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Comparative study of Schiff base using various synthesis methods and their theoretical prediction of activities

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Abstract- Aim of this paper to establish a comparison among various methods of synthesis for Schiff base (sulphanilic acid and salicylaldehyde) along with their prediction of biological activities using a computer software PASS (Prediction of Activity Spectra for Substance) for enhancing Computer Aided Drug Designing. As results shown that the facile microwave irradiation and a green protocol of grindstone method is perfectly suitable for synthesis of Schiff base in terms of yield and easy approach.

Keywords- Schiff base, compare study, PASS prediction.

1. INTRODUCTION

The environment friendly synthetic methods have attracted more attention in recent years. The synthesis of imines has been reviewed many times in recent years. Schiff bases are characteristically formed by the condensation of a primary amine and an aldehyde and were first reported by Hugo Schiff in 1864. Schiff bases are generally bi- or tri-dentate ligands competent of forming very stable complexes with transition metals. In organic synthesis, Schiff base reactions are useful in making carbon-nitrogen bonds. The metal complexes of Schiff bases are used as a catalyst in various biological systems, polymers and dyes, beside some uses as antifertility and enzymatic agents. Literature survey showed that Schiff bases and their metal complexes, whether of natural or non-natural origin, have biological applications including antibacterial, antifungal, anti-tubercular, anti-parasitic, antiviral, antioxidant, anticancer, analgesic, anti-inflammatory properties etc[1-18]. PASS (Prediction of Activity Spectra for Substance)[19-20] is a very good tool to compute hypothetically activities of any molecule based on its chemical structure. However the activities expected are apparent and not to be validated experimentally but the activities are expressed in terms of Pa (the probability of compound being active) and Pi (the probability of compound being inactive). Further in general Pa values more than 0.3 (30%) can be predictable to have the expected activities and compounds having Pa<0.3 may not possess the predicted activity.

From above literature survey, it is cleared that many work on Schiff base has been done. Each work is concern about conventional methods only. A very few reports are observed on synthesis of Schiff base from sulphanilic acid by various method approach. The present paper reports synthesis, characterisation and various methods of Schiff base derived from sulphanilic acid and salicylaldehyde. The product can be purified simply by re-crystallization using appropriate alcohol. The yield of products is good to excellent.

2. EXPERIMENTAL

Melting points are examined in open capillary tubes and are uncorrected. The purity of the compound was determined on silica gel-coated aluminium plates (Merck). IR spectra were obtained on a Bruker Optik GmbH Alpha sample compartment RT-DLaTGS ZnSe HR 0.8). ^{1}H NMR spectra were measured on at Bruker Avance II 400 MHz from SAIF Chandigarh. Microwave irradiation was carried out with commercial RAGA's LG domestic microwave oven (1000W). All reagents were commercially available. All chemicals used were analytical grade.

