Available online at **www.joac.info**

ISSN: 2278-1862

Journal of Applicable Chemistry

2023, 12 (5): 598-611

(International Peer Reviewed Journal)

Synthesis, Corrosion inhibition, and Pharmacological Activities and docking studies of (3-(4-halophenyl)-5-(4-halophenyl)-1H-pyrazol-1-yl) (2-(4-halophenyl) quinolin-4-yl) methanone hybrids

Balakrishna Kallauraya[1, 2]*, Venuprasad Kirumakki Dwarakanath[1], Priya[2], Ramesh Sooryanarayana Bhat[3], Alphonsus D'souza[4], Gururaja Rangaiah[5] and Prashant Nayak[6]

1. Department of Studies in Chemistry. Mangalore University, Mangalagangotri -574 199, Karnataka, **INDIA.**
2. Department of Chemistry, Yenepoya (Deemed to be University), YIASCM, Balmata Campus, Mangalore-575002 **INDIA.**
3. NITTE (Deemed to be University), Department of Chemistry, NMAM Institute of Technology, Nitte-574110, Karnataka, **INDIA.**
4. Department of Studies in Chemistry St.Philomenas College (Autonomous) Mysuru. 570015. Karnataka, **INDIA.**
5. Post graduate department of chemistry Sarada Vilas College, Mysuru-570015. Karnataka, **INDIA.**
6. Department of Pharmaceutical Sciences, Nitte (Deemed to be University), NGSM Institute of Pharmaceutical Sciences, Deralakatte, Mangaluru-575018, **INDIA**.

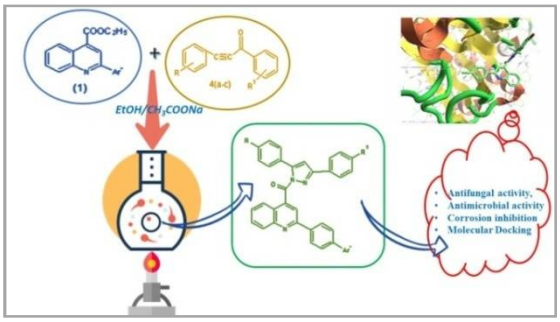
Email: bkalluraya@gmail.com

Accepted on 14th August, 2023

ABSTRACT

A novel series of 3,5-diaryl-1-(2-aryl-4-quinolinoyl) pyrazoline are synthesized by the reaction of 2-aryl-quinolinoylhydrazide (1) with 1,3-diaryl-2-propyne-1-one (3). The structures of the newly synthesized compounds are confirmed by analytical and spectral data. The biological activity study of the compounds indicated that most of the newly synthesized compounds showed good antibacterial activity. Further the docking experiments indicated that compound 5h showed good binding property with Glucosamine fructose-6-phosphateamino transferase. Similarly, the corrosion inhibition property as evaluated by potentiodynamic polarization technique. In the medium tested, the tested compound ***5a*** *demonstrated excellent inhibitory action against corrosion.*

Graphical Abstract:



Bioactive Pyrazole derivative

Keywords: Pyrazolines, Quinoline derivatives, antifungal activity, antimicrobial activity, corrosion inhibition.

INTRODUCTION

Pyrazoline,a five membered nitrogen containing heterocyclic compound is known to exhibit significant pharmacological properties. A wide range of biological activities including anticancer [**1**], anti-inflammatory [**2**], MAO-B inhibition [**3**], and antioxidant activity [**4**], have been linked to pyrazoline and its derivatives. The pyrazoline derivatives are utilized in wide variety of products, including agrochemicals, dyes, and analytical reagents [**5**]. Similarly substituted quinoline derivatives also show prominent biological activities including antibacterial, HIV-1 fusion inhibition, anticancer, anti-inflammatory, and antioxidant property, etc [**6-10**]. Prompted by these observations and in continuation of our effort to find biologically active heterocycles [**11-16**] herein we report the synthesis of 3, 5-diaryl-1-(2-arylquinolinoyl) pyrazolines (5a-i). The antibacterial activity of these compounds was assessed. Most of the newly synthesized pyrazoline derivatives showed significant antibacterial activity. Also, the newly synthesized pyrazoline derivatives showed effective corrosion inhibition against mild steel on exposure to 1N HCl.

MATERIALS AND METHODS

Materials and Methods: All the chemicals were procured from Merck Pvt. Ltd., and purified whenever needed. The structures of the newly synthesized compounds are established by analytical and spectral analysis. The melting points of the compounds are determined in open capillary tubes and are uncorrected. ^{1}H-NMR spectra were recorded on a Bruker Advance-II 400 MHz NMR spectrometer, using $CDCl_3$ as the solvent and tetramethyl silane (TMS) as the internal standard. The chemical shifts are expressed in delta scale. Water-Micro-mass Q-T of Micro LC mass spectrometer was used to record the mass spectra. Purity of the compounds was ascertained by TLC, using petroleum ether and ethyl acetate (9:1) as a mobile phase.

General Procedure for the Synthesis of 2-arylquinoline-4-carboxylic acid: A solution of NaOH (0.1mol, 4 g) and appropriately substituted is at in (0.2 mol) in water (50 mL) was heated on water bath for 45 min. To the clear solution acetophenone (0.02 mol, 3 mL) was added in small portions with occasional shaking, heating was continued for 4h and then the reaction mixture was chilled into ice bath. The solid obtained was collected by filtering through sintered glass crucible. The sodium salt of cinchonic acid thus obtained was dissolved in water (100 mL). The cinchonic acid was precipitated by neutralizing with glacial acetic acid. Melting Point: 260°C, Yield :88 %.

General procedure for the synthesis of ethyl-2-phenyl quinoline-4-carboxylate: 2-Phenylquinoline -4-carboxylic acid (0.01mol) in 20 mL of absolute alcohol and 0.5 mL conc. sulphuric acid was refluxed for 12 h. The excess alcohol was removed by distillation. The contents were cooled to room temperature, poured into ice. The product obtained was filtered through sintered glass crucible and dried. Melting Point: 138^{o}C, Yield: 82%,

General procedure for the synthesis of 2-arylquinoline -4-carbohydrazide: A mixture of ethyl-2-arylquinoline-4-carboxylate (0.01 mol) and hydrazine hydrate (0.5 mL, 0.01 mol) was taken in a round bottom flask and 20 mL of absolute alcohol was added. The contents were refluxed on a water bath, cooled to room temperature, and poured into ice. The solid product separated was collected by filtration and crystallized from absolute alcohol. Melting point: 158°C, Yield: 80 %.

General procedure for the preparation of 1,3-diaryl-2- propene-1-ones.2(a-c): To a mixture of substituted acetophenone (0.01 mol) and substituted aldehyde (0.01 mol) in ethanol (25 mL), 30% sodium hydroxide (5 mL) was added drop by drop under ice bath and the mixture was agitated for 4h

at room temperature. The solid separated was filtered, washed thoroughly with water, and recrystallized from absolute alcohol [19].

General procedure for the preparation of 2,3-dibromo-1,3-diaryl-2-propan-1-one-3(a-c): 1, 3 Diaryl -2-propene-1-one (0.01mol) in glacial acetic acid (10 mL) was added a solution of bromine (30**%** in acetic acid) drop wise with stirring until the colour of the bromine persisted. The reaction mixture was then allowed to stand at room temperature overnight. The crystals of 2,3-dibromo-1,3-diarylpropan-1-one separated was filtered and washed with petroleum ether. It was dried and recrystallized from glacial acetic acid.

