Schiff Bases & their Synthetic Methods

M. Sc. Chemistry
4th Sem (1a)
Ph. D. Course Work- Paper-II / Unit-I

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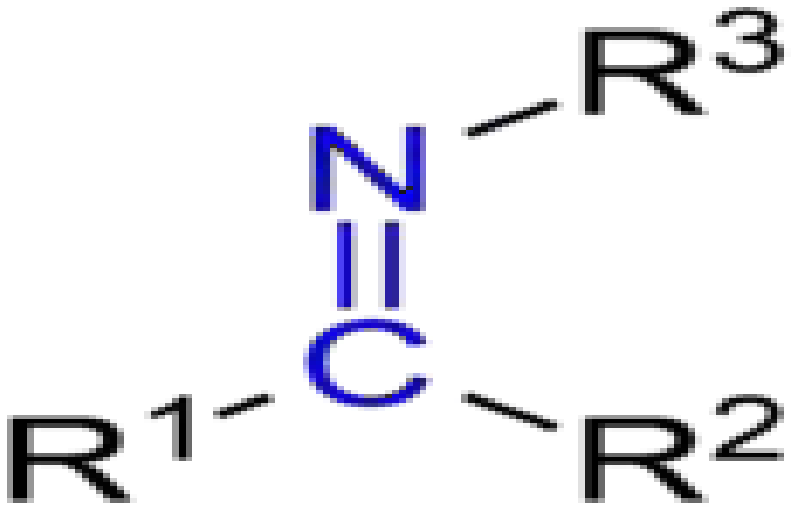
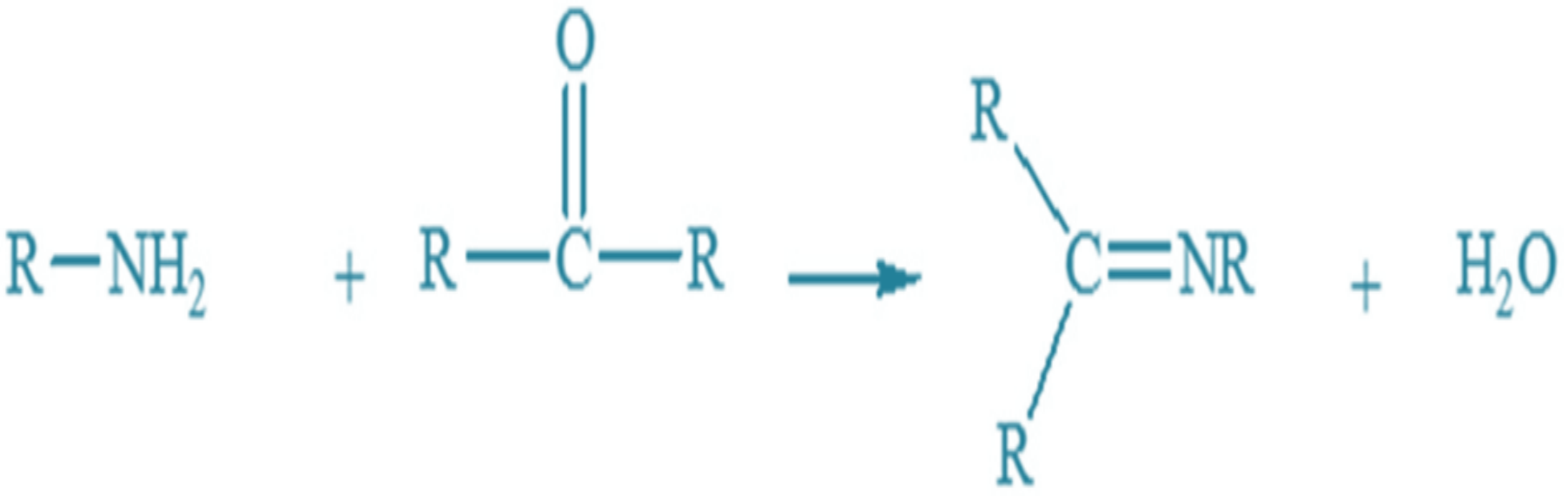
Schiff Base

Schiff base is a compound having functional group of carbon-nitrogen double bond where nitrogen atom is connected to an aryl or alkyl group.

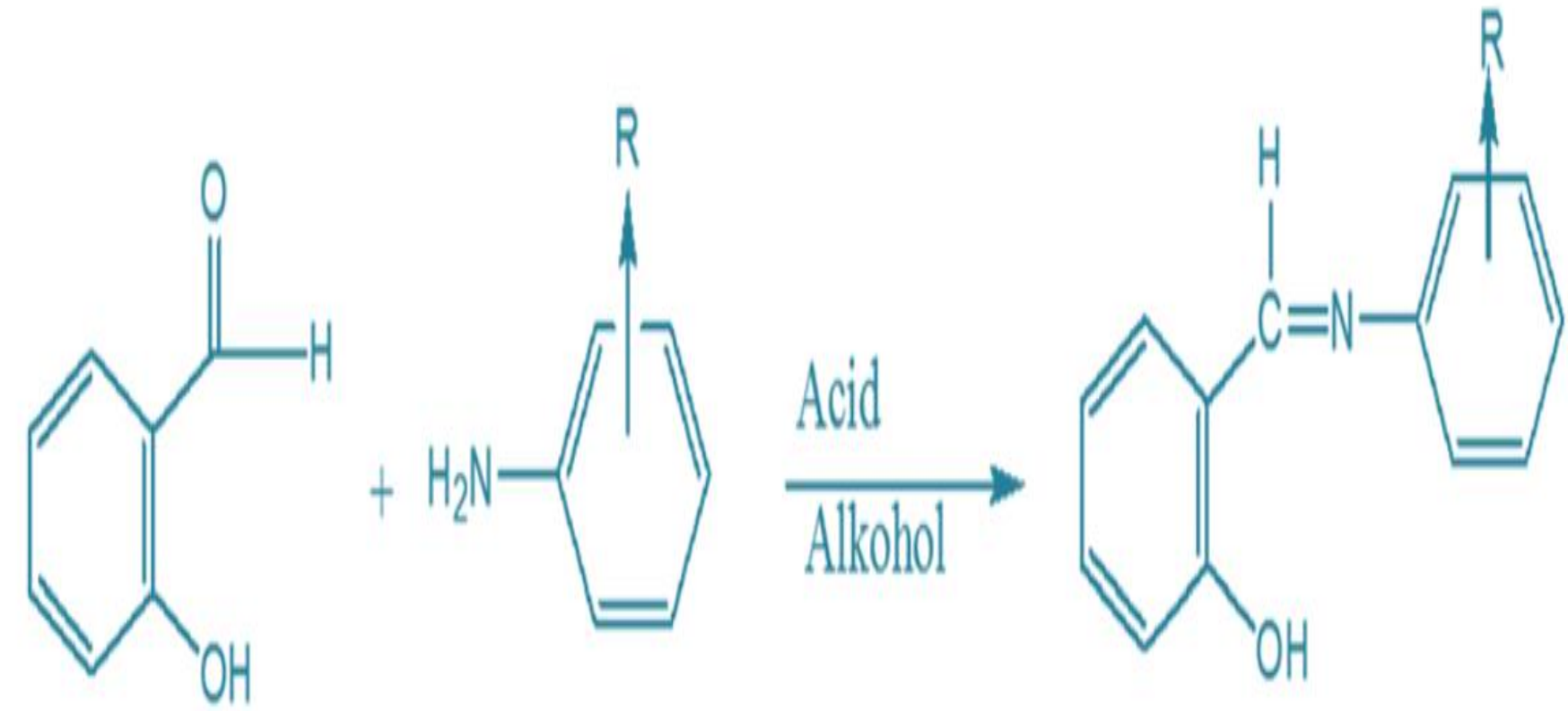
Its General formula is



Here, Carbonyl compds may be ketone or aldehyde. R1 & R2 may be similar or disimilar longer & smaller. But R3 never be H.

