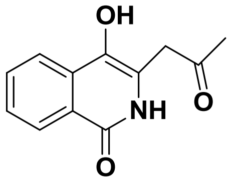
3.1.2 Characterization Data of compounds:

To access the desired compound, we have performed the model reaction between isoquinoline-1,3,4(2H)-trione and substituted indole in water at 60 °C. Indeed, after 6 h, the expected compound was isolated in excellent yield 85 %. The structure of product was ascertained by its spectroscopic data (^{1} H, ^{13} C NMR HRMS and FT-IR).

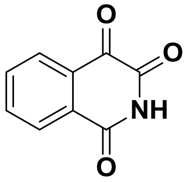
2-(2-oxopropyl)isoindoline-1,3-dione ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86-7.88 (m, 2H), 7.73-7.75 (m, 2H), 4.69 (s, 2H), 4.49 (s, 2H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.3, 170.4, 135.5, 133.9, 125.3, 56.4, 23.7; HRMS (ESI) m/z calculated for $C_{11}H_{9}O3$ $[M+H]^{+}$: 299.1278 Found 299.1287.

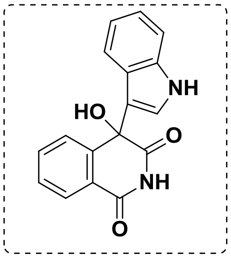


4-hydroxy-3-(2-oxopropyl)isoquinolin-1(2H)-one ^{1}H NMR (400 MHz, $CDCl_3$) 12.84 (br s, 1H), 10.54 (s, 1H), 8.16-8.29 (m, 2H), 7.79-7.92 (m, 2H), 2.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.4, 167.4, 154.7, 144.7, 138.7, 132.4, 130.5, 126.2, 120.2, 103.5, 30.1; HRMS (ESI) m/z calculated for $C_{12}H_{11}NO3$ $[M+Na]^{+}$:240.0632, found 240.051.

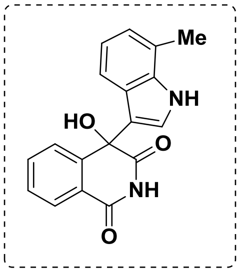


isoquinoline-1,3,4(2H)-trione ^{1}H NMR (400 MHz, $CDCl_3$) 11.95 (br s, 1H), 8.11-8.13 (d, *J= 7.28 MHz,*1H), 8.03-8.05 (d, *J= 7.28 MHz,* 1H), 7.87-7.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.7, 175.0, 169.6, 145.7, 140.6, 137.7, 134.3, 131.3, 124.3; IR (KBr)(cm^{-1})v_{max}: 3145 (broad NH), 1707(C=O), 1685, 1298, 1222, 859, 743; HRMS (ESI) m/z calculated for **$C_9H_5NO_3$** $[M+Na]^{+}$:198.0162, found 198.0122.

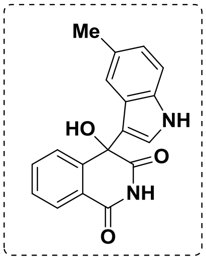




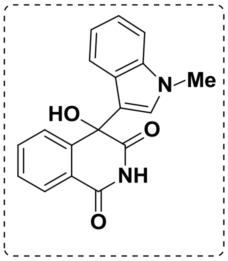
4-Hydroxy-4-(1*H*-indol-3-yl)isoquinoline-1,3(2*H*,4*H*)-dione (3aa):Yield 85 %; ^{1}H NMR (400 MHz, acetone-d$_6$) δ 10.23 (br s,1H), 10.08 (br s, 1H), 8.12-8.14 (d, *J= 7.5 MHz*, 1H), 7.87-7.89 (d, *J= 7.8 MHz*, 1H), 7.77-7.78 (d, *J= 6.0 MHz.* 2H), 7.58-7.62 (m, 1H), 7.34-7.36 (d, *J= 7.8 MHz* ,1H), 7.06-7.09 (m, 1H), 6.95-6.99 (m, 1H), 6.65 (s, 1H), 5.62 (s, 1H); ^{13}CNMR (100 MHz, acetone-d$_6$) δ 174.9, 164.7, 144.3, 138.0, 134.7, 129.2, 128.1, 127.8, 125.8, 124.8, 122.6, 122.4, 122.0,121.7, 120.1, 112.4, 74.7; IR (KBr)(cm^{-1}) v$_{max}$:3377 (broad ,OH), 3185(broad, NH), 1716 (C=O), 1683, 1124, 1078, 754, 742; HRMS (ESI) m/z calculated For $C_{17}H_{12}N_2O_3$ [M+Na]$^+$: 315.0897. Found 315.0740.



4-Hydroxy-4-(7-methyl-1*H*-indol-3-yl)isoquinoline-1,3(2*H*,4*H*)-dione (3ab): IR (KBr)(cm^{-1}) v$_{max}$: 3402 (broad, NH and OH), 3051, 2925, 2854, 1692 (C=O), 1362, 1140, 1105, 782, 752; HRMS (ESI) m/z calculated For $C_{18}H_{14}N_2O_3$ [M+Na]$^+$: 329.0897 Found 329.0805.



