Est. 1984

ORIENTAL JOURNAL OF CHEMISTRY
An International Open Access, Peer Reviewed Research Journal

www.orientjchem.org

ISSN: 0970-020 X
CODEN: OJCHEG
2019, Vol. 35, No.(2):
Pg. 863-869

Ferrocenyl Substituted Pyrazoles, Synthesis via novel route, Spectral Investigations and Their Biological Studies

MANOJ KUMAR[1]*, SHASHI SHARMA[1], HARDEEP SINGH TULI[2] and VINIT PARKASH[1]

[1]Department of Chemistry, M M University, Sadopur-Ambala, Haryana, India.
[2]Department of Biotechnology, M M D University, Mullana-Ambala, Haryana, India.
*Corresponding author E-mail: manojraju27@gmail.com

http://dx.doi.org/10.13005/ojc/350250

(Received: February 06, 2019; Accepted: April 06, 2019)

ABSTRACT

Ferrocenyl substituted heterocyclic compounds have wide range of medicinal approach. The synthesis of ferrocenyl substituted pyrazole is the new concern in these compounds with enhanced biological activities. This work focus on synthesis of ferrocenyl substituted pyrazoles via novel route. The synthesis of 1-phenyl-3-ferrocenyl-pyrazole was investigated involving Friedel Crafts acylation like reaction conditions. The reaction proceeded through three stages using addition cyclo-condensation of acetyl ferrocene with phenyl hydrazine followed by cyclization using cyclizing reagent iodine in presence of $NaHCO_3$. Individual product separated out having excellent yield (83%). Ferrocenyl substituted pyrazoles were characterized by spectroscopic methods (^{1}H NMR, IR, GC-MS) and their biological properties have been screened.

Keywords: Addition cyclo-condensation, Ferrocene, Pyrazole, Acylation, Biological-activities.

INTRODUCTION

Ferrocene are interesting and important class of molecules because of their high thermal stability, variable oxidation states, aromatic character and iron source. These properties make it more favourable for drug designing. From literature glance various alkaloids, vitamins, antibiotics are heterocyclic in nature thus heterocylic compounds have many pharmaceutical advantages. Ferrocenyl moiety increases the biological activity of heterocyclic compound basically in inhibition of tumour cell growth[1-5].

Ferrocenyl substituted pyrazole and similar series of substituted Ferrocenyl pyrazole synthesized from (2-formyl-1-chlorovinyl)Ferrocene[6] in 2005 by Goremen *et al.,* In 2007, 5-alkyl-2ferrocenyl 6,7-dihydropyrazolo[1,5-a]pyrazin-4[5H]-one complex and its derivatives having inhibitory effect towards A549 cancer cell growth was discovered[7]. New ferrocenyl derivatives of pyrazole analogues were prepared in 2014. One of them was (2-formyl-1-chlorovinyl)ferrocene prepared by using acetylferrocene. These compounds have anticancer and other biological activities[8].

(R)-N,N-dimethyl-1-[(S)-2-{3-(1-phenyl)-1H-pyrazolyl}ferrocenyl]ethylamine was synthesized from 1-(R)-N,N-dimethylferrocenylethylamine in 1999 by Burkhardt *et al.,* This research was a new approach in the field of chelating pyrazole-containing ligands[9]. Generally carbonyl compounds are raw material for the synthesis of many heterocyclic compounds but present study deals with acylation of ferrocene using little bit similar to Friedel Crafts Acylation. Novel approach reported in this study composed of two step synthesis for preparation of Ferrocenyl substituted pyrazole. Although many Friedel Craft acylation of ferrocene have been reported[10-14] earlier but this route is quite unique. This study explore novel route for synthesis of ferrocenyl substituted pyrazole under optimizing conditions.

MATERIALS & METHODS

All the chemicals used were of analytical grade procured from LOBA, MERK and OTTO. Solvents were distilled before use. Double distilled water is used. ^{1}H NMR spectra was recorded on BRUKER ADVANCE II 400 NMR Spectrometer at 400MHz. IR spectra was made using Perkin Elmer-Spectrum RX-IFTIR instrument samples were prepared as KBr pellets. Mass spectra(m/z) was made by using Gas Chromatography Mass Spectrometry through SAIF LAB Chandigarh.

