



**Ministry of Higher Education
& Scientific Research
University of Diyala – College of Science
Department of Chemistry**



Synthesis and Characterization of Novel Pyrazole Derivatives from 4-Florophenylhydrazine and Study Their Cytotoxicity as Anti-Cancer Agen

Presented by researcher

Sumaya Mahdi Salih Khammas

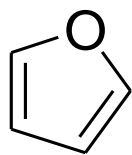
Supervised by

Assist. Prof. Dr. Fadhil Lafta Faraj

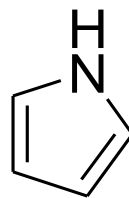
Assist. Prof. Dr. Hameed Madlool Mohammed

Introduction

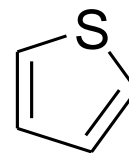
Heterocyclic compounds are organic compounds that contain heteroatoms in their ring structure in addition to carbon atoms, such as sulfur, oxygen or nitrogen, as the heteroatom. The ring may be aromatic or non-aromatic.



furan



1H-pyrrole



thiophene

Figure 1: the chemical structures of pyrrole, furan and thiophene

Indole

Indole is an aromatic heterocyclic organic compound. It has a bicyclic structure, consisting of a benzene ring and a pyrrole nucleus are fused in 2, 3 positions of the pyrrole ring Figure 2

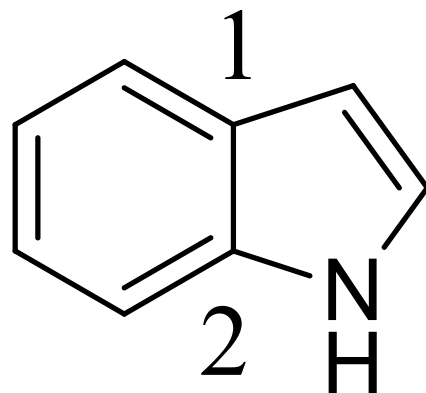
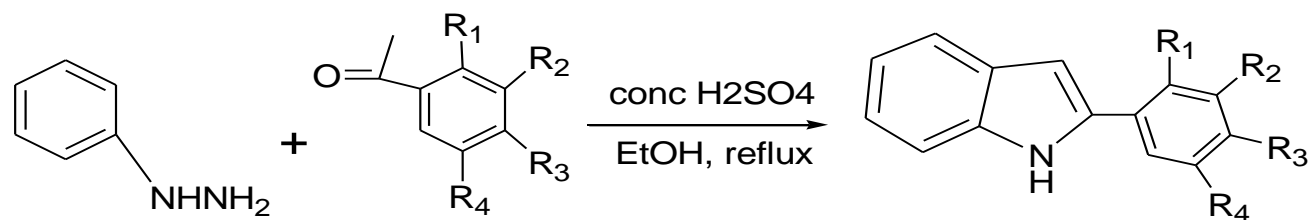


Figure 2: the chemical structures of indole ring

Indole synthesis

Fischer-Indole Synthesis

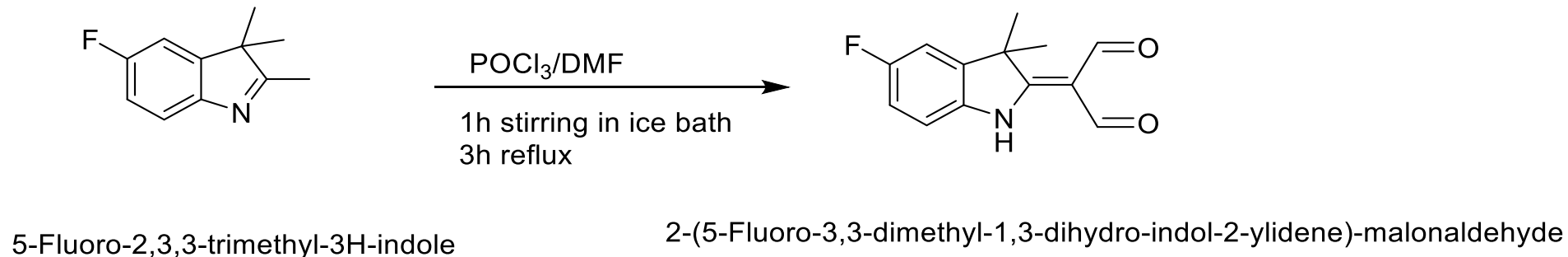
The Fischer indole synthesis is considered one of the best methods for preparing indoles. The Fischer indole synthesis converts arylhydrazones of aldehydes or ketones into indoles in the presence of an acid catalyst. Below is the overall reaction equation (1).