General procedure for the preparation of 1,3-diaryl-2-propyne-1-one. 4(a-c): To a suspension of 2, 3-dibromo-1,3-diarylpropan-1-one (0.01mol) in dry benzene (20 mL) added tri ethylamine (0.04mol in 5 mL dry benzene). The resulting yellow solution was allowed to stir at room temperature for 24h. After the completion of the reaction, the solution was filtered and the excess benzene was removed under vacuum and allowed to stand overnight. The solid crystals separated were collected by filtration. Propynones prepared as per this procedure are, 3-(4-chlorophenyl)-1-phenylprop-2-yn-1-one, 3-(4-bromophenyl)-1-(4-chlorophenyl)prop-2-yn-1-one,1,3-bis(4-chlorophenyl)prop-2-yn-1-one were prepared.

General procedure for the preparation of 3,5-diaryl-1-(2-aryl-4-quinolinoyl) pyrazoline 5(a-i): A mixture of 2-aryl-quinoline-4-carbohydrazide (0.01 mol) in alcohol (20 mL) was taken in a round bottom flask fitted with a reflux condenser, to that propynone (4a-c) (0.01 mol) was added, followed by sodium acetate (0.82 g) and the contents were refluxed for 6hrs, cooled to room temperature, and poured into ice-cold water (100 mL). The crystals separated was collected by filtration and further purified by recrystallization from absolute alcohol (Table 1).

Table 1. Characterization data of Pyrazolines (5a-i)

Comp No.	R	R^1	Ar	Melting Point / ^{0}C	Mol. Formula (Mol. Wt)	Yield / %	Elemental analysis found (calculated) / %		
							C	H	N
5a	p-Cl	Phenyl	p-Br	142	$C_{31}H_{19}BrClN_3O$ (564)	80	65.92 (65.86)	3.39 (3.36)	7.44 (7.40)
5b	p-Br	p-Cl	p-Br	145	$C_{31}H_{18}Br_2ClN_3O$ (643)	77	57.84 (57.79)	2.82 (2.78)	6.53 (6.50)
5c	p-Cl	p-Cl	p-Br	143	$C_{31}H_{18}BrCl_2N_3O$ (599)	82	62.13 (62.08)	3.03 (3.00)	7.01 (6.59)
5d	p-Cl	phenyl	Phenyl	140	$C_{31}H_{20}ClN_3O$ (485)	78	76.62 (76.70)	4.15 (4.13)	8.65 (8.62)
5e	p-Cl	p-Br	Phenyl	139	$C_{31}H_{19}BrClN_3O$ (564)	76	65.92 (65.90)	3.39 (3.36)	7.44 (7.40)
5f	p-Cl	p-Cl	Phenyl	138	$C_{31}H_{19}Cl_2N_3O$ (520)	75	71.55 (71.53)	3.68 (3.66)	8.07 (8.03)
5g	p-Cl	Phenyl	p-Cl	136	$C_{31}H_{19}Cl_2N_3O$ (520)	74	71.55 (71.52)	3.68 (3.66)	8.07 (8.03)
5h	p-Cl	p-Br	p-Cl	143	$C_{31}H_{18}BrCl_2N_3O$ (599)	82	62.13 (62.10)	3.03 (3.00)	7.01 (7.00)
5i	p-Cl	p-Cl	p-Cl	144	$C_{31}H_{18}Cl_3N_3O$ (554)	81	67.11 (67.08)	3.27 (3.25)	7.57 (7.54)

Solvent of crystallization: Ethanol

Corrosion studies:

Preparation of Specimen: Mild steel specimens of composition (0.03 %P; 0.03 % Si; 0.04 %Ni; 0.4 % Mn; 0.06 % C; 0.03 % S; 0.003 % Mo; the balance was Fe) were used for corrosion studies. Specimens of size 1 cm ×1 cm were used for electrochemical studies. The specimen was embedded in epoxy resin leaving a working area of 1 cm^2. The surface was mechanically polished with different

grades of silicon carbide sandpaper (up to 1200 grit), rinsed with deionized water, and finally cleaned with acetone, and the same procedure was performed before each experiment.

Preparation of electrolyte: The electrolyte of 1N HCl solution was prepared by diluting 37 % HCl (Merck) using deionized water which is used as a corrosive media. The inhibitor solution was prepared by dissolving 50 mg L^{-1} of inhibitor (5a) in 1N HCl acid solution and the inhibition effect was investigated.

Potentiostat (CH-instrument beta software) was used to carry out electrochemical studies of mild steel (MS). In the presence and absence of an inhibitor at 30°C, the polished MS was exposed to a corrosive medium of 1N HCl and permitted the establishment of a steady state open circuit potential (OCP). Potentiodynamic polarization measurements were produced from OCP with a scan rate of 0.1 mVs^{-1} in a potential range of ± 200 mV and the potentiodynamic current-potential (I-E) plots were recorded from the literature [**20**]. Corrosion potential (E_{corr}), corrosion current density (i_{corr}), and CR are recorded. The EIS studies were performed by impressing OCP of 10 mV amplitude AC signal with a frequency range from 10000 Hz to 0.01 Hz.

Pharmacological Activities

Antibacterial Activity: The antibacterial efficacy of the newly synthesized compounds was tested against four different pathogenic organisms, including two Gram-positive and two Gram-negative bacteria. Gram-positive bacteria include Staphylococcus aureus and Bacillus subtilis, while Gram-negative bacteria include Escherichia coli and Pseudomonas aeruginosa. The antibacterial activity of newly synthesised compounds was determined using the Minimum Inhibitory Concentration (MIC) method via serial dilution in the current experiment [**21**].

Preparation of standard and test solution: Ofloxacin was the standard employed. In separate 10 mL of DMF solutions, 10 µg of Ofloxacin and 10 µg of the test compounds were dissolved. Pipette out 0.1, 0.2, 0.4, 0.8, and 1.0 mL from this stock solution, then diluted with 10 mL of DMF.

Preparation of Nutrient agar Media: The basal medium, called nutrient agar, was made by dissolving 15 g L^{-1} of agar, 5 g $L^{-1}$of sodium chloride (bacteriological), 1.5 g L^{-1} of beef extract, and 5 g L^{-1} of the peptic digest for animal tissue. The pH of the agar medium was raised to 7.4. 28 g of nutritional agar were dissolved in 1000 mL of water and heated to boiling to completely dissolve the material. Autoclaved for 15 minutes at 121°C and 15 lbs of pressure to sterilize.