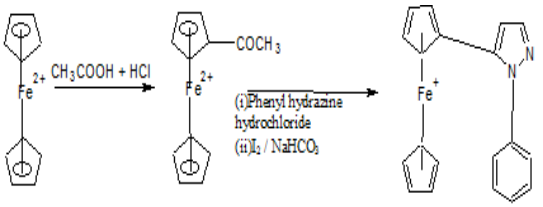
Synthesis

Synthesis of cyclopenta-2,4-dien-1-yl(2-(1-phenyl-1H-pyrazol-4-yl)cyclopenta-2,4-dien-1-yl)iron(III)

For the synthesis of 1-phenyl-3-ferrocenyl pyrazole Friedel Craft Acylation like technique was used. Although solubility of ferrocene created a problem because as such ferrocene was not soluble in acetic acid yet this situation was overcome by treatment of ferrocene with a mixture of concentrated HCl and acetic acid. A mixture of acetic acid (0.16mmol) and hydrochloric acid (0.13mmol) was treated with (0.005mole) ferrocene in presence of a pinch of Lewis acid ($AlCl_3$) by refluxing with vigorous stirring at 100^{0}C for two hour using magnetic stirrer with hot plate resulting in the synthesis of acetoferrocene.

Phenylhydrazine was added drop wise to acetoferrocene followed by refluxing with stirring using magnetic stirrer with hot plate at 60^{0}C for one hour. Reaction was carried out in addition -Cyclo condensation manner with removal of water molecule. 1-phenyl-3-ferrocenyl pyrazole was obtained as yellow solid by treatment the reaction mixture with iodine crystal (0.001mol) and 0.02mol) of sodium bicarbonate by refluxing at100^{0}C for three hours followed by quenching the reaction in ice.

IR (KBr, in cm^{-1}): 416(Cp-Fe-Cp Str.), 750(C-H Str.), 1148(C-N Str.), 1661(C=N Str.). ^{1}H nmr: (400MHz,DMSO, in ppm) δ:6.69-6.79(m,5H,Cp), δ:1.93(s,1H,allylic-H), δ:7.27-7.31(d,1H,Cis-H), δ:1.99-2.00 (d,1H,allylic-H), δ:8.75(s,1H,N-H), δ:4.30(s,1H,vinyl H), δ:2.48(s,1H,CH-N), δ: 7.00-7.16(m,5H,Ar-H). GC-MS (m/z): 328.02 found 328.17. Anal.Calc. for $C_{19}H_{17}{}^{56}FeN_2$: C, 69.54; H, 5.18; N, 8.54%. Found C, 69.09; H, 5.27; N, 8.19%.



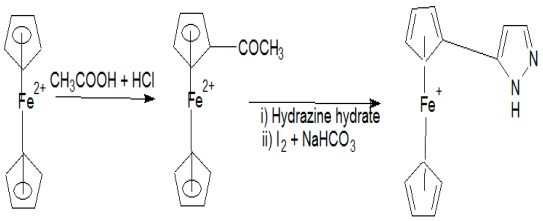
Scheme. 1

Synthesis of cyclopenta-2,4-dien-1-yl(2-(1H-pyrazol-4-yl)cyclopenta-2,4-dien-1-yl)iron(III)

1 (1-hydride pyrazole)ferrocene was synthesized by addition cyclo–condensation manner. Acetoferrocene was treated with (0.1M) hydrazine drop wise with vigorous stirring at room temperature for half an hour and mixture left undisturbed so that reaction ceases. Then the reaction mixture was refluxed using magnetic stirrer with hot plate to 100^{0}C for two hours.

Resultant product was obtained by treating reaction mixture with Iodine crystals(0.001mol)and 0.02mol) of sodium bicarbonate contained in a round bottom flask is refluxed using water bath to 100^{0}C for 2.5 hour followed by reaction in ice and solid was separated out.

IR (KBr, in cm^{-1}): 450,496(Cp-Fe-Cp Str.), 755(C-H Str.), 1158(C-N Str.), 1656(C=N Str.), 3260(N-H Str.), 3920(M-H asym. Str). ^{1}HNMR (400MHz,DMSO, in ppm): δ:6.62-6.69(m,5H,Cp), δ:1.83(s,1H,allylic-H), δ:7.17-7.21(d,1H,Cis-H), δ:8.77(s,1H,N-H), δ:4.33(s,1H,vinyl–H), δ:2.38(s,1H,CH-N), δ:7.01(s,1H). GC-MS (m/z): 252, found 252.59. Anal. Calc. for $C_{13}H_{12}{}^{56}FeN_2$: C, 61.95; H, 3.99; N, 11.11%. Found: C, 62.01; H, 3.90; N, 11.00 %.