4-hydroxy-4-(5-methyl-1H-indol-3-yl)isoquinoline-1,3(2H,4H)-dione (3ad): yield 67%;^{1}H NMR (400 MHz, acetone-d$_6$) δ 10.14 (br s, 1H), 10.06(Br s, 1H), 8.11-8.13 (d, *J= 7.8 MHz*, 1H), 7.86-7.88(d, *J= 7.7 MHz* 1H), 7.75-7.79 (t, 1H), 7.58-7.60 (d, *J= 6.3 MHz*, 1H), 7.22-7.24 (d, *J= 8.5 MHz*, 1H), 7.03-7.07 (t, 1H), 6.90-6.93 (d, *J= 6.8 MHz*, 1H), 6.54(s, 1H), 5.59 (s, 1H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, acetone-d$_6$) δ 175.0, 164.7, 144.3, 136.3, 134.6, 129.1, 128.9, 128.8, 128.4, 128.1, 127.8, 126.5, 124.8, 124.2, 121.4, 112.0, 74.7, 21.2; IR (KBr)(cm^{-1})v$_{max}$: 3398 (broad, OH), 3195 (broad, NH), 3080, 1718 (C=O), 1692, 1368, 1105, 1032, 792, 759; HRMS (ESI) m/z calcd For $C_{18}H_{14}N_2O_3$ [M+Na]$^+$: 329.1004 Found 329.0901.



4-hydroxy-4-(1-methyl-1H-indol-3-yl)isoquinoline-1,3(2H,4H)-dione(3af): IR (KBr)(cm^{-1})v$_{max}$: 3310(broad, OH), 3133 (broad, NH), 3077, 1714 (C=O), 1684, 1363, 1141, 119, 743, 754; HRMS (ESI) m/z calcd For $C_{18}H_{14}N_2O_3$ $[M+Na]^+$:329.1004. Found 329.0878.

3.1.3 NMR Spectra of compounds

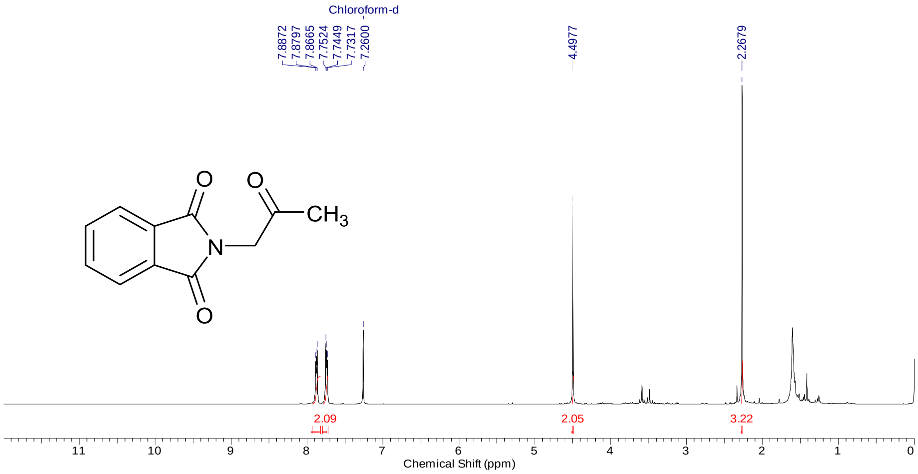


Figure 7: **^{1}H -NMR** of 1H-Isoindole-1,3(2H)-dione,2-(2-oxopropyl)

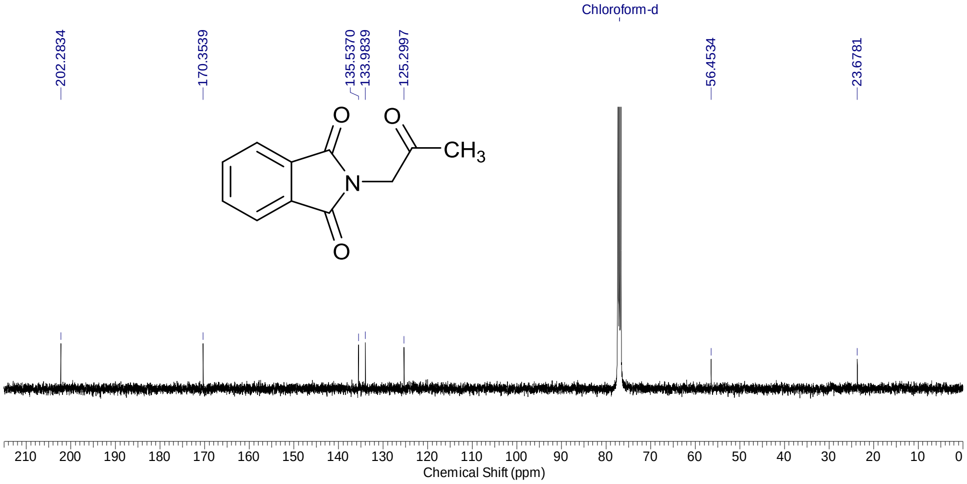


Figure 8: **^{13} C-NMR** of 1H-Isoindole-1,3(2H)-dione,2-(2-oxopropyl)

