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Design, Synthesize and Characterization the Quinazoline Derivatives as Antitubercular Agent

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Abstract
An efficient direct amination of quinazolin-4(3*H*)-ones using *N*,*N*-dimethylformamide as a nitrogen source is described that affords the corresponding 4-(dimethylamino)quinazolines in high yields. This transformation proceeds through efficient 4-toluenesulfonyl chloride mediated C–OH bond activation at room temperature. These Synthesized 4 compounds were confirmed through spectral characterization using IR, NMR, MASS Spectroscopy. The result showed significance for these compounds antitubercular activity compared with Pyrazinamide as a standard drug.
Keyword: Amination, Quinazolin-4(3*H*)-one, 4-Aminoquinazoline

INTRODUCTION

Tuberculosis (TB), which is caused by the bacteria Mycobacterium tuberculosis, is an infectious disease for which new medicines are still needed to improve treatment. In only one year, the WHO announced 8.8 million new cases and 1.4 million deaths due to the disease. Furthermore, billions of people have latent infections that have no clinical signs but have the ability to become active. TB therapy currently includes a two-month course of isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (ETH), followed by another four months of INH and RIF. These medications have been in use for decades, leading to the proliferation of M. tuberculosis strains that are multidrug resistant (MDR) and extensively drug-resistant (XDR) [1].

Tuberculosis affects the lungs in most cases, but it may also affect other parts of the body. When people with the disease cough, sneeze, or spit, it spreads through the air.

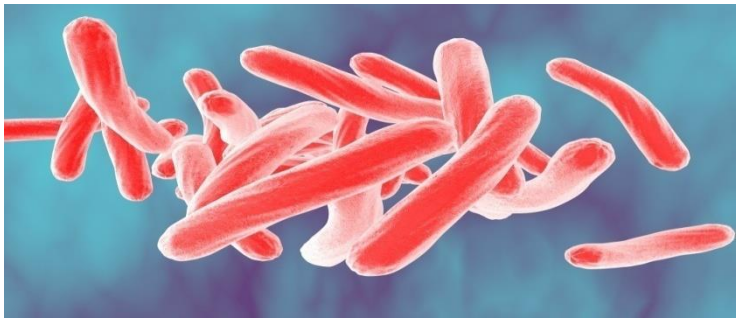


Fig 1. Mycobacterium Tuberculosis

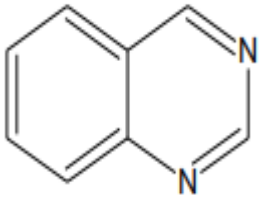


Fig -2. Structure of Quinazoline

Quinazoline is also known as 1,3-diazonaphthalene, is an organic compound with the molecular formula $C_8H_6N_2$. It is an aromatic heterocycle with a bicyclic structure consisting of two fused six-membered aromatic rings, a benzene ring and a pyrimidine ring. It is a light yellow crystalline solid and soluble in water. It has melting
point is 48^0C.[2]

Material And Methods

The reagents, solvents and chemicals used for the synthesis of compounds in the present study were acquired from Lobachem chemicals, Sigma –aldrich Co. Melting point were determined by using digital melting point apparatus. Reaction were monitored by thin layer chromatography using Pre-coated silica gel GF 250 as adsorbent Methanol : Acetonitrile : Ethyl acetate (4:4:2). IR spectra (KBR Pellets) were recorded on Shimadzu FT-IR. 1H NMR spectra (DMSO) were taken using TMS as internal standard and chemical shift are expressed in § ppm.

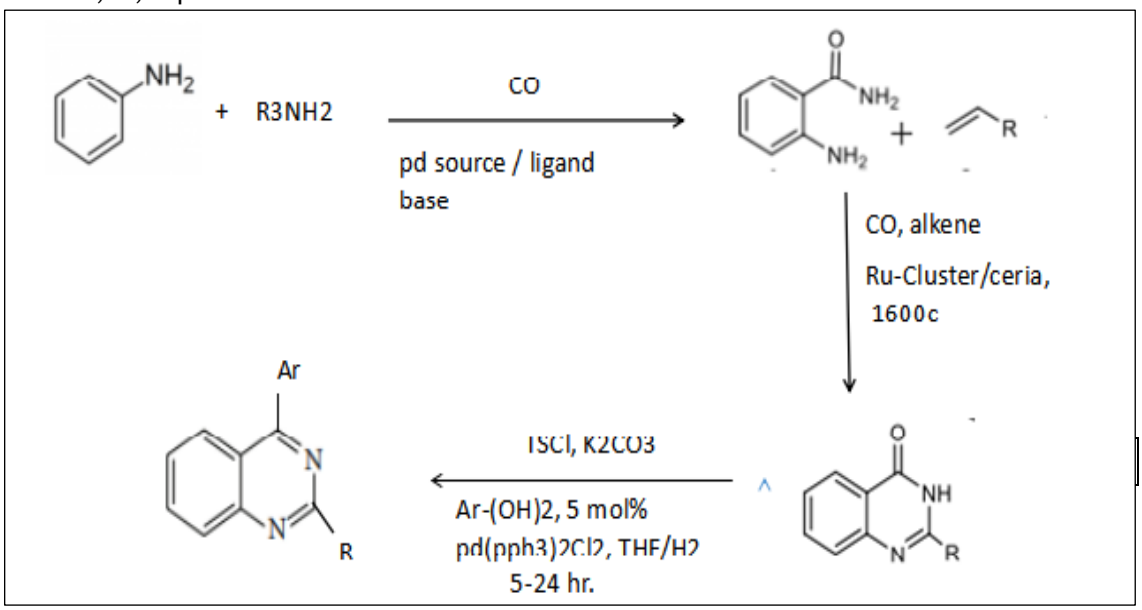
Methods

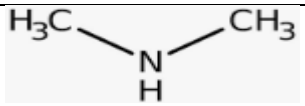
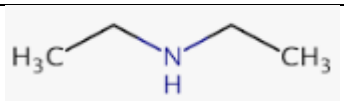
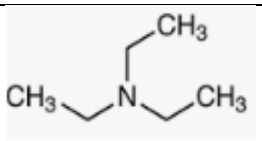
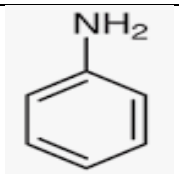
Methods used for all research and step by step explanation of work carried out.

- Synthetic scheme is highly susceptible for the reaction condition, all possible risk factors are taken into consideration and scheme is optimized time to time for good synthetic practice and safest way of result.
- Synthetic process is smart work and need to be cautions and time to time observing reaction so that avoid the errors and immediately came up with the alternative way for fluent reaction process. Chemicals reaction depends upon many variables and monitored every time, temperature, and PH etc.

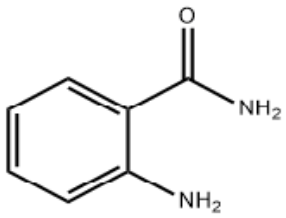
Scheme

Following scheme represent the general synthetic pathway and the possible end product,
Where R, Ar, represent the substituent to be added.