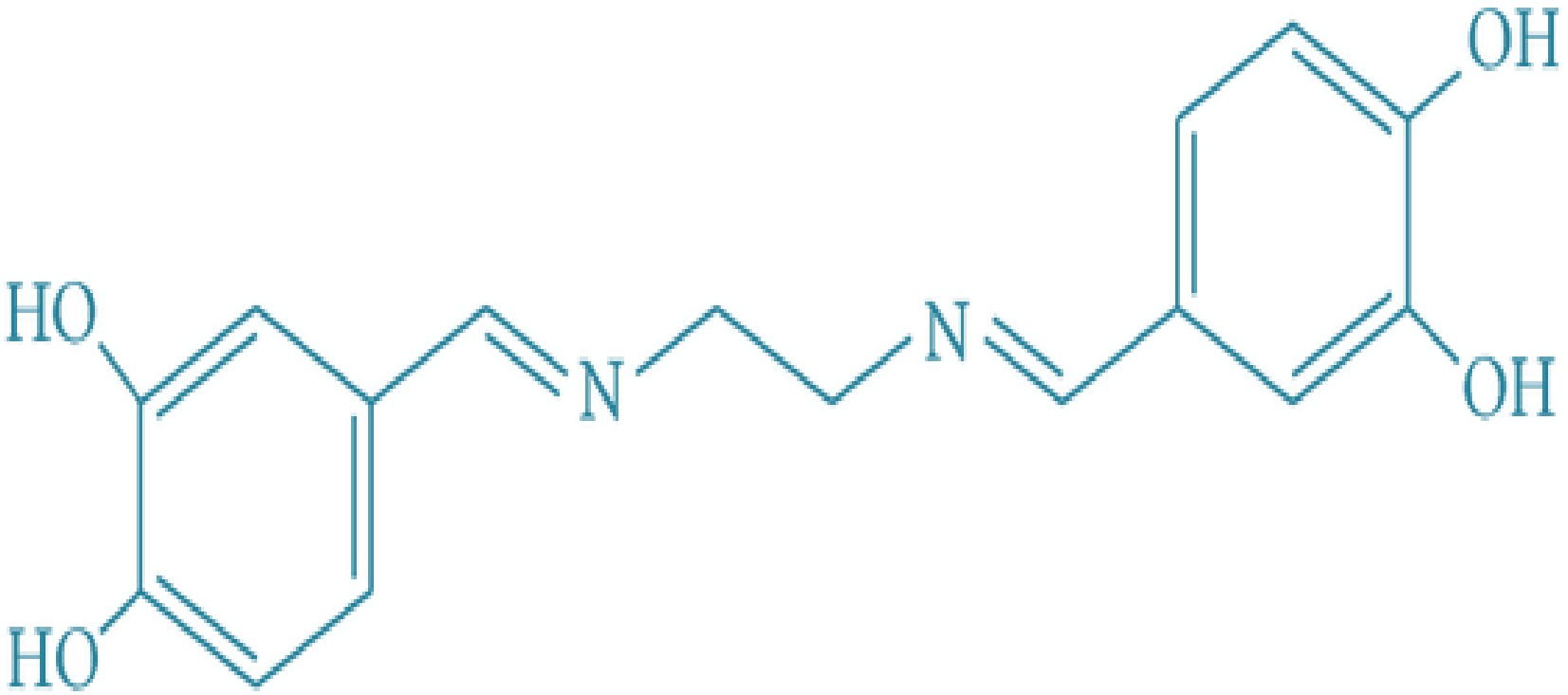


General reaction of formation of Schiff base or Aldimine

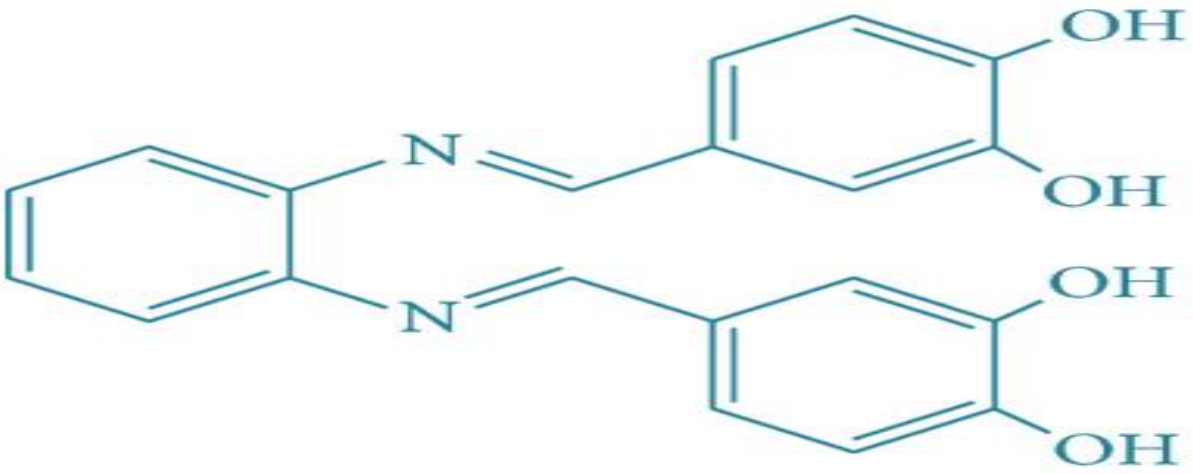


Salicylaldehyde Substituted aniline 2-(Substituted-phenyliminomethyl)-phenol

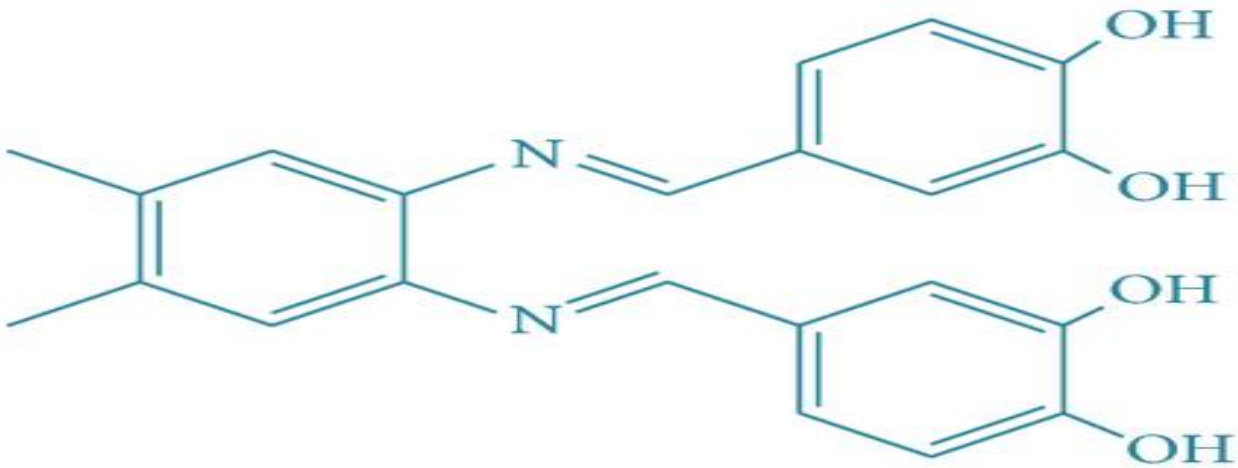
R = H- (A-1); 4-Cl (A-2); 3-Cl (A-3); 2-SH (A-4); 4-Cl, 2-NO_2 (A-5); 2-Cl (A-6);



N,N′-Bis(3,4-dihydroxybenzylidene)ethan-1,2-diamine (**EDH_4**)



N,N′-Bis(3,4-dihydroxybenzylidene)benzene-1,2-diamine (**PDH_4**)



N,N′-Bis(3,4-dihydroxybenzylidene)4,5-dimethyl-1,2-diamine (**$MPDH_4$**)

Procedures for Synthesis of Schiff Bases

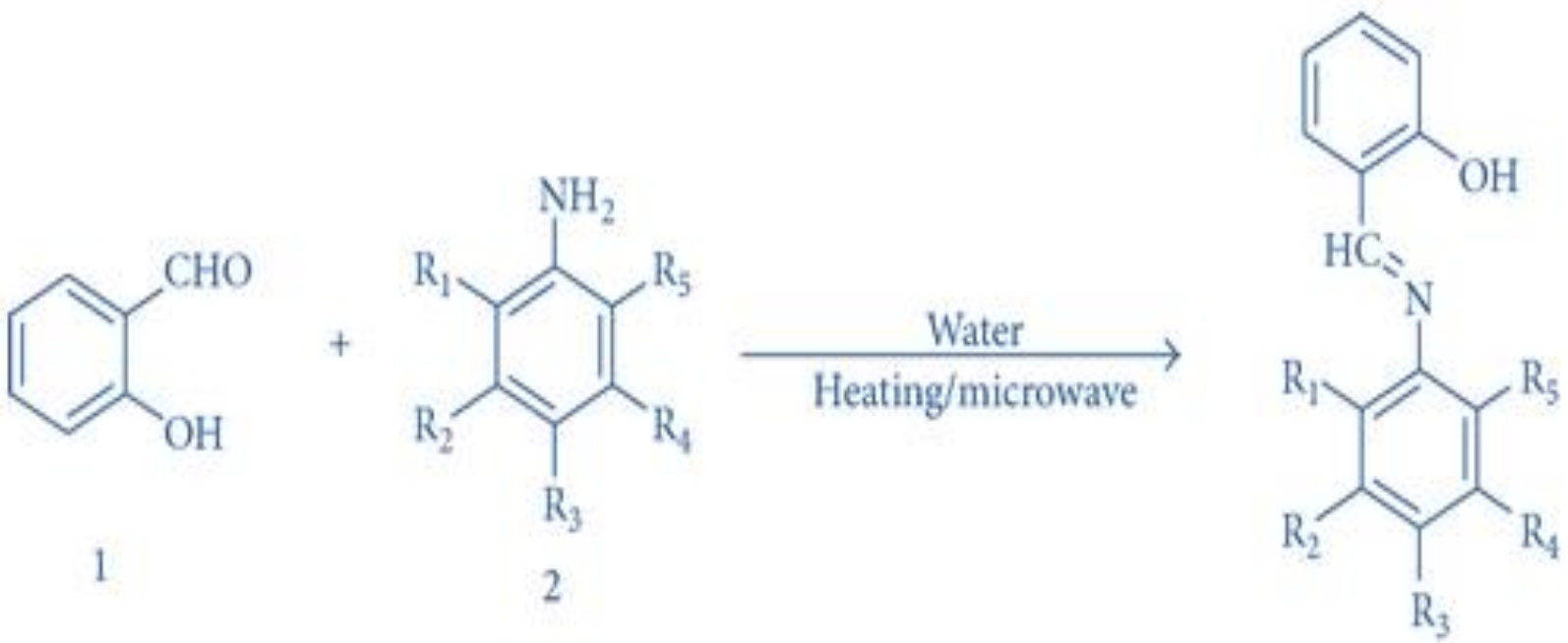
Schiff Base & there complexes have been widely used in organic chemistry, inorganic chemistry, medicinal chemistry as well as environmental chemistry due to easy formation & rich coordination with large variety of metal ions. There are several processes are available for synthesis of schiff base & their complexes. But growing concern over the environmental impact of chemicals, green reaction conditions in synthetic processes have been advocated in which greenness is required in chemical reaction i.e. minimum wastages avoid use of auxiliary substance like organic solvent additional reagents & minimum energy is required as well as maximum yield in minimum time.

In this context, the use of water as the reaction medium offers several advantages as
(a) it is cheap, non inflammable, nontoxic, and safe to use
(b) its unique physical and chemical properties often increase the reactivity or selectivity, which sometimes is unattainable in organic solvents
