The 23rd International Electronic Conference on Synthetic Organic Chemistry

Microwave assisted synthesis and its cytotoxicity study of 4*H*-pyrano[2,3-*a*]acridine-3-carbonitrile intermediate: Experiment design for optimization using Response Surface Methodology

BY

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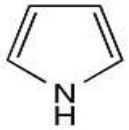
Introduction

- **Heterocycles – Cyclic compounds with 2 different atoms.**

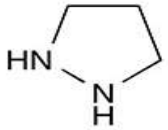
oxetane

2*H*-oxete

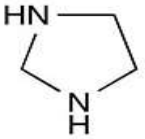
thietane



1*H*-pyrrole

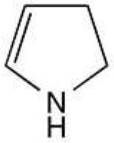


pyrazolidine



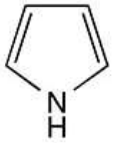
imidazolidine

- **Nitrogen heterocycles – Nitrogen atom present in the cyclic ring**

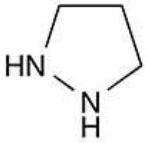


2-pyrroline

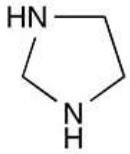
2*H*-pyrrole



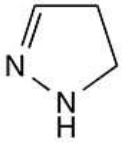
1*H*-pyrrole



pyrazolidine

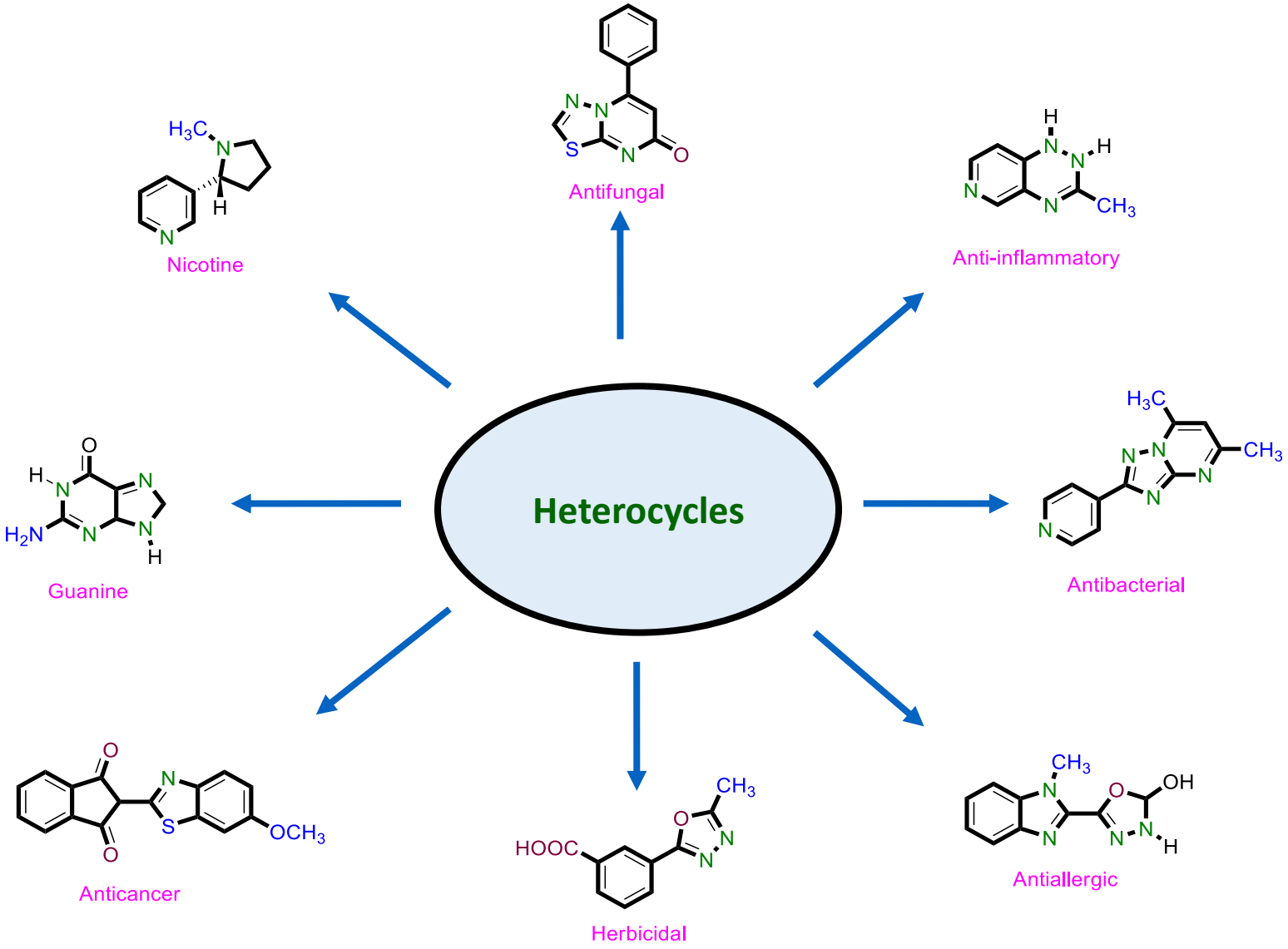


imidazolidine

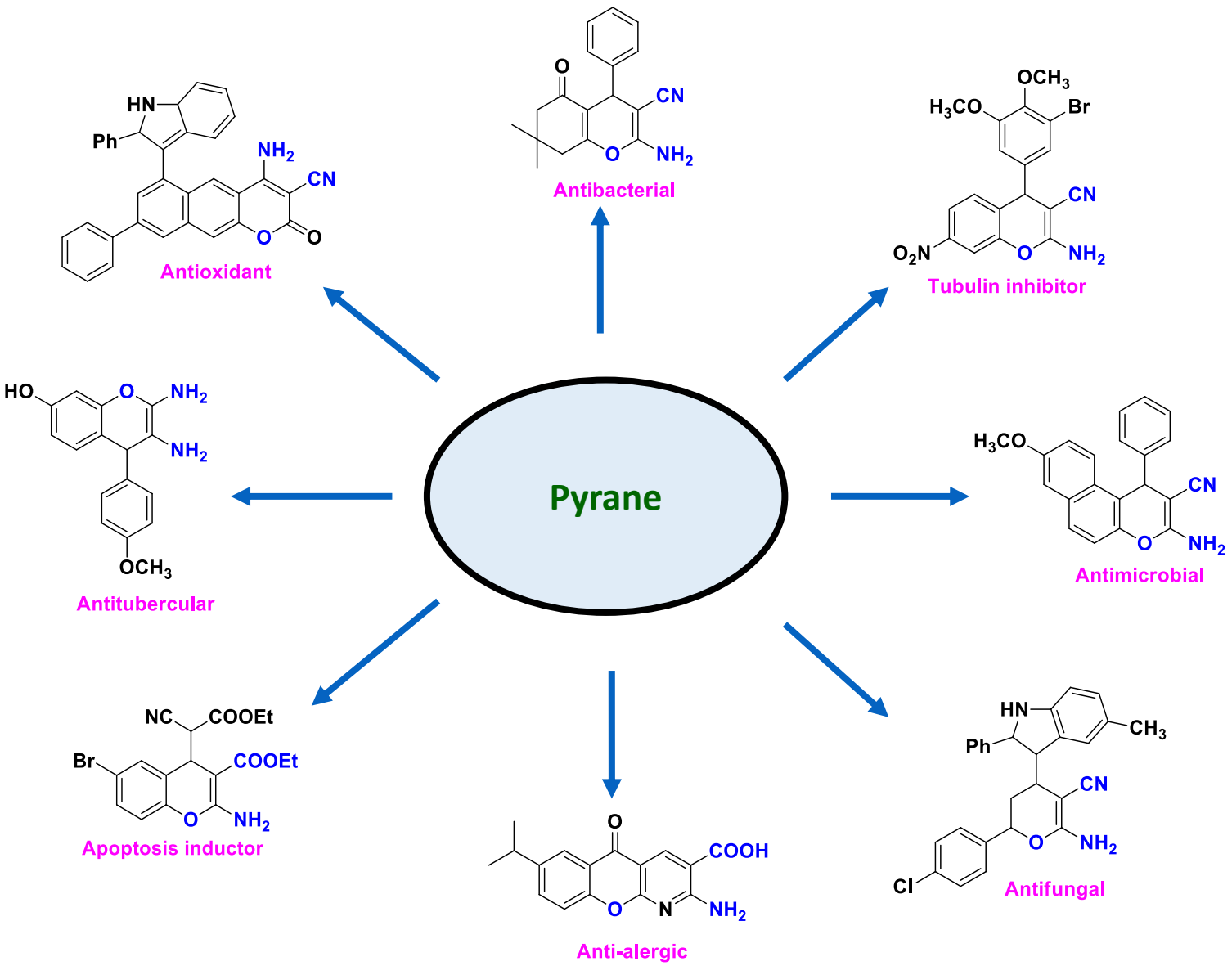


2-pyrazoline

Importance of heterocyclic compounds



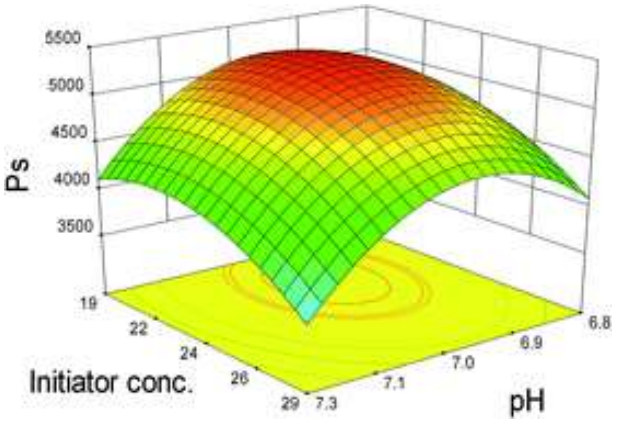
Mukhtyar. S. Saini *et al*., **A review: biological significances of heterocyclic Compounds.** *IJPSR.* 2013, 4(3), 66-77.



Vitaly A. Osyanin et al., Tetrahedron 68 (2012) 5612-5618

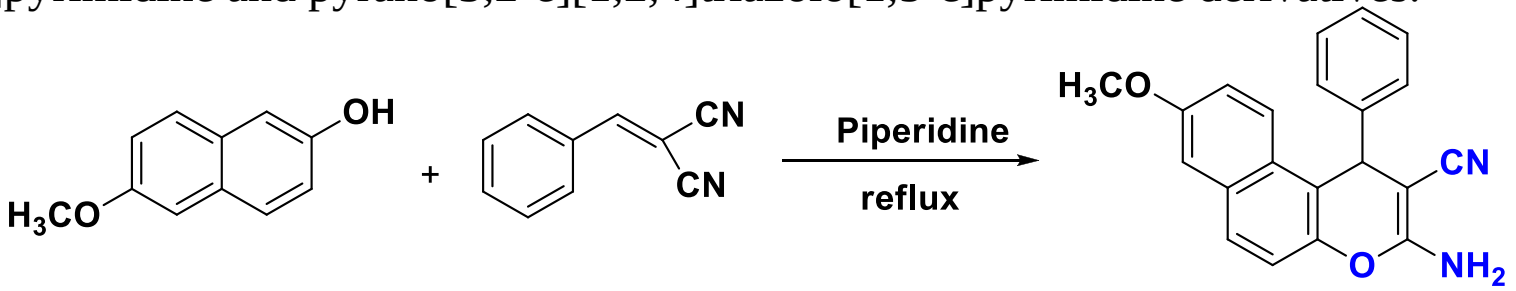
RSM (Response Surface Methodology)

- Response Surface Methodology (RSM) is useful for the modeling and analysis of programs.
- Explores the relationships between several explanatory variables and one or more response variables.
- Help to better understand and optimize your response.