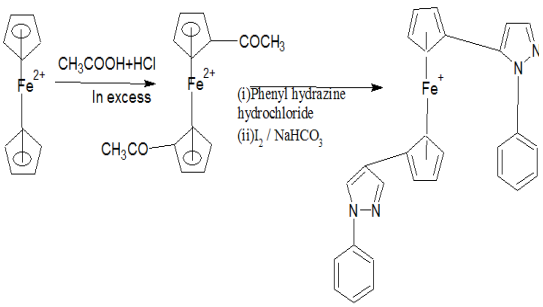
Scheme. 2

Synthesis of bis(2-(1-phenyl-1H-pyrazol-4-yl) cyclopenta-2,4-dien-1-1yl)iron(III)

bis(2-(1-phenyl-1H-pyrazol-4-yl) cyclopenta-2,4-dien-1-1yl)iron(III) was synthesized by diacetyl ferrocene treated with phenyl hydrazine hydrochloride. Diacetyl ferrocene mixed with phenyl hydrazine hydrochloride until the mixture became homogeneous at room temperature. Then the mixture was refluxed using magnetic stirrer with hot plate to 100^{0}C for 3 hour.

1,1bis(1, 1-di-phenyl-3-ferrocenyl pyrazole was obtained by treating reaction mixture with Iodine crystals(0.001mol)and 0.02mol) of sodium bicarbonate by refluxing to100^{0}C for three hour using magnetic stirrer with hot plate. Then hot mixture was poured in ice a crude solid was separated out and recrystallized with ethyl alcohol. Then new product 1,1-bis(1, 1-di-phenyl-3-ferrocenyl pyrazole was carried out.

IR (KBr, in cm^{-1}): 422(Cp-Fe–Cp Str.), 752(C-H Str.), 1133(C-N Str.), 1655(C=N Str.), 3259(N-H Str.), 3941(M-H asym. Str).^{1}HNMR (400MHz, DMSO)δ:6.44-6.49(m,5H,Cp), δ:1.96(s,1H,allylic-H), δ:7.07-7.11(d,1H,Cis-H), δ:1.98-2.00(d,1H,allylic-H), δ:8.73(s,1H,N-H), δ:4.30(s,1H,vinyl–H), δ:2.48(s,1H,CH-N), δ:7.00-7.16(m,5H,Ar-H) GC-MS (m/z): 473, found 473.18. Anal. Calc. for $C_{28}H_{24}{}^{56}FeN_4$: C,71.06; N, 11.84; H, 5.07%. Found C, 71.79; N, 11.34; H, 5.27%.



Scheme. 3

Biological Study

Antimicrobial Assay

In vitro antimicrobial activity has been evaluated for synthesized ligand against pathogenic strains of bacteria *(Staphylococcus aureus*, *Klebsiella pneumoniae*) and fungi (*Aspergillus niger, Trichophyton brubrum*) using disc plate diffusion assay. The stock solutions of ligand (1000 ppm) was prepared in DMSO. The plates of culture medium using nutrient agar and potato dextrose agar were prepared for bacterial and fungal growth respectively under sterilized condition. The various concentrations of ligand (100, 150, 200 and 250 ppm) were loaded on 5 mm sterilized filter paper discs and placed on agar plates followed by incubation at 30°C for 24 h and 72 h to evaluate the effect of compound on bacterial and fungal growth respectively. Neomycin and Fluconazole were used as standard antimicrobial agents for bacterial and fungal study respectively.

DNA photo-cleavage assay

DNA cleavage activity of the synthesized ligands were studied by agarose gel electrophoresis using supercoiled pUC19 plasmid DNA. The total volume of reaction mixture was 10 µl containing 0.5 µg of plasmid DNA in TE (Tris 10mM, EDTA 0.01mM, pH 8.0) buffer with various concentrations of synthesized ligands. The eppendorfs carrying reaction mixture were placed directly on the surface of a trans-illuminator (8000 mW/cm), at 360 nm for 30 minute. After irradiation, samples were further incubated at 37°C for 1 hour. Irradiated samples were mixed with 6X loading dye containing 0.25% bromophenol blue and 30% glycerol. The samples were then analyzed by electrophoresis on a 0.8% agarose horizontal slab gel in Tris-Acetate EDTA buffer (40 mMTris, 20 mM acetic acid, 1 mM EDTA, pH: 8.0) with comparison to untreated plasmid DNA as a control. Gel was stained with ethidium bromide (1 µg/ml) and photographed under UV light.