1.		Dimethylamine
2.		Diethylamine
3.		Triethylamine
4.		Aniline

Steps in the synthesis and Characterization of each compound
Reactant Profile:-
(1) 2-Aminobenzamide



Synonym : Anthranilamide
Molecular formula : $C_7H_8N_2O$
Molecular weight : 136.15 g/mol
Melting Point : 109-111.5^{0}C
Solubility : Ethanol, Ethyl ether, Benzene

- **Synthesized compounds are characterized by following methods-**
- **Step 1 :**
- **Preparation of Anthranilamide (1)**

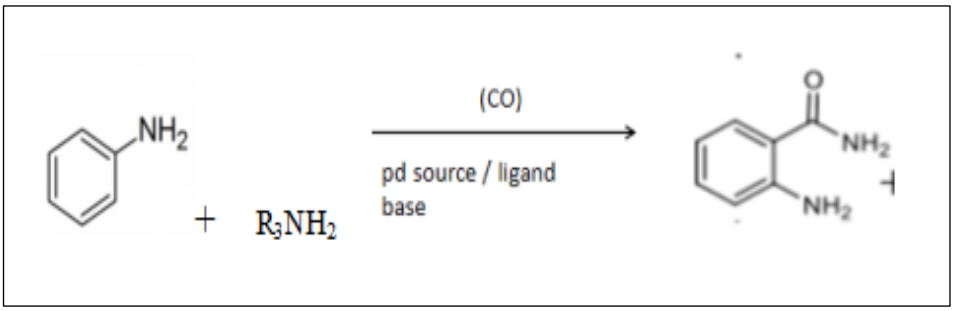


Figure 2. Steps 1 for Synthesis

First step reaction in which various substituited aniline react with amine in the

presence of palladium resulting to give Intermediate 1. In this reaction step Anthranilamide is formed.

The general procedure for reaction pathway show as below

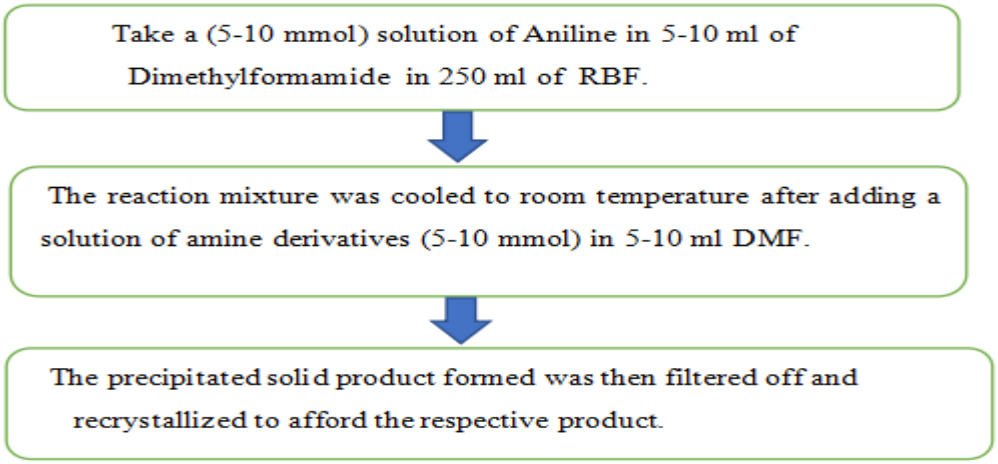


Figure 3 . Procedure for step 1.

- **Characterization of Compound**

Physical Properties

Name :2-Aminobenzamide

Colour : Light brown

Molecular Formula : $C_7H_8N_2O$

Melting point : 111-113^{0}C

Solubility : Soluble in hot water, Slightly soluble in ether and benzene.

- **Step 2 :**

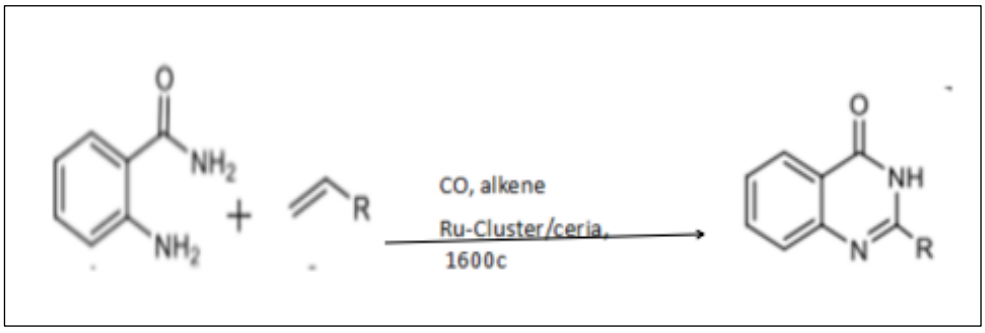


Figure 4 . step 2 for synthesis

Where intermediate (1) react with amine in presence of ruthenium cluster resulting undergoes to formation of intermediate (2).

The general procedure for reaction pathway show as below

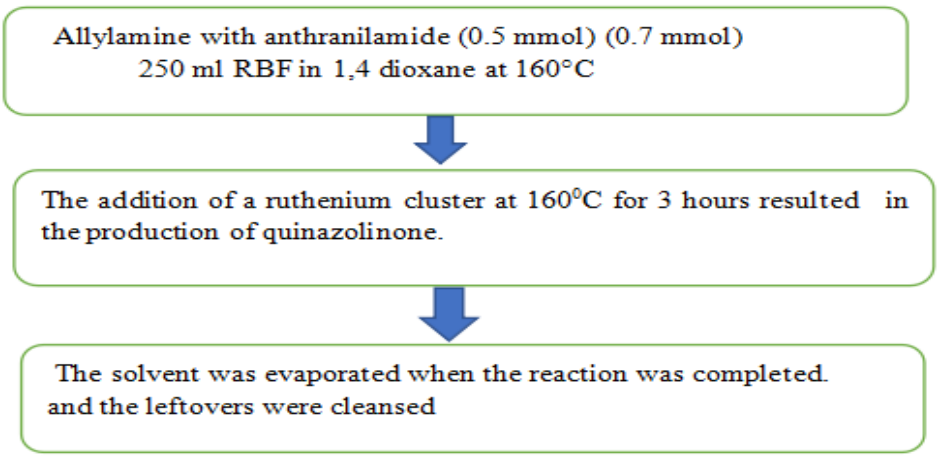


Figure 5. Procedure for step 2

- **Characterization of Compound**
  Physical Properties
  Name :Quinazolin-4(3H)-one
  Colour : Light brown
  Molecular Formula : $C_8H_6N_2O$
  Melting point : 124-127^{0}C
  Solubility : Soluble in ethyl acetate and ethanol, dichloromethane

- **Step 3 :**

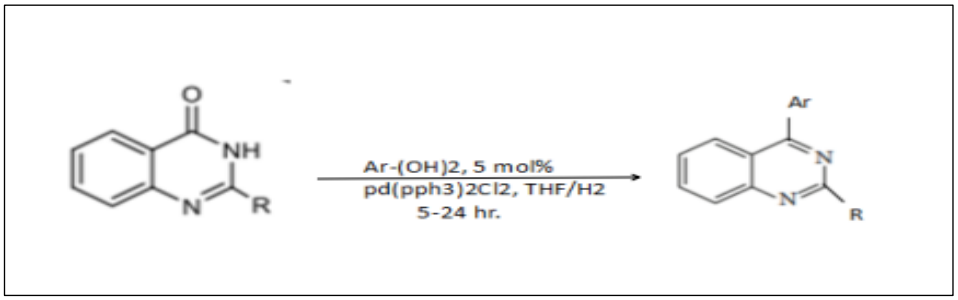


Figure 6. Step 3 for synthesis

Substituted 2,4 quinazoline compound were prepared by reaction between intermediate (2) with boronic acid in the presence of triphenylphosphine palladium and solvent resulting target product is formed.
Synthesis of the target product procedure show in a below.