(c) it eliminates the additional efforts required to make the substrates/reagents dry before use and thus reduces/eliminates the consumption of drying agents, energy, and time.

SB is formed by the condensation of a primary amine and an carbonyl compd (aldehyde or ketone)

(a) It involves the use of organic solvents like methanol, tetra hydrofuran (THF), and 1,2-dichloroethane (DCE).

(b) But in Microwave method (green synthesis method) of Schiff base without solvent has also been reported which yield is maximum.



3(a–e)

(3a) R_1 = F, R_2 = H, R_3 = F, R_4 = H, R_5 = H

(3b) R_1 = H, R_2 = H, R_3 = Cl, R_4 = H, R_5 = H

(3c) R_1 = F, R_2 = F, R_3 = F, R_4 = F, R_5 = H

(3d) R_1 = H, R_2 = H, R_3 = Br, R_4 = H, R_5 = H

(3e) R_1 = H, R_2 = H, R_3 = F, R_4 = H, R_5 = H

Experiment

Way-1

Microwave Method

A mixture of salicylaldehyde (0.004 mol) and substituted aromatic amines (2a–e) (0.004 mol) in water (1 mL) were added in microwave tube. The contents were subjected to microwave irradiation at 200 W for about 30 sec–2 min. Progress of the reaction was monitored by TLC. After the completion of the reaction, solid product was obtained in reaction mixture which was filtered and recrystallized with methanol.

Way- 2

Conventional Refluxed Method

Schiff bases are prepared by condensation of salicylaldehyde (0.004 mol) with various aromatic amines (2a–e) (0.004 mol) in benzene (10 mL) and the mixture was heated under refluxed temperature until no water is present.