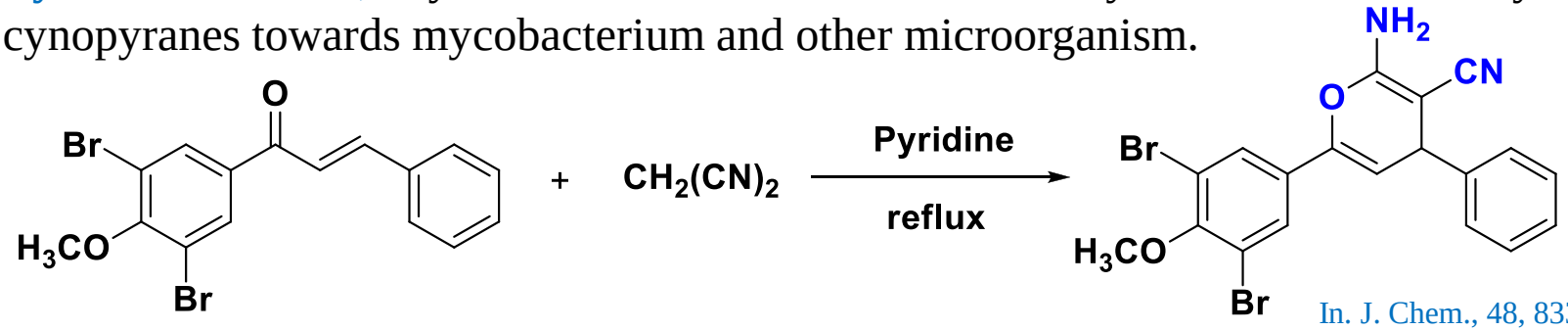
Literature review

Fathy A.E. *et al.,* Synthesis and antimicrobial evaluation of naphtho[2,1-b]pyrano[2,3-d]pyrimidine and pyrano[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine derivatives.



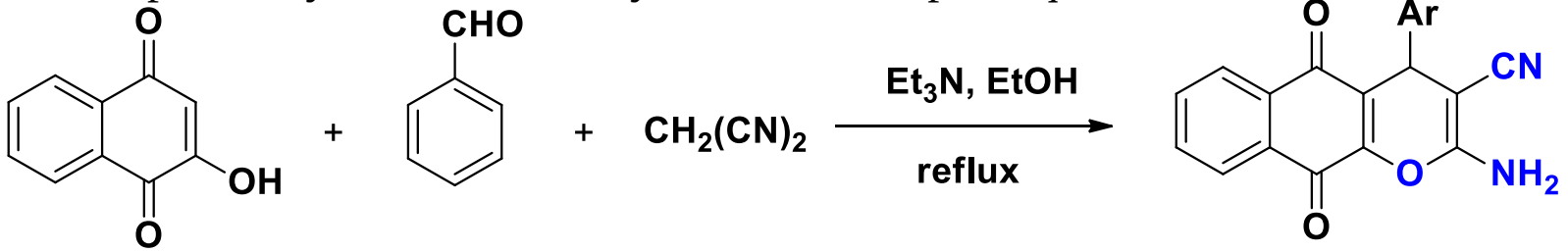
Acta. Pharm.,54, 13–26, 2004

Vyas D.H. *et al.,* Synthesis and antimicrobial activity of some new cynopyridine and cynopyranes towards mycobacterium and other microorganism.



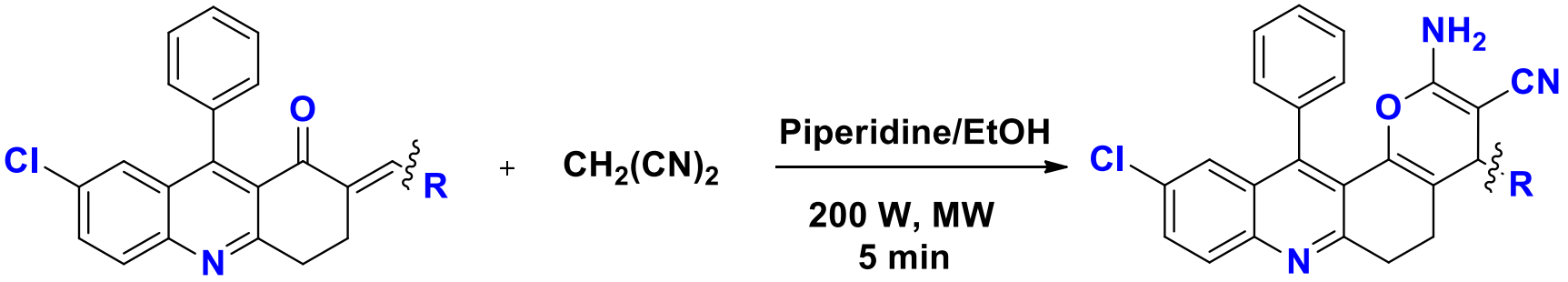
In. J. Chem., 48, 833-839, 2009

Magedov I.V. *et al.,* Structural simplification of bioactive natural products with multicomponent synthesis. 4. 4H-Pyrano-[2,3-b]naphthoquinones with anticancer activity



Bioorg. Med. Chem. Let., 22, 5195–5198, 2012

Synthesis of 2-amino-10-chloro-4-(3,4-dimethoxyphenyl)- 12-phenyl-5,6-dihydro-4H-pyrano[2,3-a]acridine-3-carbonitriles

