4 Aminoquinoline 1, 2, 4 Triazole Derivatives

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Abstract:

The drug quinoline is a substance or product used or intended to explore physiological system or pathologiacal state for the benefit of the receipt. The quinoline and triazole both are heterocyclic aromatic compound with the chemical formula C9H7N of quinoline and C3H3N3 of trizole. When the amine group is attach in the heterocyclic ring that is known as aminoquinolines. The 4 – aminoquinolines 1, 2, 4 triazole is synthesize from ethyl and hydrazine hydrate. It have anti-malarial property by which used to treat eryhtrocytic plasmodium infection while triazole derivative like flucanazole , itracanzole and ravacazole have anti – fungal property. Agar dilution methods are widely used for determination of antimicrobial activity of both gram positive and gram negative bacteria. Approximately 90% of population used 4 – aminoquinoline anti malaria to treat an attack of malaria fever 23% and take them for propylaxsis while 7% population used the drug for non – malarial agents on the other hand 1, 2 , 4 triazole moiety are widely studies as anticorrosive. The synthesis compound can be characterized by solubility studies and biological activity evaluation.

Key words: Introduction, method and methodology, characterization, antimicrobial activity studying, spectral analysis

Introduction:

There are various heterocyclic compound have shown antimicrobial and antifungal potential [1]. Quinoline is basically characterized by double ring structure compound of benzene and pyridine. The 4 – aminoquinoline 1,2,4 triazole derivative plan to establish the method of synthetic of the proposed compound elucidate the structure of synthesized compound by FT –IR, ‘ HNMR and mass spectroscopy as well as evaluate the biological activity of synthesized derivative such as anti bacterial activity and antifungal activity. 4-aminoquiniline is a therapeutic drug for combating malaria. The derivative of 4 – aminoquinoline continue to be the most sought out anti malarial agent for chemical modification [2].It is reported that during the research work on 4 – aminiquinoline 1,2,4 triazole if 7 – chloro 4 – aminoquinoline nucleus is obligatory for anti malarial activity inhibition of a- hematin formation and accumulation of drug at the target sites. 7 – chlorogroup is replaced by NH2 , OCH3 and so on electron withdrawing group like N02 the anti-malarial activity is reduced. The triazole is white to pale yellow crystalline solid with a weak, character, odour it is soluble in water and alcohol melt at 120°C and boils at 260°C [3].In recent year , the chemistry of triazole and their focus heterocyclic compound containing 1,2,4 triazole derivative has received considerable attention owing to their synthetic and effective

biological importance. 1,2, 4 triazole have antifungal, antituberculosis, anticonvulsion, anti inflammatory – analgesic as well as antimicrobial property [4].

Method and Methodology

4, 7 dichloroquinoline and methyl amine as the precursor compound to establish 4 – aminoquinolin 1, 2, 4 triazole derivatives.

- Synthetic of 7 – chloro N- methyl quinolin 4 – amine.
- Synthetic of (7 – chloroquinolin 4 –yl) carbamic acid.
- Synthesis of methyl (7- chlorouquinolin -4- yl) carbamate.
- Synthesis of N – (7- Chloroquinolin – 4 –yl) hydrazine carboxamide.
- Synthesis of N- (7 – Chlorquinolin-4 –yl) -2- (ethylcarbamothioyl) hydrazine carboxamide).
- Synthesis of N – (7 – chlorquuinolin – 4-yl) 2- (ethylcarbamothioyl) hydrazine carbaxamide.
- Synthesis of 5 (7- chloroquinolin -4-yl) amino – 4- ethyl 1,2,4 dihydro – 3H- 1,2,4 triazole -3-thione.
- Synthesis of final compound.

1. **Synthesis of 7- chloro N- methyl quinolin -4- amine:**
   A mixture of 4, 7 dichloroquinolin (1 mol) and methyl amine 9 2 mol) were refluxed for 1 hr at 80°C and next 8 hours at 110 -135°C. The resultant mixture was allowed to cool. Nextly 100 ml of dichloromethane was added to the reaction mixture. To this reaction mixture 10% solution of sodium hydroxide (100 ml) was added with stirring. If no precipitate occurs then a little excess of sodium hydroxide solution was added to make the solution alkaline. The ppt. was collected.
2. **Synthesis of (7 – chloroquinolin -4-yl) carbamic acid:**
   The mixture of (7- chloro quinolin – 4- yl) methyl amine (0.33 mol) and 136 gm of sodium dichromate dehydrate in 300 ml of water were taken in rbf fitted with dropping funnel and magnetic stirring bar. To this well stirred mixture conc. Sulphuric acid was added, the mixture was refluxed to gentle boiling for half an hour. The resultant reaction mixture was cooled and poured in to 400 – 500 ml of water. Nextly the crude product was filtered and washed with 200 ml of water. The filtrate was transferred to the beaker, 200 ml of 5% sulphuric acid was added and it was allowed to digest on water bath with agitation to remove chromium salts. The resultant mixture was cooled and filtered.
3. **Synthesis of methyl (7 – chloroquinolin – 4-yl) carbamate:**
   The mixture of (7- chloroquinolin – 4-yl) carbamic acid (0.125 mol), absolute ethanol (0.25 mol), 3.8 gm conc. Sulphuric acid and 30 ml of sodium dried benzene were taken in rbf and was refluxed for 16 hrs. The resultanat reaction mixture was cooled and 50 ml of ether was added to it. The extract was washed successively with sodium hydrogen carbonate solution and water, dried with magnese sulphate or calcium chloride and the solvent was distilled off on a water bath. The traces of benzene was removed by heating on a water bath at 110°C. Finally the residue of methyl (7 – chlorouinolin -4-yl) carbamate solidifies on cooling.
4. **Synthesis of N – (Chloroquinolin – 4- yl) hydrazine carboxamide**
   The mixture of methyl (7 – chloroquinlin – 4 –yl) carbamate (0.01 mol) and hydrazine hydrate (0.02)

in ethanol (30 ml) was refluxed for 6 hrs. From the resultant mixture excees was ethanol was removed by distillation. The product was recrystallized after cooling.