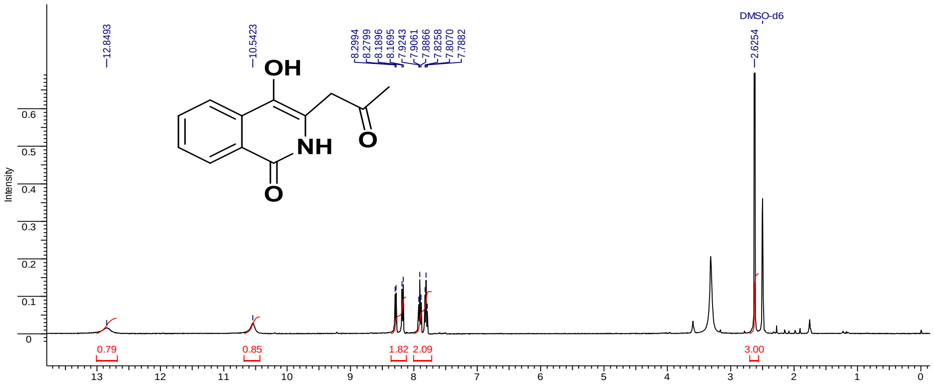


Figure 9: ^{1}**H -NMR** of 1(2*H*)-Isoquinolinone,3-acetyl-4-hydroxy

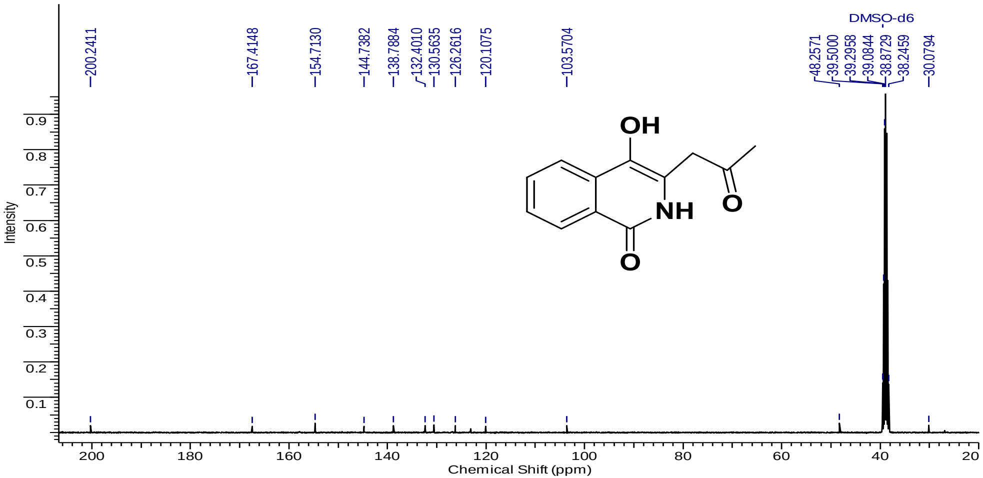


Figure 10: ^{13} **C-NMR** of 1(2*H*)-Isoquinolinone,3-acetyl-4-hydroxy

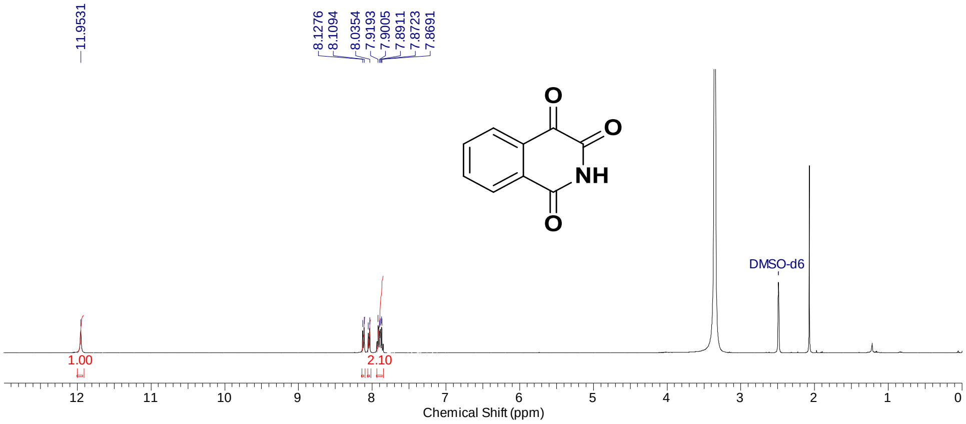


Figure 11: ^{1}**H -NMR** of Isoquinoline-1,3(2H,4H)-dione

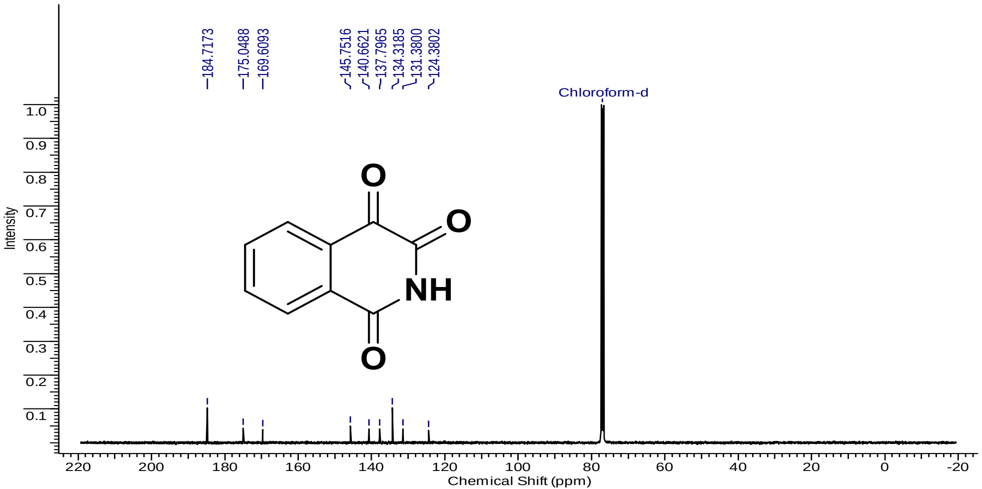


Figure 12: ^{13} **C-NMR** of Isoquinoline-1,3(2H,4H)-diones