RESULT AND DISCUSSION

Spectral study of cyclopenta-2,4-dien-1-yl(2-(1-phenyl-1H-pyrazol-4-yl)cyclopenta-2,4-dien-1-yl) iron(III)

IR study: (cm^{-1}) Eclipsed Ferrocene shows

signal in region (400-500) for ten localised Fe-C bonds which is at 416 here. For aromatic C-H stretching out of plane bending is in between (900-690) which is at 750, C-N stretching is in region (1350-1000) which is at 1148, C=N stretching in region(1690-1640) which found in 1661, while N-H stretching is lies in between (3500-3100) meanwhile here is at 3264, asymmetric M-H str. is at 3939[15-17]. ^{1}H NMR study: (400MHz, DMSO, ppm) δ:6.69-6.79(m,5H,Cp), δ:1.93(s,1H,allylic-H), δ:7.27-7.31(d,1H,Cis-H), δ:1.99-2.00(d,1H,allylic-H), δ:8.75(s,1H,N-H), δ:4.30(s,1H,vinyl H), δ:2.48(s,1H,CH-N), δ:7.00-7.16(m,5H,Ar-H). cyclopentadienyl ring give chemical shift in between 6-8ppm in this value is 6.69 to 6.79 as a multiplet, allylic hydrogen have shift value ranging from 1.6-2.6ppm this peak is identified at 1.93 as a singlet, aromatic cis proton have shift value in region of 6-8ppm which is a doublet at 7.27 to 7.31, in the actual NMR spectra of acetylferrocene cyclopentadienyl ring has sharp singlet at 4.19 and singl *et at.,* 2.39 is for three equivalent protons of acetyl methyl group. Multiplets at 4.49 and 4.77ppm integrating for two types of protons in other cyclopentadienyl ring[18-19]. GC-MS: Calc: $C_{19}H_{17}{}^{56}FeN_2$: 328.02 found :328.17.

Spectral study of cyclopenta-2,4-dien-1-yl(2-(1H-pyrazol-4-yl)cyclopenta-2,4-dien-1-yl) iron(III)

IR study: Eclipsed Ferrocene shows signal in region (400-500) for ten localised Fe-C bondswhich is at 450 and 496. Aromatic C-H stretching out of plane bending is in between (900-690) which is at 755, C-N stretching is in region (1350-1000) which is at 1158, C=N stretching in region(1690-1640) which found in 1656, while N-H stretching is lies in between (3500-3100) meanwhile here is at 3260, asymmetric M-H str. is at 3920[20-21]. ^{1}H NMR study :(400M Hz,DMSO,ppm)δ:6.62-6.69(m,5H,Cp), δ:1.83(s,1H,allylic-H), δ:7.17-7.21(d,1H,Cis-H), δ:8.77(s,1H,N-H),δ:4.33(s,1H,vinyl–H), δ:2.38 (s,1H,CH-N), δ:7.01(s,1H). cyclopentadienyl ring give chemical shift in between 6-8ppm in this value is 6.62 to 6.69 as a multiplet, allylic hydrogen have shift value ranging from 1.6-2.6ppm this peak is identified at 1.83 as a singlet, aromatic cis proton have shift value in region of 6-8ppm which is a doublet at 7.17 to 7.21, N-H peak is identified at 8.77 meanwhile CH-N peak is at 2.38[22-23]. GC-MS: Calc: $C_{13}H_{12}{}^{56}FeN_2$: 252.03 found 252.09.

Spectral study of bis(2-(1-phenyl-1H-pyrazol-4-yl) cyclopenta-2,4-dien-1-yl)iron(III)