5. **Synthesis of N- (7- chloroquinolin -4- yl) 2- (ethylcarbamothioyl) hydrazine carbaxamide:**
   N – (7- chloroquinolin – 4- yl) hydrazine carboxamide (0.023 mol) was suspended in ethanol (25 ml) and ethyl isothiocynate was also added . The resultant mixture was refluxed for 3 hrs. N- (7- chloroquinolin – 4-yl) 2- (ethylcarbamothioyl) hydrazine carbamide was isolated after cooling.
6. **Synthesis of 5 – [7- Chloroquinolin – 4-yl) amino] – 4 ethyl 1,2,4 – dihydro- 3H- 1,2,4 – triazole – 3 – thione**
   The mixture of N – (7- chloroquinolin – 4- yl) 2- (ethylcarbamide) hydrazine carbamide (0.01mol) and 10% sodium hydroxide (2ml) was refluxed for 5-12 hrs. Nextly the mixture was cooled and acidified with conc hydrochloride acid. The resultant reaction mixture was filtered. The ppt. was collected and was recrystallized with ethanol to get 5 – [(7 – chloroquinolin- 4-yl)] amino] – 4 – ethyl – 2,4, dihydro – 3H – 1,2,4 triazole- 3- thione.
7. **Synthesis of final compound:**
   Farmaldehyde (1.5 ml, 40% sol) was added to a solution of 5 –[(7 – chloroquiinolin -4- yl) Amino] 4- ethyl – 1, 2, 4 dihydro – 3H – 1,2,4 triazole – 3- thione (0.5 gm, 1.8 m mol) in ethanol (15 ml) and this reaction mixture was refluxed for 1 hr. After this each amine (0.5 gm) was added to the reaction mixture and it was added to the reaction mixture and it was again refluxed for next

Charecterization of synthetic compounds:

1. **Solubility studies:**
   Solvents like water, ethanol, chloroform, benzene, methanol, acetone and dimethyl sulphoxide was taken for solubility studies.
2. **Biological Activity Evaluation:**
   Anti malarial agents synthesized by are potential anti – malarial effect at MIC of 0.25 mg/ml against chloroquine – sensitive plasmodium falcipearum strain.
   Methods for studying anti microbial activity:
   Antimicrobial activity is determined based on the in vitro activity in pure cultures. In vitro susceptibility test are done by the following methods i.e.
   a) **Agar dilution method**
   b) **Tube dilution method**

a) **Agar dilution method:**
   In this method , petri dishes of agar are prepared by pouring method. The agar is incubated with microorganism. Bores are made in the agar plate and specific volume of anti-microbial substances are placed in cup. The plates are incubated at a temperature of 37°C for 24 hrs. The antimicrobial substances diffuses through the agar around cup and produces a clear zone of inhibition. The diameter of this zone can be measured and estimation of the degree of activity of the antimicrobial substances can be obtained.

b) **Tube dilution method:**

The method is used to determine antimicrobial susceptibility in liquid media. It can be determine MIC of the compound. The diffusion of anti microbial agents as preferred in growth medium so as conc. of the of the drug covers its clinical significance range. An equal volume of both containing

bacteria /ml is added to each tube and to control tube that contain no anti microbial agent. The tubes are examined for visible turbidity after overnight incubation[4].

Result:

Compound A:

Molecular formula : $C_{19}H_{16}ClN_7O_2S$

Molecular weight : 441.8

Soluility : water, ethanol

Percentage yield : 69.4%

Spectral features

Compound A

Molecular weight: 441.8

IR in cms $^{-1}$

Peak at 3212 corresponds to NH stretching.

Peak at 3082 corresponds to Ar.CH stretching at 1596 corresponds to C=N stretching.

Peak at 1596 corresponds to C=N stretching.

Peak at 1425 corresponds to CN stretching.

Peak at 1512 corresponds to Ar-NO_2 ass. stretching.

Peak at 1365 corresponds to Ar-NO_2 symstretching.

Peak at 1120 corresponds to C=Sstretching.

Mass: in m/z Further evidence of the structure of the compound

was obtained by recording mass spectra of the sample.

The molecular ion peak was observed at m/z 441.

NMR (δ) in PPM

6.68-8.32 (9H, m, Ar), 5.91 (1H, s, NH), 4.31-4.38 (3H, m, CH_3) 4.7 (1H, S, NH), 1.01-1.12 (2H, m, CH_2),

The mas spectrum revealed:

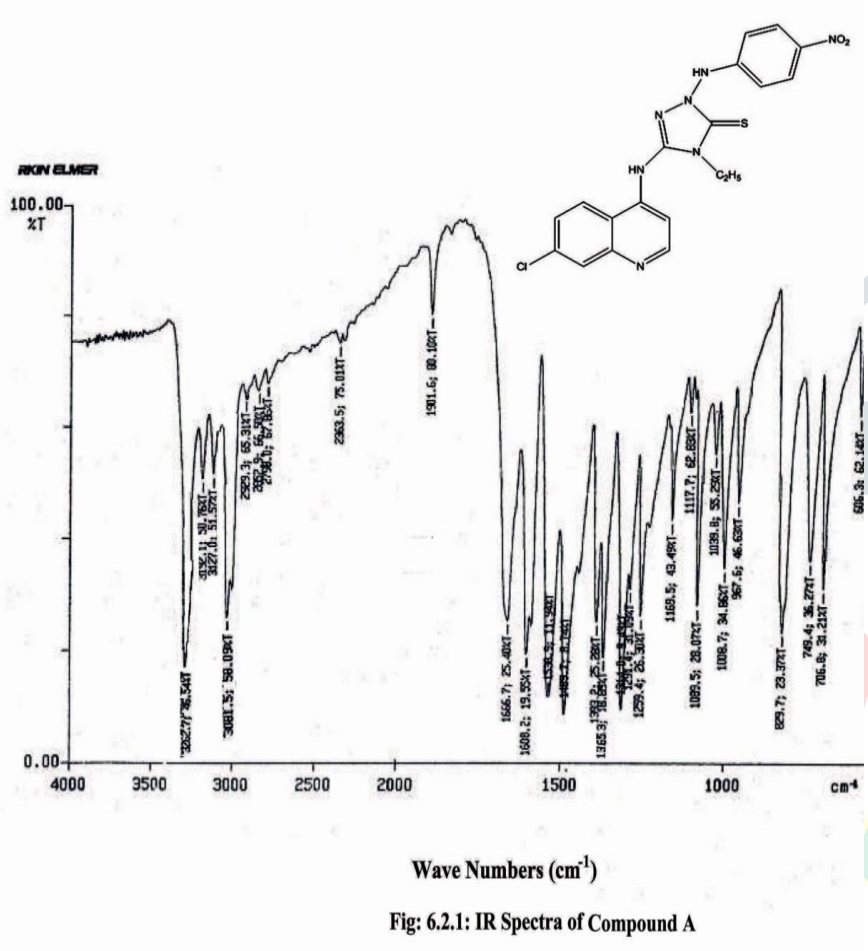

Fig: 6.2.1: IR Spectra of Compound A

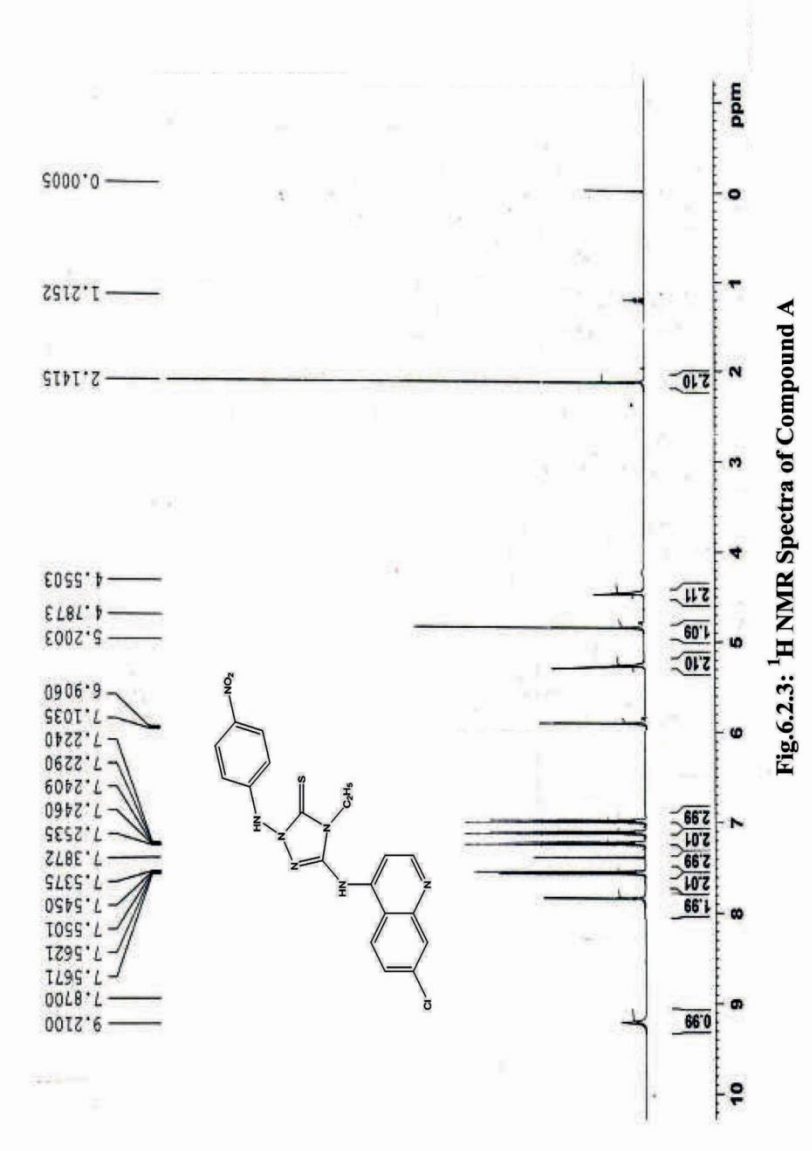

Fig.6.2.3: ^{1}H NMR Spectra of Compound A

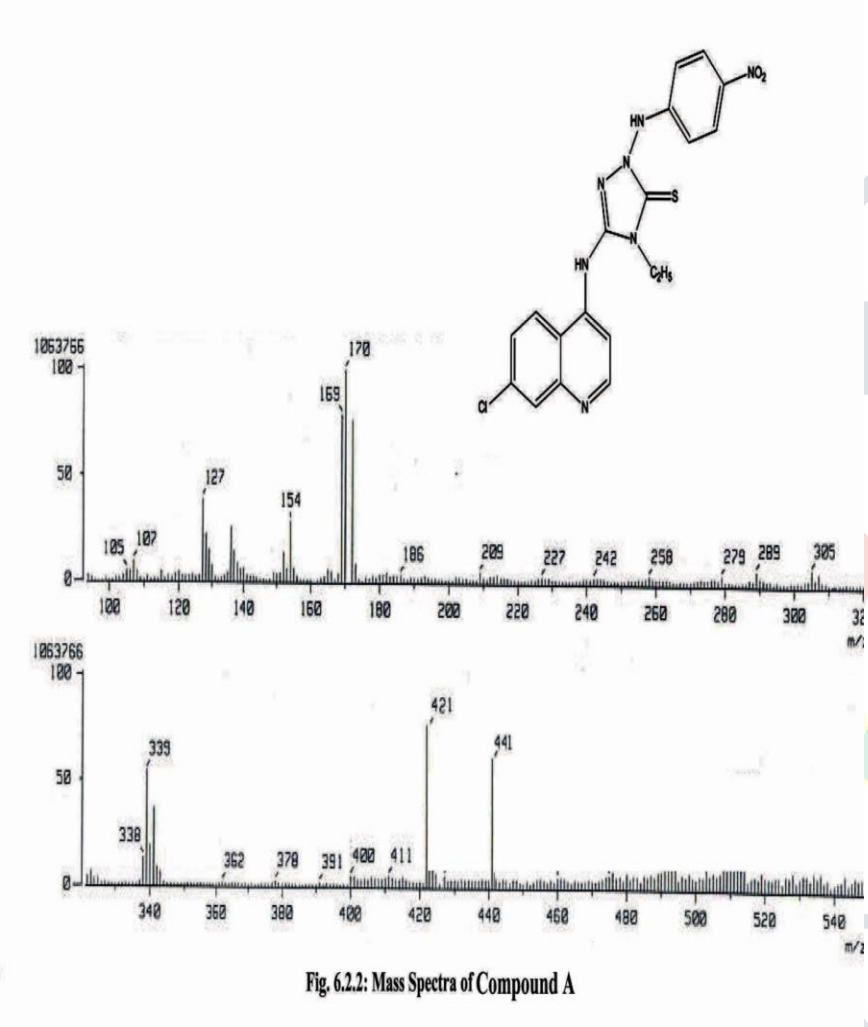

Fig. 6.2.2: Mass Spectra of Compound A

IR IN cms^{-1}

Peak at 3326 correspondece to NH stretching.

Peak at 3062 correspondece to ArCH stretching.

Peak at 3062 correspondence to C=N stretching

Peak at 1390 corresponds to C- N stretching

Peak at 1130 corresponds to C= S stretching.

Peak at 1120 corresponds to C=Cl stretching.

Mass in m/z : Further evidence of the structure of the compound was obtained by recording mass spectra of the sample. The mass spectra revealed.The molecular ion peak was observed at m/z 431.

NMR in PPM: 6.44 – 8.38 (9H,m, Ar), 5.85 (1H,s ,NH), 4.24- 4.31 (3H, m CH_3) 4.0 (1H, S ,NH)1.31- 1.38 (2H, m , CH_2).