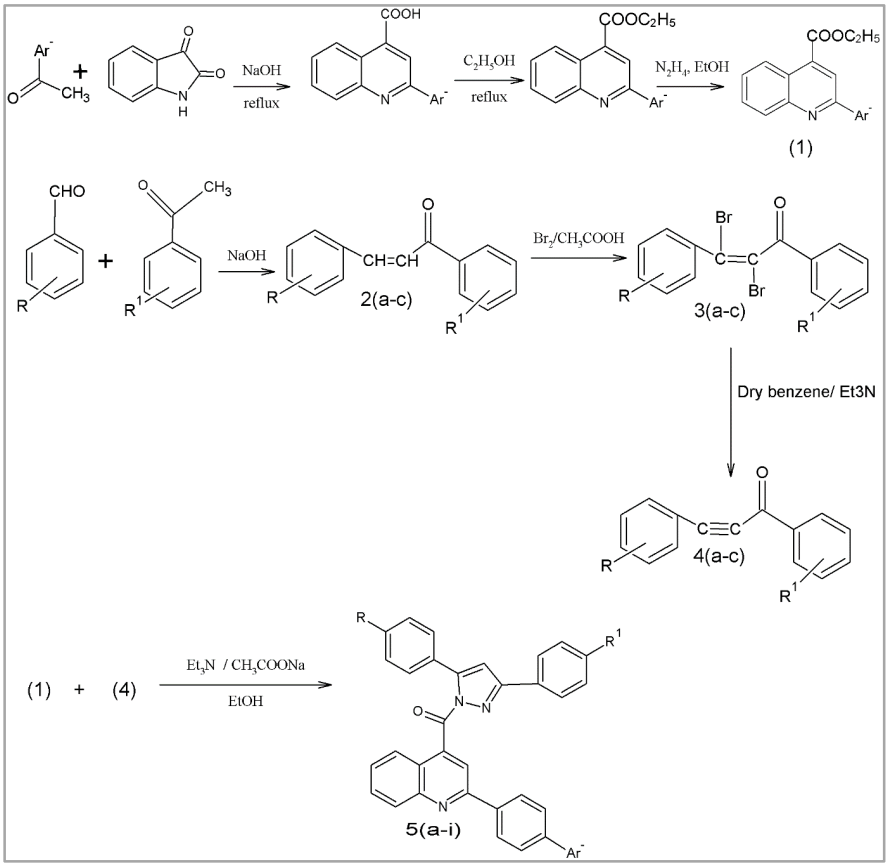
Method of testing: The sterilized media was chilled to a temperature of at 40°C; the necessary organism was inoculated with 0.2 mL of its subculture. This inoculated media was placed in 20 mL portions into sterile, previously labelled Petri plates, and allowed to solidify. The cups are then made using a cork borer. The cups were carefully filled with the test substance in various quantities together with the standard, and they were then incubated at 37°C for 24 h. After 24 h, the minimal concentration at which the zone of inhibition could be seen was observed. The results of the tested samples are shown in table 3.

RESULTS AND DISCUSSION

Chemistry: The 1,3-diaryl-2-propene-1-ones were obtained by the Claisen-Schmidt condensation of appropriate ketones and aldehydes in alcohol medium employing sodium hydroxide. These propenones on bromination with bromine in glacial acetic acid gave dibromo-propanone (3).

These di-bromopropanones, when treated with excess of triethylamine in dry benzene medium underwent dehydrobromination to give propynones (4). Quinoline-4-carboxylic acid upon esterification followed by hydrazinolysis with hydrazine hydrate gave the corresponding hydrazide (1). Reaction of propynones (4) with 2-aryl-4-quinolinoylhydrazide (1) in alcohol medium in the presence of sodium acetate as catalyst gave pyrazolines(5) [**22**]. The synthetic route for the

preparation of compounds (5) is outlined in Scheme 1. The IR spectra of propynones showed absorption bands in the region of 1690-1700 cm^{-1} for the carbonyl moiety, whereas the acetylenic stretching band was observed at 2250 cm^{-1}. The IR spectrum of compound 5 h showed an absorption band at 1717.80, due to the N-acetyl carbonyl stretching, while the C=N stretch was observed around 1214-1359cm^{-1}. In the ^{1}H - NMR spectrum of the compound, 5 h the signal due to aromatic peaks of the Quinolines ring and other phenyl ring protons overlapped with each other and appeared as multiplets in the region of 7.2-8.22 ppm. Further in the ^{13}C NMR the carbonyl carbon resonated at 176 ppm while other carbons appeared in the region of 110-120 ppm. Further the mass spectrum of this compound showed the molecular ion peak at m/z, 599, in conformity with the assigned molecular formulae $C_{31}H_{18}N_3OBrCl_2$.



Scheme 1. Synthesis of methanone hydrids.

Potentiodynamic polarization study: Investigators have investigated the impact of inhibitor concentration on corrosion rate and MS. Figure 1 displays the potentiodynamic polarization plots of MS in 1N HCl with and without inhibitors. Table 2 lists the electrochemical parameters, including the cathodic Tafel slope (βc), the anodic Tafel slope (βa), the corrosion potential (E_{corr}), the corrosion current density (i_{corr}), and more. The electrochemical data such as i_{corr} and E_{corr}, βc, and βa obtained by the CH instrument after applying the density of Fe-7.8 gcm^{-3}, the atomic weight of Fe-55.84, and the oxidation state (2) of Fe [23].

Table 2. Potentiodynamic polarization data of MS in 1 N HCl with and without inhibitor

Sample	E_{corr}/V	Ba/Vdec^{-1}	Bc/Vdec^{-1}	i_{corr}/µAcm^{-2}	IE/%
Withinhibitor(5a)	-0.604	8.12	6.25	0.550	91.14
Withoutinhibitor	-0.710	20.21	5.98	6.210	-

The percentage inhibition efficiency of the inhibitor may be calculated by using the Equation given below.

$$\%IE = \frac{i_{corr(0)} - i_{corr(in)}}{i_{corr(0)}} \times 100$$

Where the corrosion current densities in the absence and presence of the inhibitor, respectively, are denoted by $i_{corr(o)}$ and $i_{corr(in)}$. In the presence of an inhibitor, the mild steel corrosion current density decreased [**24**]. When comparing MS to a blank, the overall corrosion potential was switched to cathodic. The potentiodynamic polarisation curves inhibit both the cathodic and anodic reactions (Figure 1). As a result, the inhibitor has a mixed type action that leans more toward a cathodic effect. The inhibitor (5a) exhibits better inhibition efficiency (91.14**%**), as determined from the literature, at room temperature [**21**]. The i_{corr} decreases in the presence of an inhibitor, as demonstrated in table 2. As a result, the inhibitor's efficiency of inhibition increases [**25**].

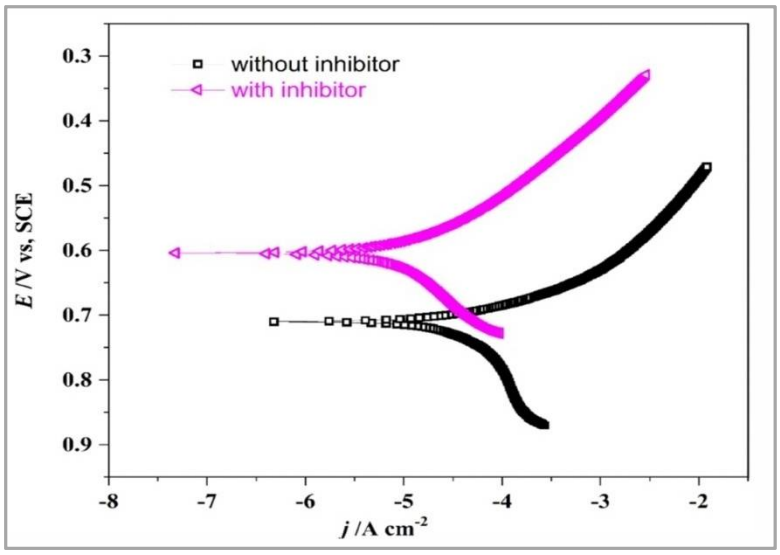


Figure 1. polarization plot for MS in 1N HCl with and without inhibitor.