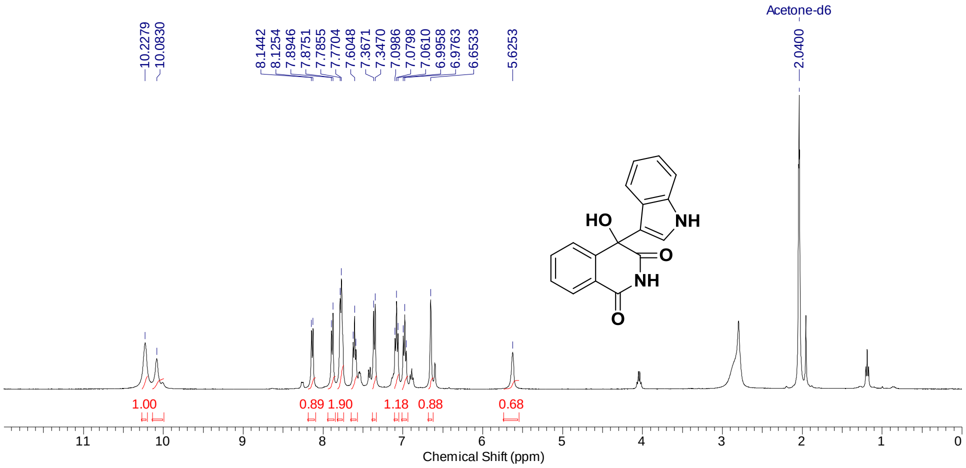


Figure 13: ^{1}**H -NMR** of 4-Hydroxy-4-(1H-indol-3-yl)isoquinoline-1,3(2H,4H)-dione

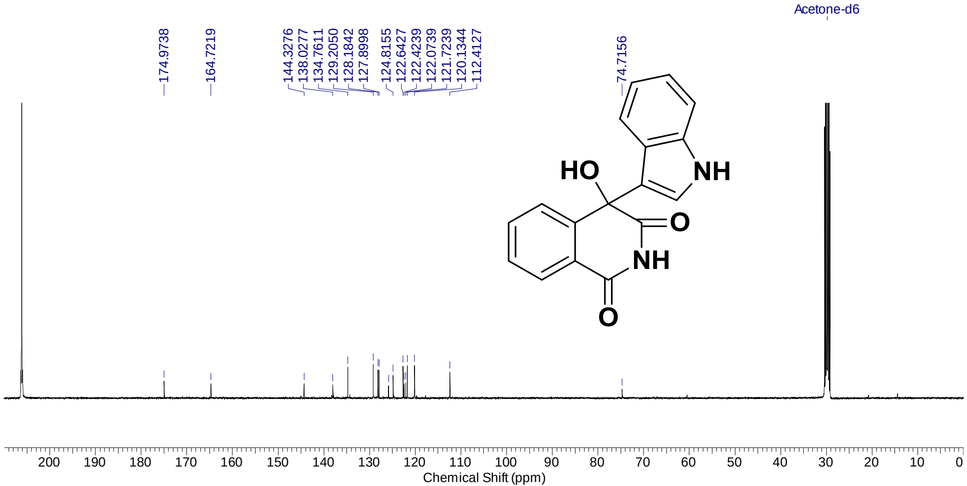


Figure 14: ^{13}**C -NMR** of 4-Hydroxy-4-(1H-indol-3-yl)isoquinoline-1,3(2H,4H)-dione

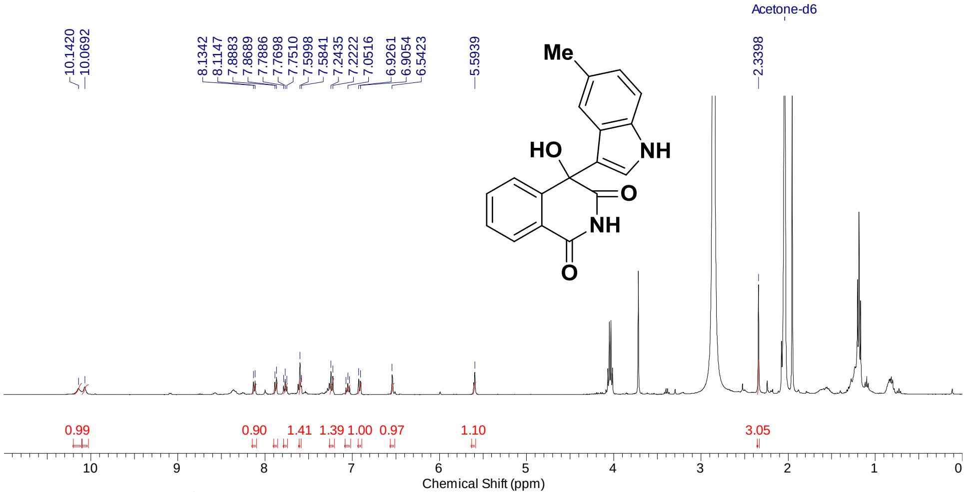


Figure 15: ^{1}**H -NMR** of 4-Hydroxy-4-(1H-indol-3-yl)isoquinoline-1,3(2H,4H)-dione