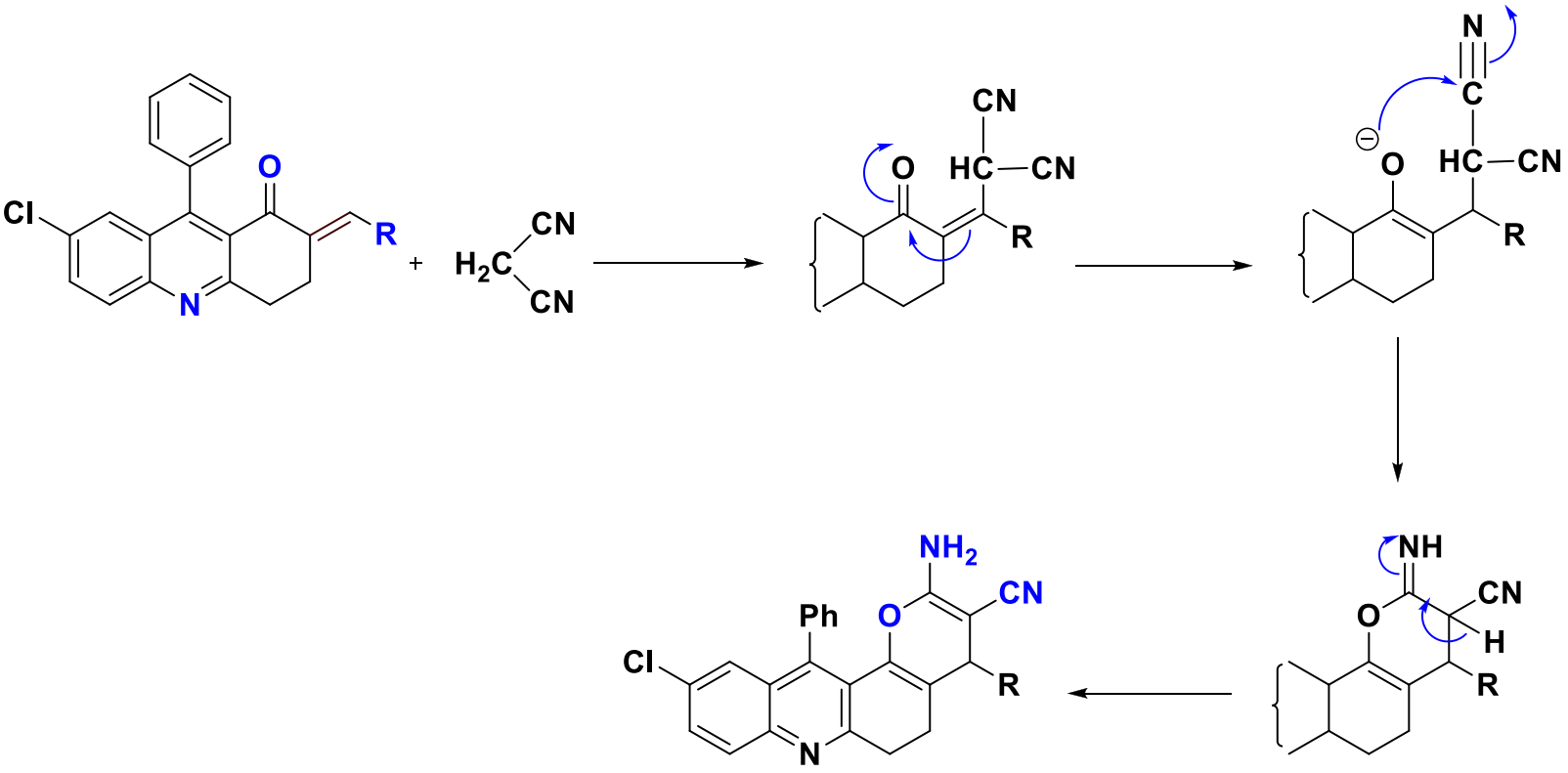


1 a-f

2

3 a-f

Mechanism of the reaction



RSM optimization of pyrane derivatives (3 a-f)

Selected variables and levels used in the CCD

Variables	Levels		
	-1	0	+1
TIME (min)	2.5	5	7.5
WATTZ (W)	100	200	300
TEMP (°C)	40	50	60

Experimental analysis of the CCD model 3a-f

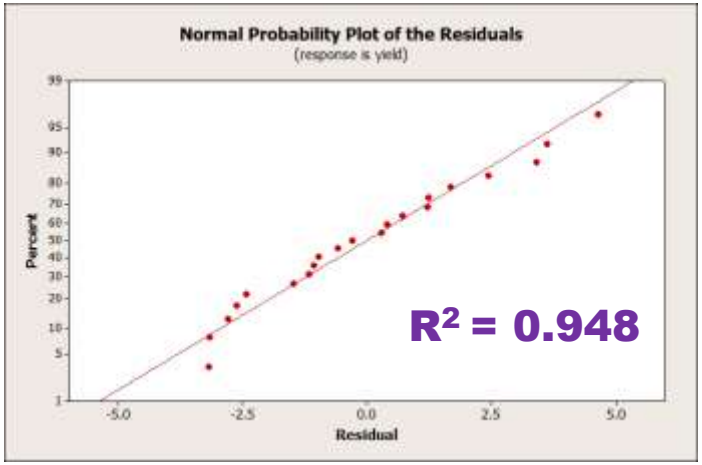
Time (Min)	Wattz (W)	Temp °C	Theoretical Yield (%)	Experimental Yield (%)
-1	-1	-1	52	52
1	-1	-1	60	62
-1	0	-1	63	63
0	0	-1	73	74
1	0	-1	75	73
-1	1	-1	62	62
0	1	-1	74	72
1	1	-1	79	84
-1	-1	0	76	78
0	-1	0	82	85
1	-1	0	81	78
-1	0	0	81	85
0	0	0	89	90
1	0	0	90	88
-1	1	0	74	73
0	1	0	84	85
1	1	0	88	87
-1	-1	1	79	76
0	-1	1	83	82
1	-1	1	80	84