2.1 *General procedure for the preparation of Schiff base*

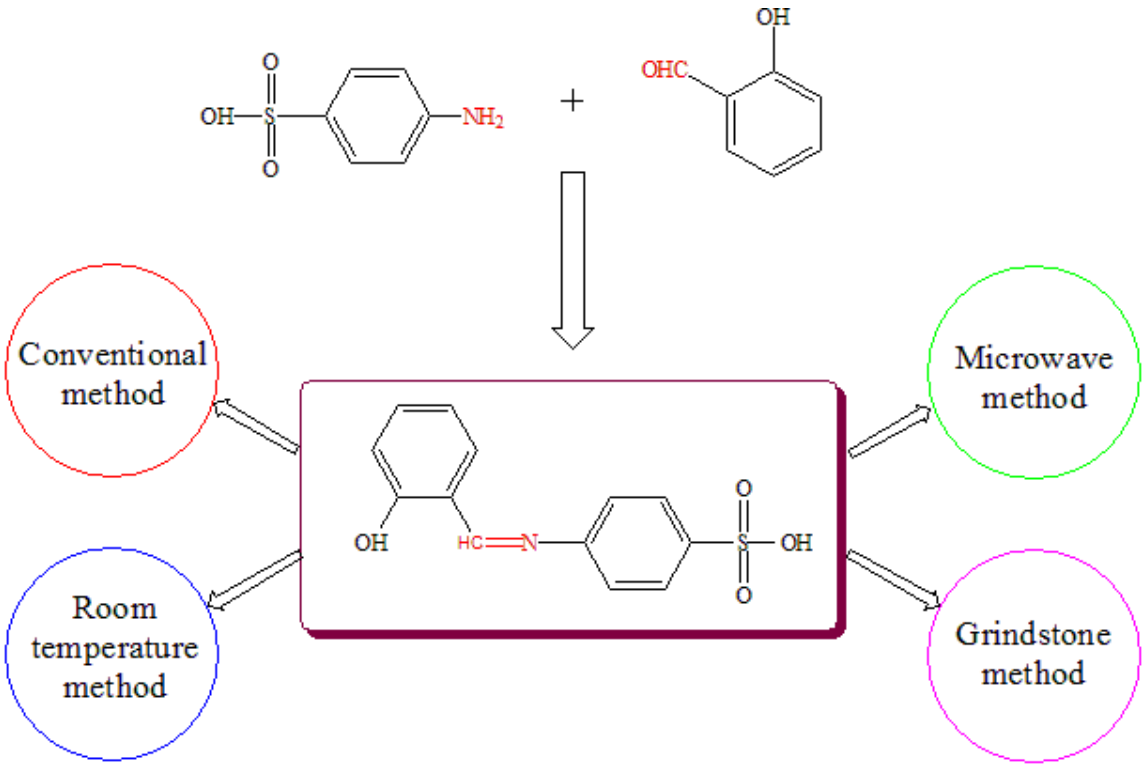
1. *Conventional method*

Schiff bases are prepared by condensation of salicylaldehyde (0.01 mol) with sulphanilic acid (0.01 mol) in ethanol (10-15mL). To the mixture these acetic acid (2-3 drops) was added and the mixture was stirred at ambient temperature for four hours. The progress of reaction was monitored by TLC. On completion of reaction the yellow- coloured amorphous product was separated. Filtered off, dried and recrystallized by ethanol.

2. *Room temperature method*
A 10 ml solution of salicylaldehyde (0.01 mol in ethanol) was added dropwise in a 10 ml solution of sulphanilic acid (0.01 mol in ethanol). The mixture was stirred on magnetic stirrer at the room temperature for one hour. Few drops of acetic acid was gradually added. The final mixture kept for about 15 minutes, filtered off and washed with cold ethanol and dried.

3. *Grindstone method*
Salicylaldehyde (0.01 mol) and sulphanilic acid (0.01 mol) were mixed in a mortar. To the mixture few drops of acetic acid was added. The reaction mixture was ground together in a mortar using a pestle to generate pale yellow coloured tacky solid within 20-40 min. After that, distilled water (20 mL) was added and solid product separated out. The separated product was filtered, washed with cold water and recrystallized from ethanol.

4. *Microwave method*
The reaction mixture of sulphanilic acid (0.01 mol) and salicylaldehyde (0.01 mol) were dissolved in ethanol (10 ml). One drop of glacial acetic acid was taken in a borosil beaker and irradiated in a microwave at a power of 20% intensity (140 W) for 2-3 minutes. The resultant solution was cooled and poured in cold water. The separated solid was filtered and recrystallized from ethanol.



Scheme 1. Synthesis of Schiff base

3. RESULTS AND DISCUSSION

The synthesis scheme has been given in scheme 1. The result summarized in table 1 by performing at different temperature and methods. Amongst

approach 3, approach 2 and approach 1, approach 4 has a great asset. However, after comparing the progress of reaction the best yields were obtained in microwave method. It can be appropriate for laboratory, industrial manufacture which consumes the least time to finish the synthesis of Schiff base. Microwave irradiation synthesis does not only use the least time, but also has the greatest yield. From

the table.1, we can know clearly that microwave irradiation is the simple way to synthesis this Schiff base. Microwave irradiation is becoming an increasingly popular method of heating which replaces the classical one because it is proved to be a clean, cheap and convenient method. Frequently, it affords higher yields and results in lesser reaction time. A result also shows that grindstone technique is better as compared to conventional method. No organic solvent required, reaction finished within 20-40 minutes with pure products in good percent yield.

Table.1 The compare of various methods of synthesis of Schiff base:

Approach	Reaction condition	Time	Yield
1.	Conventional method	4 hours	60%
2.	Room temperature method (stir)	1 hours	75%
3.	Grindstone method	20- 40 min.	65%
4.	Microwave method	2-3 min.	93%

Melting Point: 280^0C

IR frequencies: 3426, 1587, 1248, 1166.

