AN EFFICIENT SYNTHESIS, CHARACTERIZATION AND BIOEVALUATION OF SCHIFFS BASE CONTAINING BENZIMIDAZOLE MOIETY CATALYZED BY CAMPHOR SULPHONIC ACID

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Abstract : Schiff's bases possessing a significant class of medicinally and pharmaceutical important molecules.An efficient process for the synthesis for a novel Schiff bases from 2-amino benzimidazole with P-substituted aryl aldehyde by using camphor sulphonic acid in organic solvent at room temperature. The intermediate moiety (2-amino Benzimidazole) can be synthesized from o-phenyl diamine with cyanobromide in the presence of acid medium. All the newly synthesized compounds were evaluated by the advanced spectroscopic data (^{1}HNMR, ^{13}CNMR and LCMS) and also structural determination titled compounds were calculated by elemental analysis. Subsequently all newly compounds were studied by their anti microbial activity.

***Index Terms*- O-phenyldiamine, CNBr, 2-aminobenzimidazole, camphor sulphonic acid, P-substituted arylaldehydes, schiff bases, bioevaluation**.

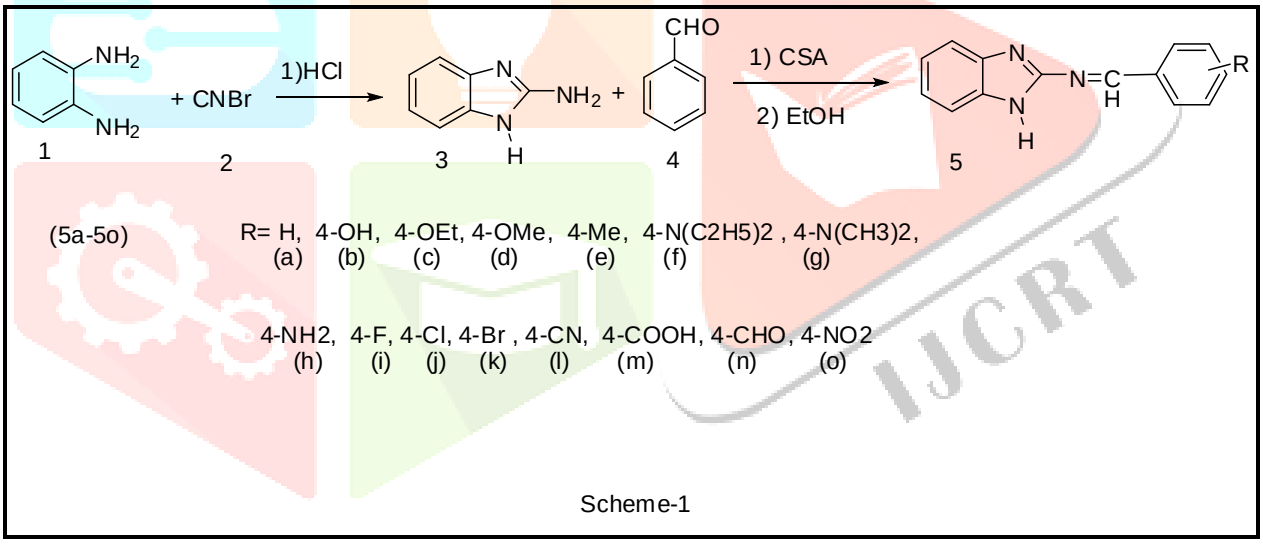
Introduction

Schiff's base synthesised from the condenation between the primary amines and substituted aldehyde which is also important class in organic, medicinally and pharmaceutical compounds. Mostly synthetic organic compounds possess imines group and also very important significat class of organic synthesis because of their applications in many fields such as biological, inorganic and also analytical chemistry.

Compounds composed of the combination of part of heterocyclic rings which are responsible for exhibit the pharmacoligical properties. The compound containing five membered heterocyclic ring.The benzimidazole is an important class of their significant biological properties against several virus like influenza, HIV, Herpus(HSV-1) and Epstein-barr[1-3] and benzimidazole moiety present in schiff bases which are show anti cancer and anti proliferate properties. Benzimidazole is being explored intermediate in the pharmaceutical industries and the benzimidazole derivatives have also been found in the diverse therapeutic applications[4,5] .The versatile core contained in several substances of benzimidazole derivatives are possess a broad spectrum of pharmacological activities [6-8] in particular, it has been

important pharmacopoeia and privi-leged structure in medicinal chemistry [10,11],encompassing a diverse Schiff bases derived from aromatic primary amines and aryl aldehyde which are also important class of organic compounds. Mostly synthetic organic compounds possess imines group and also very important class of organic compounds because of their applications in many fields such as biological, inorganic and also analytical chemistry.of biological activities including anti-microbial [12-14], antioxidant[15], anti viral [16,14], antihypertensive [18], antiprotozol [19], anti-inflammatory [20] and molluscicidal [21] agents. Further mode, benzimidazole showed anticancer activity against DNA topoisomerase [22-23] and colon cancer cell lines [24].