IR study: Eclipsed Ferrocene shows signal in region (400-500) for ten localized Fe-C bonds which is at 422. Aromatic C-H stretching out of plane bending is in between (900-690) which is at 752, C-N stretching is in region (1350-1000) which is at 1133, C=N stretching in region(1690-1640) which found in 1655, while N-H stretching is lies in between (3500-3100) meanwhile here is at 3259, asymmetric M-H str. is at 3941[24-25]. ^{1}H NMR study: (400MHz, DMSO, ppm) δ: 6.44-6.49 (m, 5H, Cp), δ:1.96 (s, 1H, allylic-H), δ:7.07-7.11(d, 1H, Cis-H), δ:1.98-2.00 (d, 1H, allylic-H), δ:8.73 (s, 1H, N-H), δ:4.30 (s, 1H, vinyl–H), δ:2.48 (s, 1H, CH-N), δ:7.00-7.16 (m, 5H, Ar-H) cyclopentadienyl ring give chemical shift in between 6-8ppm in this value is 6.44 to 6.49 as a multiplet, allylic hydrogen have shift value ranging from 1.6-2.6ppm this peak is identified at 1.96ppm as singlet, aromatic cis proton have shift value in region of 6-8ppm which is a doublet at 7.07 to 7.11[26-28]. GC-MS : Calc: $C_{28}H_{24}{}^{56}FeN_4$: 473.05 found 473.17.

Antimicrobial Activities

The antimicrobial effect of synthesized ferrocenyl substituted pyrazoles towards harmful human pathogenic microorganisms has been studied with comparison to Neomycin and Fluconazole. The compounds were found very potent against tested bacteria and fungi (Fig.1). The antimicrobial action of ferrocenyl substituted pyrazoles was measured in term of zone of inhibition (Table 1 to 3) and MIC values were found to be in the range of 75-90 µg/ml. Previous evidences have supported that pyrazole based derivatives possesses broad spectrum of antimicrobial effects. Bekhit and Abdel-Aziem investigated the antimicrobial effect of novel pyrazole[29] derivatives against *Gram-positive* and *Gram-negative* bacterial as well as pathogenic fungi. Recently Mandal et al. and Munyaneza *et al.,* have also reported the promising antimicrobial activities of metal complexes of pyrazole[30-31].

Table 1: Antimicrobial effects of cyclopenta-2,4-dien-1-yl(2-(1-phenyl-1H-pyrazol-4-yl)cyclopenta-2,4-dien-1-yl)iron(III) against bacterial and fungal strains

	Bacterial Strains (Zone of inhibition in mm)								Fungal Strains (Zone of inhibition in mm)							
	S. aureus				*K. pneumoniaae*				*A. niger*				*Trichophyton rubrum*			
Dosages	100 ppm	150 ppm	200 ppm	250 ppm	100 ppm	150 ppm	200 ppm	250 ppm	100 ppm	150 ppm	200 ppm	250 ppm	100 ppm	150 ppm	200 ppm	250 ppm
Zone of Inhibition	11 mm ±0.5	15 mm ±0.7	17 mm ±0.6	18 mm ±0.6	11 mm ±0.5	13 mm ±0.5	16 mm ±0.5	18 mm ±0.7	12 mm ±0.5	15 mm ±0.5	17 mm ±0.5	20 mm ±0.5	11 mm ±0.7	13 mm ±0.4	15 mm ±0.5	17 mm ±0.6
Standards	21 mm (Neomycin)				23 mm (Neomycin)				(24 mm) Fluconazole				(9 mm) Fluconazole			

Table 2: Antimicrobial effects of cyclopenta-2,4-dien-1-yl(2-(1H-pyrazol-4-yl)cyclopenta-2,4-dien-1-yl)iron(III) against bacterial and fungal strains

	Bacterial Strains (Zone of inhibition in mm)								Fungal Strains (Zone of inhibition in mm)							
	S. aureus				*K. pneumoniaae*				*A. niger*				*Trichophyton rubrum*			
Dosages	100 ppm	150 ppm	200 ppm	250 ppm	100 ppm	150 ppm	200 ppm	250 ppm	100 ppm	150 ppm	200 ppm	250 ppm	100 ppm	150 ppm	200 ppm	250 ppm
Zone of Inhibition	9 mm ±0.5	13 mm ±0.7	15 mm ±0.6	17 mm ±0.6	10 mm ±0.5	12 mm ±0.5	15 mm ±0.5	17 mm ±0.7	11 mm ±0.5	14 mm ±0.5	18 mm ±0.5	19 mm ±0.5	10 mm ±0.7	12 mm ±0.4	14 mm ±0.5	16 mm ±0.6
Standards	21 mm (Neomycin)				23 mm (Neomycin)				(24 mm) Fluconazole				(9 mm) Fluconazole			

Table 3: Antimicrobial effects of bis(2-(1-phenyl-1H-pyrazol-4-yl)cyclopenta-2,4-dien-1-1yl)iron(III) against bacterial and fungal strains