Way- 3

Room Temperature Method

To a stirred solution of carbonyl compd and p-amine in 10ml DCM, anhydrous MgSO4 was added. The reaction mixture was stirred 2 hours at room temperature. The resulting mixture was filtered through a sintered glass funnel with the aid of two 2ml portions of DCM, and then the filtrate was concentrated under reduced pressure by rotary evaporation at room temperature to afford yellow oil. The residual was dissolved in ethanol heated in an 80°C water bath while hot water was added with stirring. The resulting solution was allowed to cool to room temperature and then was cooled in an ice-water bath for 2 hr. Filtration provide the title compound (75%) as white lamellar crystal.

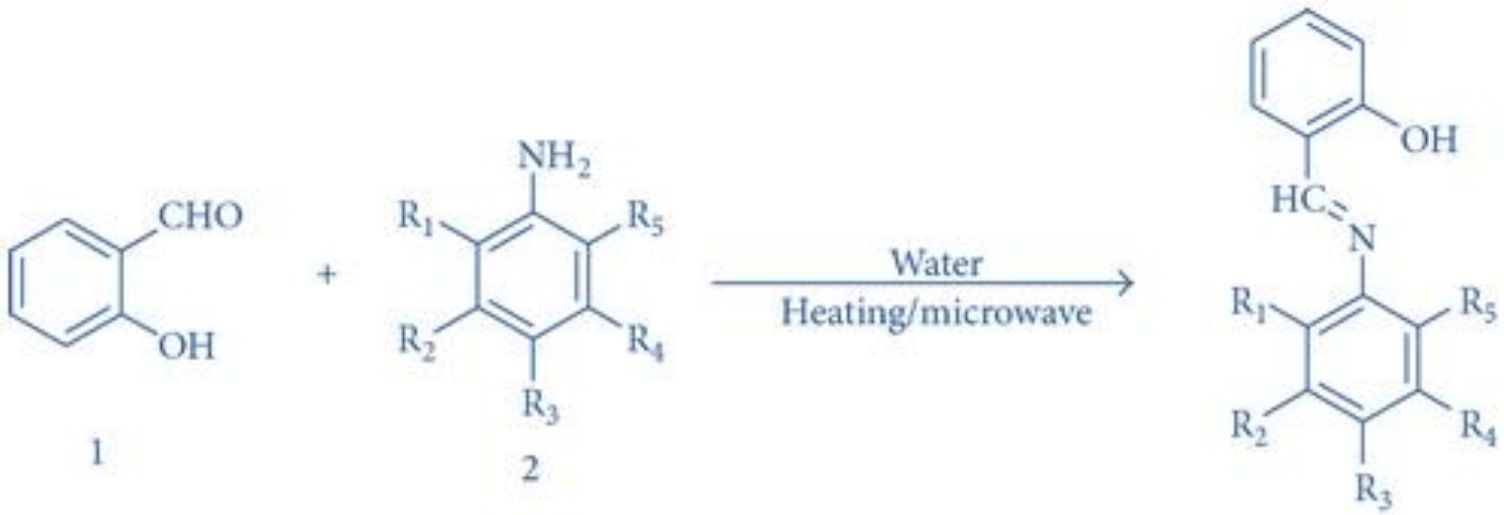
Result & Discussion

All above three methods were compared & was found that time taken & percentage yield were summarised in this table which indicates microwave method is best method.

The compare of three way of synthesis of Schiff base

Way	Reaction condition	Time	Yield
1	microwave irradiation	4min	85%
2	reflux	over 7h	72%
3	rt stir	4h	75%

Novel green method using water as solvent for synthesis of schiff's base has been established. The synthetic scheme has been given in following **Scheme 1**.



3(a–e)

(3a) $R_1 = F, R_2 = H, R_3 = F, R_4 = H, R_5 = H$

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(3c) $R_1 = F, R_2 = F, R_3 = F, R_4 = F, R_5 = H$

(3d) $R_1 = H, R_2 = H, R_3 = Br, R_4 = H, R_5 = H$

(3e) $R_1 = H, R_2 = H, R_3 = F, R_4 = H, R_5 = H$

Synthesis of 3a at different temperatures starting from ambient temperature to 80°C as shown in Table 1. However, on comparing the progress of reaction, the best yields were obtained at a temperature of 70°C, therefore synthesis of compounds (3b–e) was carried out at this temperature. Moreover reaction time reported was according to the completion of reaction at a microwave power of 200 W. The results summarized in Table 1.

TABLE 1: Comparison of yield of Schiff base (3a) at different temperatures under microwave condition.

Compound	Microwave method		Yield %
	Power	Temp.	
3a	200 W	Ambient	30
3a	200 W	50°C	65
3a	200 W	60°C	80
3a	200 W	70°C	95
3a	200 W	80°C	96

The Microwave irradiation method is compared (in terms of time and yield %) with conventional Reflux method for the synthesis of Schiff bases as illustrated in **Table 2.**

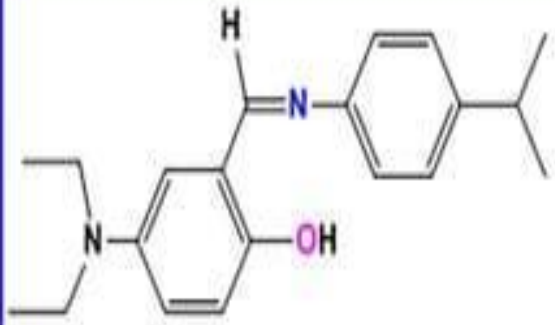
TABLE 2: Comparison of microwave and conventional method.

Comp.	Microwave method				Conventional method		
	Power	Temp.	Time (sec)	Yield %	Temp.	Time (hrs)	Yield %
3a	200 W	70°C	60	95	Ambient	2	70
3b	200 W	70°C	30	92	Ambient	1.5	75
3c	200 W	70°C	60	96	Ambient	1.5	75
3d	200 W	70°C	30	94	Ambient	1	72
3e	200 W	70°C	120	90	Ambient	1.5	70

Classification of Schiff bases and their metal complexes

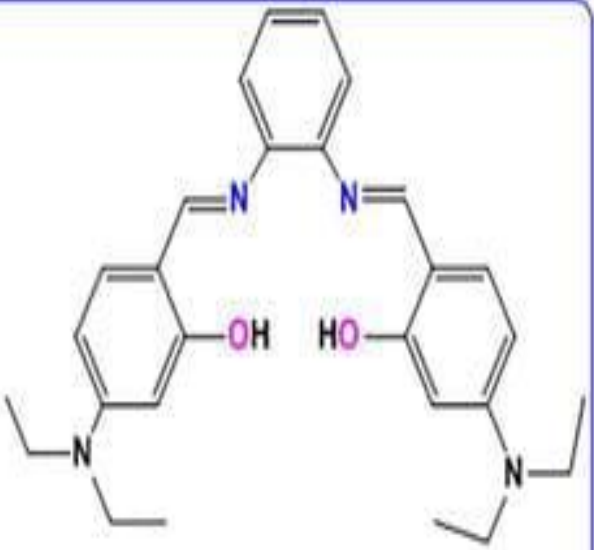
By coordinating the d-block metal ion with the electron-donating ligand atom, a complex is created that modifies the metal's steric and electrical properties. By doing so, the metal ion's reactivity is stabilized and regulated, which is especially helpful for ions at higher oxidation states where they are less stable. Auxiliary ligands, or Schiff bases, are compounds that modify the structure and reactivity of a transition metal ion inside a complex. On the other hand, they do not incur any irreversible modifications, unlike reactive ligands. Atoms like nitrogen, sulfur, or oxygen can act as donors in the coordination process.