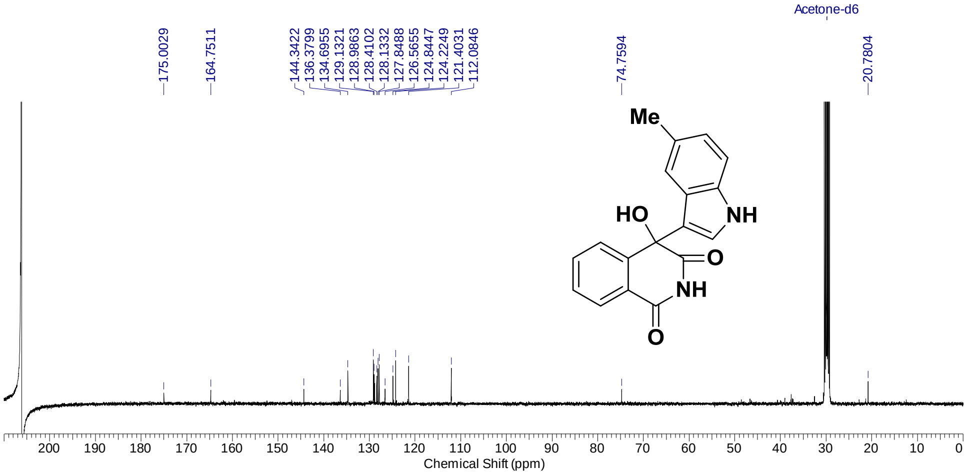


Figure 16: ^{13}**C -NMR** of 4-Hydroxy-4-(1H-indol-3-yl)isoquinoline-1,3(2H,4H)-dione

3.1.4 <u>FT-IR spectra of Compounds</u>

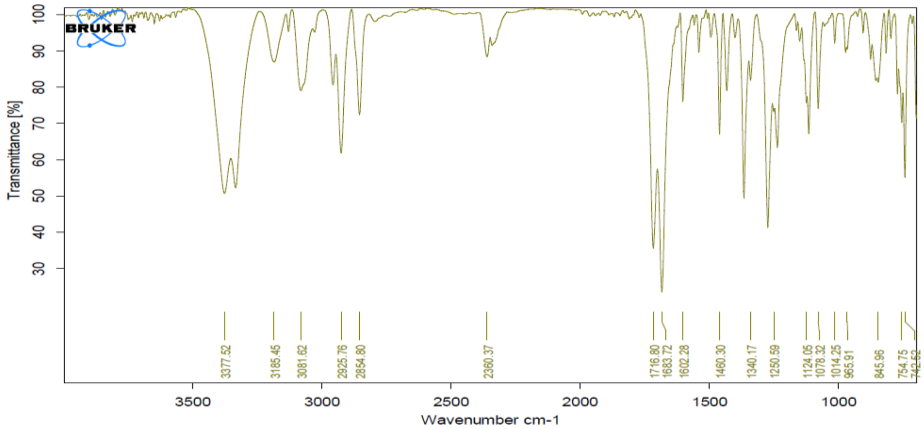


Figure.17: **FT-IR** of 4-Hydroxy-4-(1H-indol-3-yl)isoquinoline-1,3(2H,4H)-dione

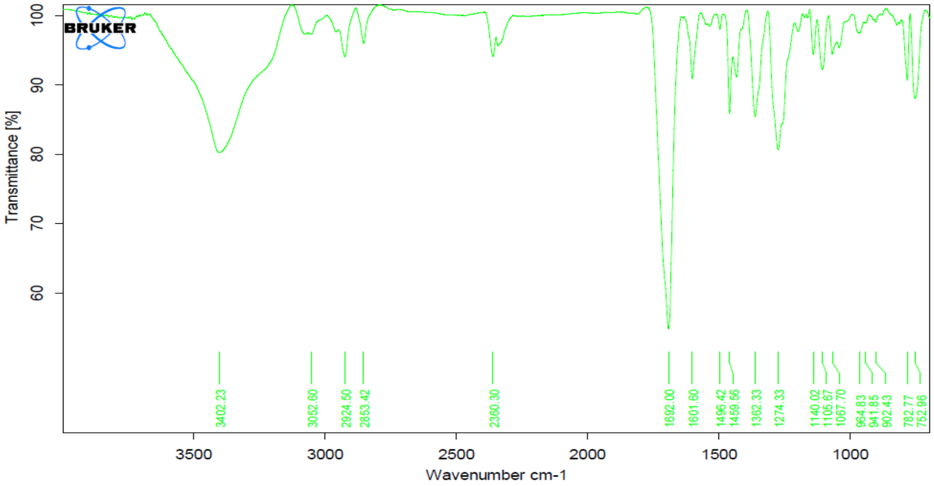


Figure.18: FT-IR of 4-Hydroxy-4-(7-methyl-1*H*-indol-3-yl)isoquinoline-1,3(2*H*,4*H*)-dione

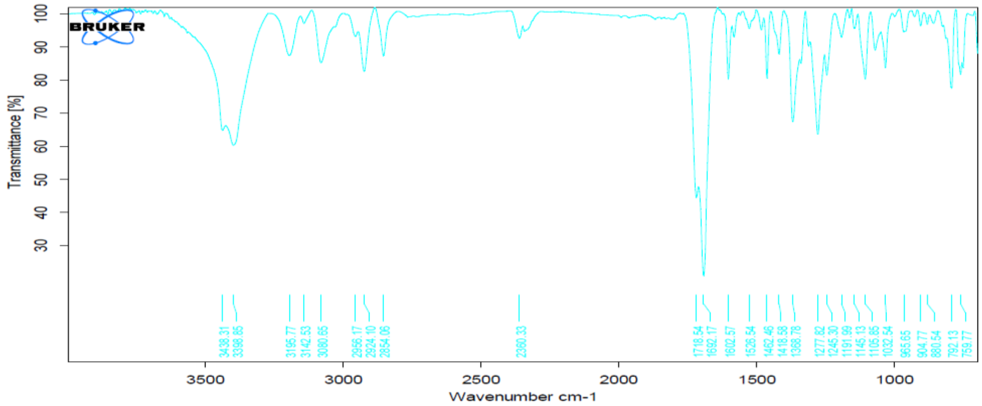


Figure 19: FT-IR of 4-hydroxy-4-(5-methyl-1H-indol-3-yl) isoquinoline-1,3(2H,4H)-dione