Equation (1): Synthesis of substituted 2-aryl-1H-indoles

The Vilsmeier–Haack reagent

The Vilsmeier-Haack reagent (POCl₃+DMF) is most commonly used for the introduction of CHO group into aromatic rings, since it is one of the most common functional group for carbon-carbon bond formation.



Equation (2): The reaction of Vilsmeier-Haack reagent

Pyrazole ring

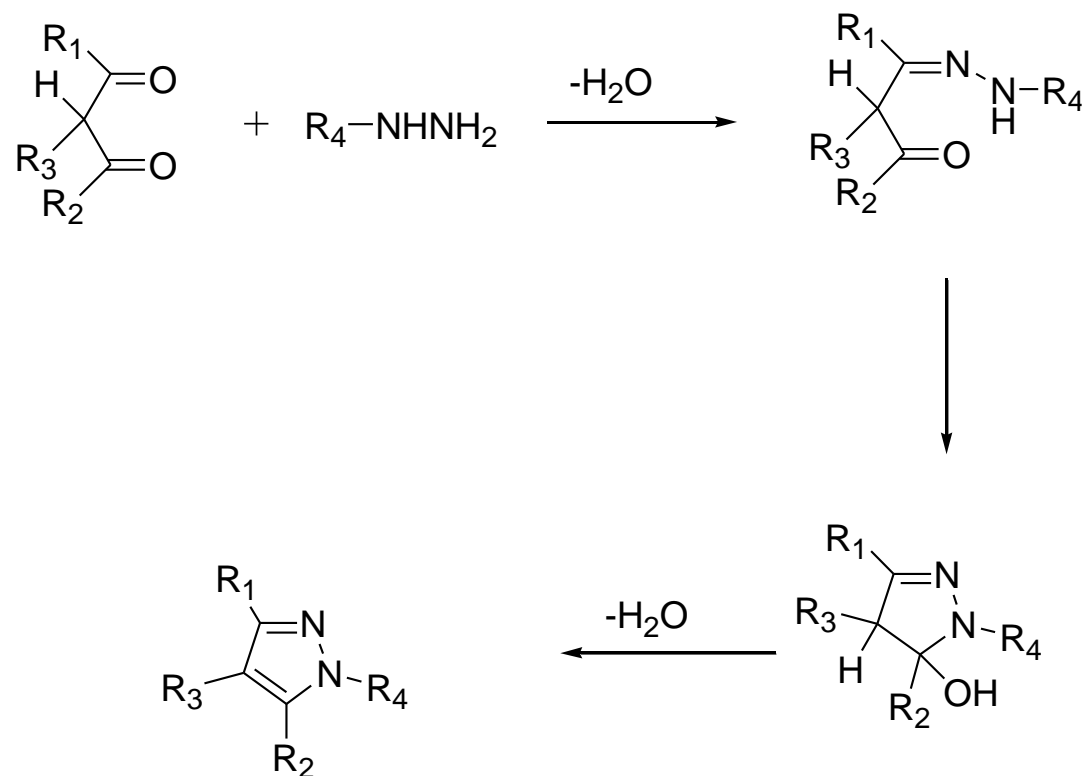
Pyrazole is a chemical compound that has a five-membered heterocycle with two nitrogen atoms and three adjacent carbons

Pyrazole synthesis

Pyrazole derivatives are preparing in many synthetic pathways which represent an interesting topic since these compounds have various applications in the pharmaceutical and agrochemical industry

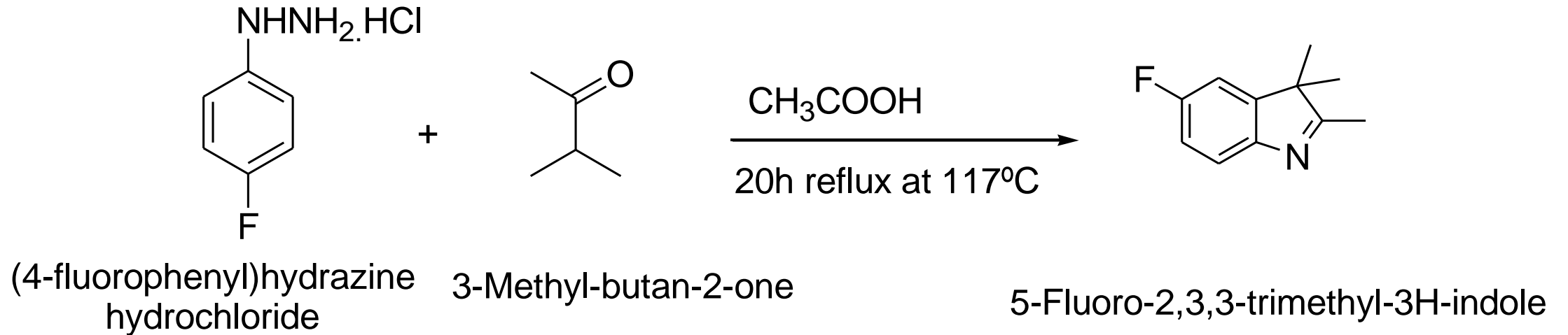
Knorr pyrazole synthesis.