Electrochemical impedance analysis: Figure 2 displays the Nyquist plots of mild steel (MS) in 1N HCl solutions in both the absence and presence of the inhibitor (5a) at 30**℃**. The depression (Figure 2) is a sign of the metal surface in homogeneities during corrosion [**18**]. Corrosion resistance is represented by the diameter of the capacitive loop, and as the diameter of the capacitive loop lowers, the corrosion resistance also considerably reduces. The size of the capacitive loop grew with inhibitor concentration, increasing corrosion resistance, as seen by the electrochemical impedance plot (Figure 2). By utilizing ZSimpWin software version 3.21 to fit an appropriate equivalent circuit to the Nyquist plots under the experimental findings, the impedance parameters were examined. The electrical equivalent circuit made up of inductive/resistive/capacitive elements in series and parallel, with circuit description code LR(Q(R(C(R(LR)(CR)), was proposed. It is depicted in figure 3 and was used to replicate the impedance plot for mild steel with inhibitor. There are nine components in the circuit. The comparable circuit is composed of the solution resistance (R_s), charge transfer resistance (R_{ct}), inductive resistance (R_L), and the inductive element (L). The capacitor series C_1 and C_2 as well as the constant phase element (CPE), Q, is parallel to the resistor series R_1, R_2, R_L, and R_{ct}. The oxide layer is responsible for the parallel circuit because of its ionic conduction, and capacitance. The parallel circuit of a resistor is attributed to an oxide film due to the ionic conduction in oxide film and the capacitance due to its dielectric properties. The results of electrochemical impedance and potentiodynamic polarisation measurements are in strong agreement with each other. This indicates

that the CR depends more on the type of inhibitor used not on the measurement. Therefore, inhibitors can effectively prevent the corrosion of MS [17].

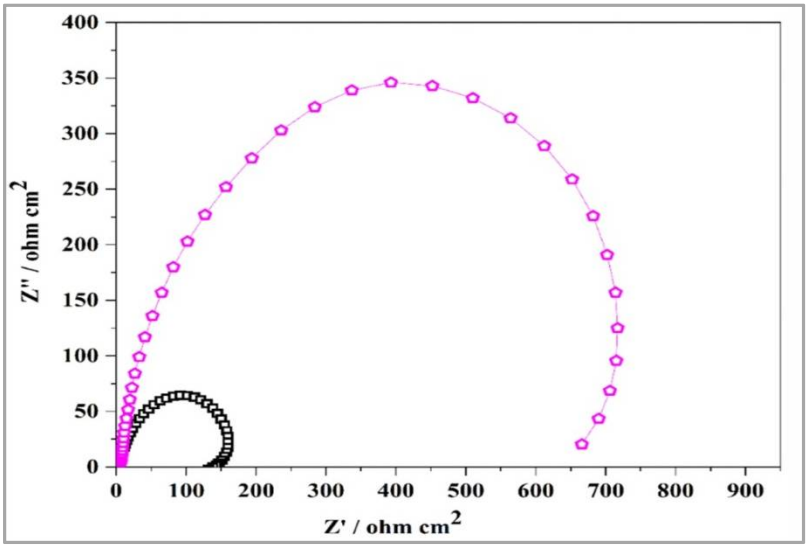


Figure 2. EIS plot of MS in 1 N HCl with and without inhibitor

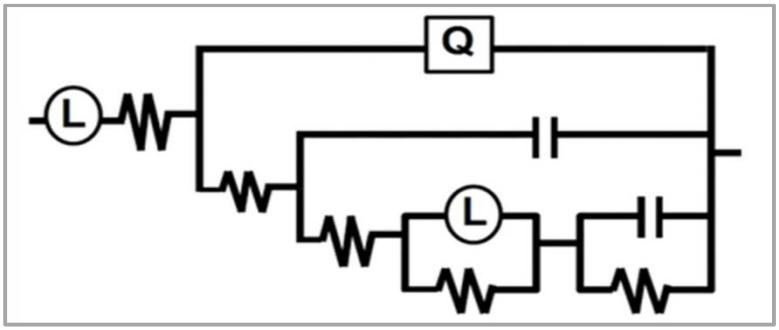


Figure 3. Equivalent circuit was employed to reproduce the impedance curve for MS with inhibitor (5a).

Antibacterial activity: The newly synthesized compounds were tested for their antibacterial effectiveness against four pathogenic bacteria, including *S. aureus*, *B. subtilis* (Gram-positive), *Escherichia coli, and P. aeruginosa* (Gram-negative). Most of the compounds showed antibacterial activity that was moderate to good and comparable to that of standard *ofloxacin*. Among the substances examined, compound 5h demonstrated antibacterial activity that was comparable to that of standards.The bacterial zones of inhibition values are presented in table 3.

Table 3. Antibacterial activity data of compounds (5a-5i)

Sl.No	*E.Coli*	*S.Aureus*	*P. Aureginosa*	*B.Subtilis*
5a	22.4±0.21	17.2±0.28	21.8±0.31	16.2±0.12
5b	21.7±0.40	18.2±0.46	20.5±0.23	15.2±0.94
5c	20.7±0.29	29.3±0.15	31.2± 0.23	30.2±0.83
5d	20.1±0.38	16.8±0.27	22.3±0.12	14.8±0.64
5e	19.7±0.16	15.2±0.46	18.5±0.79	19.2±0.73
5f	18.5±0.23	17.8±0.87	17.6±0.42	20.4±0.61
5g	19.5±0.20	22.4±0.36	23.5±0.38	26.2±0.86
5h	**30.4±0.35**	**29.6±0.19**	**31.2± 0.23**	**30.2±0.83**
5i	18.4±0.25	19.0±0.34	19.6±0.26	25.5± 0.46
Ofloxacin	31.2±0.28	30.4±0.18	30.9± 024	29.3±0.26

Molecular docking

Protein preparation: In the present study, the structure of Glutaminase domain of GLMS complexes with glutamate (PDB ID: 1XFF) was downloaded from a protein data bank (https://www.rcsb.org/) and prepared using the protein preparation module available in cresset flare. During the preparation, missing residues, side chain atoms, and hydrogens were added. Further, a series of energy minimizations were undertaken to attain the overall stability of the protein. The minimized protein conformation was used for molecular docking. The results are presented in table 4.

Table 4. Docking energy of (2-(4-halosubstituted phenyl) quinolin-4-yl) (5-(4-halosubstituted phenyl)-3-phenyl-1H-pyrazol-1-yl) methanonederivatives with Glutaminase domain of Glucosamine--fructose-6-phosphate aminotransferase (1XFF).

Compounds	Docking energy kcalmol^{-1}
5a	-6.18
5b	-6.62
5c	-6.39
5d	-6.08
5e	-5.25
5f	-5.07
5g	-6.43
5h	**-7.22**
5i	-6.01

Rationale for target selection: Glucosamine-fructose-6-phosphate aminotransferase (GLMS) also called as Glucosamine-6-phosphate synthase catalyzes the first step in hexosamine metabolism, converting fructose-6P into glucosamine-6P using glutamine as a nitrogen source. There are several inhibitors of GLMS which show antibacterial and antifungal activity [21-24]. All the compounds (5a-5i) were screened for docking studies and the docking energies are shown in table 4. To dock (2-(4-halosubstituted phenyl) quinolin-4-yl) (5-(4-halosubstituted phenyl)-3-phenyl-1H-pyrazol-1-yl) methanone and its derivatives to GLMS, the co-crystal (Glutamic acid) binding site was considered as a substrate-binding/catalytic site. Hence, the co-crystal centric grid box with 10Å was generated on the GLMS structure. The molecular docking was performed using a cresset flare to find the lowest energy conformation in which 5h derivative (Figure 4) can interact with GLMS.