RSM optimization of pyrane derivatives (3 a-f)

Analysis of Variance (ANOVA)

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Regression	9	1942.32	1942.324	215.814	22.51	0.000
Linear	3	1285.21	378.138	126.046	13.14	0.001
Square	3	447.82	574.436	191.479	19.97	0.000
Interaction	3	209.29	209.294	69.765	7.28	0.006
Residual Error	11	105.49	105.485	9.590		
Total	20	2047.81				

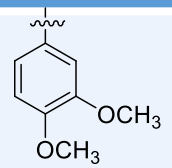
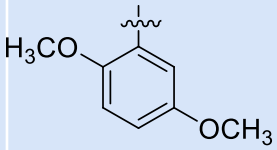
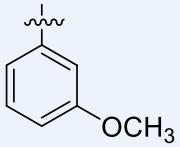
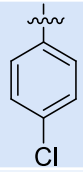
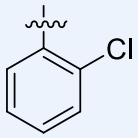
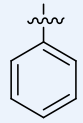
Where DF – Degree of freedom, SS- Sum of Squares, MS- Mean Square



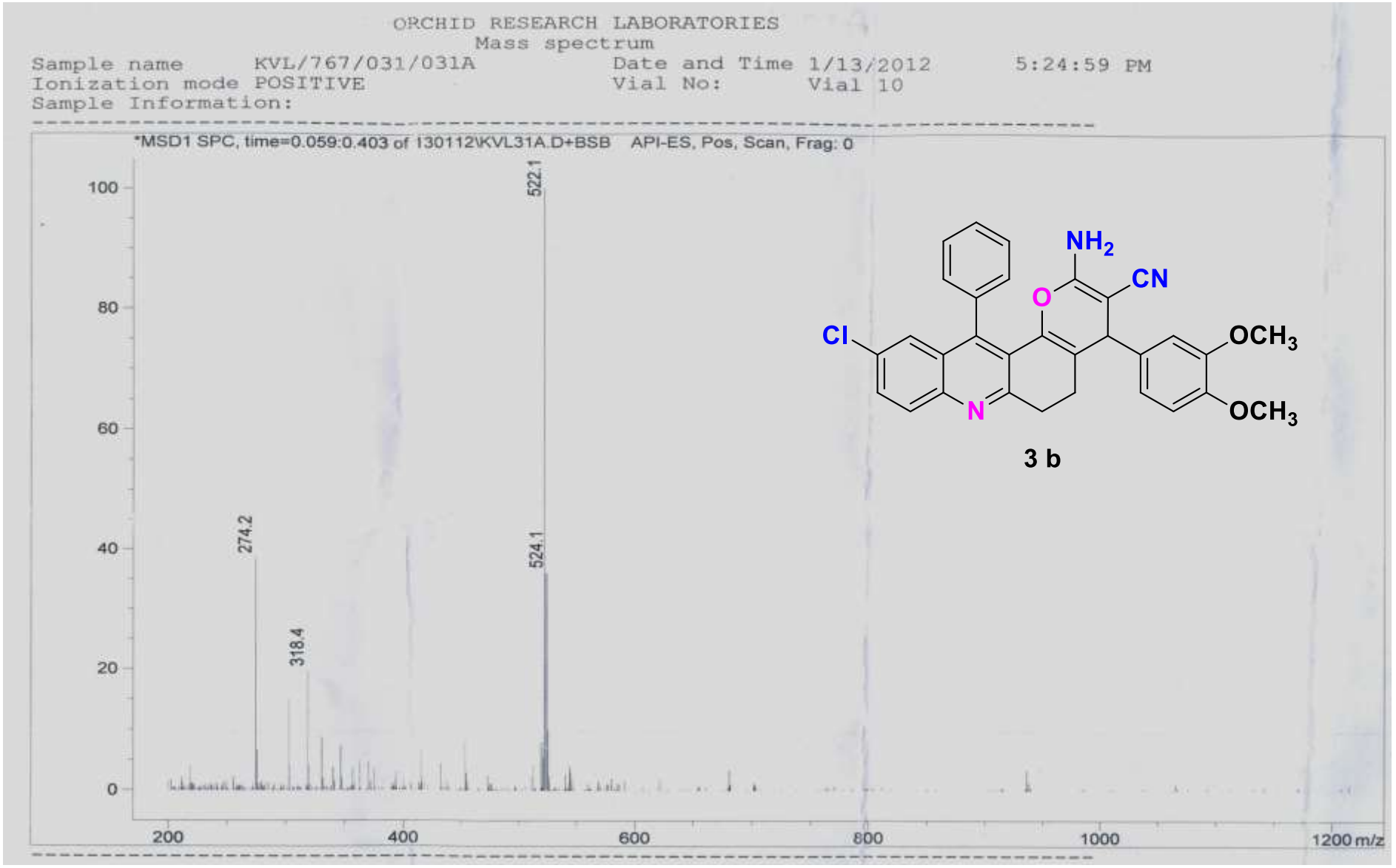
Quadratic Polynomial Equation

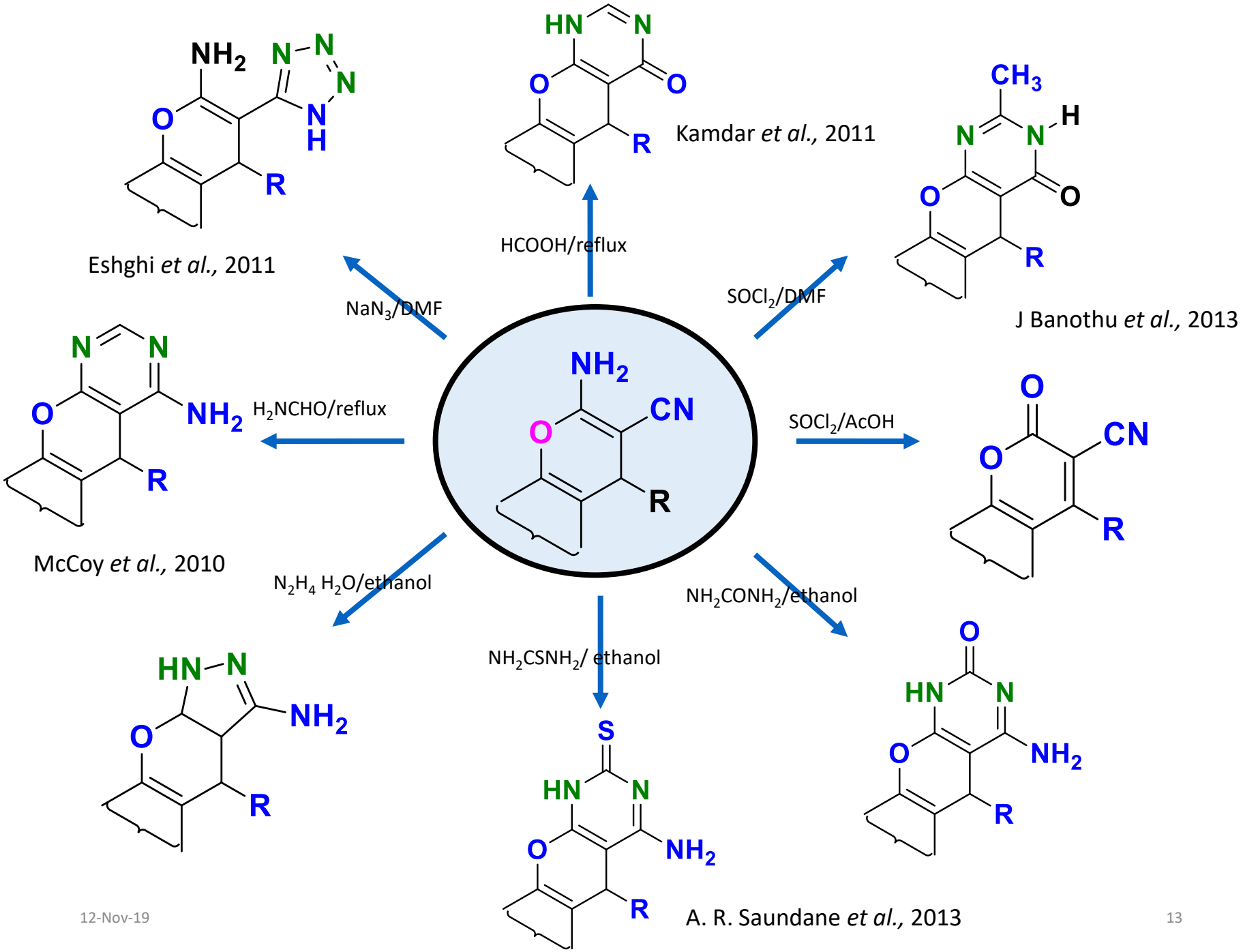
Yield = 89.58 + 4.619 Time + 1.08 Wattz + 5.61 Temp - 3.59 Time*Time - 5.96 Wattz*Wattz - 10.70 Temp*Temp + 2.43 Time*Wattz - 1.49 Time*Temp - 6.01 Wattz*Temp

Summary of synthesized pyrane derivatives (4.1a-f)

Compounds	R	M. P. (^{o}C)	Yield %
3 a		206-208	90
3 b		228-230	82
3 c		136-138	84
3 d		162-164	82
3 e		154-156	82
3 f		235-237	83

LC-Mass of 2-amino-10-chloro-4-(3,4-dimethoxyphenyl)-12-phenyl-5,6-dihydro-4H-pyrano[2,3-a]acridine-3-carbonitrile (3b)