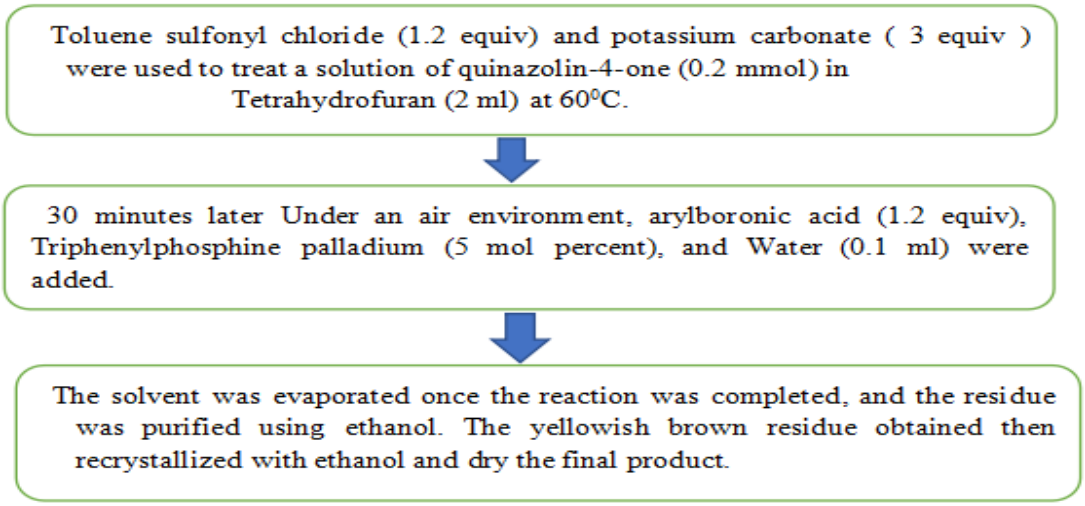


Figure 6. Procedure for step 3

- **Characterization of Compound**

Physical Properties

Name :2-alkyl,4-aryl-quinazoline

Colour : Light brown

Melting point : 124-127^{0}C

Solubility : Soluble in ethanol, dichloromethane and ethyl acetate.

❖ **Characterization of synthesized compound carry out by various available technique**

➢ **Thin layer chromatography :**

Thin layer chromatography of compounds carried out by using pre-coated TLC plate with silica gel GF 250[(12)]. Samples and products are prepared in suitable solvents, various mobile phases used such as-

Stationary phase : Pre-coated silica gel GF 250

Mobile phases : Methanol : Dichloromethane (2:8)

Methanol : Acetonitrile : Ethyl acetate (4:4:2)

Detection : UV-chamber, Iodine chamber.

➢ **Melting point :**

The melting points were determined by capillary tube method. The compounds its crystallinity at particular temperature were found.

➢ **Infrared Spectroscopy :**

ATR-IR spectroscopy used for the IR spectra of synthesized compounds. These instrument does not need of a sample preparation as other instrument needs 'KBr pellets' in this solid sample directly placed on ATR crystal and the spectra is obtained.

IR spectroscopy have finger print region (500 cm^{-1} to 1450 cm^{-1}) and functional group region (1450 cm^{-1} to 4000 cm^{-1}) are powerful ranges for confirming functional groups, except few diatomic molecules such as Cl_2, N_2, O_2.[63]

➢ **NMR Spectroscopy :**

To obtained "1H NMR" spectrum of a compounds the solvent used must be free from hydrogen because their the chances of solvent protons interfere with compounds proton.

NMR involve the interaction between electromagnetic radiation and the magnetic field of hydrogen nucleus. NMR provide information about equivalent protons and their different electronic environment and help us to find, structure of molecules.

The number of signals denotes the number of equivalent proton in molecule. The nature of proton like aromatic, vinyl, aliphatic etc. Confirmed.[64]

- **Mass Spectroscopy :**

Mass Spectroscopy is a technique to find exact molecular mass of compounds. Ionization source and magnetic detector, the commonly used methods as

- Soft ionization technique
- Hard ionization technique

Here, the molecule fragmented into ionic forms by beam of electron. The relative abundance of fragmentation is depend on stability of ions. The charge particle then separated with their masses.[65]

- **Biological Evaluation of synthesized compounds :-**

Biological activity is done by using "Microplate Alamar Blue Dye Methods which is based on inhibition of cell wall growth .

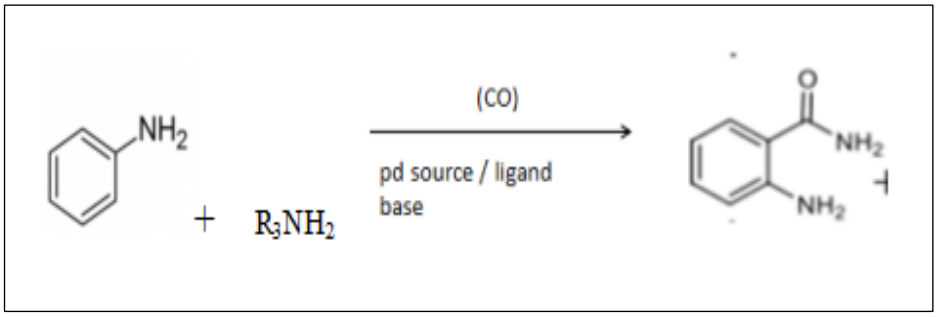
Assay procedure of microplate Alamar Blue Dye Method :-

The biological activity of the molecules was tested using the MABA (Microplate Alamar Blue Assay) against M. tuberculosis. MABA (Microplate Alamar Blue Assay) is a non-toxic, thermostable reagent that correlates with the BACTEC radiometric process. 200 litres of sterile water is poured into each of the 96 wells. On the pan, dilutions of test solutions were rendered using 100l of middlebrook 7H9. The research samples were incubated for 5 days at 37^0C after being measured at 100 to 0.2 l conc. Incubate for 24 hours after adding a 1:1 mixture of alamer blue dye and tween 80 to the plate.The pink and blue colours in the wells were examined; blue indicates no bacterial development, while pink indicates growth. The cheapest medicine on the market. It's MIC to keep the colour from changing from blue to pink.