Compound B

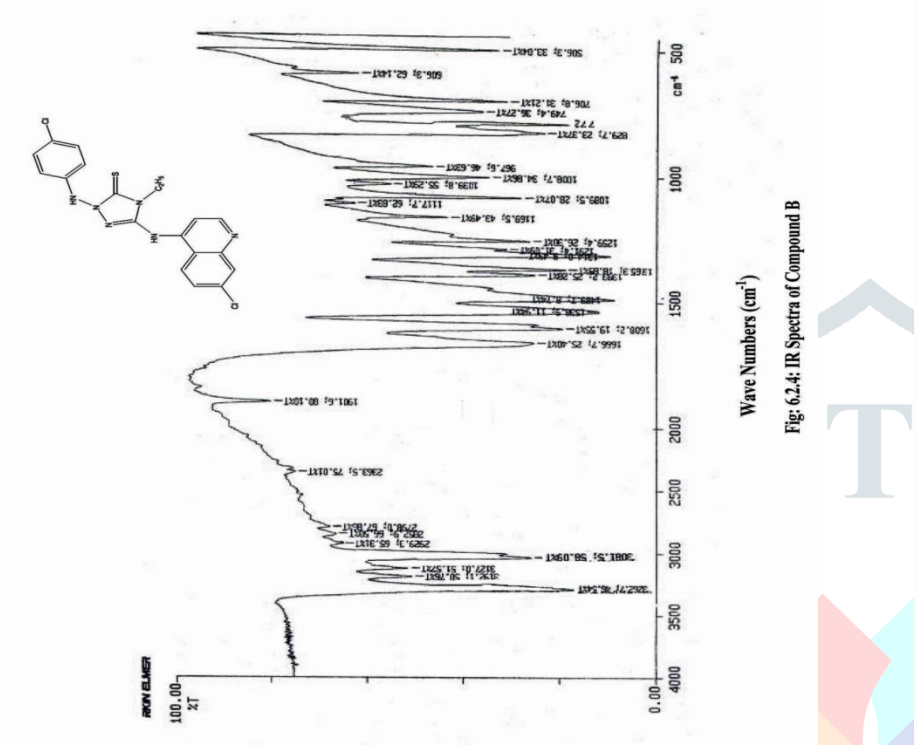

Fig: 6.2.4: IR Spectra of Compound B

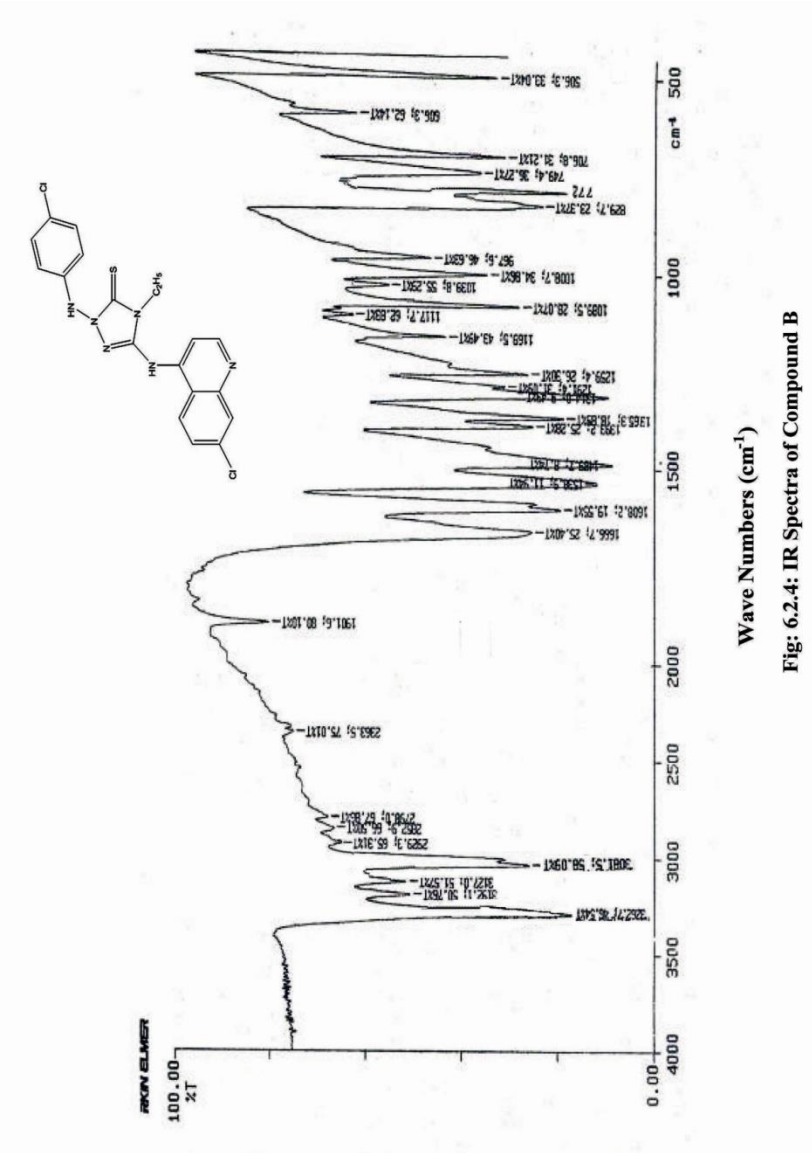

Fig: 6.2.4: IR Spectra of Compound B

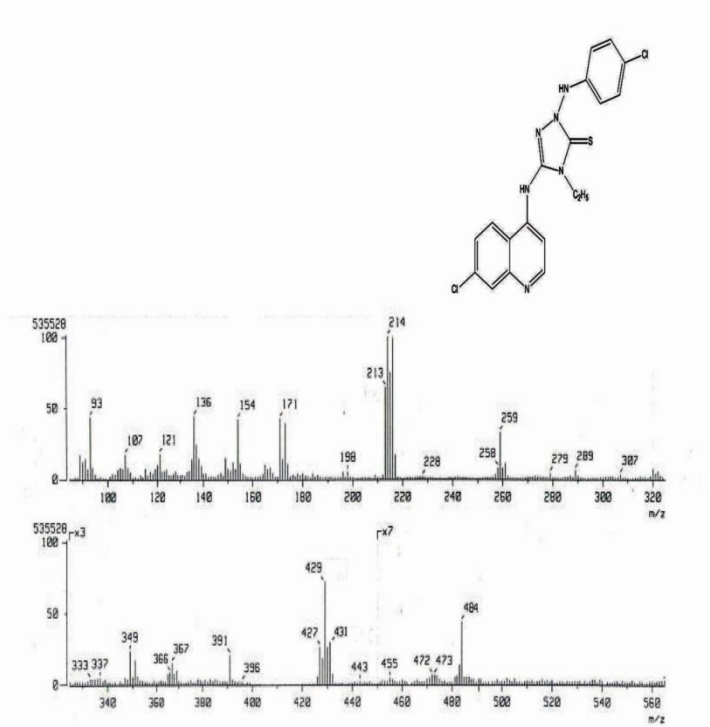

Fig. 6.2.5: Mass Spectra of Compound B

Molecular formula : $C_{19}H_{16}BrClN_6S$

Molecular weight : 475

Solubility : water, ethanol

Perentage yield : 70%

IR in cms $^{-1}$

Peak at 3292 corresponds to NH stretching.

Peak at 3035 corresponds to Ar.CH stretching.

Peak at 1592 corresponds to C=N stretching.

Peak at 1354 corresponds to C-Nstretching.

Peak at 1144 corresponds toC=Sstretching.

Peak at 690 corresponds to C-Brstretching.

Mass: in m/z: Further evidence of the structure of the compound was obtained by recording mass spectra of the sample. The mass spectrum revealed.

The molecular ion peak was observed at m/z 474.

NMR (δ) in PPM

6.54-8.29 (9H, m, Ar), 5.90 (1H, s, NH), 4.21-4.27 (3H, m, CH_3) 3.9 (1H, S, NH), 1.29-1.39 (2H, m, CH_2).