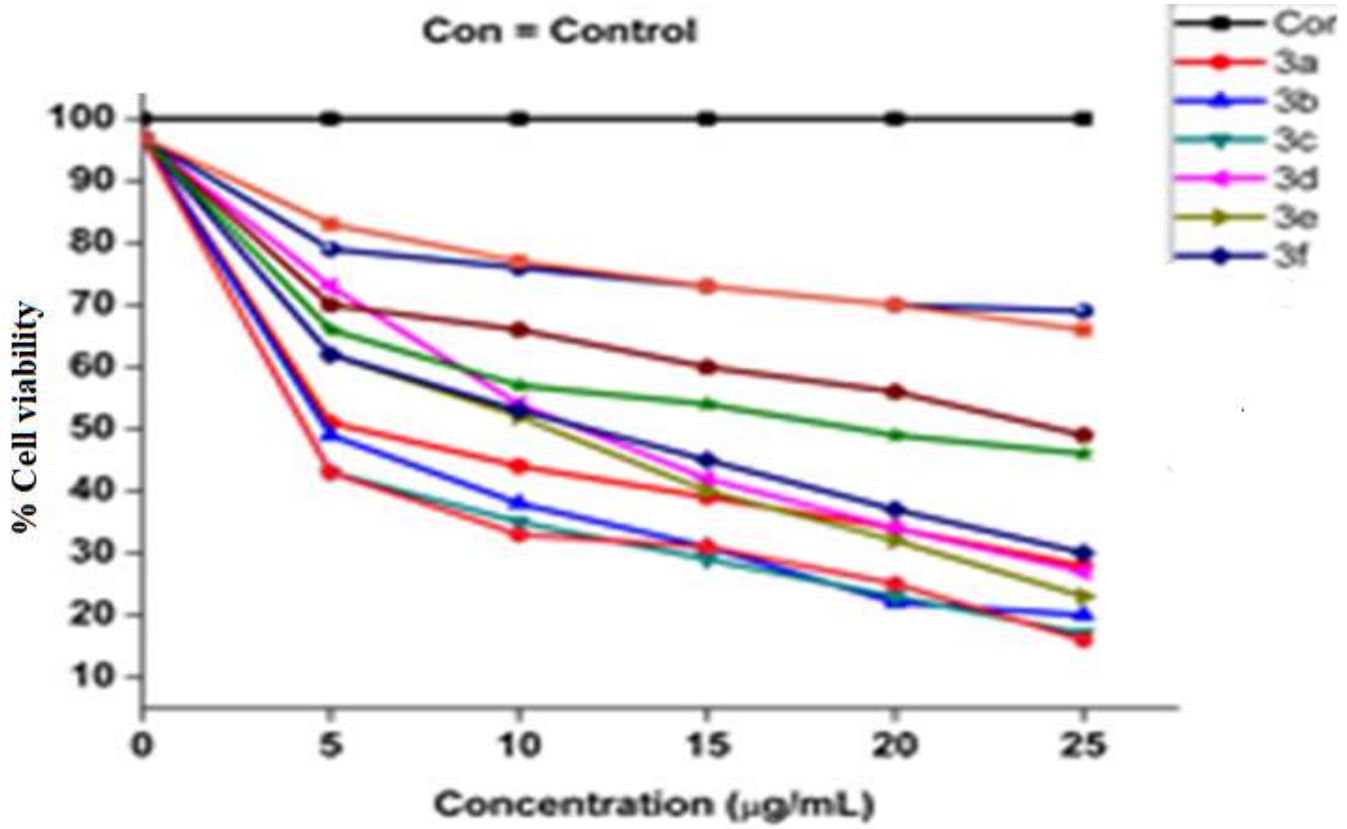



Eshghi *et al.,* 2011
Kamdar *et al.,* 2011
J Banothu *et al.,* 2013
McCoy *et al.,* 2010
A. R. Saundane *et al.,* 2013
HCOOH/reflux
NaN3/DMF
SOCl2/DMF
H2NCHO/reflux
SOCl2/AcOH
N2H4 H2O/ethanol
NH2CONH2/ethanol
NH2CSNH2/ ethanol

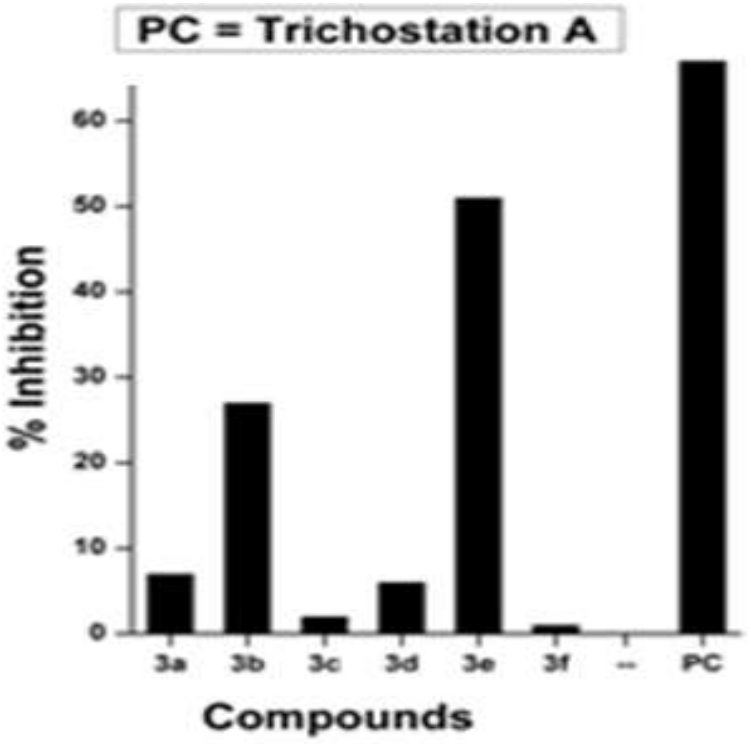
Cytotoxicity study

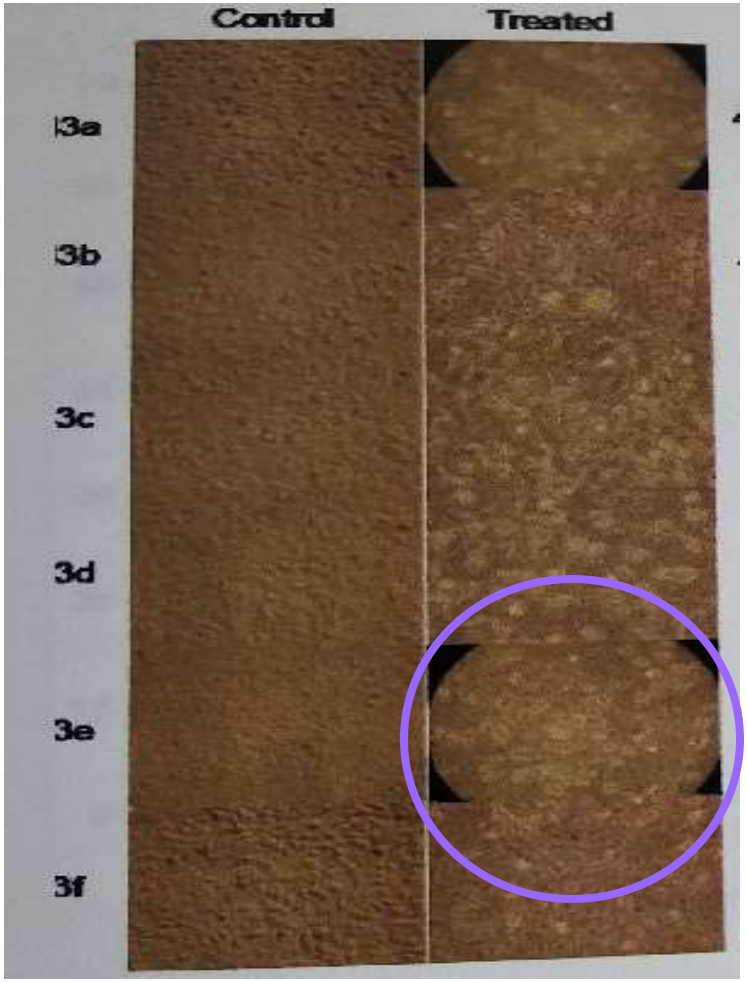
- Discovery of **synthetic drugs** with potential anti cancer activity is very initiative trend in various countries.
- **HeLa cell line** is an immortal cell line used most commonly in medical research.
- **MTT** assay is widely used to measure cell escalation and screening of **anticancer** drugs.
- **HDAC enzyme** play crucial roles in various biological functions, including cell growth, differentiation, and apoptosis.
- Recent studies have utilized HDACs as a promising target **enzyme** in **anticancer drug** development.