Result And Discussion:-

Synthesized compound:-

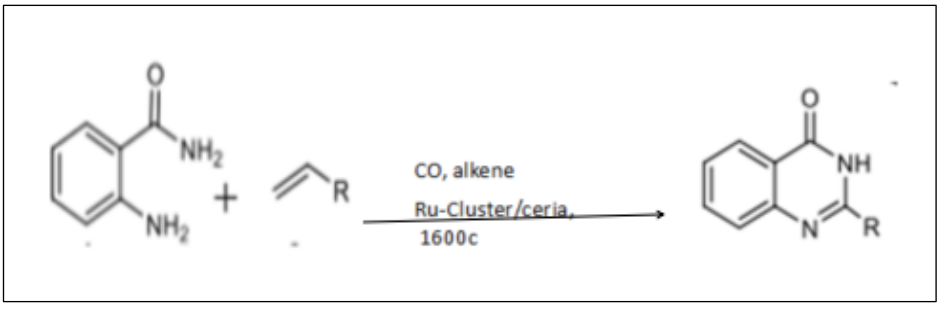
- **Step 1:-**



First step of reaction aniline react with amine in presence of palladium source to give intermediate 1. And percentage practical yield was found to be-

Theoretical yield was found to be = 8.35 gm
Practical yield was found to be = 6.8 gm
Percentage practical yield was found to be = 81.5 %

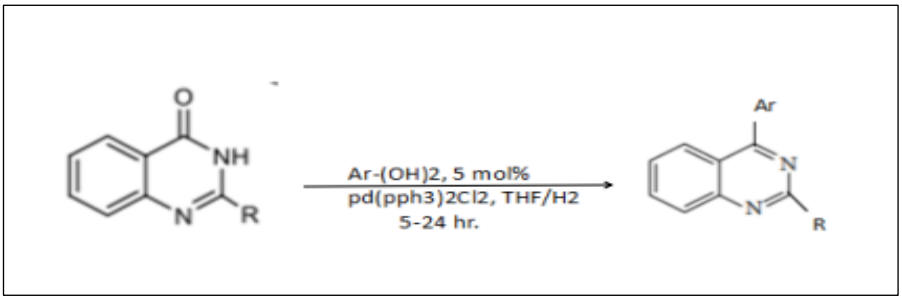
Step 2 :



In this step of reaction of anthranilamide react in presence ruthenium cluster and alkene at 160^{0}c to give intermediate 2. And percentage practicalyield was found to be-

Theoretical yield was found to be = 7.57 gm
Practical yield was found to be = 4.80 gm
Percentage practical yield was found to be = 63.4 %

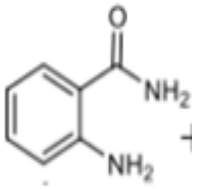
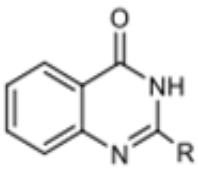
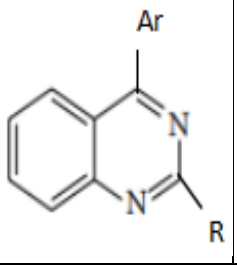
Step 3 :



In this step of the synthesis reaction between intermediate 2 react with boronic acid in the presence of triphenylphosphine palladium and solvent under the condensation at 160^{0}C for 5-24 hr.

Theoretical yield was found to be = 2.53 gm
Practical yield was found to be = 2.17 gm
Percentage practical yield was found to be = 85.7 %

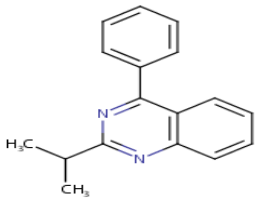
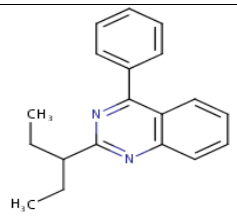
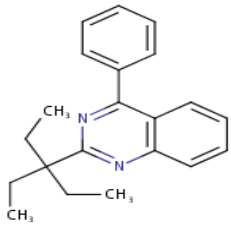
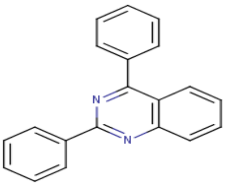
Table 3. Physiochemical data

Sr. No.	Structure	Intermediate	Yield and M. P.
1.		2-aminobenzamide	Theoretical yield was found to be = 8.35 gm Practical yield was found to be = 6.8 gm Percentage practical yield was found to be =81.5% Melting point = 98-100^{0}c
2.		Quinazolin-4-one	Theoretical yield was found to be = 7.57 gm Practical yield was found to be = 4.80 gm Percentage practical yield was found to be =63.4% Melting point = 134-136^{0}c
3.		2-alkyl-4-aryl-quinzoline	Theoretical yield waas found to be = 2.53 gm Practical yield waas found to be = 2.17 gm Percentage practical yield was found to be =85.7% Melting point = 122-126^{0}c

Characterization :

Result of which is characterization of the synthesized end product. As depicted below hence forth the abbreviation use for corresponding structure. Synthesized all compound are interpreted by the IR, NMR and MASS spectroscopic methods.

Table 4. Synthesized Compounds

Sr. No.	Structure	Name of Compound
A.		2-Isopropyl-4-phenylquinazoline
B.		2-Diethyl-4-phenylquinazoline
C.		2-Triethyyl-4-phenylquinazoline
D.		2,4-Diphenylquinazoline

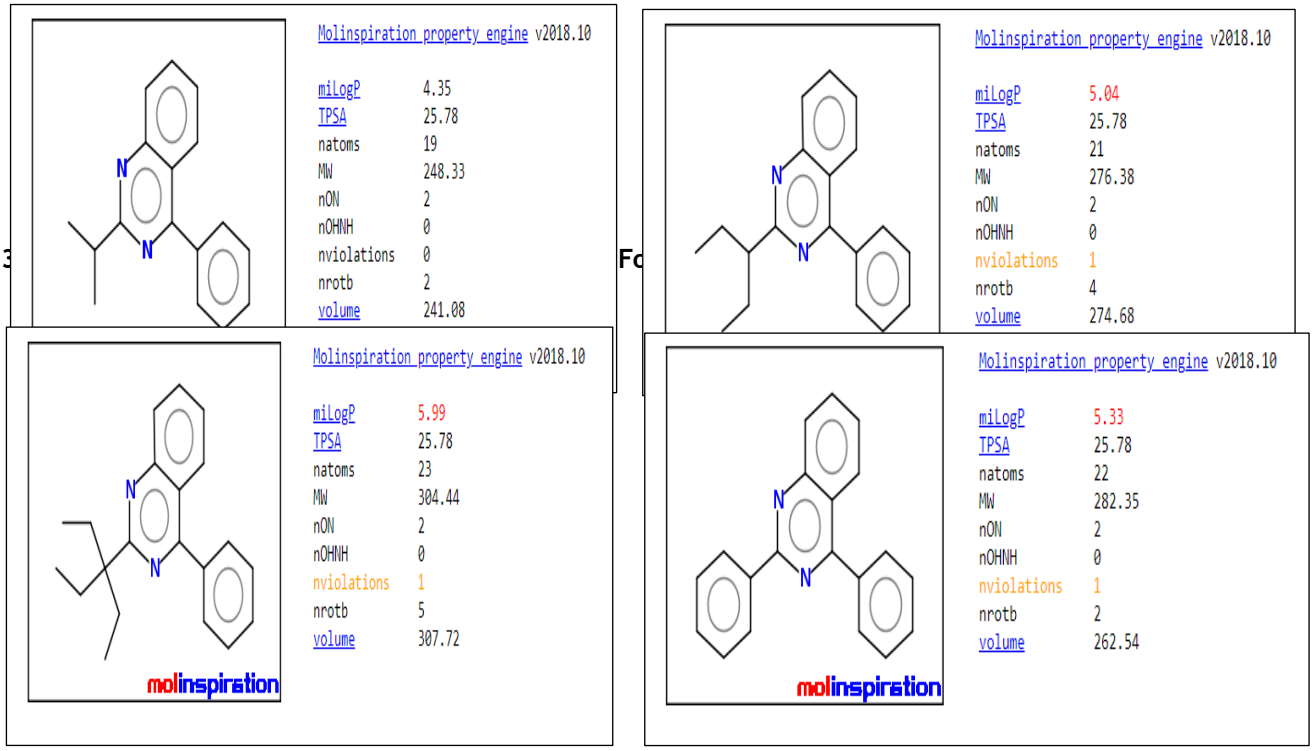
- ✓ Above structures are studied by means of in-silico method i.e. by software technique includes-
- ❖ Molinpiration
- ❖ OSIRIs toxicity predictor

