Universal Journal of Chemistry 5(2): 36-42, 2017 http://www.hrpub.org
DOI: 10.13189/ujc.2017.050202

Synthesis and Biological Activity of Some Schiff Bases from Phthalimides

Girish Kumar Sinha[1,*], Akanksha Priya[2], Sonal Priya[3], Satyendra Narayan[1]

[1]Post Graduate Centre of Chemistry, College of Commerce, Arts and Science Patna (M.U.), India
[2]Department of Botany, University of Delhi, India
[3]Department of Chemistry, Oklahoma State University, USA

Abstract An innovative protocol to the synthesis of this material emerged on exploring the potential of the various form of N-aminophthalimides on its reaction with a number of aromatic aldehydes. New series of biologically active substituted Schiff bases with general formula, R1N=CHR2 where R1 = 3-nitro-N-aminophthalimide, 3-bromo-N-aminophthalimide, 4-nitro-N-aminophthalimide, 4-bromo-N-aminophthalimide, R2 =2, 6-dichlorobenzaldehyde, o-anisaldehyde and o-vanillin were synthesized by the reaction of substituted N-aminophthalimides and substituted aldehydes in ethanol. Moreover N-aminophthalimides (50-70% yield) were synthesized by reactions of corresponding phthalimides and hydrazine hydrate. Such compounds were characterized by different physico-chemical techniques like, melting point, elemental analysis, multinuclear NMR (1H, 13C).The synthesized compounds were screened for antibacterial and antifungal activities. The explorations of the biological properties of the compounds are mentioned in this paper.

Keywords N-aminophthalimide, Schiff Bases, Antimicrobial Activity, Aromatic Aldehydes, Azomethine

1. Introduction

Recent years have witnessed a great deal of interest in the synthesis and characterisation of Schiff bases [1]. They have a wide variety of applications in various fields, *e.g*., biological, inorganic and analytical chemistry [2-6]. They are used in optical and electrochemical sensors as well as in various chromatographic methods, to enable detection of enhance selectivity and sensitivity [7-9]. They possess excellent characteristics structural similarities with natural biological substances. Relatively easy preparation procedures and the synthetic flexibility enables design of suitable structural properties [10-16]. Schiff bases are also effective corrosion inhibitor because of ability of forming monolayer on the surface to be protected due to interaction with C=N by electron transfer, chemisorptions [17-19]. In addition to this the atoms of the benzene rings create multiple adsorption sites for the inhibitor in forming stable monolayer formation. Imine linkage formed between the aldehyde derived from vitamin A and the protein opsin present in the retina of the eye plays a vital role in the chemistry of vision. Vitamin B_6 serves as a coenzyme and is capable to form an imine with amino acid of protein. This is helpful in the transfer of the amino group from one amino acid to another, the transamination reactions, which is important in the metabolism and the biosynthesis of amino acids. Reports have shown that the presence of a lone pair of electrons in sp^2 hybridized orbital of nitrogen atom present on the azomethine group has a vital role in exhibiting chemical and biological importance [20]. Schiff bases have been reported in their biological properties, such as, antibacterial, antifungal activities [21-24]. They are active against a wide range of organisms for example; *Candida albicans, Escherichia coli, Staphylococcus aureus, Bacillus polymyxa, Trichophyton gypseum, Mycobacteria, Erysiphe graminis* and *Plasmopara viticola* [25-28]. Ortho--phenylenediamine Schiff bases show clinical properties [29]. Isatin Schiff bases were reported to possess antiviral, anti-HIV, antiprotozoal and anthelmintic activities [30]. They also exhibit significant anticonvulsant activity, apart from other pharmacological properties [31]. Certain cobalt Schiff base complexes are potent antiviral agents [32]. Schiff bases derived from 4-dimethylamine benzaldehyde shows antibacterial activity, in medicines used as antibodies and anti-inflammatory agents [33-38]. All these facts prompted us to extend such works and we focused to synthesise Schiff bases with heterocyclic moieties such as phthalimides [39]. We also planned to screen such newly synthesized Schiff bases against microbial activities.