It's one of the essential methods for synthesis involving the reaction of 1,3-dicarbonyls with hydrazine derivatives.



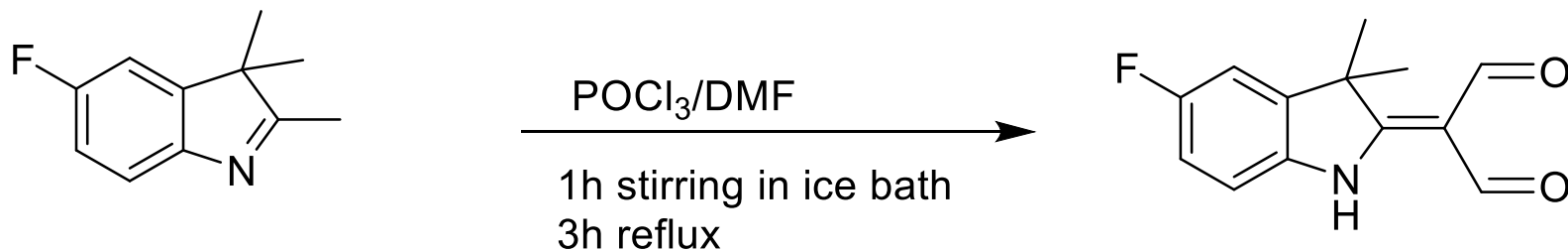
Scheme 1 : Knorr pyrazole synthesis

**Synthesis of the starting material by two steps:
The first step by: Fischer indole synthesis.**



Equation 3 : The synthetic pathway of 5-fluoro -2,3,3-trimethyl-3H-indole. (1)

The second step: by Vilsmeier Haack reaction



5-Fluoro-2,3,3-trimethyl-3H-indole

2-(5-Fluoro-3,3-dimethyl-1,3-dihydro-indol-2-ylidene)-malonaldehyde

Equation 4 : The synthetic pathway of 2-(5-Fluoro-3,3-dimethyl-1,3-dihydro-indol-2-ylidene)-malonaldehyde (2).

Results and Discussion

A series of new pyrazole derivatives have been synthesized via condensation reaction of **2-(5- Fluoro-3,3-dimethyl-1,3-dihydro-indol-2ylidene)-malonaldehyde (2)** with various **substituted phenyl hydrazine hydrochloride** in the ratio (1:1) according to the synthetic pathway, as shown in the figure (1):