In this investigation, we synthesized Schiff base from 2-amino benzimidazole and various P-substituted aryl aldehyde (Electron donating , aElectron withrwing and halogen containing) using camphor sulphonic acid as a acid catalyst. We aimed tothesynthesis of new schiff's bases using organicaci(camphor sulphonic acid) catalyst due to improved better yield as well as completion of the reaction time is less and also the intermediate of this reaction such as benzimidazole can be synthesized O-phenyl diamine with cyanobromide. In addition to studied the biological activity. In the view of these facts as a continues search of antimicrobial activity of Schiff base and its derivatives with benzimidazole are synthesized in the present work.



scheme-1 : synthetic protocol of the compounds

Methods & Materials

Experimental

All the synthetic grade reagents and analytical chemicals were procured from Meric and Fine chemicals. Organic solvent used as absolute alcohol .The melting point of the all newly synthesized compounds were find out using an Agrwal thermal apparatus and uncorrected. The NMR spectra of selective compounds were recorded on a Bruker for 400 ^{1}H NMR spectra and 100 MHz for ^{13}C NMR spectra in $CDCl_3$ solvent using TMS as internal standard. Chemical shifts (δ) are referred in terms of ppm and J -coupling constants are given in Hz. Abbreviations for multiplicity is as follows: s (singulet), d (doublet), t (triplet), q (quadruplet), m (multiplet). The reaction was monitored by thin layer chromatography using silica gel as an adsorbent and ethyl acetate-hexane in different ratios as eluent. All the synthesized compounds find the molecular weight using LCMS.

Procedure for the synthesis of 2-aminobenzimidazole:

A mixture of O-phenyl diamine (**1, 1 equiv**) and cyano bromide (**2, 1 equiv**) are introduced 100ml RB flask and addition of an organic solvent acetonitrile to the above mixture. The reaction carried out on magnetic stirrer with reflux condition. After completion of the reaction, the mixture product extracted with ethyl acetate and washed with saturated solution of anhydrous sodium bicarbonate. The intermediate compound such as benzimidazole can be separated using column chromatography (4:6, ethyl acetate: n-hexane). The reaction was checked using TLC (4:6 ethyl acetate and n-hexane). The final compound obtained. (Ref -25).

Synthesis of 2-aminobenzimidazole (3):

Orange red color, m.p-155^{0}c, yield-91%

^{1}HNMR (400MHz, $CDCl_3$) δ in ppm:12.27 (s,1H,NH),9.26(s,1H,CH), and 7.23-7.11(m,4H,A-r H), 6.60(s,2H,NH_2). **^{13}CNMR (100MHz, $CDCl_3$)** δ in ppm:157.0, 135.92, 122.87, 115.1. **LCMS (m/z):132.95**. **Molecular formula:**$C_7H_7N_3$. **Elemental analysis**: Caliculated:C-63.14,H-5.30,N-31.56. Obtained:C-63.18,H-5.28,N-31.54.

General procedure for the synthesis of Schiff base:

1) 2-aminobenimidazole **(3,1 equiv)**introduced in 100 ml RB flask in acetonitrile and P-substituted aryl aldehyde**(4,1 equiv)** added to the RB flask. The reaction carried on magnetic stirrer at RT. A catalytic amount of camphor sulphonic acid added to the above mixture. The reaction was monitored after all the reactants are consumed during the reaction time, after completion of the reaction, cold water added to the product. The product can be washed with brine solution and solid product was separated out. We desired compound can be recrystalized from ethanol.

2) N-benzylidene-1H-benzo[d]imidazol-2-amine (5a):

Brickred solid; yield-91%; m.p – 151^{0}c

^{1}HNMR (400MHz, $CDCl_3$) δ in ppm:12.38 (s,1H,NH),9.35(s,1H,CH), and 8.07-6.86(m,9H,A-r H). **^{13}CNMR** (100MHz, $CDCl_3$) δ in ppm: 167.7,156.4, 136.7, 135.4,133.0, 129.6, 129.4, 122.4, 119.0, 111.5. **LCMS (m/z):**221.33. **Molecular formula:**$C_{14}H_{11}N_3$. **Elemental analysis**: Caliculated:C-76.00,H-5.01,N-18.99. Obtained: C-76.02,H-5.00,N-18.98.

3) *N*-(4-hydroxybenzylidene)-1H-benzo[d]imidazol-2-amine (5b):

Red solid; yield-93%; m.p – 219^{0}c

^{1}HNMR (400MHz, $CDCl_3$) δ in ppm: 12.51(s,1H, NH), 9.35(s,1H,NH), 9.18(s,1H,-OH), 7.89-6.86(m,8H,Ar-H). **^{13}CNMR (100MHz, $CDCl_3$)** δ in ppm: 160.1, 159.1, 157.1, 135.4, 129.8, 129.0, 122.6, 115.9, 11.8. **LCMS** (m/z):236.98. **Molecular formula**: $C_{14}H_{11}N_3O$. **Elemental analysis**: calculated: C-70.87, H-4.67, N-17.71, 0-6.74. Obtained:C-70.90, H-4.66, N-4.16 O6.73.