Following is the schematic diagram for preparation of Schiff bases which we followed:

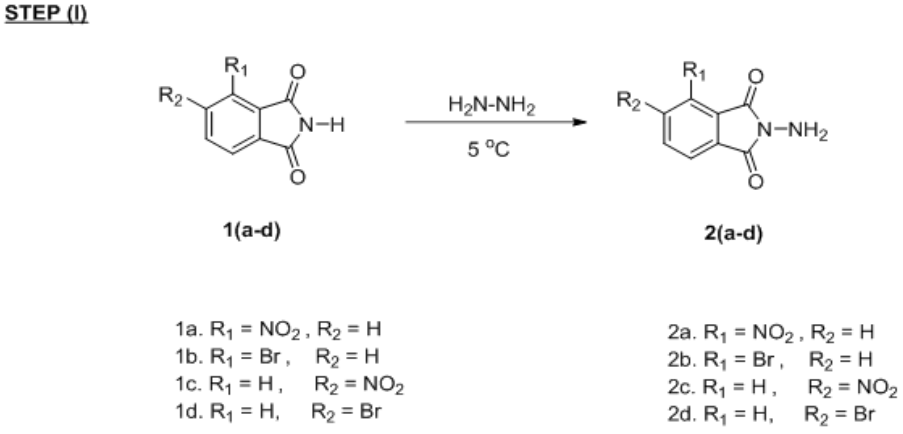

Figure 1. Synthesis of N-aminophthalimides from phthalimides

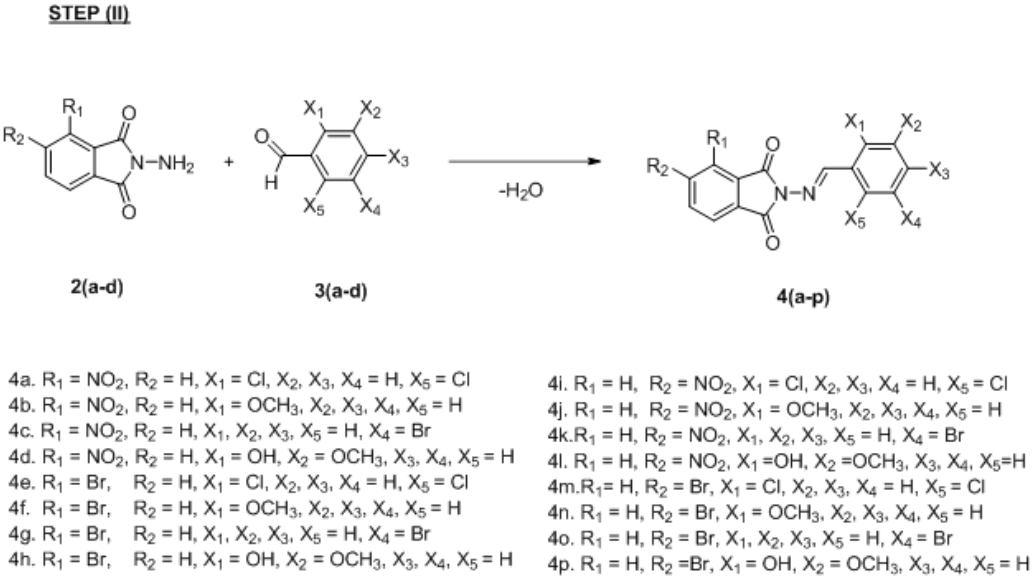

Figure 2. Synthesis of Schiff bases from N-aminophthalimides

The formation of compounds was confirmed on the basis of elemental analysis, IR and PMR spectroscopical data.

2. Experimental

All the chemicals and reagents used were of AR quality. Materials used for the synthesis of the reported compounds were from reputed companies. Traditional method was used in the preparation of Schiff bases. Melting points were taken in open capillaries and are uncorrected. Purity of compounds was monitored on silica gel 'G' coated TLC plates. The IR spectra was taken on 157 spectrophotometer in KBr and PMR spectra on a varian A 60 D instrument using TMS as internal standard.