Bacterial Strains (Zone of inhibition in mm)					Fungal Strains (Zone of inhibition in mm)											
	S. aureus				*K. pneumoniaae*				*A. niger*				*Trichophyton rubrum*			
Dosages	100 ppm	150 ppm	200 ppm	250 ppm	100 ppm	150 ppm	200 ppm	250 ppm	100 ppm	150 ppm	200 ppm	250 ppm	100 ppm	150 ppm	200 ppm	250 ppm
Zone of Inhibition	12 mm ±0.5	17 mm ±0.7	19 mm ±0.6	20 mm ±0.6	14 mm ±0.5	16 mm ±0.5	18 mm ±0.5	21 mm ±0.7	13 mm ±0.5	16 mm ±0.5	20 mm ±0.5	22 mm ±0.5	11 mm ±0.7	16 mm ±0.4	18 mm ±0.5	19 mm ±0.6
Standards	21 mm (Neomycin)				23 mm (Neomycin)				(24 mm) Fluconazole				(9 mm) Fluconazole			

Fig.1. Antimicrobial Study of ferrocenyl substituted pyrazoles

DNA Photo-cleavage assay

The photo-induced DNA cleavage has been carried out using super coiled plasmid DNA by gel electrophoresis. The super coiled DNA (form I) migrate relatively fast with comparison to nicked DNA (form II). The conversion of form I to form II was observed with the treatment of synthesized ferrocenyl substituted pyrazoles in comparison to untreated plasmid DNA (Fig. 2) which indicates that ferrocenyl substituted pyrazoles have significant DNA-cleavage potential. Previously, Han *et al.,* have reported the role of pyrazole based ligands as promising DNA cleaving action[32] via hydrolytic mechanisms. More recently, Feng *et al.,* have investigated DNA binding capabilities of pyrazole derivatives and suggested their promising role in designing the chemotherapeutic drugs[33].

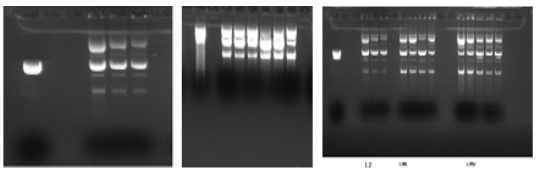


Fig. 2. DNA Photo-cleavage activity of ferrocenyl substituted pyrazoles

CONCLUSION

Three ferrocenyl substituted pyrazoles have been synthesized via novel route and characterized. It is clear from the evidences that such bonding is possible. The results of the experimental study of ferrocenyl substituted pyrazoles give new approach towards new structural motif and lights the probability that these compounds can be explored as potential biological agents which leads to further new research.

ACKNOWLEDGEMENT

The authors are thankful to MM University Trust, Ambala for the financial support during the course of this study.

Conflict of Interest

There is no conflict of interest among the authors regarding the publication of this manuscript.