A. Molinspiration property engine :-

Molinspiration technique gives the idea regarding the basic properties of molecules depending upon *in-silico* technique, properties of compounds given below-

1. For molecule - A

2. For molecule - B

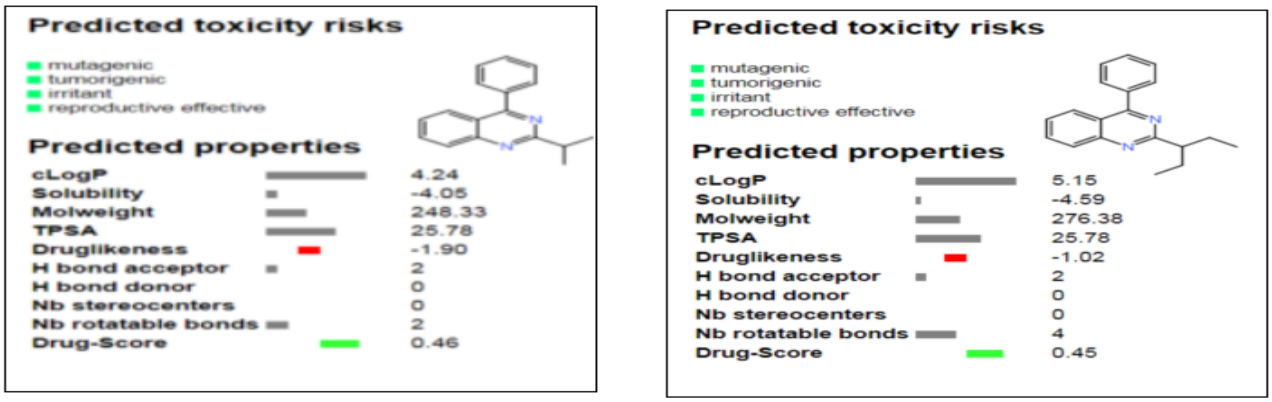


B. OSIRIs toxicity predictor :-

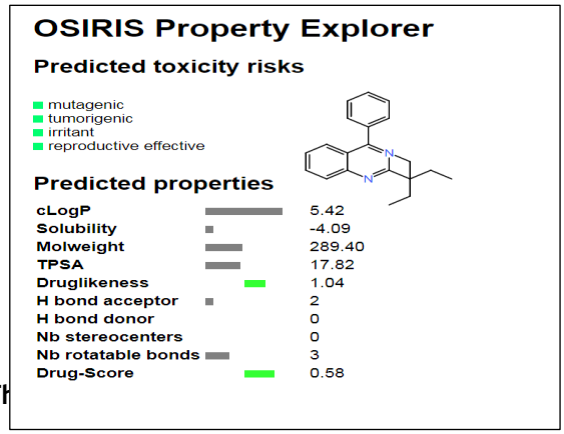
- ✓ To predicting toxicity of compounds, OSIRIs proprietary being used such as mutagenicity tumorogenecity. Green colour is similar to drug-like conformational behaviour. It provide data such as
- ✓ Toxicity calculator
- ✓ cLogP
- ✓ Solubility
- ✓ Molecular mass
- ✓ Extrapolation of drug likeness

1. For Molecule A :-

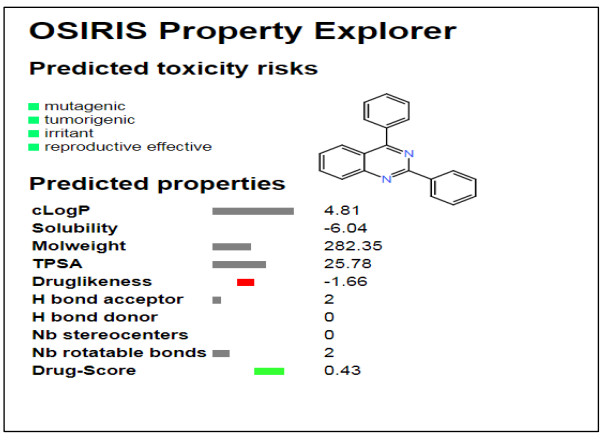
2. For Molecule B :-



3.For Molecule C :-



4. For Molecule D :-



C.Th

Table No. 4 :- TLC data of synthesized compounds

Compounds	Mobile Phase	Rf Value
A	Methanol : Acetonitrile : Ethyl acetate	0.41
B	Methanol : Acetonitrile : Ethyl acetate	0.53
C	Methanol : Actonitrile : Ethyl acetate	0.57
D	Methanol : Acetonitrile : Ethyl acetate	0.84

❖ **Characterization of synthesized compounds :-**

Characterization is done by following spectrroscopic methods.

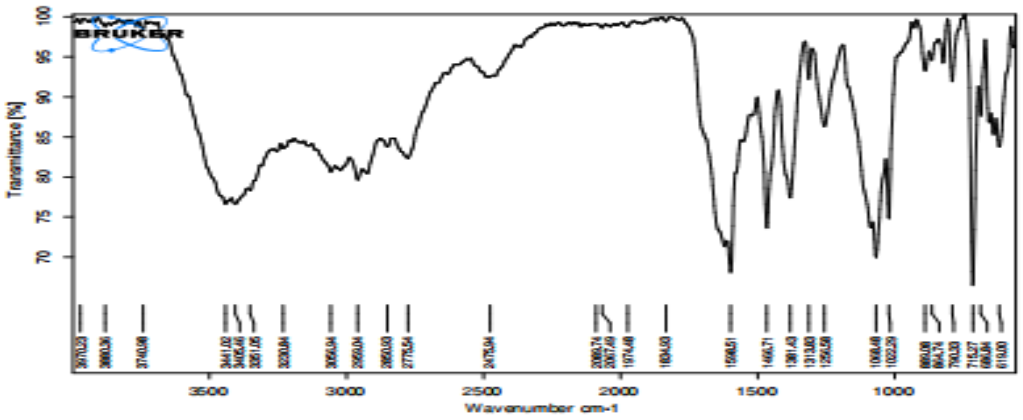
- IR
- Mass
- NMR

✓ IR gives the information about the different types of frequencies that a particular bond exhibit and that specific.

✓ Molecular mass related information obtained from the MASS spectroscopy.