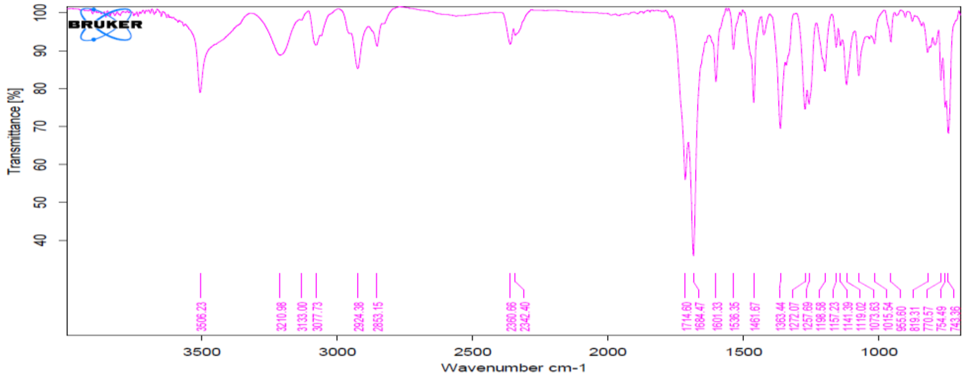


Figure 20: FT-IR of 4-hydroxy-4-(1-methyl-1H-indol-3-yl)isoquinoline-1,3(2H, 4H)-dione

3.1.5 <u>Mass spectra of Compounds</u>

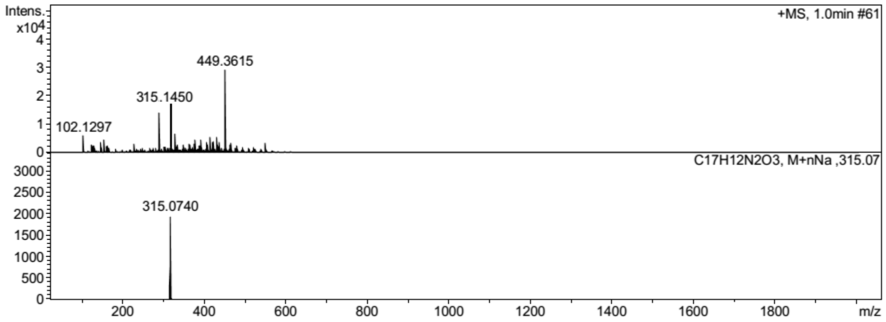


Figure 21: **Mass spectrum** of 4-Hydroxy-4-(1H-indol-3-yl)isoquinoline-1,3(2H,4H)-dione

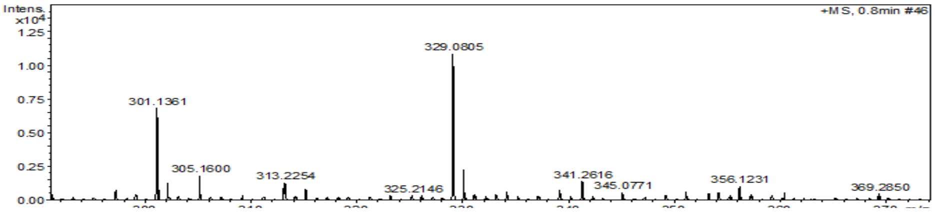


Figure 22: Mass spectrum of 4-Hydroxy-4-(7-methyl-1*H*-indol-3-yl)isoquinoline-1,3(2*H*,4*H*)-dione

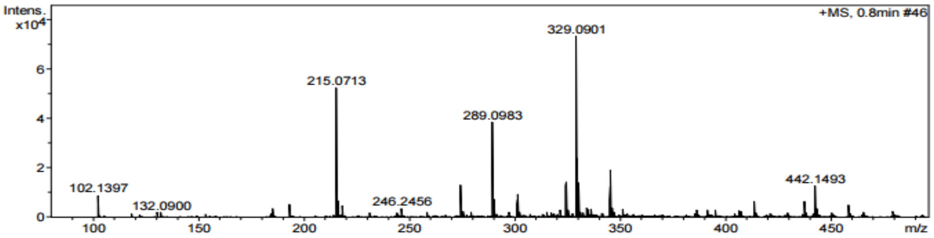


Figure 23: Mass spectrum of 4-hydroxy-4-(5-methyl-1H-indol-3-yl)isoquinoline-1,3(2H,4H)-dione

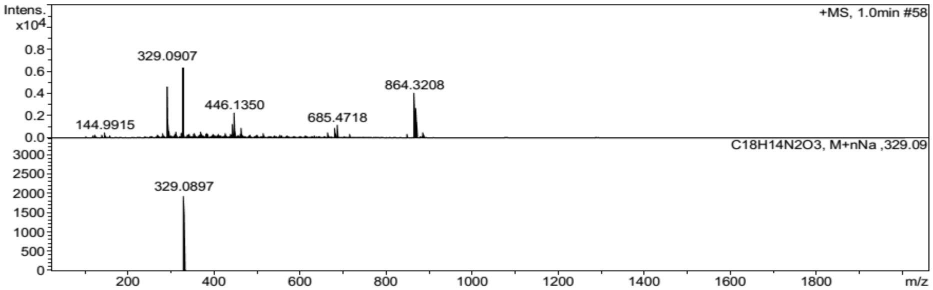


Figure 24: Mass spectrum of 4-hydroxy-4-(1-methyl-1H-indol-3-yl)isoquinoline-1,3(2H,4H)-dione