Preparation of 3- and 4-Substituted Phthalimides (1a-1d)

3-and 4-nitrophthalimides were prepared by heating corresponding nitrophthalic acid with ammonium carbonate [39]. 4-aminophthalimide (m.p. 264^0C,d) was obtained as yellow crystals by stirring 4- nitrophthalimide (11.20 g, 0.11 mol) with a solution of stannous chloride(84g, 0.11 mol) in HCl (450 ml) and water (150 ml), cooling the resulting solid at 0^0C, washing it with hot water and crystallised as yellow needles. Similarly 3-aminophthalimide (m.p. 270^oC) was prepared in the same way which was yellow powder. These compounds were converted into 3- and 4-bromosubstituted derivatives by Sandmeyer reaction using cuprous bromide and HBr [40].

Preparation of N-Aminophthalimides-(2a-2d)

1:1 mole of phthalimides (1a-1d) and hydrazine in 90-100 ml of absolute ethanol were stirred under water-ice bath at 0-5 °C for 25 min. 1.5-2 ml of 99 % hydrazine were added to flask drop by drop. The mixture was well stirred at 0-5 °C for 2.30 *h*. Gradually viscosity of reaction medium increased with time. 60-80 ml of ice-water was added to the reaction mixture. It was then filtered with vacuum pump. The precipitate obtained was washed with 5 ml of water and dried well. The yield of the compounds was 50-73 %.

Table 1. Physical Data of Compounds 4a-4p

Entry	Molecular Formula	State	Melting Point (°C)	Color	Yield (%)	% of Elements		
						C	H	N
4a	$C_{15}H_7N_3O_4Cl_2$	Solid	177-179	Yellow	63	49.01	2.01	11.71
						49.45	1.92	11.54
4b	$C_{16}H_{11}N_3O_5$	Solid	135-137	Yellow	71	59.28	3.47	13.01
						59.08	3.38	12.92
4c	$C_{15}H_8N_3O_4Br$	Solid	127-129	White	73	48.31	2.18	11.41
						48.13	2.14	11.23
4d	$C_{16}H_{11}N_3O_6$	Solid	231-232	Yellow	62	56.25	3.13	12.12
						56.31	4.23	12.32
4e	$C_{15}H_7N_2O_2BrCl_2$	Solid	188-189	Pale yellow	65	45.42	1.82	7.08
						45.23	1.76	7.06
4f	$C_{16}H_{11}N_2O_3Br$	Solid	125-127	Cream	73	53.81	3.09	8.1
						53.48	3.06	7.8
4g	$C_{15}H_8O_2Br_2N_2$	Solid	128-130	Pale yellow	61	44.28	1.91	6.81
						44.12	1.96	6.86
4h	$C_{16}H_{11}N_2O_4Br$	Solid	214-217	Pale yellow	55	50.88	2.98	7.54
						51.20	2.93	7.47
4i	$C_{15}H_7N_3O_4Cl_2$	Solid	182-184	White	50	49.81	1.98	11.71
						49.45	1.92	11.54
4j	$C_{16}H_{11}N_3O_5$	Solid	165-167	Deep yellow	68	59.28	3.27	12.85
						59.08	3.38	12.92
4k	$C_{15}H_8N_3O_4Br$	Solid	129-131	Cream	62	48.25	2.08	11.28
						48.13	2.14	11.23
4l	$C_{16}H_{11}N_3O_6$	Solid	219-221	Yellow	74	56.15	3.18	12.42
						56.31	4.23	12.32
4m	$C_{15}H_7N_2O_2BrCl_2$	Solid	156-158	White	67	45.12	1.88	7.10
						45.23	1.76	7.06
4n	$C_{16}H_{11}N_2O_3Br$	Solid	145-147	Pale yellow	71	53.68	3.12	7.97
						53.48	3.06	7.8
4o	$C_{15}H_8O_2Br_2N_2$	Solid	115-117	Pale yellow	52	44.19	1.85	6.91
						44.12	1.96	6.86
4p	$C_{16}H_{11}N_2O_4Br$	Solid	207-209	White	67	51.12	2.88	7.58
						51.20	2.93	7.47

Preparation of Schiff Bases (4a-4p)

The compounds **2a-2d** were condensed with aromatic aldehydes, **3a-3d**, to produce the corresponding Schiff bases **4a-4p**. Equimolar quantities of the N-aminophthalimides (0.01 mol) and aromatic aldehydes (0.01 mol) were taken in 80-100 ml of xylene. Anhydrous $ZnCl_2$ (3-5 g) was added to this solution. The mixture was refluxed for 6-8 h. The crystals were separated and filtered under suction. The mother liquor of the above reactions were diluted with dry ether (50-70 ml) and then saturated with dry HCl gas. Viscous liquid formed were separated and exposed to the atmosphere which turned into dark solid with metallic lustre. The compounds crystallized from alcohol have white, yellow or creamy colour crystal appearance in general. Melting points were determined, yield 50-78%.