REFERENCES

1. Bioani, M.; Gonzalez, M. *Med. Chem.,* **2005**, *5*, 409-418.
2. Lee, K.Y.; Kim , J.M.; Kim, J.N. *Tetrahedron Lett.*, **2003**, *44*, 6737-6742.
3. Jain, K.S.; Schitre, T.S.; Miniyar, P.B.; Kathiravan, M.K.; Bendre, V.S.; Veer, V.S.; Shahane, S.R.; Shishoo, C. *J. Curr. Sci.*, **2006**, *90*, 793-799.
4. Jin, Z. *Nat. Prod. Rep.*, **2006**, *23*, 464-496.
5. Melo, P.E.; Teresa, M.V.D. *Curr. Org. Chem.*, **2005**, *9*, 925-958.
6. Zora, M.; Gormen, M. *Jour. Organ. Chem.*, **2007**, *692*, 5026-5032.
7. Xia, Y.; Dong, Z.W.; Zhao, B.X.; Ge ,X.; Meng, N.; Shin, D.S. *Bioorg. Med. Chem.*, **2007**, *15*, 6893–6899.
8. Mandal, S.; Sadhukhan, R.; Ghosh, U.; Mandal,S.; Saha, M.; Ray J. *Jour. Corrd. Chem.*, **2016**, *69*, 1618-1634.
9. Burkhardt, U.; Drommi, D. *Inorganic chimica Acta.*, **1999**, *296*, 183-194.
10. Bishop, B.C.; Brands, K.M.J.; Gibb, A.A.; Kennedy, D. *J. Synthesis.*, **2004**, *1*, 43-52.
11. Szarka, Z.; Skoda-Foldes, R.; Balogh, J.; Kollar, L. *Tetrahedron Lett.*, **2001**, *42*, 539-768.
12. Szarka, Z.; Skoda-Foldes, R.; Kuik, A.; Berente, Z.; Kollar, L. *Synthesis.*, **2003**, *4*, 545-550.
13. Kuik, A.; Skoda- Foldes, R.; Balogh, J.; Kollar, L. *J. Organomet. Chem.*, **2005**, *690*, 3237-3242.
14. Balogh, J.; Zsoldos-Mady, V.; Frigyes, D.; Benyei, A.C.; Skoda Foldes, R.; Sohar, P. *J. Organomet. Chem.*, **2007**, *692*, 1614-1618.
15. Plazuk, D.; Zakrzewski, J. *J. Organomet. Chem.*, **2009**, *694*, 1802-18069.
16. Werner Angew, H. *Chem. Int. Ed.*, **2012**, *51*, 6052-6058.
17. Tirkey,V.; Mishra, S.; Dash, H.R.; Das, S.; Nayak, B.P.; Mobin, S. N.; Chatterjee, S. *J. Organomet. Chem.*, **2013**, *732*, 122-129.
18. Maguene, G.M.; Jakhlal, J.; Ladyman, M.; Vallin, A.; Ralambomanana, D.A.; Bousquet, T.; Maugein, J.; Lebibi, J.; Pelinski, L. *Eur. J. Med. Chem.*, **2011**, *46*, 31-38.
19. Astruc, D. *Tetrahedron.*, **1983**, *39*, 4027-4095.
20. Sahu, K. S.; Banerjee, M.; Samantray, A.; Behera, C.; Azam, A.M. *Tropical J. Pharma Res.*, **2008**, *2*, 961-968.
21. Holla, S.B.; Mahalinga, M.; Karthikeyau, S.M.; Akberali, M.P.; Shetty, S.N. *Bioorg. Med. Chem.*, **2006**, *14*, 2040-2047.
22. Katritzky, A.R.; Vakulenko, A.V.; Gedu, R.A.; Rogers, J.W. *ARKIVOC i.*, **2007**, *60*, 8555-8560.
23. Zhao, Li.J.; Zhao, Y.F.; Yuan, X.L.; Gong, P. Arech. *Pharm. Chem. Life Sci.*, **2006**, *339*, 593-597.
24. Yan, Z.R.; Liu, Y.X.; Xu F.W.; Pannecouque, C.; Trrouw, M.W.; Clereg, E. De. *Arech. Pharm. Res.*, **2006**, *29*, 957-962.
25. Perez-Rebolledo, A.; Ayala, J.D.; De Lima, G. M.; Marehini, N.; Bo-Mbieri, G.; Zani, C. L.; Souza-Fagundes E.M. *Eur. J. Med. Chem.*, **2005**, *40*, 467-472.
26. Tan, W.; Yu, Z.; He, W.; Wang, L.; Sun, J.; Chen, *J. Organometallics.,* **2008**, *27*, 4833-4836.
27. Kumar, M.; Verma. G.R. *Orient. J. Chem.*, **2010**, *26*, 517-525.
28. Kumar, M.; Jaipal. *Orient. J. Chem.*, **2007**, *23*, 705-712.
29. Bekhit, A. A.; Abdel-Aziem, T. *Bioorg. Med. Chem.*, **2004**, *12*, 1935–1945.
30. Mandal, S.; Mondal, M.; Biswas, J.K.; Cordes, D.B.; Slawin, A.M.Z.; Butcher, R.J.; Saha, M.; Saha, N.C. *J. Mol. Struct.*, **2018**, *1152*, 189–198.
31. Munyaneza, A.; Kumar, G. *Morobe I.C.*, **2018**, *3*, 1-8.
32. Han, C.; Guo, Y.C.; Wang, D.D.; Dai, X.J.; Wu, F.J.; Liu, H.F.; Dai, G.F.; Tao, J. C. Chin. *Chem. Lett.*, **2015**, *26*, 534–538.
33. Jiajia, F.; Hui ,Q.; Xiaoyang, Sun.; Siran, Feng.; Zhenming, Liu.; Yali, Song.; Xiaoqiang, Qiao. *Chem. Pharm. Bull.*, **2018**, *66*, 1065-1071.