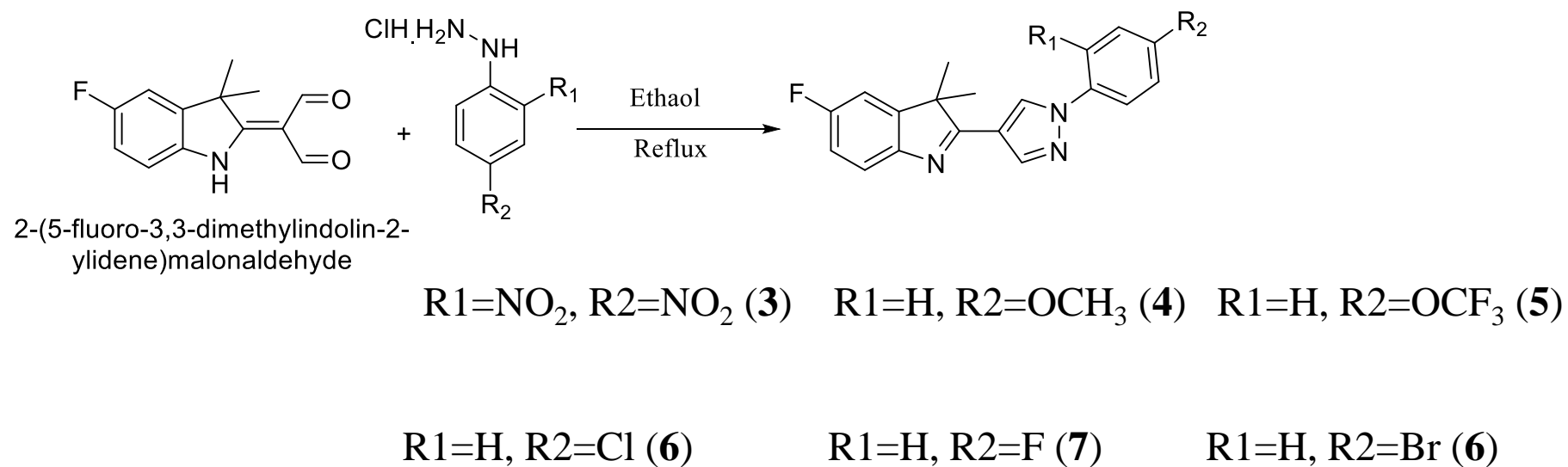
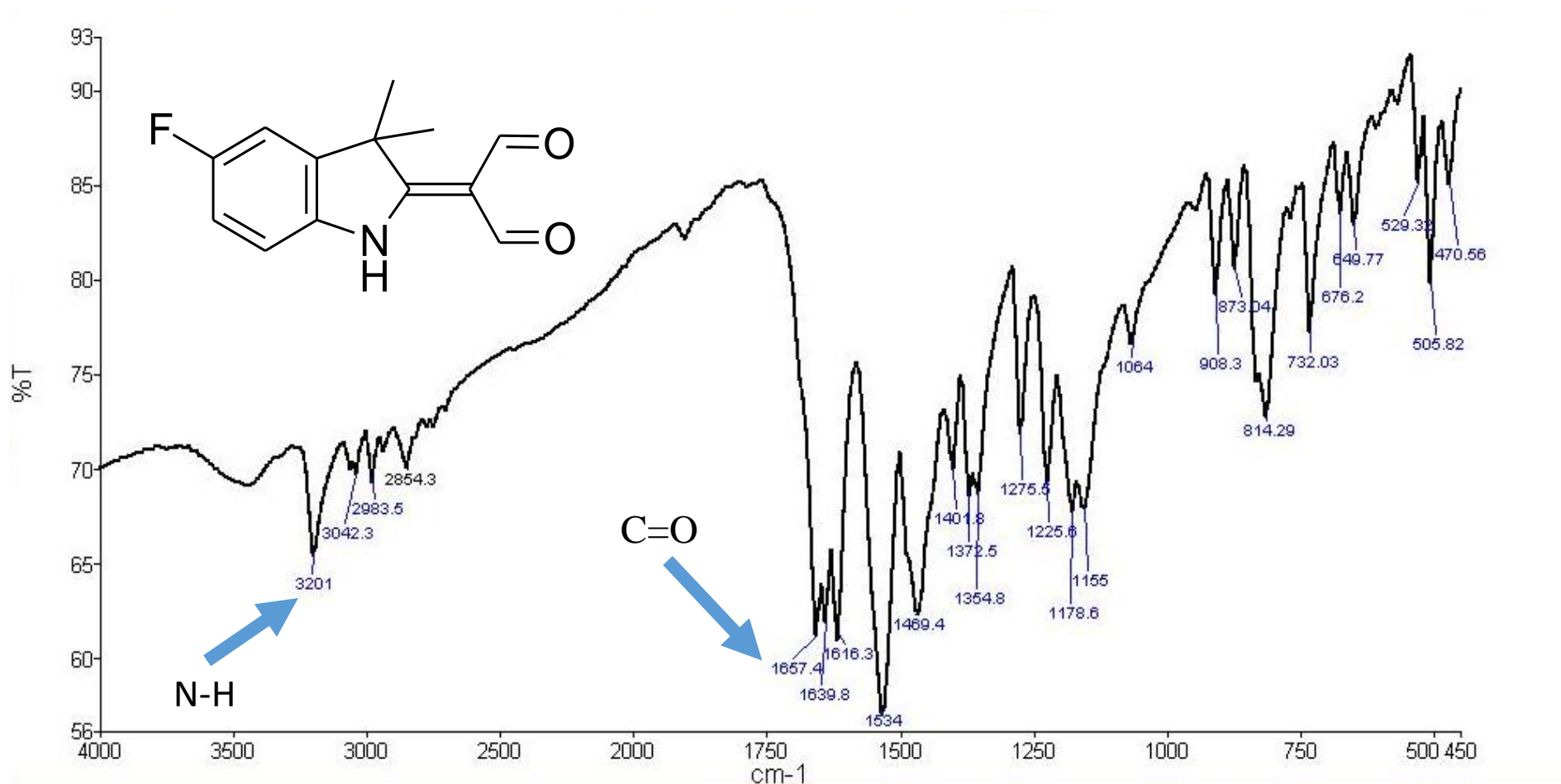