Denticity of Schiff base ligands Schiff bases are classified into bidentate, tridentate, tetradentate, and polydentate ligands, which can form extremely stable complexes with transition metal ions (Figure 5). Assume they have different functional groups such as -OH, -NH2, or -SH; the resulting Schiff bases can act as mixed-donor ligands in bi-, tri-, tetra-, and higher coordination modes [48, 49, 50, 51]. Multivalent Schiff base ligands easily form complexes with bidentate, tridentate, and tetra- or polydentate metal ions at different oxidation states. Donor atoms (N, O, S) can be found in bidentate ligand (NN or ON), tridentate ligands (NNN, ONO, NNS or ONS), and tetradentate ligands (ONNO, NNNN, NSNO).



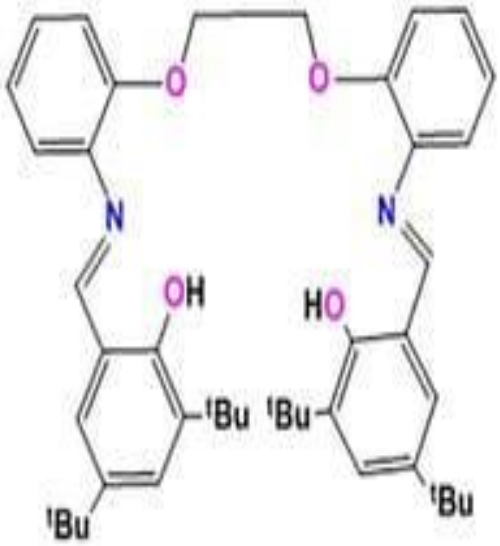
Bidentate

Tridentate



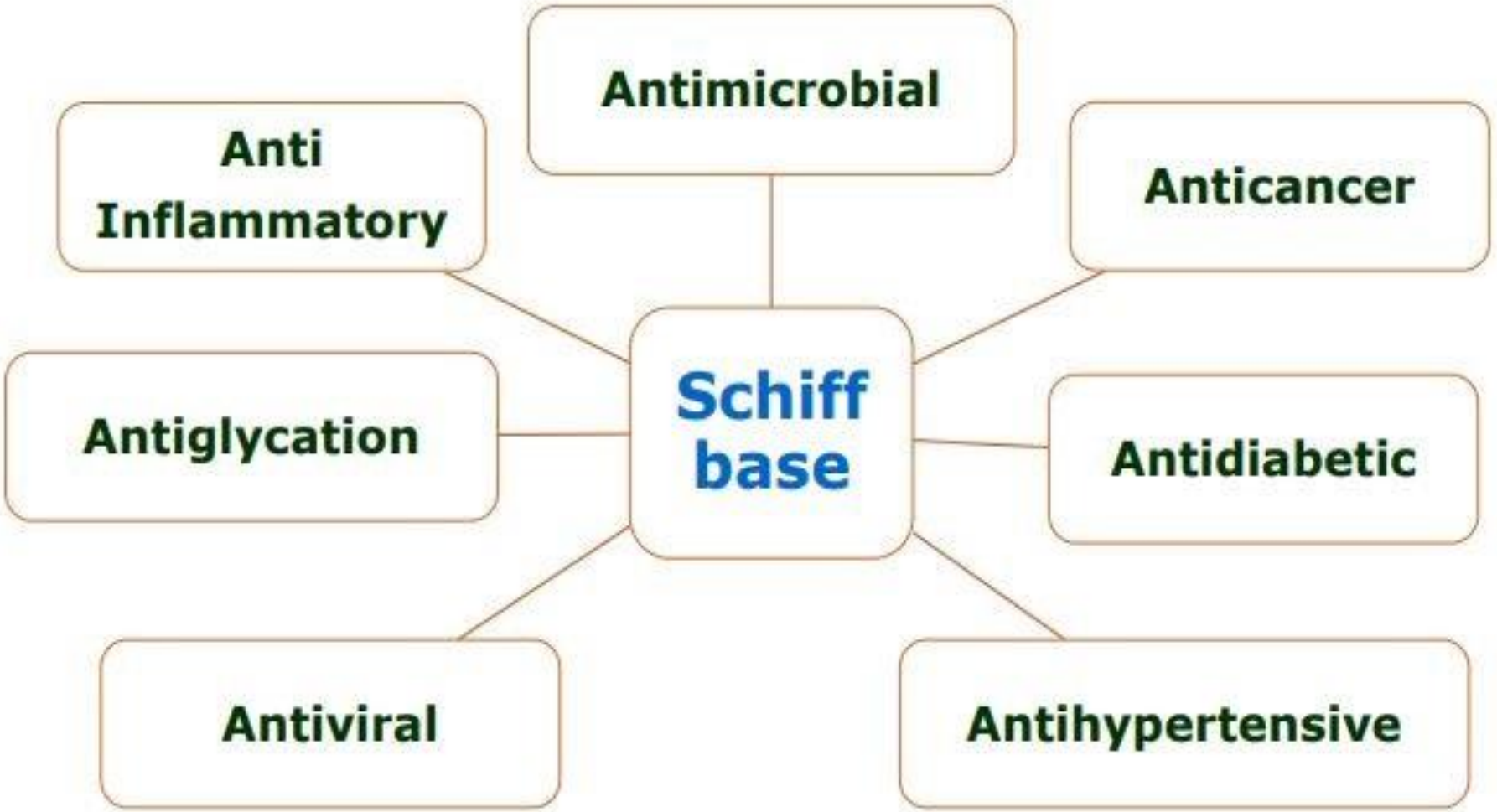
Tetradentate

Pentadentate



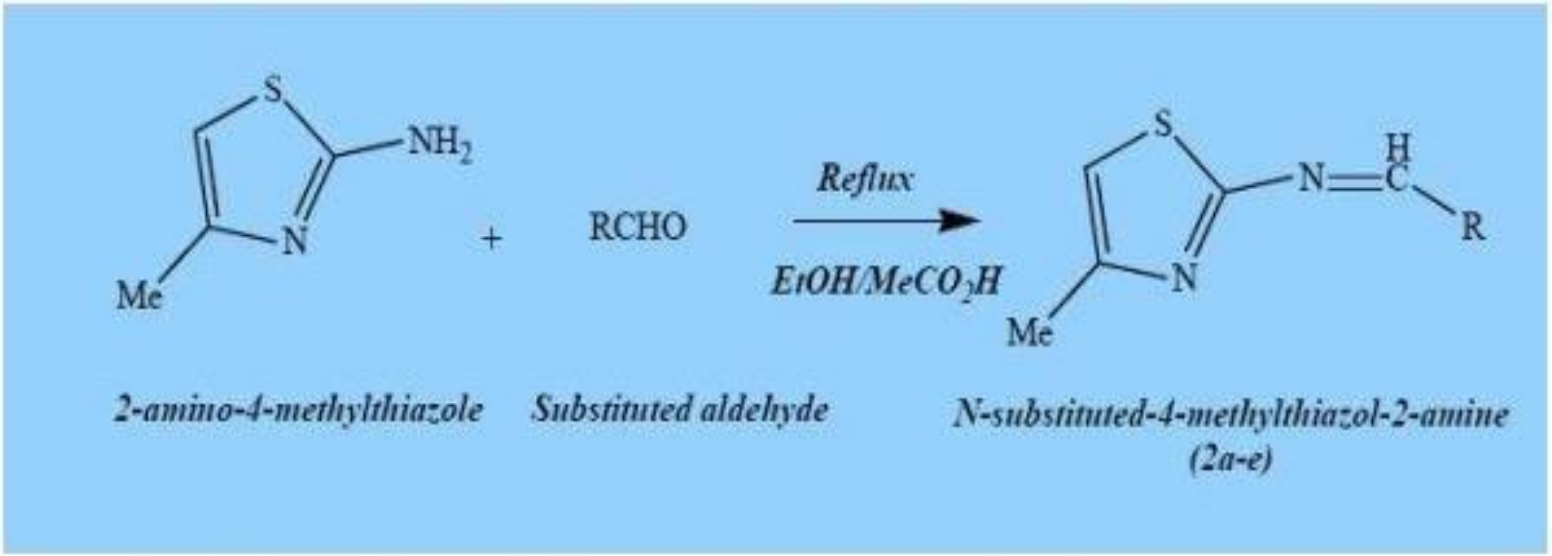