Compound A :-

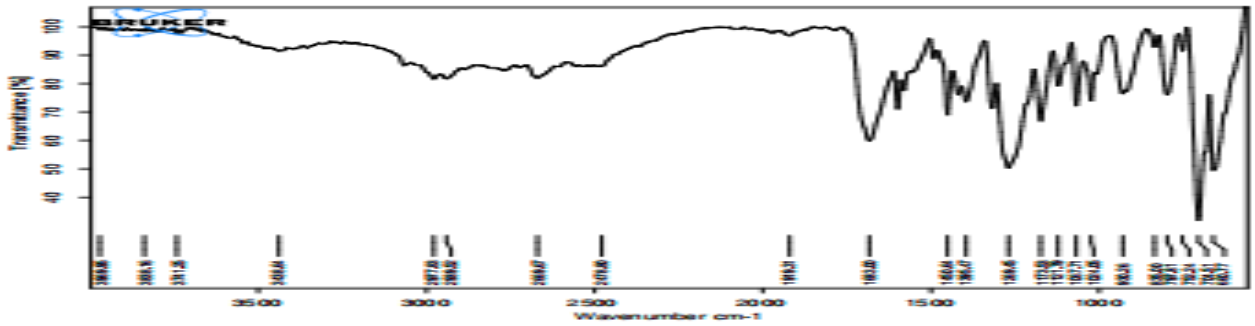
❖ **IR spectrum of A :-**



Functional groups	Standard frequencies (cm^{-1})	Observed frequencies (cm^{-1})
C-H stretch	2850-2960	2850.93
C=C stretch	1620-1680	1598.51
C=N	2210-2260	2089.74
C-N	1180-1360	1313.83
Aromatic C-H Stretch	3000-3100	3056.94
N-H	3300-3500	3441.02

- ✓ Spectra shows the presence of all functional groups with their respective frequencies.
- ✓ The approximate value for all functional group is given into the above table.

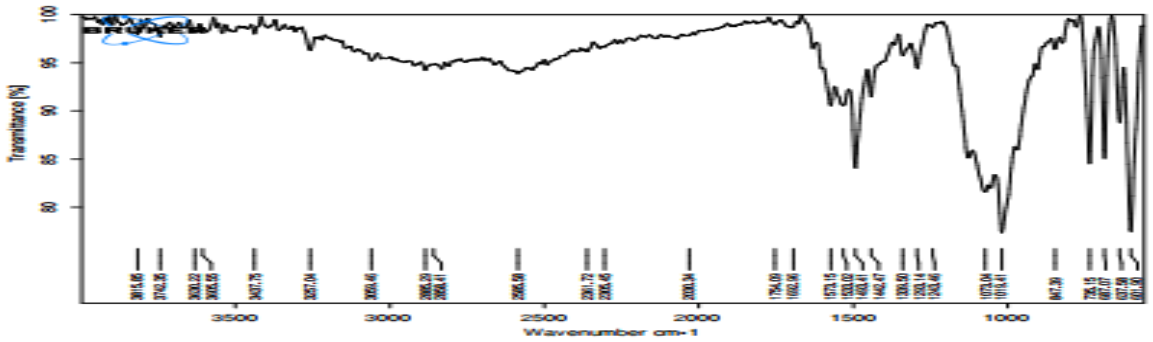
❖ **IR spectrum of B :-**



Functional groups	Standard frequencies (cm^{-1})	Observed frequencies (cm^{-1})
C-H Stretch	2850-2960	2939.52
C=C Stretch	1620-1680	1683.00
C=N	2210-2260	1919.31
C-N	1180-1360	1269.45
Aromatic C-H Stretch	3000-3100	2977.83
N-H	3300-3500	3438.64

- ✓ Spectra shows the presence of all functional groups with their respective frequencies.
- ✓ The appropriate value for all functional group is given into the above table.

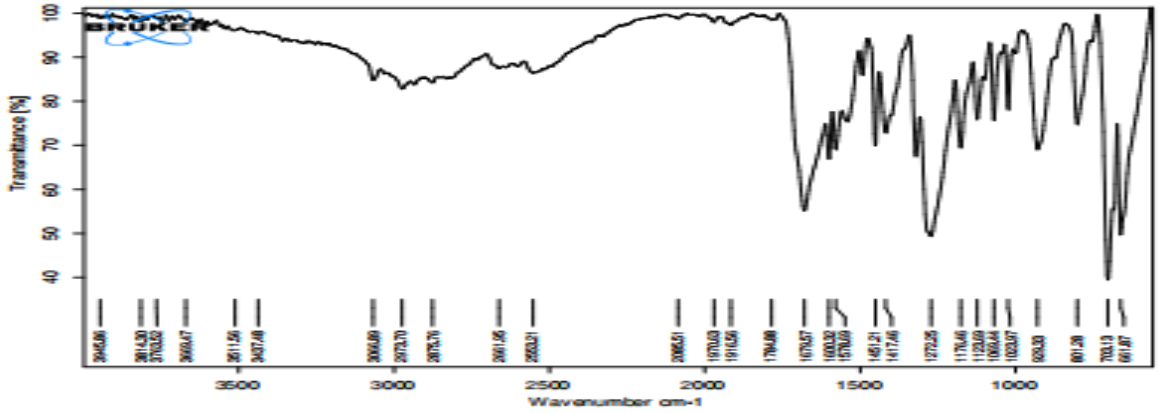
❖ **IR spectrum of C :-**



Functional group	Standard frequencies (cm^{-1})	Observed frequencies (cm^{-1})
C-H Stretch	2850-2960	2885.29
C=C Stretch	1620-1680	1692.96
C=N	2210-2260	2030.34
C-N	1180-1360	1339.50
Aromatic C-H Stretch	3000-3100	3059.46
N-H	3300-3500	3437.75

✓ Spectra shows the presence of all functional groups with their respective frequencies.
✓ The approximate value for all functional group is given into the above table.

❖ **IR spectrum of D :**



Functional group	Standard frequencies (cm^{-1})	Observed frequencies (cm^{-1})
C-H Stretch	2850-2960	2875.76
C=C Stretch	1620-1680	1679.57
C=N	2210-2260	2085.51
C-N	1180-1360	1272.25
Aromatic C-H Stretch	3000-3100	3066.89
N-H	3300-3500	3437.48

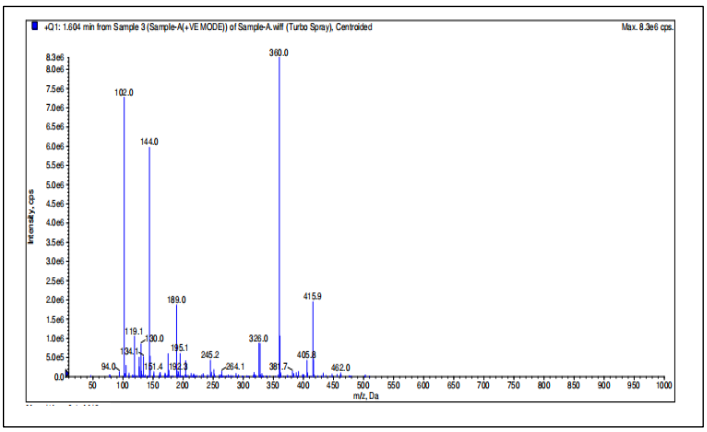
✓ Spectra shows the presence of all functional groups with their respective frequencies.

✓ The approximate value for all functional group is given into the above table.