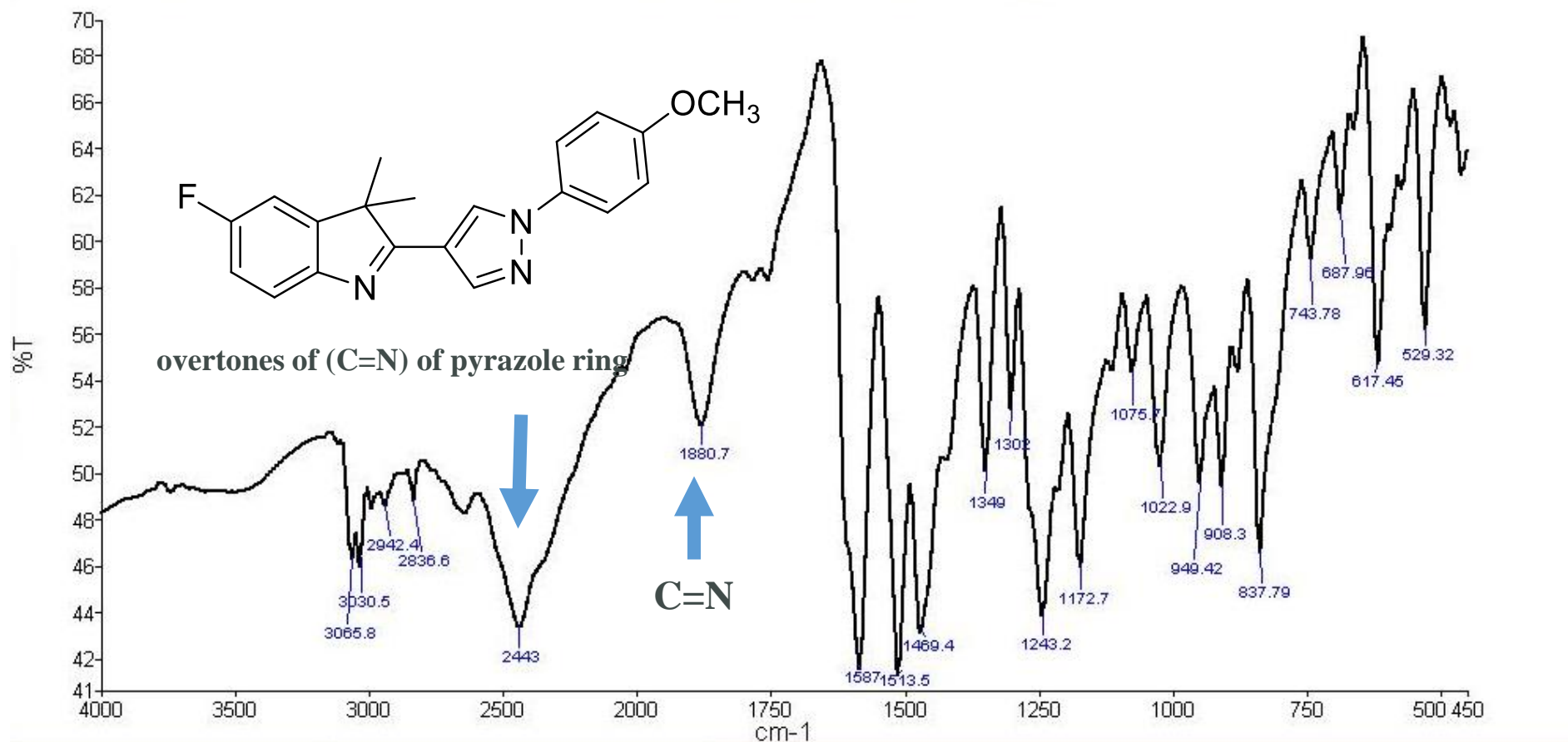
Figure 1: The synthetic pathway of the synthesized compounds (3-8)

FT-IR Study

The results of the FT-IR for the newly synthesized compounds displayed absorption bands in the range between 400-4000 cm^{-1} .