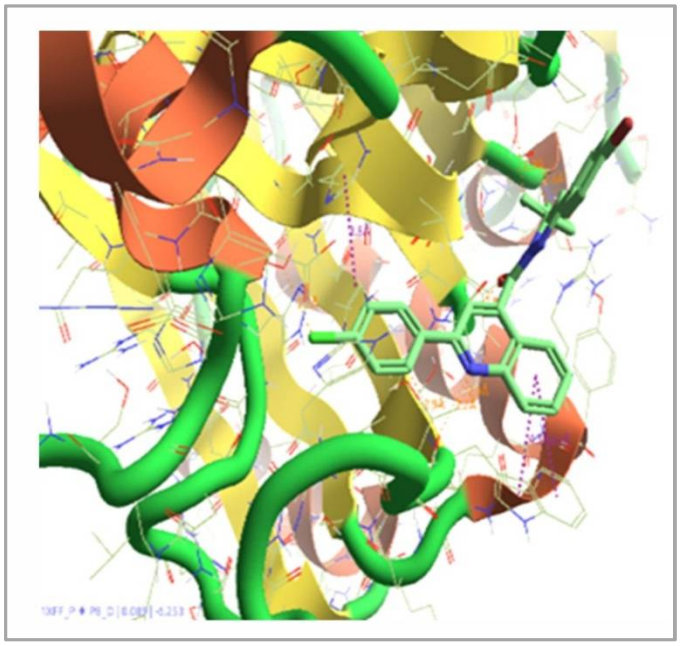


Figure 4. Visualizations of 2D diagrams, binding pocket compound (5h).

APPLICATION

The work is both theoretical and applied .it involves synthesis of new derivatives of nitrogen compound and its pharmacological and corrosion inhibition property studies.

CONCLUSION

Syntheses of a novel series of pyrazoline carrying quinolone moiety are reported. The newly synthesized compounds showed reasonably good antibacterial activity and compound 5h showed significant corrosion inhibition property. The synthesized compounds are tested for their ability to combat microbes and all of them had considerable antibacterial activity at 0.1 mL dilution in that compound 5h showed highest activity. Therefore, these derivatives might be regarded as effective antibacterial agent. Finally, all the compounds were screened for docking studies. The docking was performed using a cresset flare to find the lowest energy conformation in which 5h derivative can interact with GLMS.

Conflict of interests: The authors declare that there is no conflict of interest.

ACKNOWLEDGMENT

The authors are thankful to the Nitte University, St.Philomenas College (Autonomous), Mysuru, PURSE, Mangalore University, Mangalore, for spectral and analytical data.

Supplementary data of Synthesized Compounds

Spectral data of Synthesized compounds:

Compound 2c: IR (A.T.R, cm^{-1}): 690 (C-Br Stretch), 1600(C=C Stretch), 1696(C=O Stretch), 3096(C-H stretch, Aromatic).

Compound 3c: IR (A.T. R, cm^{-1}): 2250 (-C≡C- Stretch), 1696(C=O stretch), 3096(C-H Stretch, Aromatic). Melting Point is 188°C.

Compound 5a: ^{1}H NMR (400 MHz, DMSO-d^6): δ 8.942-8.919 (s, 3H), 8.882 (d, J = 8.5, 1.4 Hz, 2H), 8.229 – 7.98 (m, 6H), 7.752 – 7.296 (m, 8H).
13C NMR (100 MHz, DMSO-d^6):δ 176.171 (s), 173.046 (s),173.042 (s), 172.024 (s), 171.993(s), 170.964(s), 168.948 (s), 139.171 (s), 136.042 (s), 135.024 (s), 134.021 (s), 133.974-133.952(m), 132.940 (s), 131.928(s), 120.564 (s), 120.554 (s), 115.375(s), 114.355 (s), 113.366 (s), 113.317 (s), 112.296 (s), 112.269 (s),110.174(s),109.155(s).m/z:(M^+):565; **IR(A.T.R,cm^{-1})**:1720.56(-C=O-stretching),1212.30-1357.93(C=N stretching).

Compound 5b: ^{1}H NMR (400 MHz): δ9.947(s, 1H), 8.881-8.845 (d, J = 8.6, 0.8 Hz, 2H), 8.824-8.802 (d, J = 7.2, 1.9 Hz, 1H), 8.740-7.991(m, 6H), 7.991-7.576 (m, 3H), 6.846-6.823 (m, 3H). ^{13}C NMR (100MHz)δ: 176.571 (s), 173.146 (s), 172.024(s),171.793 (s), 170.764-168.848 (m), 139.371(s),137.246(s),136.342(s),135.224(s),134.121(s),133.974133.952(m),132.840(s),131.828(s),120.964(s),120.654(s),120.444(s),115.575(s),114.455(s),113.436(s),113.417(s),112.396(s),111.369(s), 110.274(s),109.255(s).m/z(M^{+2}):645; IR (A.T.R, cm^{-1}):1719.81(-C=O-stretching),1215-1359.86(C=N stretching).

Compound 5c: ^{1}H NMR (400 MHz, DMSO-d^6) δ**:** 9.562 (s, 1H), 7.843-7.821 (d, J = 9, 0.8 Hz, 2H), 7.728-7.707(s,1H),7.686-7.589(s,1H),7.567-7.131(m,3H),6.973-6.554(m,9H). ^{13}C-NMR(100MHz, DMSOd^6)δ**:**175.571(s),173.246(s),173.242(s),171.793(s),171.024(s),171.764169.048(m),139.971(s),137.146(s),136.342(s),135.124(s),134.021(s),133.774133.652(m),132.840(s),131.828(s),120.964(s),12

0.654(s),120.444(s),115.575(s),114.455(s),113.436(s),113.417(s),112.396(s),113.369(s),110.274(s),109.255(s).m/z(M^+):599; IR (A.T.R, cm^{-1}):1702.24(-C=O-stretching),1211.34-1356.97(C=N stretching).

Compound 5d: ^{1}H NMR (400 MHz, DMSO-d^6) δ**:** 8.947-8.918 (s, 3H), 8.884 (d, *J* = 8.5, 1.4 Hz, 2H), 8.227 – 7.97 (m, 6H), 7.751 – 7.295 (m, 8H). ^{13}C NMR (100 MHz, DMSO-d^6): δ 176.170 (s), 173.05 (s),173.041 (s), 172.023 (s), 171.992(s), 170.962(s), 168.946 (s), 139.170 (s), 136.041 (s), 135.023 (s), 134.022 (s), 133.972-133.951(m), 132.939 (s), 131.926(s), 120.562 (s), 120.552 (s), 115.374(s), 114.353 (s), 113.362 (s), 113.313 (s), 112.294 (s), 112.267 (s),110.172(s), 109.153(s).m/z(M^+):609; IR (A.T.R, cm^{-1}):1720.53(-C=O- stretching),1212.29-1357.89(C=N stretching).