^{1}H-NMR (400 MHz, CDCl3): δ= 9.23 (s, 1H, N=CH), 7.70 (dd, 2H, Ar-H), 7.67 (dd, 2H, Ar-H), 7.30 (m, Ar-H), 7.27 (m, Ar-H), 2.50 (s, -OH).

Table 2: Predicted activity of synthesized compound (Schiff base) by PASS:

Predicted Activity	Synthesized Schiff base		Predicted Activity	Synthesized Schiff base	
	Pa	Pi		Pa	Pi
Glycosylphosphatidylinositol phospholipase D inhibitor	0.948	0.002	2-Haloacid dehalogenase inhibitor	0.849	0.002
Arylacetonitrilase inhibitor	0.938	0.003	Gly-X carboxypeptidase inhibitor	0.833	0.001
Feruloyl esterase inhibitor	0.926	0.003	Nicotine dehydrogenase inhibitor	0.831	0.002
IgA-specific metalloendopeptidase inhibitor	0.923	0.002	Antihemorrhagic	0.831	0.002
Gamma-guanidinobutyraldehyde dehydrogenase inhibitor	0.921	0.002	Cyanoalanine nitrilase inhibitor	0.829	0.002
(S)-6-hydroxynicotine oxidase inhibitor	0.920	0.001	Shikimate O-hydroxycinnamoyltransferase inhibitor	0.821	0.003

Cholestanetriol 26-monooxygenase inhibitor	0.918	0.002	Alcohol O-acetyltransferase inhibitor	0.817	0.002
3-Hydroxybenzoate 6-monooxygenase inhibitor	0.917	0.002	Peroxidase inhibitor	0.819	0.004
Cl--transporting ATPase inhibitor	0.909	0.003	Mucomembranous protector	0.824	0.013
Glyceryl-ether monooxygenase inhibitor	0.908	0.003	2-Hydroxy-3-oxoadipate synthase inhibitor	0.811	0.002
Superoxide dismutase inhibitor	0.895	0.004	Myosin ATPase inhibitor	0.807	0.003
Crotonoyl-[acyl-carrier-protein] hydratase inhibitor	0.889	0.002	Antiinfective	0.801	0.005
Bisphosphoglycerate phosphatase inhibitor	0.886	0.003	Linoleoyl-CoA desaturase inhibitor	0.796	0.002
2-Hydroxyquinoline 8-monooxygenase inhibitor	0.881	0.003	Poly(alpha-L-guluronate) lyase inhibitor	0.798	0.004
IgA-specific serine endopeptidase inhibitor	0.880	0.003	Glucan endo-1,6-beta-glucosidase inhibitor	0.799	0.008
Aminobutyraldehyde dehydrogenase inhibitor	0.868	0.002	Benzoate-CoA ligase inhibitor	0.801	0.017
Ferredoxin hydrogenase inhibitor	0.866	0.002	Glyoxylate oxidase inhibitor	0.787	0.003
Rhamnulose-1-phosphate aldolase inhibitor	0.862	0.003	Antituberculosic	0.785	0.003
CDP-4-dehydro-6-deoxyglucose reductase inhibitor	0.860	0.002	Pyruvate decarboxylase inhibitor	0.784	0.004
Monodehydroascorbate reductase (NADH) inhibitor	0.861	0.005	Protein-glutamate methylesterase inhibitor	0.790	0.014
2,5-Dihydroxypyridine 5,6-dioxygenase inhibitor	0.758	0.003	Vasoprotector	0.706	0.010
Alanine-tRNA ligase inhibitor	0.757	0.003	Maleate isomerase inhibitor	0.692	0.001
Antiviral (Picornavirus)	0.743	0.004	Carboxypeptidase Taq inhibitor	0.687	0.021
Glycine-tRNA ligase inhibitor	0.737	0.002	Subtilisin inhibitor	0.668	0.005
Beta-mannosidase inhibitor	0.735	0.004	Membrane permeability inhibitor	0.697	0.040
Beta-amylase inhibitor	0.731	0.003	Metallocarboxypeptidase D inhibitor	0.656	0.003
Antimycobacterial	0.728	0.005	D-lactate dehydrogenase (cytochrome) inhibitor	0.650	0.002
Venom exonuclease inhibitor	0.648	0.005	Acetate kinase inhibitor	0.651	0.004