Cell viability under concentration of 25 µ/L of synthetic compounds, 3a-f.

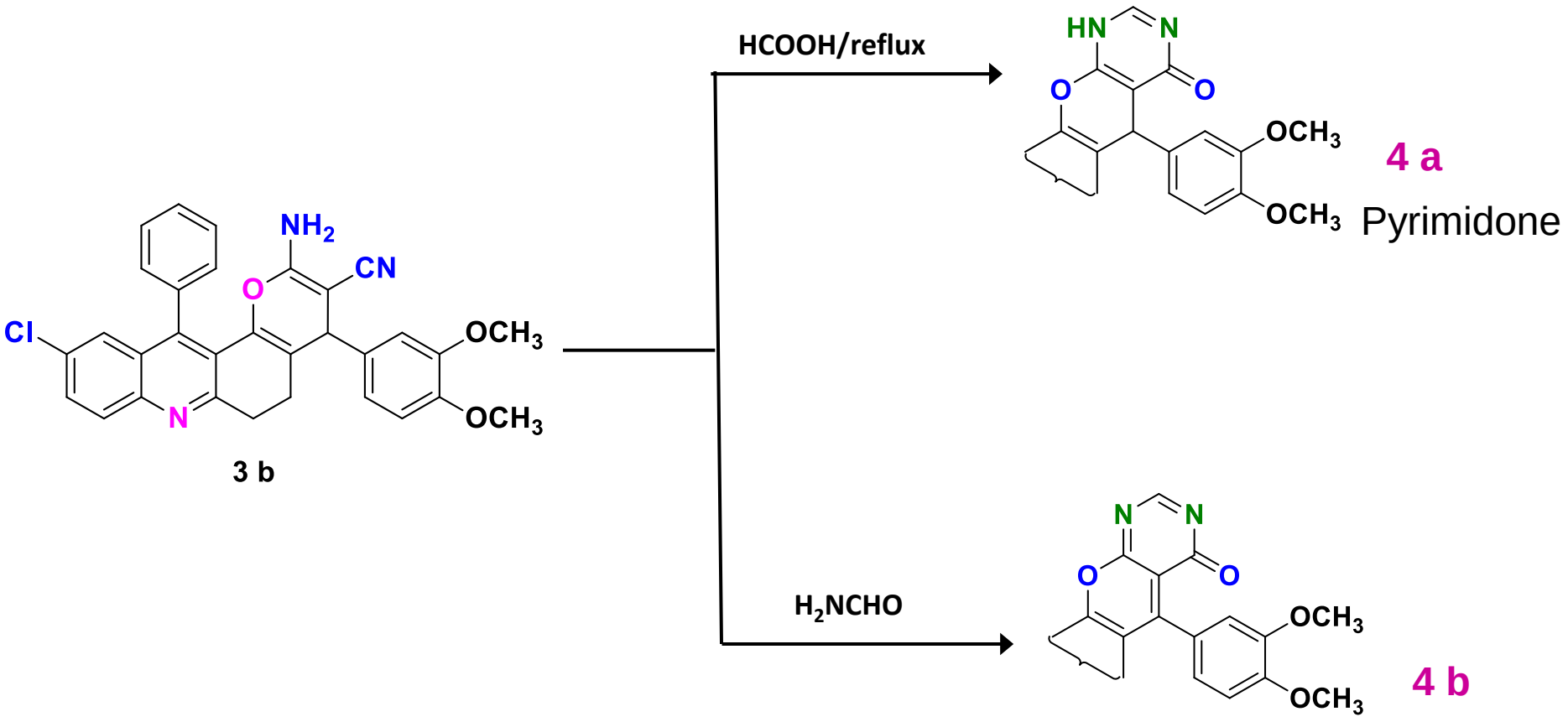


Dose-dependent inhibition of histone deacetylase enzyme activity by synthetic compounds (3a-f).





Future plan :Synthesis of pyrane derivatives, (4 a-e)



Conclusion

- A series of novel **Quinazalinone, Pyrimido, Pyrano** compounds were synthesized.

- All Synthesized derivatives were confirmed with FT-IR, ESI-MS, ^{1}H and ^{13}C NMR **spectroscopic** techniques.

- Cancer cell line studies, Apoptosis studies and HDAC enzymatic activities of synthesized derivatives were carried out.

References

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12. Roopan, S.M.; Bharathi, A.; Al-Dhabi, N.A.; Arasu, M.V.; Madhumitha, G. Sci Rep. 2017, 7, 39753.

Acknowledgement

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Thank you