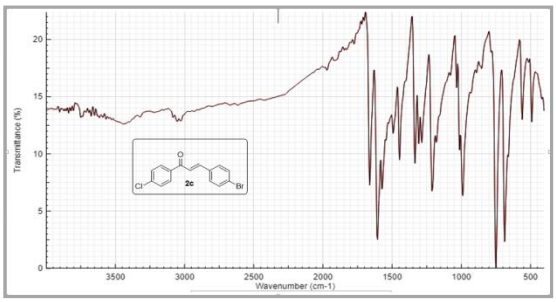
Compound 5e: ^{1}H- NMR (400 MHz):δ 9.946(s, 1H), 8.880-8.843 (d, J = 8.6, 0.8 Hz, 2H), 8.822-8.801 (d, J = 7.2, 1.9 Hz, 1H), 8.739-7.889(m, 6H), 7.992-7.577 (m, 3H), 6.847-6.824 (m, 3H).
^{13}C- NMR (100MHz) δ: 176.572 (s), 173.148 (s), 172.025(s),171.794 (s), 170.765-168.849 (m),139.372(s),137.248(s),136.344(s),135.225(s),134.120(s),133.975,133.953(m),132.841(s),131.829 (s),120.965(s),120.656(s),120.445(s),115.576(s),114.458(s),113.437(s),113.418(s),112.397(s),111.370 (s),110.275(s),109.256(s). m/z(M^+):563; IR(A.T.R,cm^{-1}):1717.80(-C=O-stretching),1214-1359.84 (C=N stretching).

Compound 5f: ^{1}H- NMR (400 MHz, DMSO-d^6) δ: 9.564 (s, 1H), 7.842-7.820 (d, J = 9, 0.8 Hz, 2H), 7.729-7.706(s,1H),7.685-7.590(s,1H),7.566-7.130(m,3H),6.972-6.552(m,9H). ^{13}C-NMR (100MHz, DMSOd^6)δ**:**175.572(s),173.246(s),173.241(s),171.792(s),171.025(s),171.765(s)169.048(m),139.970(s),137.142(s),136.340(s),135.123(s),134.021(s),133.774133.652(m),132.840(s),131.828(s),120.965(s), 120.655(s),120.445(s),115.576(s),114.456(s),113.437(s),113.418(s),112.397(s),113.367(s),110.273(s), 109.253(s). m/z(M^{+2}):521; IR (A.T.R, cm^{-1}):1702.21(-C=O-stretching), 1211.32-1356.94 (C=N stretching).

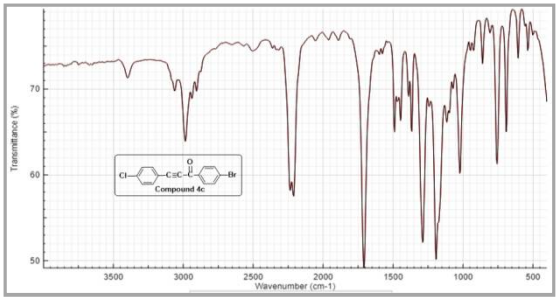
Compound 5g: ^{1}H- NMR (400 MHz, DMSO-d^6) δ: 8.943-8.920(s, 3H), 8.885 (d, J = 8.5, 1.4 Hz, 2H), 8.228 – 7.98 (m, 6H), 7.753 – 7.28 (m, 8H). ^{13}C- NMR (100 MHz, DMSO-d^6): δ 176.171 (s), 173.04 (s),173.042 (s), 172.024 (s), 171.993(s), 170.963(s), 168.947 (s), 139.171 (s), 136.042 (s), 135.024 (s), 134.023 (s), 133.973-133.952(m), 132.940 (s), 131.927(s), 120.564(s), 120.553 (s), 115.375(s), 114.356 (s), 113.363(s), 113.314 (s), 112.295 (s), 112.268 (s),110.173(s),109.152(s). m/z(M^+):521; IR (A.T.R, cm^{-1}):1720.51(-C=O- stretching), 1212.27-1357.86(C=N stretching).

Compound 5h: ^{1}H -NMR (400 MHz): δ 9.945 (s, 1H), 8.880-8.843 (d, J = 8.6, 0.8 Hz, 2H), 8.822-8.801 (d, J = 7.2, 1.9 Hz, 1H), 8.742-7.993 (m, 6H), 7.993-7.578 (m, 3H), 6.845-6.822 (m, 3H).
^{13}C-NMR(100MHz)δ: 176.572 (s), 173.147 (s), 172.025(s),171.792 (s), 170.765-168.849 (m), 139.373(s),137.247(s),136.343(s),135.225(s),134.120(s),133.975,133.954(m),132.842(s),131.830(s),120.965(s),120.657(s),120.445(s),115.576(s),114.457(s),113.437(s),113.414(s),112.398(s),111.365(s),110.273(s),109.254(s). m/z(M+2):599; IR (A.T.R, cm^{-1}):1719.812(-C=O-stretching), 1216-1359.88 (C=N stretching).

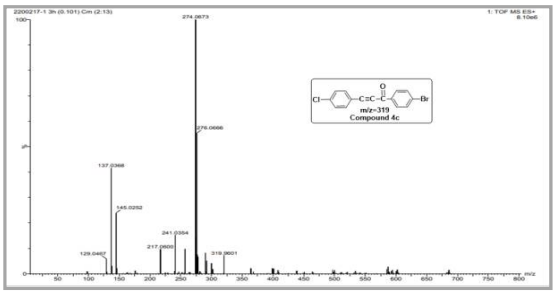
Compound 5i: ^{1}H- NMR (400 MHz, DMSO-d^6) δ: 8.943-8.920(s, 3H), 8.885 (d, J = 8.5, 1.4 Hz, 2H), 8.228 – 7.98 (m, 6H), 7.753 – 7.28 (m, 8H). ^{13}C- NMR(100 MHz, DMSO-d^6): δ 176.171 (s), 173.04 (s),173.042 (s), 172.024 (s), 171.993(s), 170.963(s), 168.947 (s), 139.171 (s), 136.042 (s), 135.024 (s), 134.023 (s), 133.973-133.952(m), 132.940 (s), 131.927(s), 120.564(s), 120.553 (s), 115.375(s), 114.356 (s), 113.363(s), 113.314 (s), 112.295 (s), 112.268 (s),110.173(s),109.152(s). m/z(M^+):521; IR(A.T.R,cm^{-1}):1720.51(-C=O- stretching),1212.27-1357.86(C=N stretching).