Glyoxylate reductase inhibitor	0.641	0.010	Protein-tyrosine phosphatase beta inhibitor	0.577	0.001
Sugar-phosphatase inhibitor	0.669	0.040	Phthalate 4,5-dioxygenase inhibitor	0.606	0.035
Phosphoglycerate mutase inhibitor	0.627	0.004	Deoxyribonuclease (pyrimidine dimer) inhibitor	0.568	0.002
Acetoin dehydrogenase inhibitor	0.623	0.004	Antiviral (Influenza A)	0.565	0.003
Urease inhibitor	0.623	0.004	Gastrin inhibitor	0.587	0.027
Antiviral (Poxvirus)	0.622	0.014	Phospholipid-translocating ATPase inhibitor	0.579	0.036
Polyporopepsin inhibitor	0.654	0.051	Glucarate dehydratase inhibitor	0.543	0.002
Glutamyl endopeptidase II inhibitor	0.643	0.041	Lactose synthase inhibitor	0.544	0.005
Antiprotozoal (Amoeba)	0.599	0.005	Serine-phosphoethanolamine synthase inhibitor	0.537	0.004
Antiseptic	0.525	0.011	Pyruvate dehydrogenase inhibitor	0.471	0.008
Alcohol dehydrogenase (NADP+) inhibitor	0.519	0.008	Membrane integrity antagonist	0.505	0.043
NADPH peroxidase inhibitor	0.563	0.053	Anthrax lethal factor inhibitor	0.465	0.003
Antiviral (Influenza)	0.516	0.020	Antiparasitic	0.479	0.018
Eye irritation, inactive	0.512	0.020	Lactate 2-monooxygenase inhibitor	0.461	0.008
Urethanase inhibitor	0.516	0.025	Dehydro-L-gulonate decarboxylase inhibitor	0.504	0.052
Antihelmintic	0.496	0.006	Anthranilate-CoA ligase inhibitor	0.468	0.017
L-amino-acid oxidase inhibitor	0.494	0.005	Omptin inhibitor	0.520	0.070
Cutinase inhibitor	0.509	0.021	Radioprotector	0.473	0.029
Gluconate 5-dehydrogenase inhibitor	0.522	0.034	Venombin AB inhibitor	0.495	0.057
Cystathionine gamma-lyase inhibitor	0.487	0.004	Endopeptidase So inhibitor	0.482	0.044
Magnolysin inhibitor	0.481	0.001	D-lactate dehydrogenase inhibitor	0.440	0.004
Lipoprotein lipase inhibitor	0.521	0.044	HIV-2 reverse transcriptase inhibitor	0.438	0.003

Histone deacetylase SIRT2 inhibitor	0.478	0.003	Cysteine synthase inhibitor	0.439	0.004
Alcohol dehydrogenase inhibitor	0.478	0.005	Thiosulfate sulfurtransferase inhibitor	0.434	0.007
Antipyretic	0.488	0.014	Insulysin inhibitor	0.483	0.056
Antiprotozoal (Trichomonas)	0.407	0.005	Antibacterial	0.425	0.025
Sweetener	0.408	0.014	Skin irritation, inactive	0.416	0.024
Analgesic stimulant	0.382	0.007	NADH dehydrogenase inhibitor	0.366	0.010
Antiprotozoal (Trypanosoma)	0.401	0.038	Antihematotoxic	0.330	0.004
Diuretic inhibitor	0.372	0.031	Antileprosy	0.325	0.007
Diuretic	0.312	0.022	Antiprotozoal (Coccidial)	0.317	0.052
Antifungal	0.307	0.078	Antiulcerative	0.311	0.089

4. CONCLUSION

This paper defines computer aided drug designing of expected activity information given in table 2. The method shown here is the most appropriate way to synthesize the salicylaldimine in which microwave method and grindstone method play an important role for encouraging the condensation of reaction of aldehyde and amines. The grindstone method procedure is maintaining environmental friendly approach for the synthesis of Schiff base. The attractive features of these procedures including good adaptations, simple workup and short time reaction, making them a useful practical approach for the synthesis of Schiff bases.

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