Hexadentate

Schiff Bases: A Versatile Pharmacophore



Schiff bases-antimicrobial activity

M. Rudrapal *et al* synthesised Schiff bases of 2-aminothiazole and evaluated their antibacterial activity



Their results indicated that compounds having either aromatic substituted phenyl rings or aromatic heterocycles possess more activity.

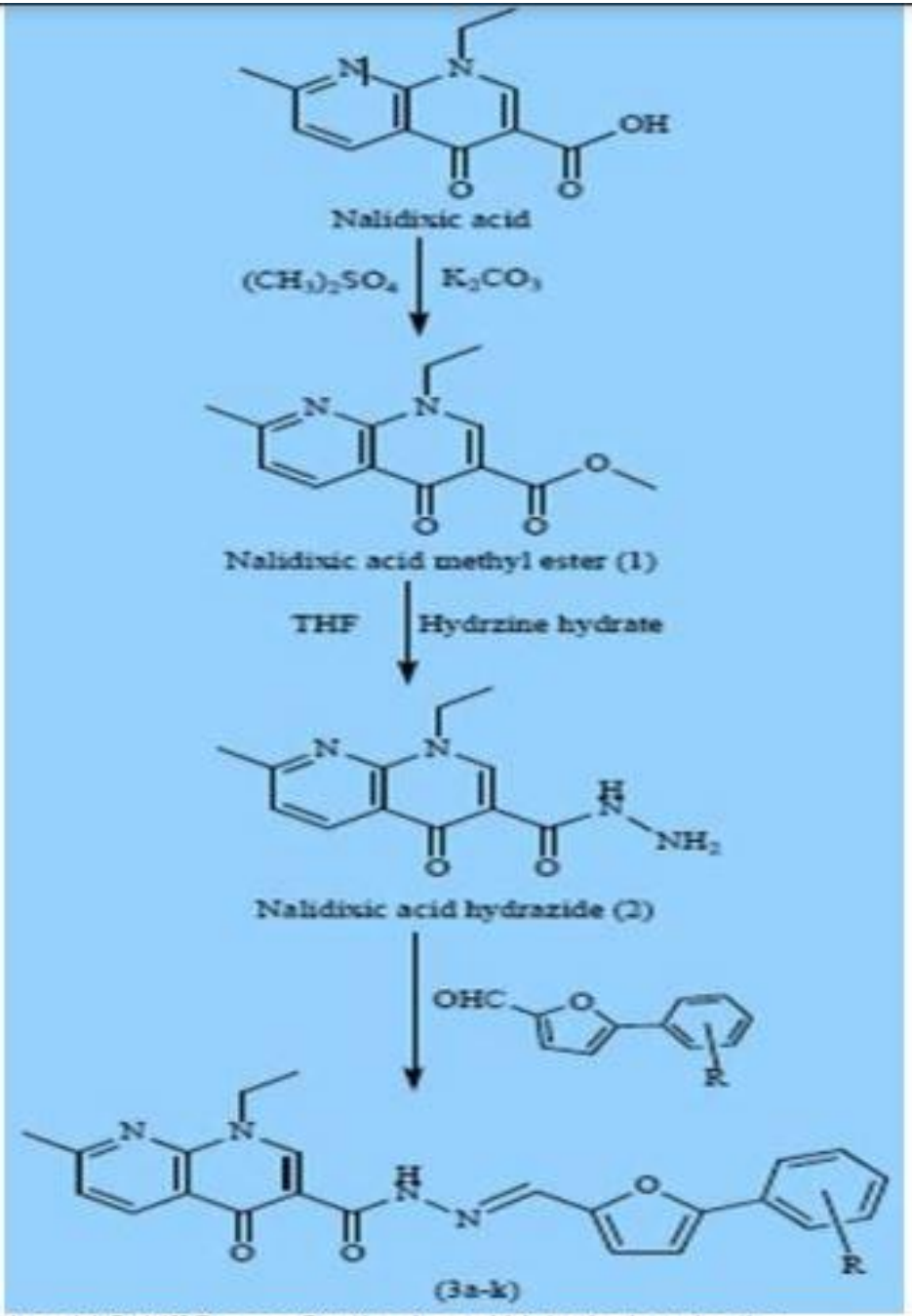
Rudrapal, M.; De, B,; Devanna, N. Synthesis and antimicrobial activity of some novel Schiff's bases of 4-methyl-2-thiazolamine. Antiinfect. Agents, 2012, 10, 72-74

Schiff bases of nalidixic acid hydrazide

Asif Husain *et al* synthesized 11 Schiff bases of nalidixic acid hydrazide.

Evaluated their antibacterial activity against four gram +ve *S.aureus*, *B. cereus*, *E. faecalis* and *S. epidermidis* and four gram -ve bacterial strains, *E. coli*, *S. typhi*, *S. dysenteriae* and *P. aeruginosa*.