Compound C

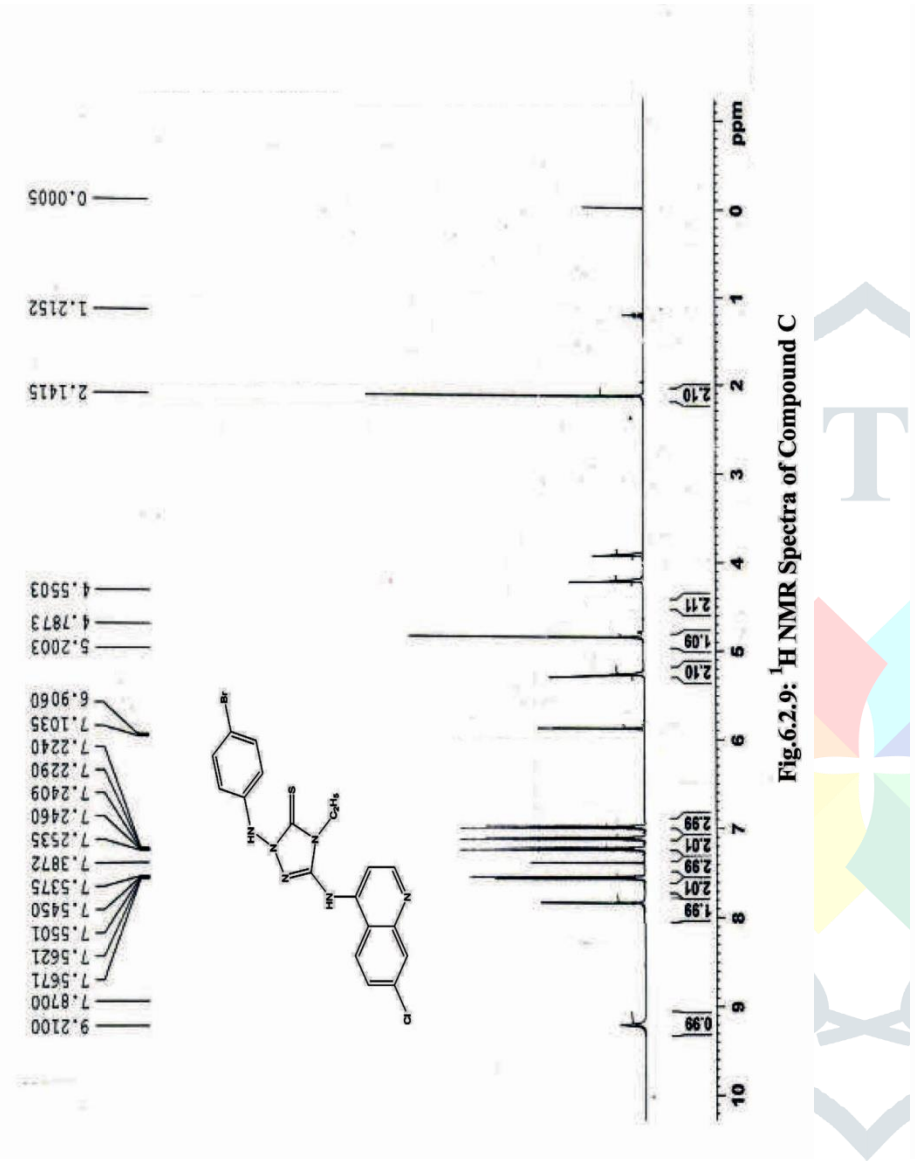

Fig.6.2.9: ^{1}H NMR Spectra of Compound C

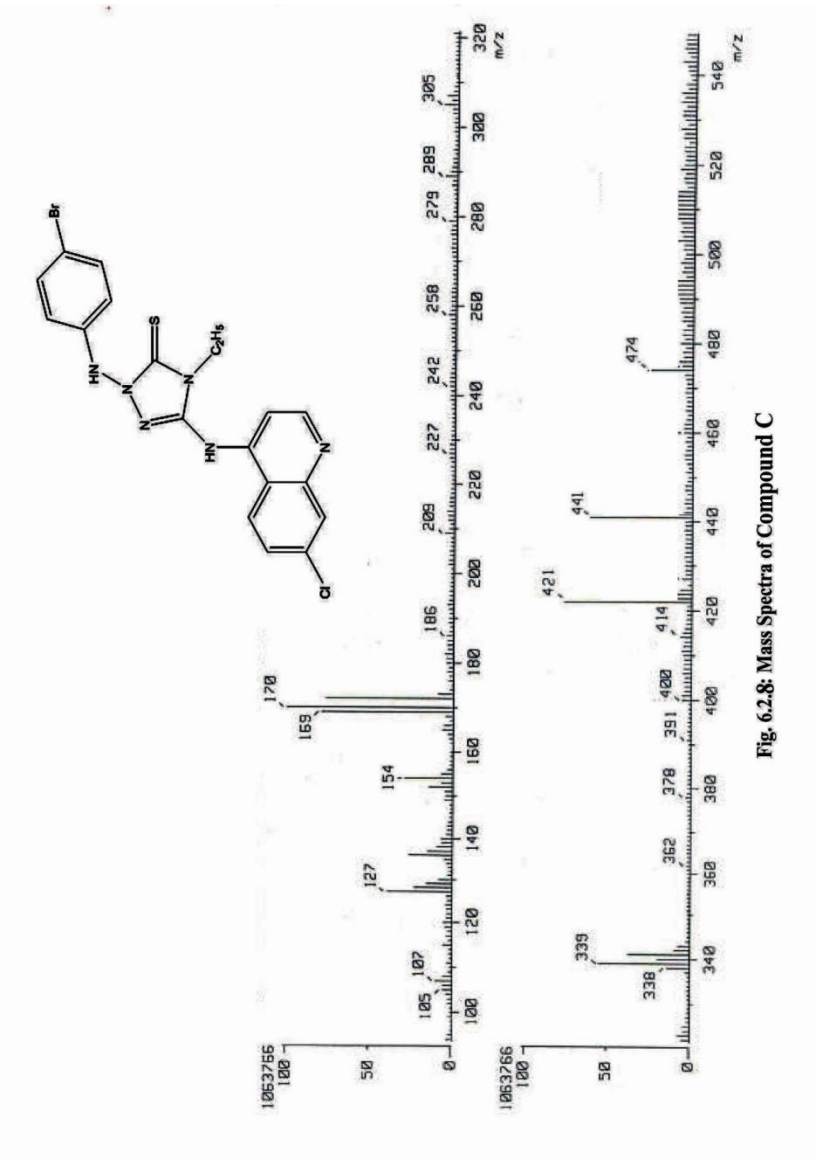

Fig. 6.2.8: Mass Spectra of Compound C

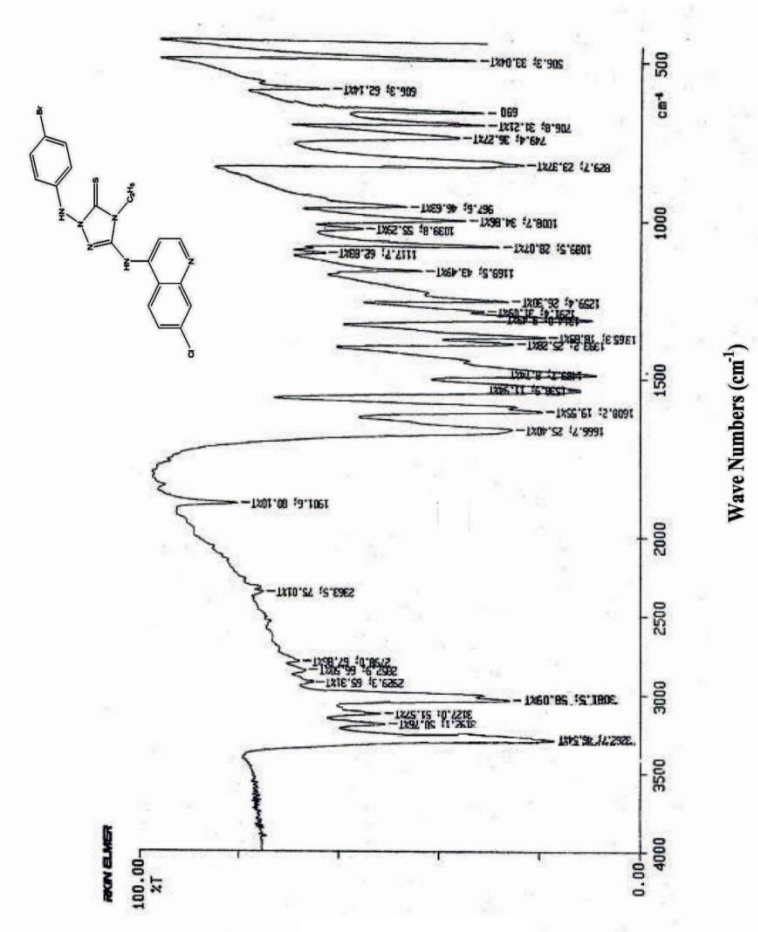

Fig: 6.2.7: IR Spectra of Compound C

Fig 6.2: 2-[(4-

Compound D:

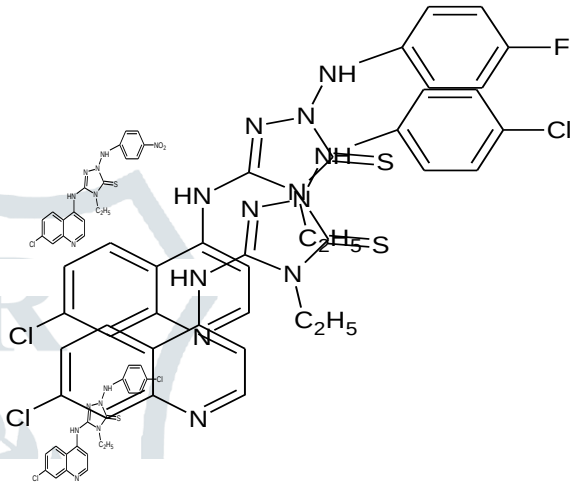

Fig 6.4:5-[(7-chloroquinolin-4-yl)amino]-4-ethyl-2-[(4-fluorophenyl)amino]-2,4-dihydro-3*H*-1,2,4-triazole-3-thione

Molecular formula : $C_{19}H_{16}ClFN_6S$

Molecular weight : 414.8

Solubility : water, ethanol

Percentage yield : 69%

IR in cms $^{-1}$

Peak at 3292 corresponds to NH stretching.

Peak at 3035 corresponds to Ar.CH stretching.

Peak at 1592 corresponds to C=N stretching.

Peak at 1354 corresponds to C-Nstretching.

Peak at 1144 corresponds toC=Sstretching.

Peak at 690 corresponds to C-Fstretching.

Mass: in m/z: Further evidence of the structure of the compound was obtained by recording mass spectra of the sample. The mass spectrum revealed:

The molecular ion peak was observed at m/z 414.

NMR (δ) in PPM: 6.47-8.10 (9H, m, Ar), 5.86 (1H, s, NH), 4.19-4.29 (3H, m, CH_3), 4.08 (1H, S, NH), 1.19-1.29 (2H, m, CH_2).