Mass Spectroscopy :-

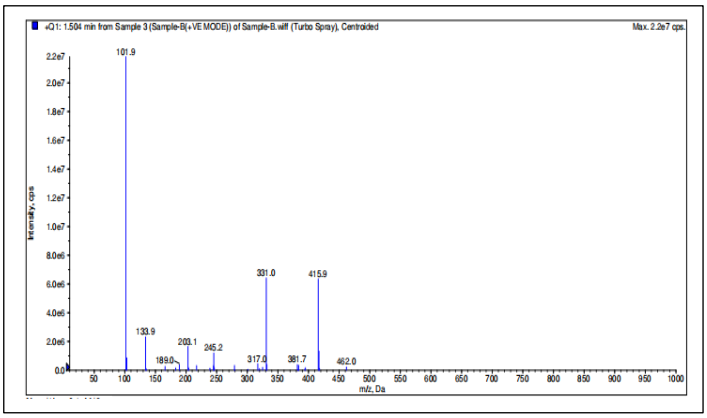
Mass spectroscopy is a technique to find exact molecular mass of compounds, the relative abundance of fragmentation is depend on stabiliity of ions. The charge particle then separated with their masses.

MASS spectra Molecule A :



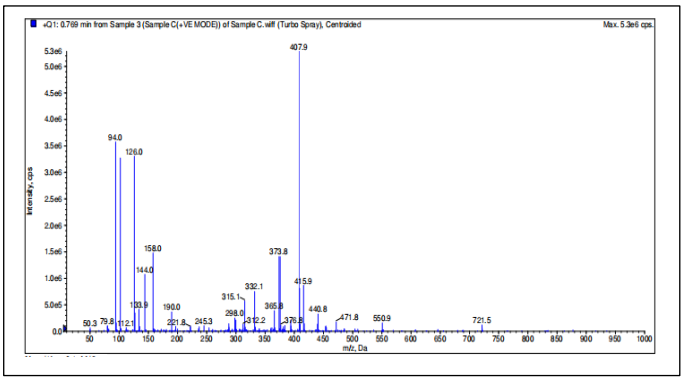
✓ The mass spectroscopy is done in positive mode.
✓ There is obtained molecular ion peak at the 360.0 m/e ratio and their some charge particles.
✓ From this spectrum the molar mass of synthesized compound was confirmed.

MASS spectra Molecule B :



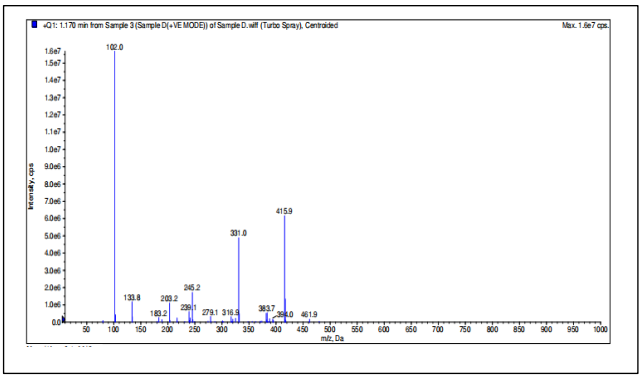
✓ The mass spectroscopy is done in positive mode.
✓ There is obtained molecular ion peak at the 101.9 m/e ratio and their some charge particles.
✓ From this spectrum the molar mass of synthesized compound was confirmed

MASS spectra Molecule C :



- ✓ The mass spectroscopy is done in positive mode.
- ✓ There is obtained molecular ion peak at the 407.9 m/e ratio and their some charge particles.
- ✓ From this spectrum the molar mass of synthesized compound was confirmed.

MASS spectra Molecule D :



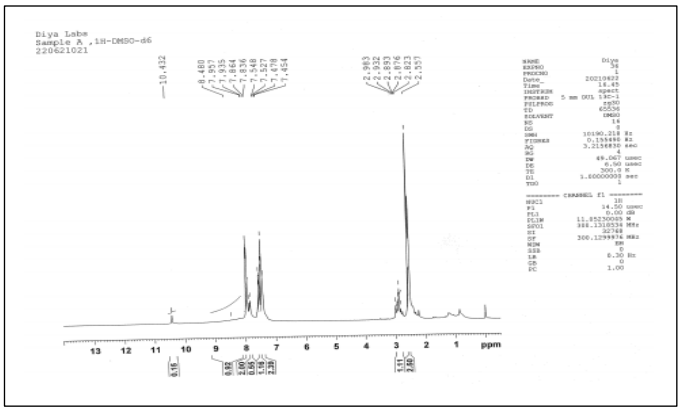
- ✓ The mass spectroscopy is done in positive mode.
- ✓ There is obtained molecular ion peak at the 102.0 m/z ratio and some of their fragments charge particles
- ✓ From this spectrum the molar mass of the synthesized compound was confirmed.

7.3 NMR Spectroscopy :-

To obtained “1H NMR” spectrum of a ny compounds the solvent used must be free from hydrogen because their the chances of solvent protons interfere with compounds proton.

NMR involve the interaction between electromagnetic radiation and the magnetic field of hydrogen nucleus. NMR provide information about equivalent protons and their different electronic environment and help us to find, structure of molecules. The number of signals denotesthe number of equivalent proton in molecule. The nature of proton like aromatic, vinyl, aliphatic etc. Confirmed.

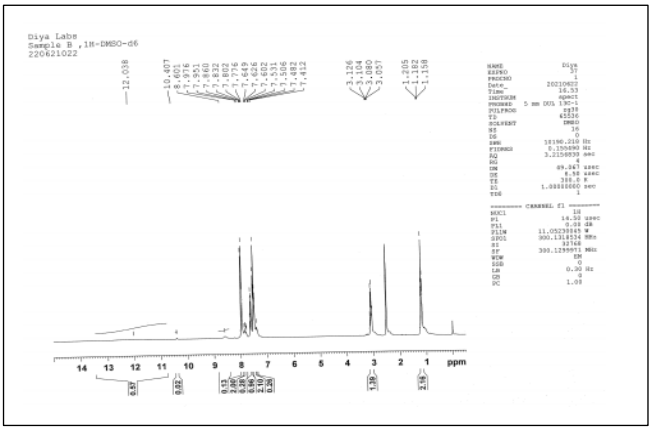
❖ **NMR Spetrrum of Compound A :-**



^{1}HNMR (DMSO)	**Chemical Shift in delta values**
Ar-H	7.5
CH_3	2.4

- NMR of compound is the only due to the neighbouring proton the peaks are interpreted by the influence of substituent groups.
- NMR chemical shifts is affected due to the presence of electron withdrawing functional group like CH_3 group affect the proton at the ortho position and meta less affected and shows the multiplate in the range of the 7.3-8.3 ppm.