3. Result and Discussion

Melting Points

It is expected that there are intramolecular hydrogen bonding in compounds **4d, 4h, 4l** and **4p** hydroxy groups and so the melting point of these compounds (231-32, 214-15,219-21 and 207-9 ºC, respectively), are higher than those of the other Schiff bases.

Spectral Analysis

The IR spectra of the Schiff bases show medium or strong bands at 1615–1650 cm^{-1} assigned to C=N stretching mode. The absence of bands characteristic of (C=O) and primary amine (NH_2) confirms the formation of the proposed Schiff base framework. The broad bands between 2800 and 2400 cm^{-1} in the spectra of the compounds **4d, 4h, 4l** and **4p** have indicated the formation of the OH···N intramolecular hydrogen bond between the salicyl part OH proton and the nitrogen atoms. The C–O stretching vibrations appear at the 1251–1298 cm^{-1} range as strong bands. The C–Cl stretching vibration is seen at the range 610–648 cm^{-1} as medium or weak bands for all of the compounds. In the IR spectrum of **4a-4d** and **4i-4l**, the strong or medium bands at 1549-1528cm^{-1} and at 1360-1365 cm^{-1} can be assigned to the symmetric and asymmetric vibrations of NO_2, respectively. The higher **δ** values (in NMR spectra using $CDCl_3$) of the Schiff bases also confirm their formation and the presence of intra-molecular hydrogen bondings in the said compounds **4d,4h,4l** and **4p (**13.64,13.95,13.93 and 13.87 respectively). Methoxy group (OCH_3) in the compounds **4b,4d,4f,4h,4j,4l,4n** and **4p** appears as singlet (**δ** values 3.82-3.88) and is also supported by IR spectra (ν_{max}1170-1175 cm^{-1}).