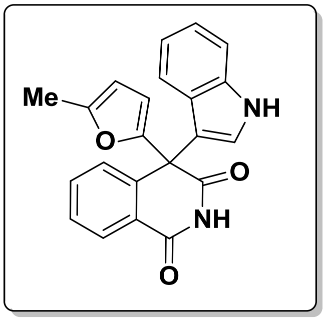
CHAPTER 4

4.1 Conclusions

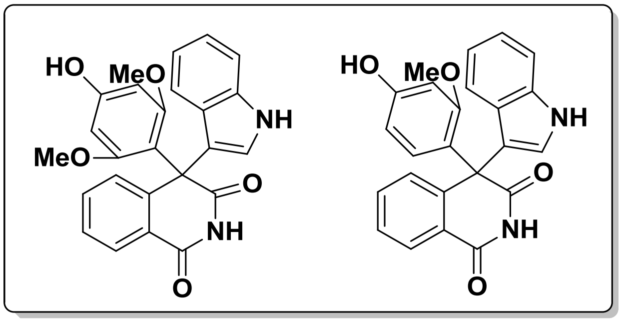
We have shown that magnetically separable Fe_3O_4 nanoparticle promoted hydroxyalkylation of isoquinoline 1,3,4 trione with indoles. This method offers some advantages in terms of clean reaction conditions, easy work-up procedure. Isoquinoline 1,3,4 trione are most important in biologically and in research area .

4.2 Scope of Future work

Future works will focus on the application of this transformation in the synthesis of natural products and try to synthesis of electrophilic substitution reaction of hydroxyindolyl derivatives with various types of Lewis or bronsted acid / bases to construct a series of possible unsymetrically as well as biologically importance.



I want to synthesis, and also various types of Lewis or Brønsted acid/bases are given below as follows:


HO
MeO
MeO
NH
O
NH
O
HO
MeO
NH
O
NH
O

References:

1. Sundberg, R. J. The Chemistry of Indoles; Academic Press: San Diego, **1996**; (b) Toyota, M.; Ihara, N. *Nat. Prod. Rep.* **1998,** *15,* 327; (c) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105,* 2873; (d) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006,** *106,* 2875; (e) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009,** *48,* 9608.

[2]. (a) Praveen, P. J.; Parameswaran, P. S.; Majik, M. S. *Synthesis* **2015**,47, 1827; (b) Gong, H.; Xie, Z. F. *Chin. J. Org. Chem*. **2012**, *32*, 1195; Original papers, see (c) Sharma, G. V. M.; Reddy, J. J.; Lakshmi, P. S.; Krishna, P. R.*Tetrahedron Lett.* **2004**, *45*, 7729; (d) Mahmoudi, H.; Jafari, A. A.; Saeedi, S.;Firouzabadi, H. *RSC Adv*. **2015,** *5*, 3023; (e) Sasaki, S.; Ikekame, Y.;Tanayama,M.;Yamauchi, T.; Higashiyama, K. *Synlett* **2012**, 2699; (f) Bandini, M.; Sinisi, R. *Org.Lett*. **2009**, *10*, 2093; (g) Abid, M.; Török, B. *Adv. Synth. Catal*. **2005**, *347*, 1797; (h)Wang, Y.; Yuan, Y.; Xing, C.-H.; Lu, *Tetrahedron Lett*. **2014,** *55*, 1045; (i) Taheri,A.; Lai, B.; Cheng, C.; Gu, Y. *Green Chem*. **2015**, *17,* 812; (j) Kumar, V. P.; Reddy, V.P.; Sridhar, R.; Srinivas, B.; Narender, M.; Rao, K. R. *J. Org. Chem.* **2008**, *73*, 1646;(k) Tayade, Y. A.; Patil, D. R.; Wagh, Y. B.; Jangle, A. D.; Dalal, D. S. *Tetrahedron Lett.* **2015**, *56*, 666; (l) Srihari, G.; Murthy, M. M. *Chem. Lett*. **2008**, *37,* 268; (m) Rad-Moghadam, K.; Sharifi-Kiasaraie, M.; Taheri-Amlashi, H. *Tetrahedron* **2010**, *66*, 2316; (n) Deb, M. L.; Bhuyan, P. *J. Synth. Commun*. **2009**, *39*, 2240; (o)Hanhan, N. V.; Sahin, A. H.; Chang, T. W.; Fettinger, J. C.; Franz, A. K. Angew.Chem., *Int. Ed*. **2010**, *49,* 744; (p) Rad-Moghadam, K.; Dehghan, N. J. Mol. Catal. *A:Chem*. **2014**, *97,* 392; (q) Li, H.; Wang, Y.-Q.; Deng, L. *Org. Lett*. **2006**, *8,* 4063; (r)Nakamura, S.; Hyodo, K.; Nakamura, Y.; Shibata, N.; Toru, T. *Adv. Synth. Catal*. **2008**, *350,* 1443.

[3].DiPoto MC, Hughes RP, Wu J (**2015**) *J Am Chem Soc 137*:14861.

[4].Inman M, Moody CJ (**2013**) *Chem Sci 4*:29.

[5].G. Cihan-Ustundağ, E. Gursoy, L. Naesens, N. Ulusoy- Guzeldemirci and G Capan, *Bioorg. Med. Chem*., **2016**, 4240.