❖ **NMR Spectrum of Compound B :-**

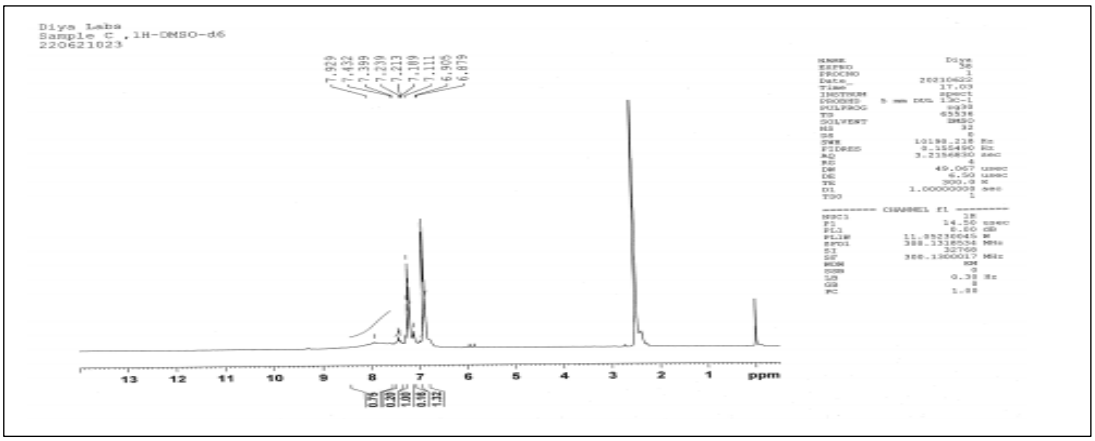


^{1}HNMR (DMSO)	**Chemical Shift in delta values**
Ar-H	7.4
CH_3	2.5

- NMR of compound is the only due to the neighbouring proton the peaks are interpreted by the influence of substituent groups.

- NMR chemical shifts is affected due to the presence of electron withdrawing functional group like CH_3 group affect the proton at the ortho position and meta less affected and shows the multiplate in the range of the 7.2-8.4 ppm.

❖ **NMR Spectrum of Compound C :-**

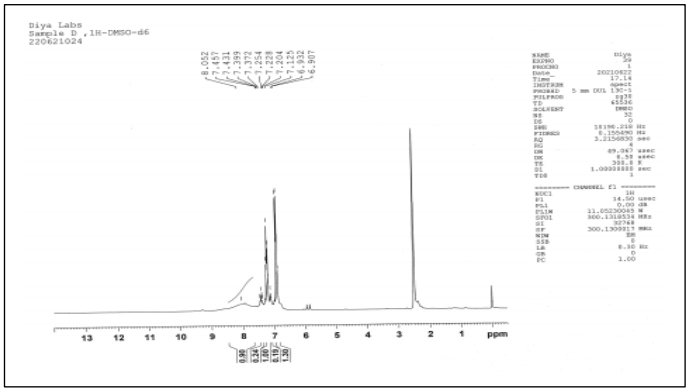


^{1}HNMR (DMSO)	**Chemical Shift in delta values**
Ar-H	7.1
CH_3	2.6

- NMR of compound is the only due to the neighbouring proton the peaks are interpreted by the influence of substituent groups.

- NMR chemical shifts is affected due to the presence of electron withdrawing functional group like CH_3 group affect the proton at the ortho position and meta less affected and shows the multiplate in the range of the 5.8-7.8 ppm.

❖ **NMR Spectrum of Compound D :-**



^{1}HNMR (DMSO)	Chemical Shift in delta values
Ar-H	7.2
CH_3	2.7

- NMR of compound is the only due to the neighbouring proton the peaks are interpreted by the influence of substituent groups.
- NMR chemical shifts is affected due to the presence of electron withdrawing functional group like CH_3 group affect the proton at the ortho position and meta less affected and shows the multiplate in the range of the 5.7-7.6 ppm.

Biological Activity :-

Assay procedure of microplate Alamar Blue Dye Method :-

✧ **Standard used for Biological Activity :-**

Pyrazinamide - 3.125 µg/ml

Standard used for this assay is Pyrazinamide to comapre the test compunds and DMSO used as control.

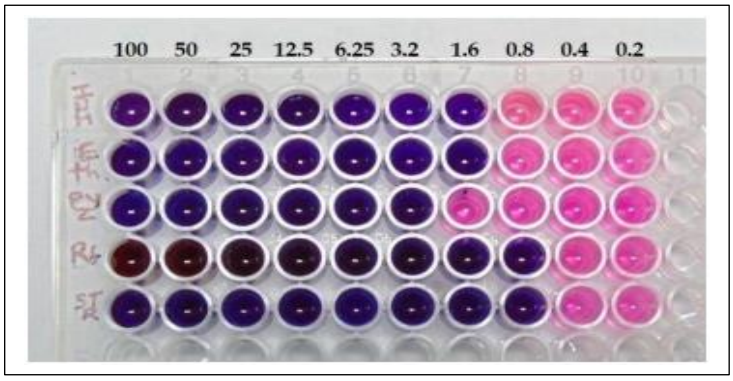


Fig. 10: Antitubercular Activity of Standard Compound

✧ **Results for Synthesized molecules**

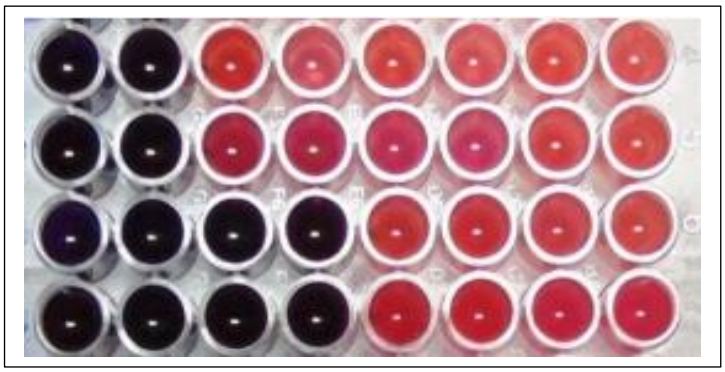


Fig. 11 : Antitubercular Activity of Synthesized Compound

7.3.3 : Observation table

(Table No.7 MIC of Synthesized compounds, S= Sensitive & R= Resistance)

Sr No.	Sample	100 µg/ml	50 µg/ml	25 µg/ml	12.5 µg/ml	6.25 µg/ml	3.12 µg/ml	1.6 µg/ml	0.8 µg/ml
1.	Compound A	S	S	R	R	R	R	R	R
2.	Compound B	S	S	R	R	R	R	R	R
3.	Compound C	S	S	S	S	R	R	R	R
4.	Compound D	S	S	S	S	R	R	R	R

❖ evaluation we can say that

✓ Molecule A-1 is sensitive up to 50 µg/ml.

✓ MIC vlue of Molecule B is sensitive up to 50 µg/ml.

✓ MIC value of Molecule C is sensitive up to 12.5 µg/ml.

✓ MIC value of Molecule D is sensitive upto 12.5 µg/ml.

Conclusion

The synthesized molecules are effective in inhibition of cell wall growth which play important role in mycolic bacterial cell wall growth. All compounds are showing the significant effect on target enzyme.

Depending upon the biological activity we can conclude that the presence of functional groups like NH2, Alkyl, Aryl group increases the activity, this groups has been selected according to electron withdrawing groups and electron donating groups.

Other than this there is again scope of various structure activity relationship and synthesized other such novel molecules.

The toxicity profile of compounds were studied by in-silico method software based by□

✓ OSIRIS

✓ Molinspiration toxicity predictor

During the synthesis of derivatives the all methods should be optimized to obtained good yield and desired product purity

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