Table 2. Spectral Data (I.R. and PMR) for 4a-4p

	IR Spectra (KBr cm^{-1})	**PMR Spectra (δ) values**
4a. $C_{15}H_7N_3O_4Cl_2$	1365, 1528(nitro),1260(C-O),	6.4d,6.7t,7.2d,7.8d,
	1792(OCN),1640(N=C), 648(C-Cl)	8.96 s (N=CH),
4b. $C_{16}H_{11}N_3O_5$	1360, 1549(nitro),1258(C-O),	6.3d,6.4t,6.7t,7.3d,7.5t
	1170(OCH_3), 1797(OCN),1640(N=C),	3.82s (OCH_3), 8.97s(N=CH)
4c. $C_{15}H_8N_3O_4Br$	1362,1546(nitro),1287(C-O),	6.50t,6.62t,7.2d,7.5t,8.0d
	1792(OCN),1625(N=C),	8.2d(Ar-H),8.96s(N=CH),
	540(C-Br)	
4d. $C_{16}H_{11}N_3O_6$	1366, 1532 (nitro),1295(C-O),	6.4t,6.7t,7.21d,7.5s,7.8t,
	1792(OCN),1640(N=C), 630(C-Cl), 2800 (OH hydrogen bonding)	8.96s (N=CH),
	11.74(OCH_3) ,3280(OH)	9.92s (OH),3.88s (OCH_3) 13.64(OH hydrogen bonding)
4e. $C_{15}H_7N_2O_2BrCl$	1295 (C-O), 625,640 (C-Cl),578(Br)	6.4d,6.7d,7.2t,7.8t,
	1780(OCN),1630(N=C)	8.96s (N=CH)
4f. $C_{16}H_{11}N_2O_3Br$	1269 (C-O), 621,568 (C-Br)	6.5d,6.7t,6.9t,7.3t,7.5d,,
	1171(OCH_3), 1778 (OCN),1615 (N=C)	3.41s (OCH_3) 8.96s(N=CH)
4g. $C_{15}H_8O_2Br_2N_2$	1277(C-O),1771(OCN),	6.50t,6.7d,7.23d,7.4d,7.8t,8.1d
	1660(N=C), 587(C-Br))	8.96s(N=CH),
4h. $C_{16}H_{11}N_2O_4Br$	1260(C-O), 548(C-Br))	6.4s,6.7t,7.4d,7.6d,7.8t
	1792(OCN),1640(N=C),	,8.96(N=CH),
	3165(OH),1170(OCH_3), 2598 (OH hydrogen bonding)	9.93s(OH), 3.87s (OCH_3) 13.95s (OH hydrogen bonding)
4i. $C_{15}H_7N_3O_4Cl_2$	1365, 1528(nitro),1260(C-O),	6.4d,6.7d,7.5s,7.8t,
	1792(OCN),1640(N=C), 648(C-Cl)	8.1d(Ar-H),8.96 s (N=CH),
4j. $C_{16}H_{11}N_3O_5$	1365, 1528(nitro),1260(C-O),	6.4d,6.7d,6.90d,7.10d,,7.8t
	1171(OCH_3), 1792(OCN),1640(N=C), 648(C-Cl)	3.85s(OCH_3), 8.96 s (N=CH),
4k. $C_{15}H_8N_3O_4Br$	1362,1546(nitro),1287(C-O),	6.50t,6.72d,7.21t,7.6d,7.82s
	1792(OCN),	8.96s(N=CH),
	1625(N=C),	
4l. $C_{16}H_{11}N_3O_6$	1366, 1532 (nitro),1295(C-O),	6.4d,6.7s,7.2d,7.4d,7.6d,7.9s
	1792(OCN),1640(N=C),	8.96s(N=CH),
	1175(OCH_3),3280(OH), 2800 (OH hydrogen bonding)	9.92s (OH), 3.85s(OCH_3), 13.93s (OH hydrogen bonding)
4m. $C_{15}H_7N_2O_2BrC$	1280 (C-O), 620,644 (C-Cl),585(C-Br)	6.2s.4d,6.7d,7.2d,7.51d,7.8t
	1786(OCN),1615(N=C)	8.96(N=CH)
4n. $C_{16}H_{11}N_2O_3Br$	1280 (C-O), 544 (C-Br)	6.4d,6.7t,7.2s, 7.8t,
	1172(OCH_3), 786(OCN),1615(N=C)	3.78 (OCH_3), 8.94s(N=CH)
4o. $C_{15}H_8O_2Br_2N_2$	1277(C-O), 1771(OCN),	6.50t,6.70t,7.24d, 7.82s,
	1660(N=C), 610, 589(C-Br))	8.96s (N=CH),
4p. $C_{16}H_{11}N_2O_4Br$	1260(C-O), 548(C-Br)	6.4s,6.7t,7.4d,7.6d,7.86d
	1792(OCN),1640(N=C),	8.1d(Ar-H ,8.96(N=CH), 9.92s (OH), 3.82(OCH_3),
	3089(OH),1171(OCH_3), 2598 (OH hydrogen bonding)	13.87s (OH hydrogen bonding)

Table 3. Antibacterial Activity of Schiff's Bases (*4a-4p)*

Compounds	Zone of Inhibition of Sample (in mm)								
	E.coli			*B.subtilis*			*S.aureus*		
	20mg/ml	10mg/ml	5mg/ml	20mg/ml	10mg/ml	5mg/ml	20mg/ml	10mg/ml	5mg/ml
4a	31	24	23	30	22	20	31	22	18
4b	32	26	25	33	30	24	32	23	20
4c	27	22	21	23	19	18	30	18	21
4d	26	20	18	23	19	16	30	16	18
4e	22	19	18	17	11	10	28	18	16
4f	19	16	14	16	9	10	22	13	11
4g	17	14	11	15	12	9	21	9	10
4h	16	12	12	12	8	5	20	8	11
4i	31	24	23	26	22	20	31	18	16
4j	28	25	26	28	24	22	29	21	18
4k	24	20	22	22	18	15	28	16	16
4l	26	16	14	24	20	17	30	12	17
4m	18	15	14	14	10	12	21	11	11
4n	14	13	11	12	9	8	12	10	7
4o	13	12	11	10	8	5	18	8	8
4p	11	10	8	9	7	4	15	8	6