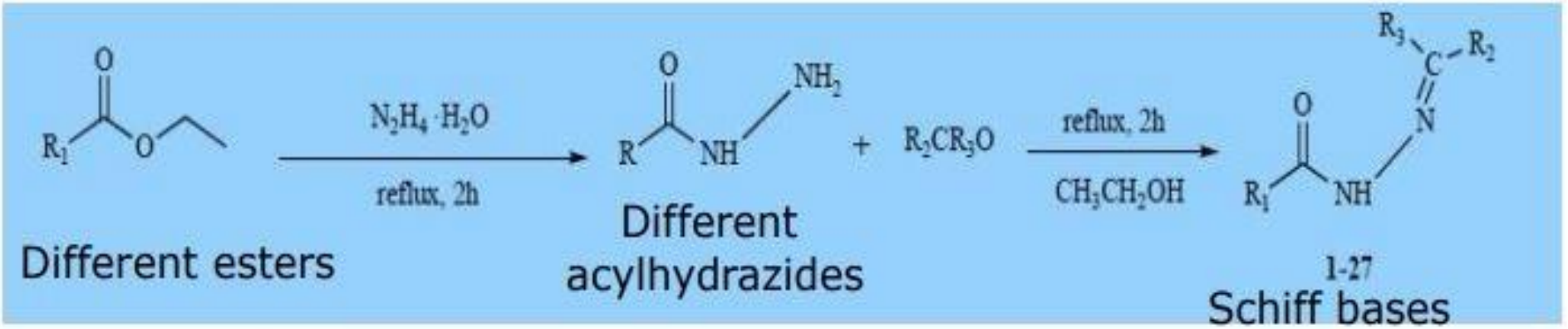
Results indicated that the substitution of aromatic ring at C-5 of furfuryl heterocyclic ring shows exciting antibacterial and anthelmintic actions.



Asif, H.; Munendra, M. V.; Versha, P.; Aftab, A.; Shah, A. K. Nalidixic acid Schiff Bases: Synthesis and biological evaluation. Lett. Drug Des. Discov. 2017, 14, 1-9

Schiff base-antioxidant activity

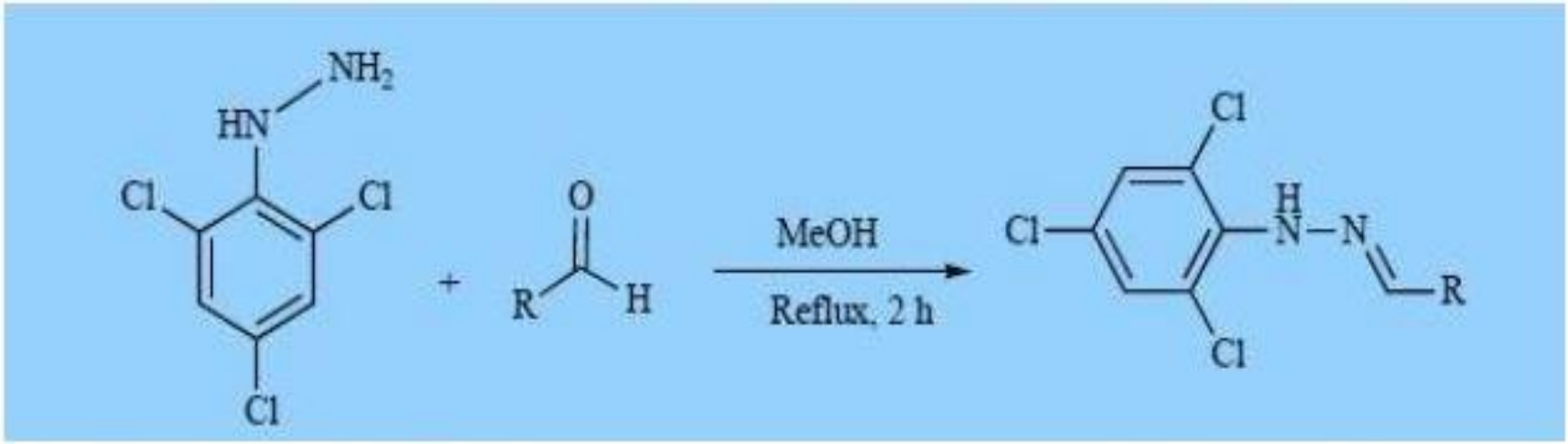
- Khalid Mohammed Khan reported the synthesis of acylhydrazide Schiff bases (1-27) from acylhydrazides which were synthesized from different esters.
- Compounds 1-27 have shown a varying degree of DPPH radical scavenging activity.



Khalid, M.K.; Muhammad, T.; Farzana, N.; Salman, S.; Sajjad, A.; Fazal, R.; Shahnaz, P.; Iqbal, C.M. Acylhydrazide Schiff bases: DPPH radical and superoxide anion scavengers. Med. Chem. 2012, 8, 705-710

Schiff bases-antioxidant activity

- Khalid Mohammed Khan et al reported antioxidant activity of 30 Schiff bases from 2,4,6-trichlorophenyl hydrazine by *in vitro* superoxide anion radical scavenger activity.