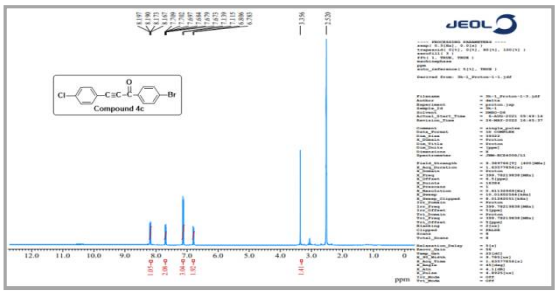
IR spectra of Compound 2c



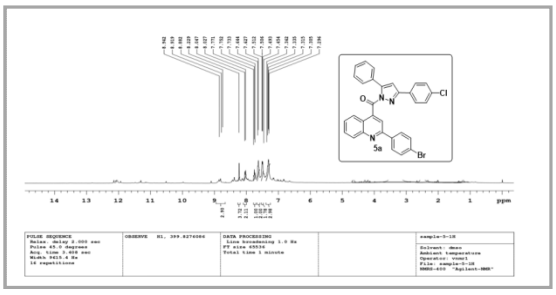
IR spectra of Compound 3c



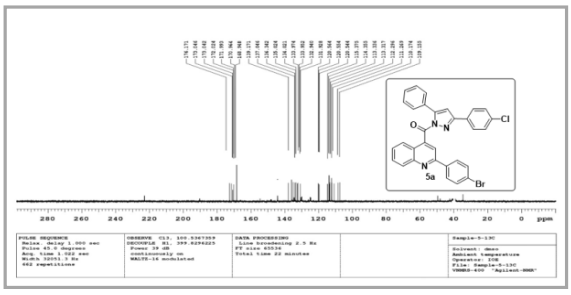
Mass spectra of Compound 3c



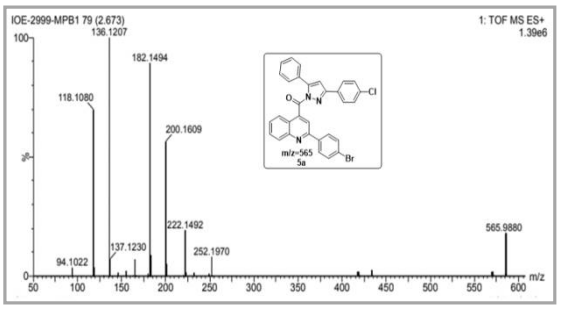
^{1}HNMR spectra of Compound 3c



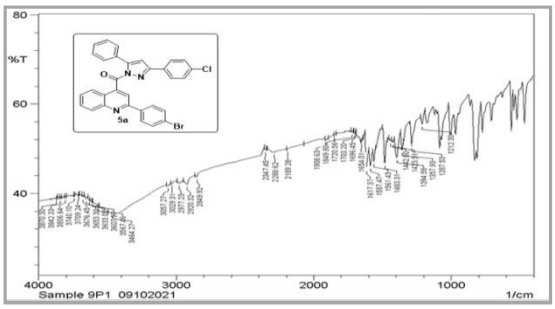
^{1}HNMR of Compound 5a



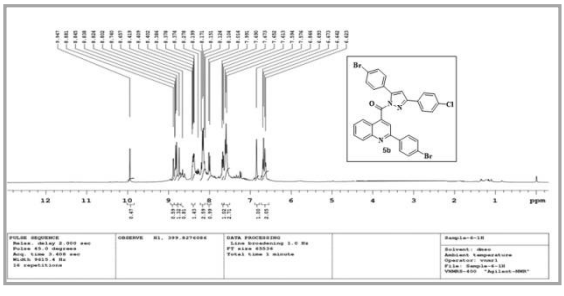
C^{13}NMR of Compound 5a



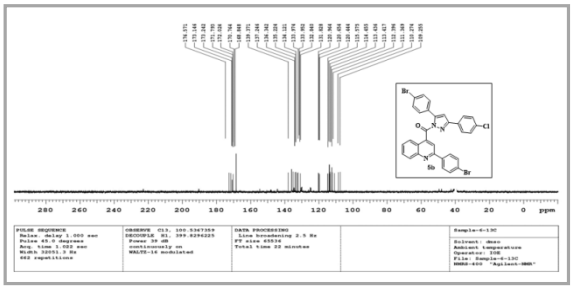
Mass spectra of Compound 5a



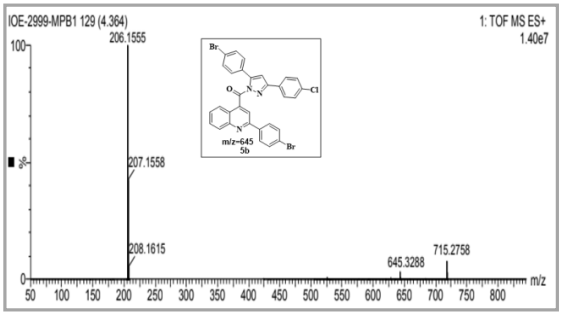
IR spectra of Compound 5a



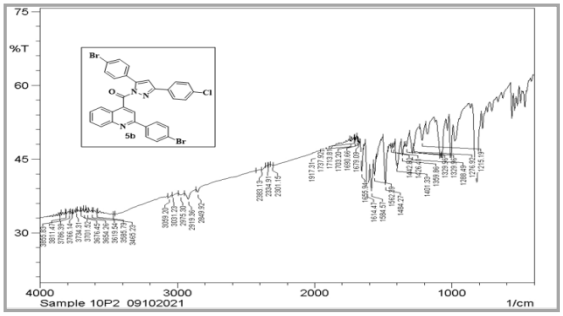
^{1}HNMR of Compound 5b



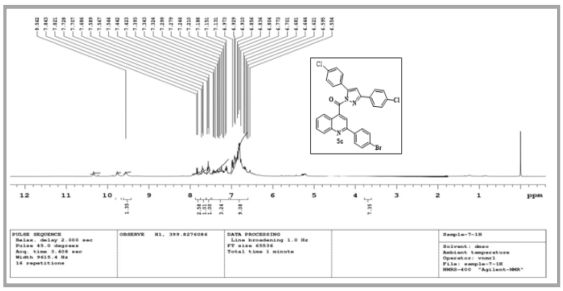
C^{13}NMR of Compound 5b



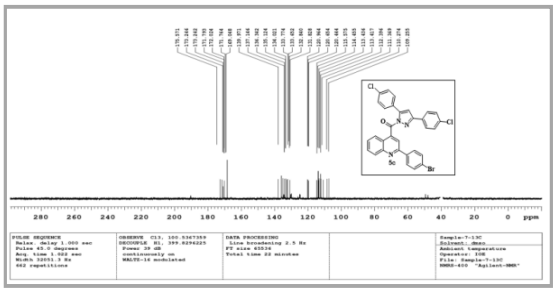
Mass Spectra of Compound 5b



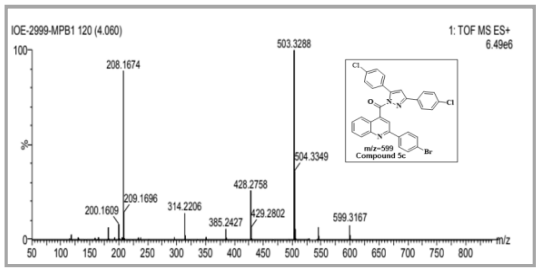
IR Spectra of Compound 5b



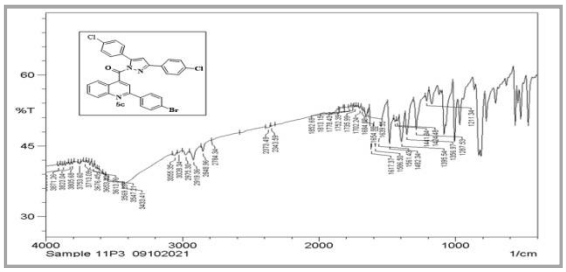
^{1}HNMR Spectra of Compound 5c



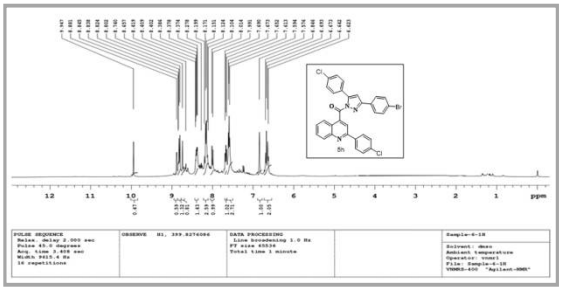
C^{13}NMR Spectra of Compound 5c



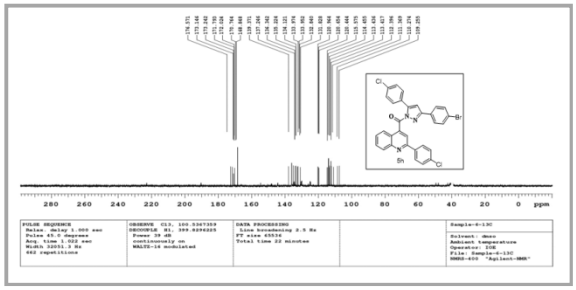
Mass Spectra of Compound 5c



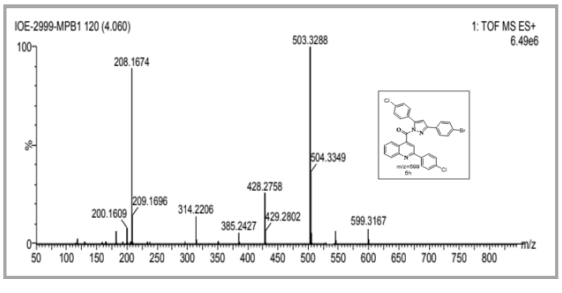
IR Spectra of Compound 5c



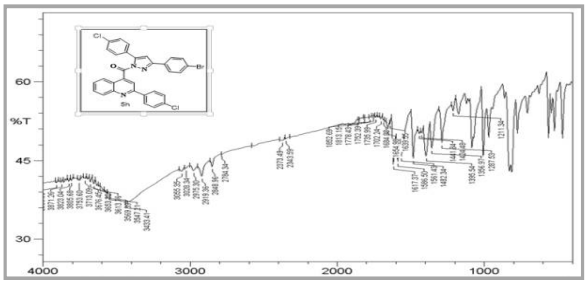
^{1}HNMR Spectra of Compound 5h



C^{13}NMR Spectra of Compound 5h



Mass Spectra of Compound 5h



IR Spectra of Compound 5h

REFERENCES

[1]. C. Congiu, V. Onnis, L. Vescil, M. Castorina, C. Pisano, *Bioorg. Med. Chem*., **2010**, 18, 6238-6248. (https://doi.org/10.1016/j.bmc.2010.07.037)

[2]. E. Bansal, V. K. Srivastava, A. Kumar, *Eur. J. Med. Chem*., **2001**, 36, 81-92. (https://doi.org/10.1016/S0223-5234(00)01179-X)

[3]. N. Gokhan-Kelekci, S. Yabanoglu, E. Kupeli, U. Salgin, O. Ozgen, G. Ucar, E. Yesilada,E. Kendi, A. Yesilade, A. Bilgin, *Bioorg. Med. Chem*., 2007, 15(17), 5775-5786. (https://doi.org/10.1016/j.bmc.2007.06.004)

[4]. T. S. Jeong, K. S. Kim, J. R. Kim, K. H. Cho, S. Lee, W. S. Lee, *Bioorg. Med. Chem.Lett.*, **2004**, 14, 27-19.(https://doi.org/10.1016/j.bmcl.2004.03.079)

[5]. R. Mulder, K. Wellinga, J. J. Van Daalen, Naturwissenschaften., **1975**, 62, 531.(https://doi.org/10.1007/BF00609070)

[6]. Z. P. Xiao, H. Ouyang, X.-D. Wang, P.-C. Lv, Z.-J. Haang, S.-R. Yu, T.-F. Yi, Y.-L.Yang, H.-L. Zhu, *Bioorg. Med. Chem*., **2011**, 19, 38-84.(https://doi.org/10.1016/j.bmc.2011.05.042)

[7]. S. Jiang, S. R. Tala, H. Lu, P. Zou, I. Avan, T. S. Ibrahim, N. E. Abo-Dya, A. Abdel-Majeid, A. K. Debnath, A. R. Katritzky, *Bioorg. Med. Chem. Lett.*, **2011**, 21, 68-95. (https://doi.org/10.1016/j.bmcl.2011.08.081)