FT-IR for compound 2-(5-Fluoro-3,3-dimethyl-1,3-dihydro-indol-2-ylidene)-malonaldehyde (2)



FT-IR for compound 5-Fluoro-2-[1-(4-methoxy-phenyl)-1Hpyrazol-4-yl]-3,3-dimethyl-3H-indole (3)

The table shows the FT- IR Spectra For other Synthetic Compounds

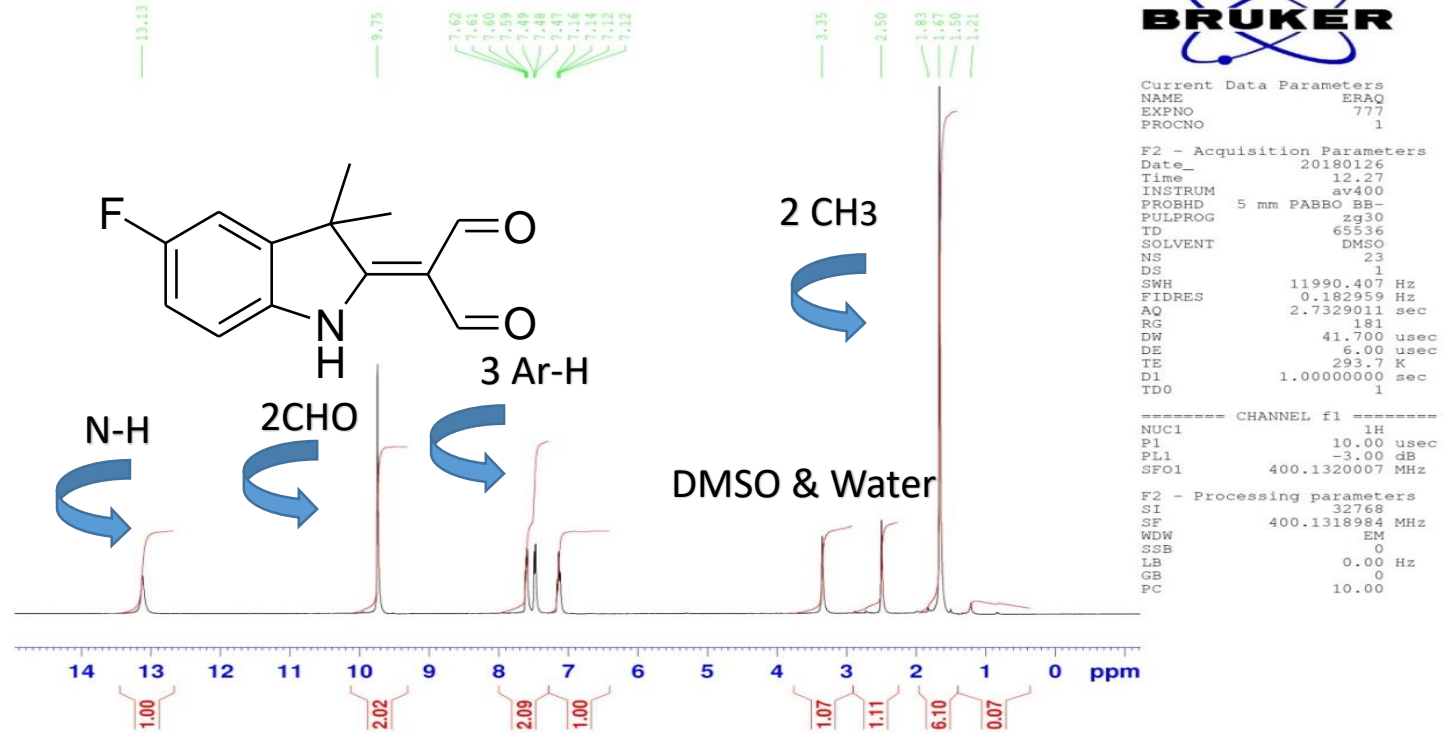
Com. No.	N-H	C-H Asym.	C-H Sym.	overtones (C=N) of pyrazole	C=O	C=N	C=C	CH₃	C-N	C-O	Others
2	3201	3042	2983	-	1657	1616	1534	1372	1275	1178	-
3	-	3065	2942	2443	-	1880	1587	1349	1243	1172	-
4	-	3259	2977	2352	-	1871	1540	1331	1272	-	1381 and 1487 (N-O)
5	-	3077	2983	2425	-	1883	1584	1352	1260	-	826 (C-Cl)
6	-	3065	2977	2290	-	1895	1592	1357	1260	1166	1075 (C-F)
7	-	3065	2980	2325	-	1901	1598	1354	1269	-	685 (C-Br)
8	-	3083	2971	2360	-	1895	1587	1331	1231	-	1081 (C-F)