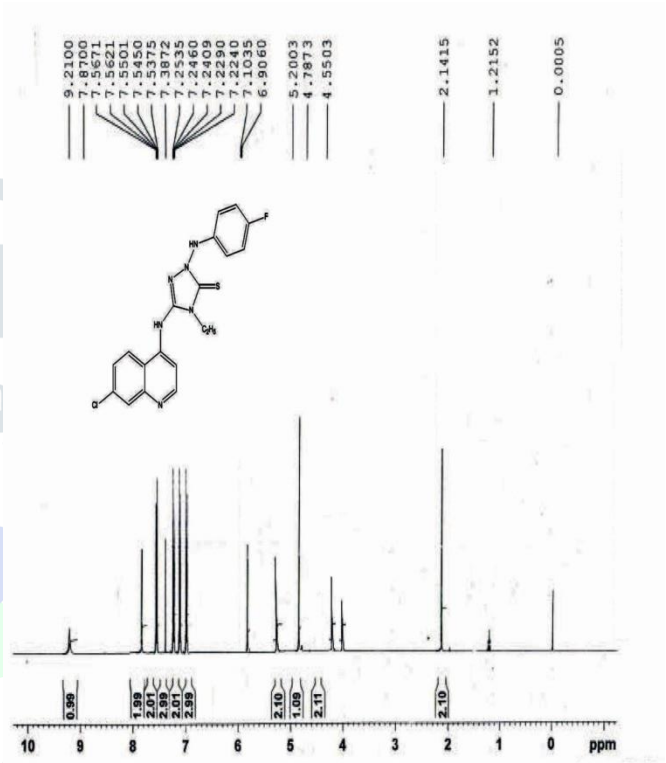

Fig.6.2.12 : ^{1}H NMR Spectra of Compound D

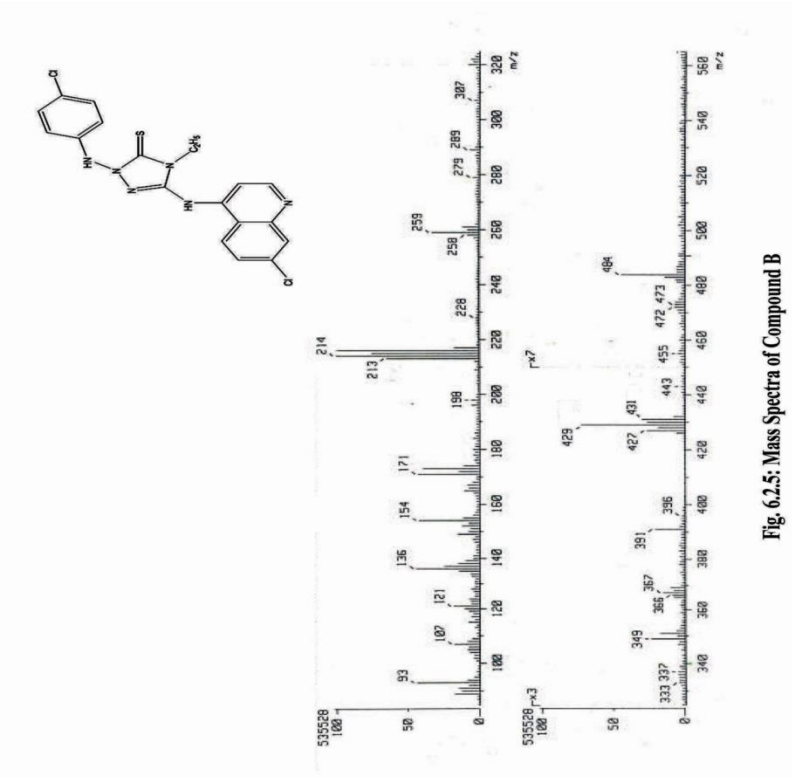

Fig. 6.2.5: Mass Spectra of Compound B

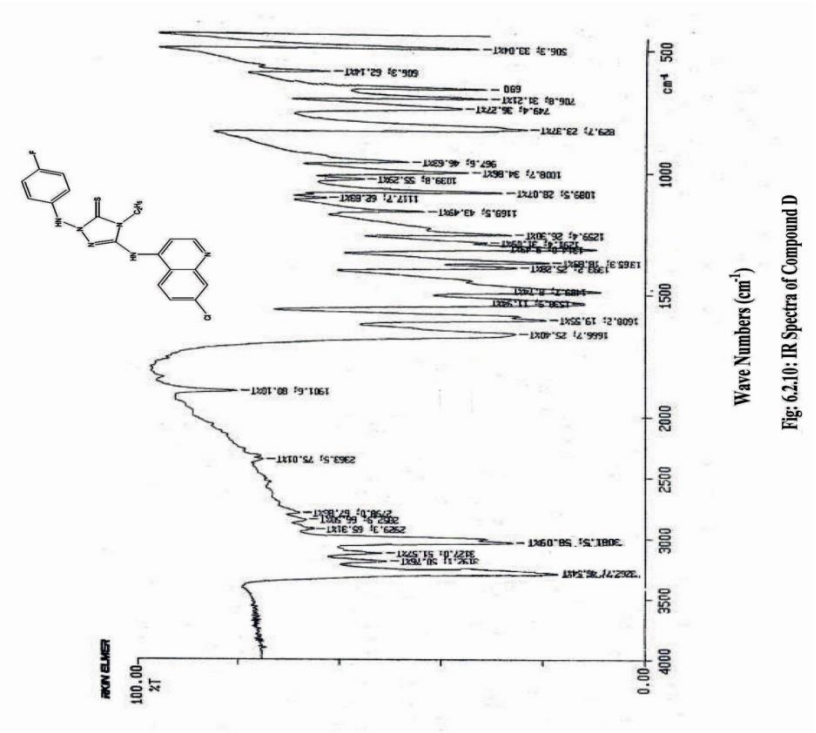

Fig: 6.2.10: IR Spectra of Compound D

Biological evaluation

Table: Data of antimicrobial activity of 4-aminoquinoline 1,2,4-triazole derivatives.

Sl. no.	Compound number	Diameter of zone of inhibition (mm)				
		S.aureus	*B.subtitis*	*E.coli*	*P.aeruod yieldginosa*	*C.albicans*
1	Compound A	16	13	19	8	-

2	Compound B	15	14	20	7	-
3	Compound C	-	8	12	-	14
4	Compound D	11	11	17	5	10
5	Ampicillin	15	14	22	10	-
6	Griseofulvin	-	-	-	-	16

(-) Indicates no inhibition zone (no activity).

Conclusion:

The objective of the present studies was synthesized and characterized by some novel 4 – aminoquinoline 1,2, 4 – triazole derivative and to carry out the antibacterial as well as antifungal activituies. Synthesis of all the 4 – aminoquinoline 1,2,4 triiazole derivatives by the above describe method result in product with good yields. IR , H NMR and mass spectroscopic analysis was done to confirm the structure of the newly synthesized compounds. Some of the synthesized compound showed moderate to good antibacterial and antifungal activity whem compared the standard drugs ampicillin and grisofulvin.

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