[8]. A. A. Fadda, E. Abdel-Latif, R. E. El-Mekawy, *Pharmacol. Pharm*., **2012**, 3, 148-157.

a. (http:/doi.org/10.4236/pp.2012.32022)

[9]. H. A. Stefani, G. V. Botteselle, J. Zukerman-Schpector, I. Caracelli, D. da Silva Corrêa,S. H. P. Farsky, I. D. Machado, J. R. Santin, C. B. Hebeda, *Eur. J. Med. Chem.*, **2012**, 47, 52. https://doi.org/10.1016/j.ejmech.2011.10.018)

[10]. J. J. Harnett, M. Auguet, I. Viossat, C. Dolo, D. Bigg, P.-E Chabrier, *Bioorg. Med. Chem. Lett.*, **2002**, 12, 14-39. (https://doi.org/10.1016/S0960-894X(02)00216-0)

[11]. Nithinchandra, B. Kalluraya, S. Aamir, A. R. Shabaraya, *Eur. J. Med. Chem.*, **2012**, 54, 597-604. (http:/doi.org/10.1016/j.ejmech.2012.06.011)

[12]. K. V. Sujith, B. Kalluraya, A. Adhikari, K. Vijayanarayana, *Med. Chem. Res.*, **2012**, 21, 543-551. (http:/doi.org/10.1007/s00044-011-9569-5)

[13]. K. S. Girisha, B. Kallurya, *Synth. Commun*., **2012**, 42, 3097. (http:/doi.org/10.1080/00397911.2011.576323)

[14]. K. S. Girisha, B. Kallurya, J. H. S. Vidyahsree, *Indian J. Chem.,B.,* **2013**, 51, 1767. (https://doi.org/10.2298/JSC140109090J)

[15]. E. A. Rawins, 'Bentleys Text Book of Pharmaceutics' (Cassell Ltd., London). **1982**, 8, 498-525.

[16]. B. S. Holla, B. Kalluraya, S. N. Shetty, *Indian J. Heterocycl. Chem.,* **2002**, 2, 61.

[17]. K. Raviprabha, R. S. Bhat, *Prot. Met. Phys. Chem*., **2021**, 57, 181-189. (http:/doi.org/10.1134/S2070205120060209)

[18]. K. Raviprabha, R. S. Bhat, *J Fail. Anal. and Preven*., **2020**, 20 (5), 1598-1608. (http:/doi.org/10.1007/s11668-020-00954-2)

[19]. B. Kallurya, K. S. Girisha, J. H. S. Vidyahsree, *J.serb.Chem.Soc.,* **2014**, 79(12), 1469–1475 (https://doi.org/10.2298/JSC140109090J)

[20]. Raviprabha K, R. S. Bhat, *Surf. Eng. Appl. Electrochem*., **2020**, 55(6), 723-733 (http:/doi.org/10.3103/S1068375519060103)

[21]. Raviprabha K, R. S. Bhat, *J Fail. Anal. Preven.*, **2019**, 19(5), 1464–1474. (http:/doi.org/10.1007/s11668-019-00744-5)

[22]. B. B. Molloy, D. H. lively, R. M. Gale, M. Gorman, and L. D. Boeck, *J. Antibiot* (Tokyo). 1972, 137, 25. (https://doi.org/10.7164/antibiotics.25.137)

[23]. R. Cooper, A.C. Horan, F. Gentile, V. Gullo, D. Loebenberg, J. Marquez, M. Patel, M.S. Puar, and I. Truumees, *J. Antibiot* (Tokyo),. **1988**, 41, 13. (https://doi.org/10.7164/antibiotics.41.13)

[24]. C. Rapp, G. Jung, W. Katzer, W. Loeffler, Angre. *Chem, Int. Ed. Engl*., 1988, 27, 1733. https://doi.org/10.1002/anie.198817331)

[25]. J. E. Walker and E. P. Abraham, *Biochem. J.*, 1970, 118, 557. (https://doi.org/10.1042/bj1180557)