NMR Study

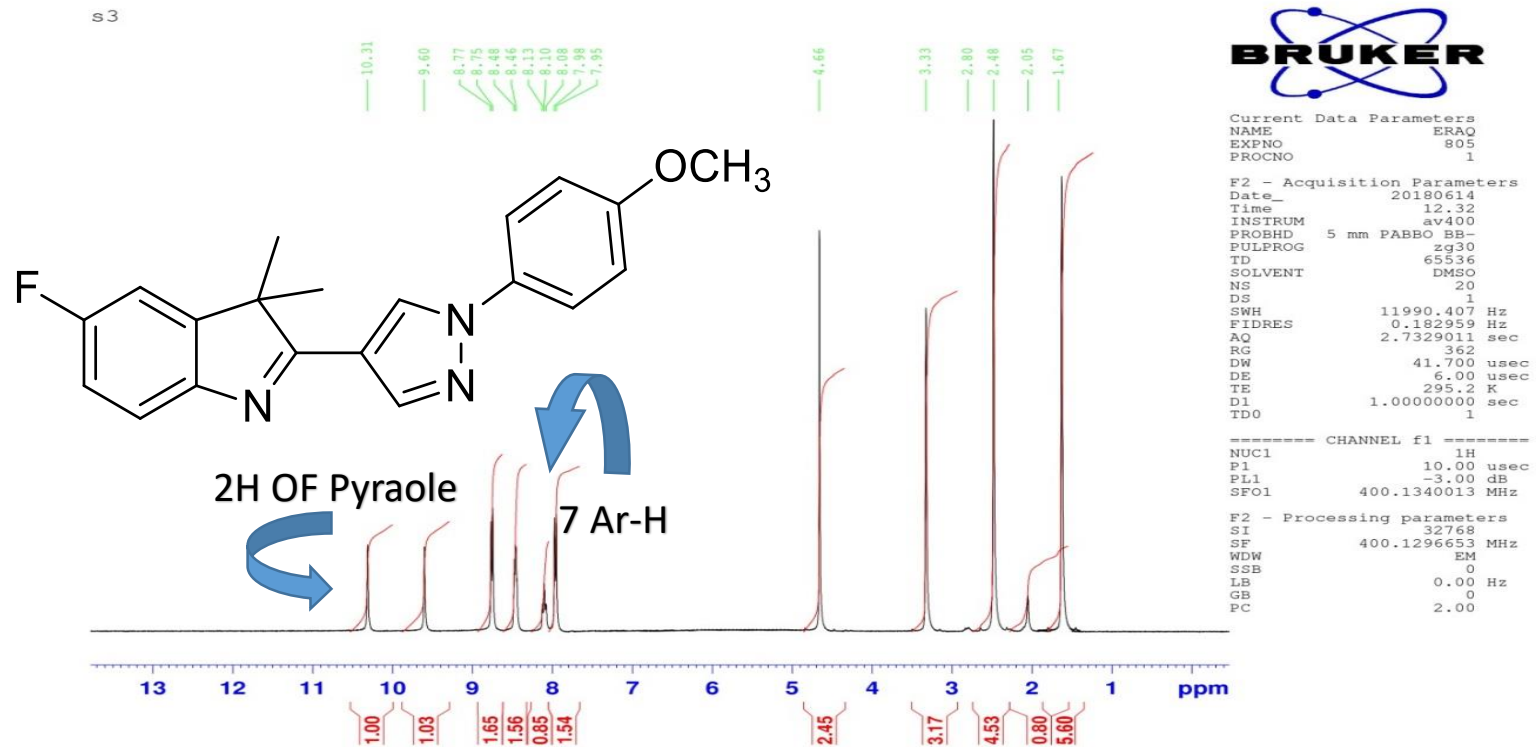
$^1\text{H-NMR}$ results of the newly synthesized compounds (1-8) showed the disappearance signals of starting materials and appearance of new signals. Such as the disappeared of two protons atoms of the carbonyl groups and appearance new signals of two protons atoms of pyrazole ring.

$^1\text{H-NMR}$ results of 2-(5-Fluoro-3,3-dimethyl-1,3-dihydro-indol-2ylidene)-malonaldehyde (2)

S2



A long single signal at 9.75 ppm which belonged to two protons of two aldehyde groups (2 x $\underline{C}HO$).



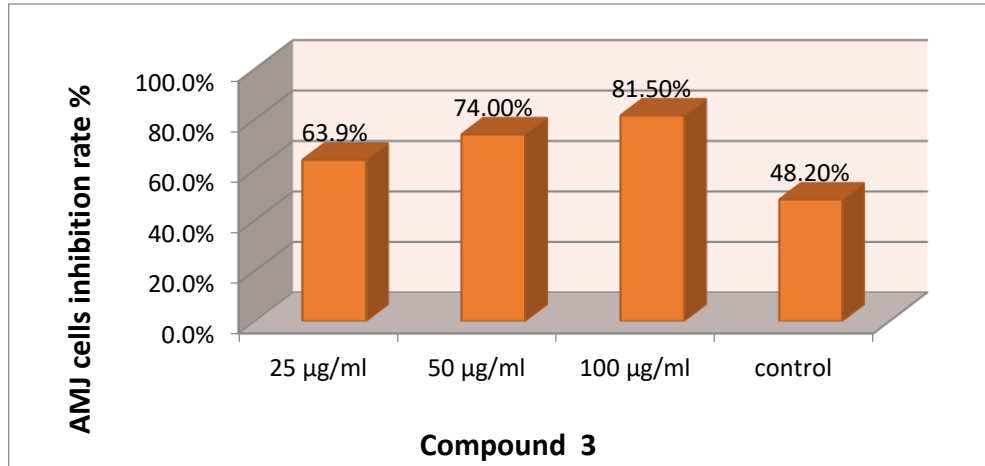
a single signal at 10.31 and 9.60 ppm belonged to the two proton atoms of the pyrazole ring