[6]. E. Garcia Prado, M. D. Garcia Gimenez, R. De la Puerta Vazquez, J. L. Espartero Sanchez and M. T. Saenz Rodriguez, *Phytomedicine*, **2007,** *14*, 280.

[7]. C. B. Cui, H. Kakeya and H. Osada, *Tetrahedron*, **1996,** 52, 12651.

[8]. C. B. Cui, H. Kakeya and H. Osada, *J. Antibiot*., **1996,** *49*, 832.

[9]. Harizi Hedi and Gualde Norbert *Journal of Biomedicine and Biotechnology***2004**:*2*,299. [10].Yan-Yan Han a,c, Zhi-Jun Wub,c, Xiao-Mei Zhang a, Wei-Cheng Yuan, Y.-Y. Han et al. / *Tetrahedron Letters 51* (**2010**) 2023.

[11].(a) Johannsen, M. *Chem. Commun*. **1999**, 2233; (b) Janczuk, A.; Zhang, W.; Xie, W. H.; Lou, S. Z.; Cheng, J. P.; Wang, P. G. *Tetrahedron Lett*. **2002**, *43*, 4271; (c) Endo, A.; Yanagisawa, A.; Abe, M.;Tohma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 6552; (d) Lei,F.; Chen, Y.-J.; Sui, Y.; Liu, L.; Wang, D. *Synlett*, **2003**, 1160.

[12]. Sevilla M, Valde´s-Solis T, Tartaj P, Fuertes AB (**2009**) *J Colloid Interface Sci 340*:230.

[13]. Bruce IJ, Sen T (**2005**) *Langmuir 21*:7029.

[14]. Baby TT, Ramaprabhu S (**2010**) *Talanta 80*:2016.

[15]. Alexiou C, Jurgons R, Schmid R, Hilpert A, Bergemann C, Parak F, Iro H (**2005**) *J Magn Magn Mater 293*:389.

[16]. Huh YM, Lee ES, Lee JH, Jun YW, Kim PH, Yun CO, Kim JH,Suh JS (**2007**) *Adv Mater 19*:3109.

[17]. Kircher MF, Mahmood U, King RS, Weissleder R, Josephson LA(**2003**) *Cancer Res 63*:8122.

[18]. Wong EW, Bronikowski MJ, Hoenk ME, Kowalczyk RS, HuntBD (**2005**) *Chem Mater 17*:237.

[19].Mohapatra and Anand / *International Journal of Engineering, Science and Technology* , Vol. *2*, No. 8, **2010**, pp. 127.

[20] a) A. Roucoux, J. Schulz, H. Patin, *Chem. Rev*.**2002**, *102*, 3757 –; b) J. M. Thomas, B. F. G. Johnson, R. Raja, G.Sankar, P. A. Midgley, *Acc. Chem. Res*. **2003**, *36*, 20.

[21]. Ch. Prasad1• S. Gangadhara1 • P. Venkateswarlu1 (**2015**)*Appl Nanosci* :-1-6.

[22].Y.-H. Zhang et al.,*FEBS Journal 273* (**2006**) 4842.

[23]. Michel C. Maillard1 , Celia Dominguez1 , Mark J. Gemkow2 , Florian Krieger2 , Hyunsun Park1 , Sabine Schaertl2 , Dirk Winkler2 , and Ignacio Muñoz-Sanjuán, *J Biomol* **September 2013** vol. *18* no. *8* **868-878.**

[24].Chen YH, Zhang YH, Zhang HJ, Liu DZ, Gu M, Li JY, Wu F, Zhu XZ, Li *J & Nan FJ* (**2006**) Design, Synthesis, and Biological Evaluation of Isoquinoline-1,3,4-trione Derivatives as Potent Caspase-3 Inhibitors. *J Med Chem* **49**, 1613.

[25]. M. P. Morales, S. Veintemillas-Verdaguer and C. J. Serna, *J. Mater. Res*., **1999**, *14*, 3066.

[26]. Qiu, X.P., “Preparation and characterization of Fe3O4, magnetic nanoparticles”, *J. Xiamen Uni. (Nat. Sci. Ed.)*., **38** (5), 711 (**2008**). (in Chinese)

[27]. Teja, A.S.; Koh, P. Synthesis, properties, and applications of magnetic iron oxidenanoparticles. *Prog. Cryst. Growth Charact. Mater*. **2009**, *55*, *22*.

[28]. Massart, R.J., “Preparation of magnetite nanoparticles”, *IEEE Trans Magn*., *17*, 11247 (**1981**).

[29].Ang, B.C., Iskandar, I.Y., “Synthesis and characterization of magnetic iron oxide nanoparticles *via* w/o microemulsion and Massart’sprocedure”, *J. Mater. Process. Technol*., *191*, 235(**2007**).

[30]. Cabrera, L., Gutierrez, S., Menendezb, N., Morales, M.P.,Herrasti, P.: *Electrochim. Acta* **53**, 3436 (**2008**).

[31]. Teo, B.M.; Chen, F.; Hatton, T.A.; Grieser, F.; Ashokkumar, M. Novel one-pot synthesis ofmagnetite latex nanoparticles by ultrasound irradiation. *Langmuir* **2009**, *25*, 2593.

[32]. Maiyong Zhu and Guowang Diao*, *J. Phys. Chem. C*, **2011**, *115* (39), pp 18923.

[33]. J.-P. Jolivet, C. Chaneac and E. Tronc, *Chem. Commun*., **2004**,481.