Biological Activity

Antibacterial Activity Data of Compounds (in vitro)

The bacterial cultures for *B. subtilis, S. aureus,* and *E. coli* were obtained from Department of Microbiology, College of Commerce, Patna. The bacterial cultures were incubated at 30 ± 0.1^{o}C for 24 hours by inoculation into nutrient agar. Schiff bases were stored dry at room temperature and dissolved in 20mg/ml dimethylsulfoxide (DMSO). Antibacterial activities of each compound were evaluated by standard petridisc method [39, 41]. All plates were prepared with an equal thickness of nutrient agar. At the end period, inhibition zones formed on media were measured with a zone reader in millimetres. Similar results were also recorded for 10 mg/ml and 5 mg/ml respectively for each compound. A filter paper disc (5 mm diameter) was impregnated with the different Schiff's bases (at specific concentrations) and the disc was then placed on the nutrient agar in a petridish and left for 24 hrs at 30 ± 0.1^{o}C.

Antifungal Activity of Compounds (in vitro), 4a-4p

Antifungal activities of compounds **4** were carried out at different concentrations using spores of *Aspergillus flavus* and *Chalara corda* by petridish method [42-44]. Spores of *Aspergillus flavus* suspended in 1.0 ml of sterile water were mixed with 9.0 ml of lukewarm molten agar and poured into a sterile petridish. After solidification of the agar, isolated single spores were marked under a microscope on an inverted petridish. Now, a circular agar area was cut off and aseptically transferred to PDA slants for growth at 25^{0}C. After one week of the growth, mycelia discs of 5 mm diameter were cut off from the maintained pure culture of the organism for inoculation into sterilized PDA medium in seven different petridishes for blotter disc studies. Small Whatman filter paper (no.44) discs of 15 mm were soaked in 5 mg/ml, 2.5 mg/ml & 1.25 mg/ml concentrations of each Schiff's base in ethyl alcohol and sterile double distilled water were put in the middle of the inoculated petridishes one each separately. The petriplate containing the disc soaked in sterile distilled water served as the control. Paired petriplates were incubated at 25^{o}C in inverted position for 6 days for the growth of the organism after which inhibitory effect of the compound was studied. Inhibitory zone was measured in each case.

4. Conclusions

All the newly formed Schiff'bases **4a-4p** were found to be effective against bacterial and fungal activities to a greater extent. It was also found that the Schiff bases having nitro and chloro groups (electron withdrawing groups), **4a-4d** and **4i-4l** were more effective than the compounds having methoxy and hydroxyl groups (electron donating groups). The activity decreases with decrease in concentration.

Acknowledgements

The authors are thankful to the CDRI, Lucknow for the spectra lR, NMR, and CHN analyses and Department of Botany, College of Commerce, Arts and Science, Patna for biological activity tests. Financial support from the University Grants Commission (UGC), Kolkata, Minor project is gratefully acknowledged.

Table 4. Antifungal Activity Data of Schiff's Bases [*4a-4p*]

Compounds	Zone of Inhibition of Sample in mm)					
	Aspergillus flavus			*Chalara corda*		
	5mg/ml	*2.5mg/ml*	*1.25mg/ml*	*5mg/ml*	*2.5mg/ml*	*1.25mg/ml*
4a	42	25	18	38	28	12
4b	47	29	22	36	26	16
4c	40	21	14	30	21	14
4d	39	20	16	32	22	12
4e	24	12	10	36	26	16
4f	26	10	8	34	24	14
4g	22	14	12	36	23	13
4h	20	12	21	22	21	11
4i	43	25	21	37	25	17
4j	47	28	21	38	24	16
4k	40	20	18	35	26	16
4l	38	18	12	26	12	10
4m	26	17	14	30	18	12
4n	20	12	9	21	11	9
4o	18	11	8	20	8	7
4p	17	8	6	21	7	5

REFERENCES

[1] Schiff, H.S. [1864], *Ann. Chem. (Paris)*. 131,118.