The table shows the ¹H-NMR results of new synthetic compounds are listed in table

Com.No	pyrazole ring	Ar-H	2xCH₃	Others
1	-	6.71-7.57	1.40	2.17 CH₃
2	-	7.12-7.62	1.67	13.13 NH, 9.75 2xCHO
3	10.31 and 9.6	7.95-8.77	1.67	4.66 OCH₃
4	10.35and9.56	8.12-8.96	1.73	-
5	9.50 and 8.74	7.25-8.06	1.62	-
6	10.66and9.89	8.30-9.20	1.85	-
7	10.52and9.78	8.12-9.35	1.67	-
8	10.42and9.69	8.08-8.91	1.66	-

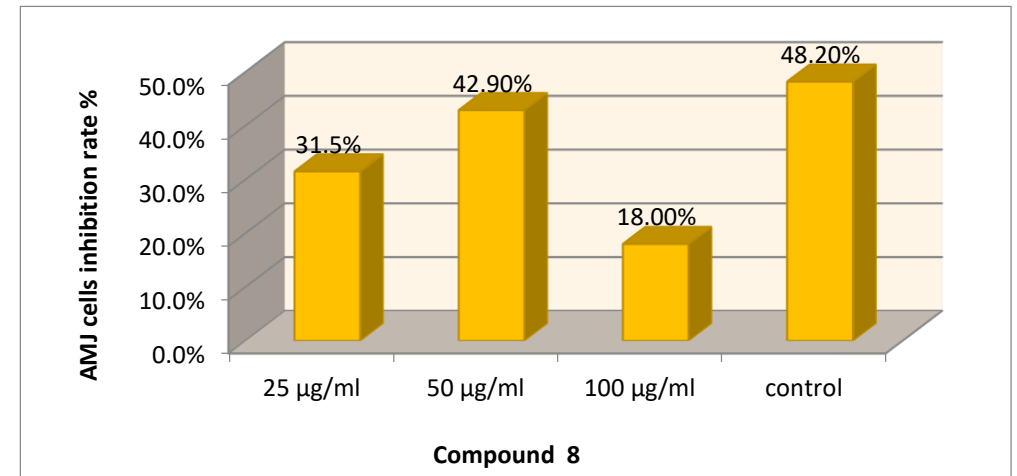
Biological study

This study showed that Cancer cell line AMJ13 were seeded as 2×10^4 cells / well in 96 well plats and after 24 h. when the cells become confluent monolayer, they were exposed to the compound's concentrations at 25, 50 and 100 $\mu\text{g/ml}$ and incubated in 37°C for 48 h, then stained with crystal violate dye and calculated the inhibition rate (%) for each compound



5-Fluoro-2-[1-(4-methoxy-phenyl)-1H-pyrazol-4-yl]-3,3-dimethyl-3H-indole (3) was the best compound which gives highest inhibitory compare to with other compounds

2-[1-(4-Fluoro-phenyl)-1H-pyrazol-4-yl]-5 Fluoro- 3,3-dimethyl-3H-indole (8) showed less inhibitory percent among all other compounds



Conclusion

- 1. Eight new pyrazole derivatives have been synthesized from the reaction of variously substituted phenyl hydrazine with 2-(5-Fluoro-3,3-dimethyl-1,3-dihydro-indol-2-ylidene)-malonaldehyde (2) which prepared by Fischer indole synthesis and Vilsmeier Hack reaction.**
- 2. 5-Fluoro-2-[1-(4-methoxy-phenyl)-1H-pyrazol-4-yl]-3,3-dimethyl-3H-indole (3) was the best compound which gives highest inhibitory compare to with other compounds**
- 3. The compound 2-[1-(4-Fluoro-phenyl)-1H-pyrazol-4-yl]-5 Fluoro- 3,3-dimethyl-3H-indole (8) showed less inhibitory percent among all other compounds.**



Thank You