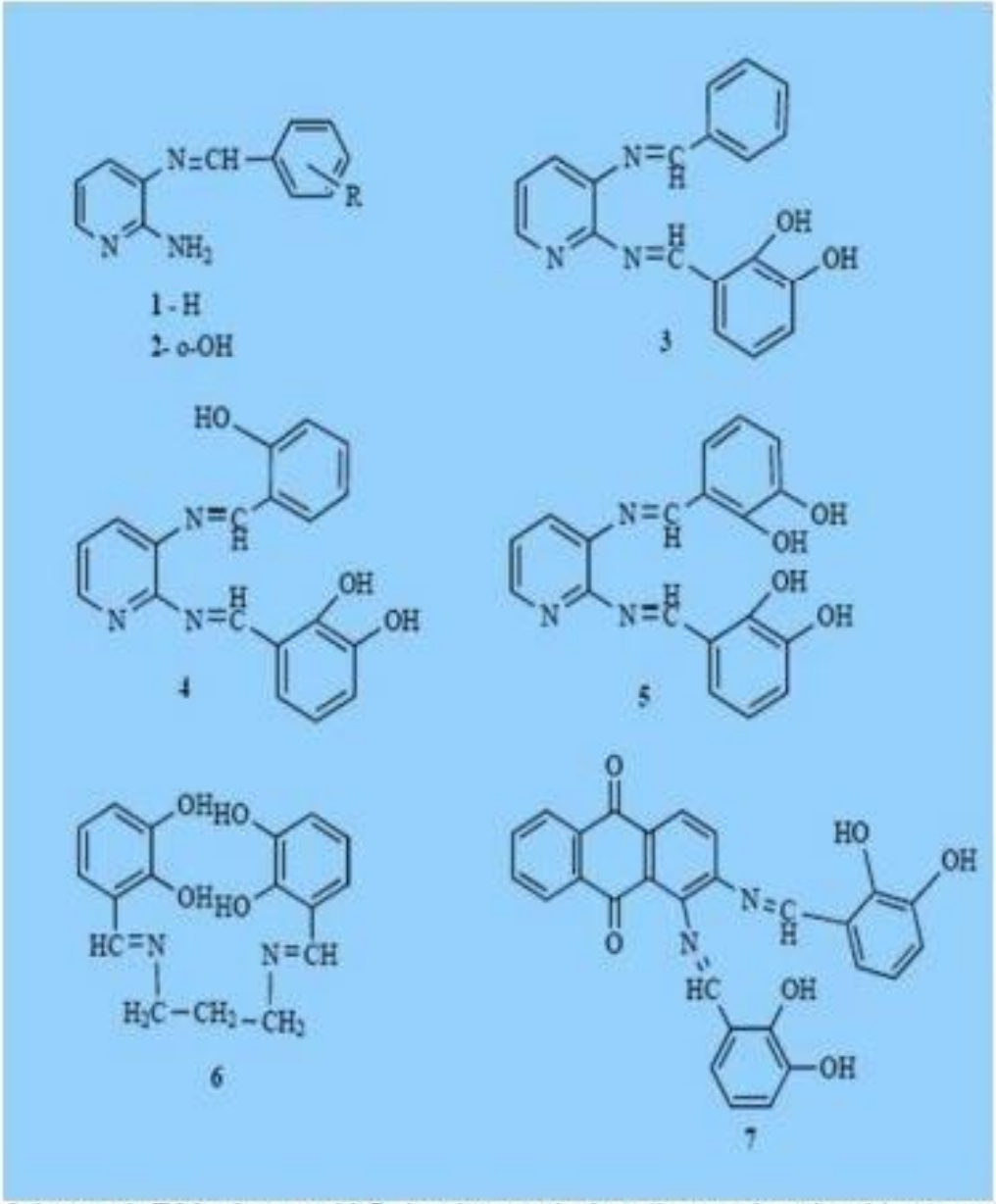
2,4,6-trichlorophenyl hydrazine

Schiff bases

Khalid, M.K.; Zarbad, S.; Viqar, U.A.; Momin, K.; Muhammad, T.; Fazal, R.; Sajjad, A.; Nida, A.; Shahnaz, P.; Iqbal C.M.; Wolfgang, V. Med. Chem. 2012, 8, 452-461

Schiff bases-antiglycation activity

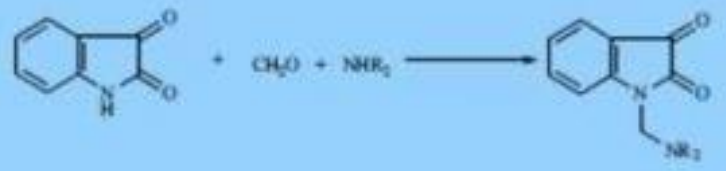
- Antiglycation property of mono, and bis Schiff bases were reported by Sabina et al.
- Mono condensed Schiff bases showed least activity
- Bis condensed schiff bases were more active.



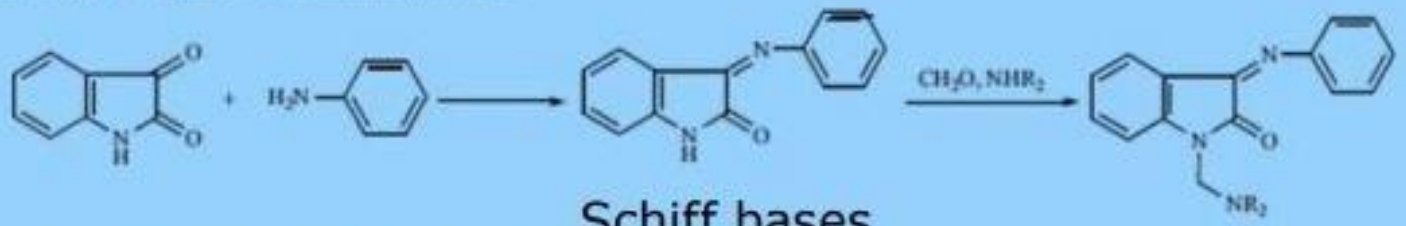
Sabina, J.L.; Minu, G.B.; Shabneez, M.; Mohamad, F.M.; Anwar, H.S. In vitro anti-glycation and anti-oxidant properties of synthesized Schiff bases. Med.Chem. 2012, 8, 409-414

Schiff bases-anticancer activity

Gang Chen et al synthesized Isatin Schiff bases which show some protection activity on the PC12 cells apoptosis induced by H_2O_2

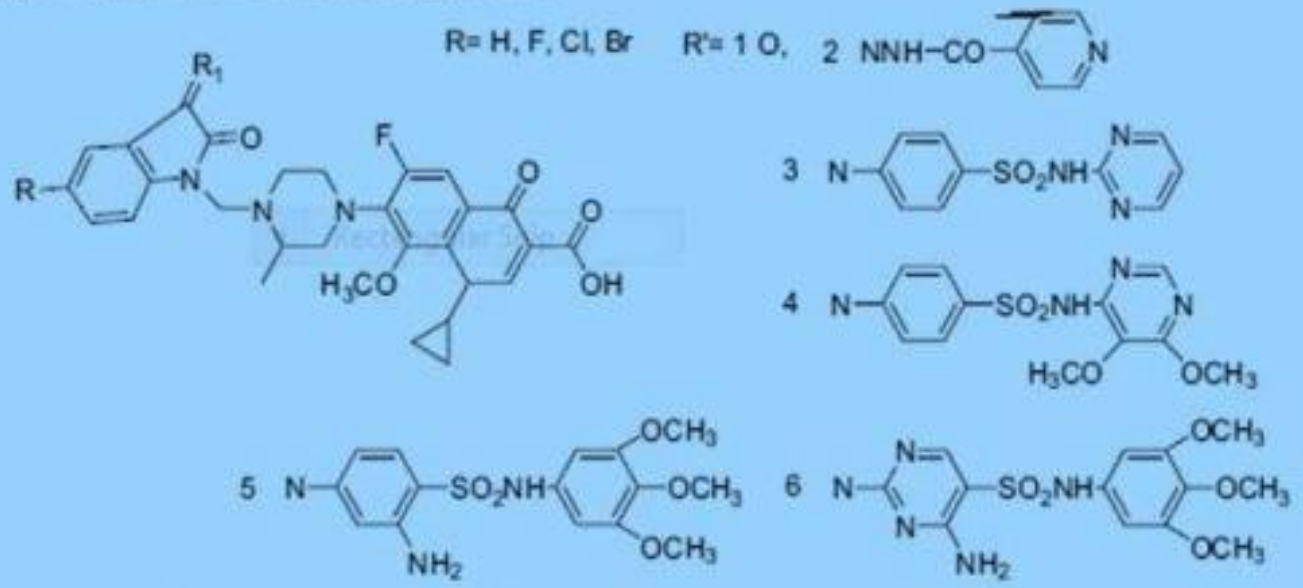


Scheme (1). The synthesis of isatin Mannich bases.



Schiff bases

Scheme (2). The synthesis of isatin Mannich and Schiff bases.



The structure of the isatin gatifloxacin Mannich bases.

Gang, C.; Yang, N.; Wei, Z.; Yanqiu, Z.; Yu, Z.; Xiaojiang, H.; Ye, W.; Shuzhen, M. Synthesis, neuro-protection and anti-cancer activities of simple isatin Mannich and Schiff bases. Lett. Drug Des. Discov. 2016, 13, 395-400

Conclusion

From all above methods which shown that microwave irradiation plays an important role for promoting the condensation reaction of carbonyl compound (aldehyde) and p-amine where water plays the role of eco-friendly solvent.

i.e. a simple efficient and fast method has been developed for the synthesis of novel Schiff bases in aqueous media under microwave irradiation method which gives maximum yield with minimum energy & wastage.

Thank You