[2] Cimerman, Z., Miljanic, S. & Galic, N. [2000]. *Croatica Chemica Acta*, 73 (1), 81- 95.

[3] Singh, P., Goel, R. L. & Singh, B. P. [1975]. *J. Indian Chem. Soc.*, 52, 958.

[4] Perry, B. F., Beezer, A. E., Miles, R. J., Smith, B. W., Miller , J. & Nascimento, M. G.[1988]. *Microbois.*, 45, 181.

[5] Elmali, A., Kabak, M. & Elerman, Y. [2000]. *J.Mol. Struct.*, 477, 151.

[6] (a) Patel, P. R., Thaker, B. T. & Zele, S.[1999]. *Indian J. Chem.*, 38 A, 563. (b) Hodnett, E.M., Dunn, W. J., [1970], *J .Med. Chem*., 13, 768.

[7] Valcarcel, M. & Laque de Castro, M. D.[1994]. "Flow-Through Biochemical Sensors", *Elsevier, Amsterdam.*

[8] Spichiger-Keller, U. [1998]. "Chemical Sensors and Biosensors for Medical and Biological Applications", *Wiley-VCH, Weinheim.*

[9] (a) Lawrence, J. F. & Frei, R. W. [1976]. "Chemical Derivatization in Chromatography", *Elsevier, Amsterdam.* (b) Olie, G. H. and Olive, S. [194] Springer, Berlin.

[10] More, S.V., Dongarkhadekar, D.V., Chavan, R.N., Jadhav, W.N., Bhusare, S.R. and Pawar, R.P.[2002]. *J. Indian Chem. Soc.*, 79, 768.

[11] Bhendkar, A.K., Vijay, K. & Raul, A.W. [2004]. *Acta Cien. Indica*, 30C, 29.

[12] Vaghasiya, Y.K., Nair, R.S., Baluja, M. & Chanda, S.S. [2004]. *J. Serb. Chem.* Soc., 69, 991.

[13] Vashi, K. & Naik, H.B. [2004]. *Eur. J. Chem.*, 1, 272.

[14] Rhodes, J. H. Chen, Hall, S.R., Beesley, J.E., Jenkins, Collins D.C. P. & Zheng, B. [1995]. *Nature*, 377, 71.

[15] Safwat, H.M., Ragab, F.A., Eid, N.M. & Abdel, G.M. [1988]. *Egypt.J. Pharm. Sci.*, 29, 99

[16] Mtrei, Yadawe, R. M. and Patil, S. ([1996]. *Orient. J. Chem.*, 12, 101.

[17] Quan, Z., Chen, S. and Li, Y. [2001]. *Corros. Sci.*, 43, 1071.

[18] Ashassi, Sorkhabi, Shabani, H. B., Aligholipour, B. and Seifzadeh, D. [2006] *Appl. Surf. Sci.*, 252, 4039.

[19] Li, S., Chen, S., Ma, H., Yu, R. and Liu, D., [1999]. *Corros. Sci*, 41, 1273.

[20] (a) Aurea, E.,Maria da, G. N., Vanilde, G., Joseph Mand Astréa ,G. J. [1999] *Braz. Chem. Soc.*, 10 ,60 (b) Kuzmin, V. E., Lozitsky, V. P., Kamalov, G. L., Lozitskaya ,R. N., Zheltvay, A. .I, Fedtchouk, A .S. and Kryzhanovsky, D. N. [2000]. *Acta Biochemical Polonica.*, 47, 867.

[21] (a) Williams, D.R. [1972]. *Chem. Rev.*, 72, 203. (b) Campos, A., Anacona, J.R. and Campos-Vallette, M.M. [1999]. *Mian group Metal chem*., 22, 283. (c) Arslan, N. S., Logoglu, E. and Sakiyan, I. [2003*]. G.U.J. Sci.*, 16, 283.

[22] (a) Safwat, H.M., Ragab, F. A., Eid, N.M. & Abdel, G.M. [1988]. *Egypt. J. Pharm. Sci.*, 29, 99 (1988). (b) Bilgramy, K. S., Prasad, T., Sinha, K. K. & Singh, P. [1980]. *J. Indian Bot.*

Soc. 59: 123-12.

[23] Davis, W., Roberts, J. J & Ross, W. C. J. [1995]. *J. Chem. Soc*. 890.

[24] Dhar, M. L., Dhar, M. M., Dhawan, B. N., Mehrotra, B. N. & Ray, C. [1968]. *Indian J. Exp Biol*.6**:** 232-248.

[25] Ebbole, D. J. [1996]. *J. Genet*.75**,** 361-374. and Barreiro, E.J.[2002]. *Bioorg. Med. Chem. Lett.*, 12, pp. 1533.

[26] Siliva Regina Tozato Prado et al. [2004]. *Z. Naturforsch,* 59, pp.663.

[27] Sami, S. M, Dorr, R.T., Alberts, D.S., Solyom, A. M. and Remers, W.A. [2000] .*J. Med. Chem*., 43, 3067.

[28] Wang, T., Zhang, Y.H., Ji, H., Chen, Y.P. and Peng, S.X. [2008]. *Chinese Chem. Lett*., 19, 26.

[29] Sandmeyer, T. [1884].Berichte der deutschen chemischen Gesellschaft. 17(4), 2650-2653.

[30] Mahindra A.M. and Fisher, J.M. [1983].*Nature (London)*, 303, 64.

[31] Pandeya, S.N., Yogecswari P., Sriram, D. [1999]. *Chemotherapy*, 45, 192.

[32] Sawodny, W.J. and Riederer, M.[1977]. *Angew. Chem. Int. Edn. Engi.* 16, 859.

[33] Bottcher, A., Takeuchi, Simon, T. M.I., Meade T.J. and Gray, H.B., [1995].*J. Inorg. Bio-Chem.*, 59, 221.

[34] Britovsek, G.L.P., Gibson, V.V., Mastroianni, S., Oakes, D.C.H., Redshaw, C., Solan, G.A. White, A.J.P., Williams, .J. [2001]. *Eur. J. Inorg. Chem.*, 431, 2.

[35] Sun, B., Chen, J., Hu J.Y. [201], *Lix., J. Chin. Chem. Soc*, 12, 1043.

[36] Boghaei D.M. and Mohebi, S., [2002]. *Tetrahederon*, 58, 5357.

[37] Liu, S.Y., Nocera, D.G., [2006]. *Tetrahedron Lett.*, 47, 1923.

[38] Budakoti A., Abid M. and Azam, A., [2006]. *Eur. J.Med. Chem.*, 41, 63.

[39] (a) Sinha, G.K., Pandey, B., Singh, N.N.[1999]. *J.Indian Chem. Soc*., 76, pp. 110-11., (b) Sinha, Girish Kumar, Singh N.N. 2ooo, ChemInform ,Vol.31, Issue 18, page no May 2, Wiley Online Library, 111 River Street, Hoboken, NJ 07030-5774, North America (USA)); (c) Sinha, G.K., Narayan, S., Yadav, S.N., Priya, A.[2014].,'Synthesis and Biological Activity of Some Schiff's Bases(N-Aminophthalimide Series)', *Advances in Scientific and Technological Research(ASTR), USA*, [online] 1 (4), 149-160. (d) Sinha, Girish Kumar, Singh N.N.[1999], "Synthesis Of Some Nitrogen Mustards", *Journal Of Indian Chemical Society Calcutta*,, Vol.76,February1999, pp.110-111.

[40] (a) Sandmeyer Reaction." Chem. Rev. 40(2); 251-277.; (b) Doyle, M.P., Siegfried, B. and Dellaria, J.F. (1977), J. Org. Chem. 42 (14); 2426-2431.

[41] Atan M.S., Dzulkefly K.A., Aspollah S. Mohd., Anuar K. & Vijay S. [2011]. "Isolation and antibacterial activity of alkaloids from *Phaeanthusopthalmicus*." *Asian Journal of Chemistry*. 23, 3824-3826.

[42] Verma R. S. and Imam S. A. [1973]. *Indian J. Microbiol*.13, pp. 45.

[43] Siliva Regina Tozato Prado et al. [2004]. *Z. Naturforsch,* 59, pp.663.

[44] Sami, S. M, Dorr, R.T., Alberts, D.S., Solyom, A. M. and Remers, W.A. [2000] .*J. Med. Chem*., 43,. 3067.