4) 3 N-(4-ethoxybenzylidene)-1H-benzo[d]imidazol-2-amine (5c):

Orange red solid; yield-93%; m.p – 227^{0}c

^{1}HNMR (400MHz, $CDCl_3$) δ in ppm:12.51(s,1H,NH), 9.35(s,1H,CH), 8.02-7.12(m,8H,Ar-H), 2.87(OC_2H_5). **^{13}CNMR (100MHz, $CDCl_3$)** δ in ppm: 164.8, 161.6, 156.4, 131.1, 128.1, 122.0, 118.8, 114.9,

110.4, 53.7, 20.7. **LCMS** (m/z):265.53. **Molecular formula**: $C_{16}H_{15}N_3O$. **Elemental analysis**: calculated: C-72.43, H-5.70, N-1584, O-6.03. Obtained:C-72.47, H-5.69, N-15.82, O-6.02.

5) N-(methoxybenzylidene)-1H-benzo[d]imidazol-2-amine (5d):

Orange red solid; yield-92%; m.p – 226^0c

^{1}HNMR (400MHz, $CDCl_3$) δ in ppm: 12.60(s,1H,NH), 9.35(s,1H,CH), 8.01-7.10(m,8H,Ar-H) & 3.72(s,3H,OMe). **^{13}CNMR (100MHz, $CDCl_3$)** δ in ppm: 165.2, 163.5, 155.9, 131.8, 128.6, 122.2, 118.9, 114.7, 110.9 & 55.45(OMe). **LCMS** (m/z):258.35. **Molecular formula**: $C_{15}H_{13}N_3O$. **Elemental analysis**: calculated: C-71.70, H-5.21, N-16.72, O-6.37. Obtained: C-71.75, H-5.20, N-16.70, O-6.35

6) N-(4-methylbenzylidene)-1H-benzo[d]imidazol-2-amine (5e):

Orange red solid; yield-91%; m.p – 225^0c

^{1}HNMR (400MHz, $CDCl_3$) δ in ppm:12.01(s,1H,NH), 9.39(s,1H.CH),7.90-7.12(m,8H,Ar-H) & 3.52(s,3H,Me). **^{13}CNMR (100MHz, $CDCl_3$)** δ in ppm: 164.9, 155.8, 143.7, 132.8, 130.0, 122.4, 118.7, 11.8 & 36 (CH_3). **LCMS** (m/z):235.08. **Molecular formula**: $C_{15}H_{13}N_3$. **Elemental analysis**: calculated: C-76.57, H-5.57, N-17.86. Obtained: C-76.59, H-5.56, N-17.85.

7) N-(4-N,N-diethylbenzylidene)-1H-benzo[d]imidazol-2-amine (5f):

Brick red solid; yield-92%; m.p – 232^0c

^{1}HNMR (400MHz, $CDCl_3$) δ in ppm: 12.51(s,1H,NH), 9.20(s,1H,CH), 7.67-7.00(m,9H,Ar-H), 3.43(CH_2), 1.28(CH_3). **^{13}CNMR (100MHz, $CDCl_3$)** δ in ppm: 159.1, 158.7, 147.9, 135.4, 127.8, 124.9, 123.1, 112.9, 110.6, 43.9, 12.6. **LCMS** (m/z): 292.18. **Molecular formula**: $C_{18}H_2ON_4$. **Elemental analysis**: Calculated: C-73.94, H-6.89, N-19.16. Obtained:73.96, H-6.88, N-19.15.

8) N-(4-N,N-dimethylbenzylidene)-1H-benzo[d]imidazol-2-amine (5g):

Brick red solid; yield-92%; m.p – 223^0c

^{1}HNMR (400MHz, $CDCl_3$) δ in ppm:12.43(s,1H,NH), 9.29(s,1H,CH), 7.68-6.90(m,8H,Ar-H), 3.07(s,6H,2CH_3). **^{13}CNMR (100MHz, $CDCl_3$)** δ in ppm: 160.5, 159.0, 152.8, 134.4, 128.1, 125.3, 122.9, 118.9, 111.2, 39.4.**LCMS** (m/z): 264.56. **Molecular formula**: $C_{16}H_{16}N_4$. **Elemental analysis**: Calculated: C-72.70, H-6.10, N-21.20. Obtained: C-72.72, H-6.09,N-21.19.

9) N-(4-aminobenzylidene)-1H-benzo[d]imidazol-2-amine (5h):

Orange red solid; yield-92%; m.p – 220^0c

^{1}HNMR (400MHz, $CDCl_3$) δ in ppm:12.28(s,1H,NH), 9.38(s,1H,CH), 7.87-6.86(m,8H,Ar-H),5.20(s,2H,NH2). **^{13}CNMR (100MHz, $CDCl_3$)** δ in ppm: 165.6, 156.4, 149.4, 136.7, 135.4, 133.1, 129.6, 129.4, 122.4, 118.9, 111.5. **LCMS** (m/z):236.46. **Molecular formula**: $C_{14}H_{12}N_4$. **Elemental analysis**: calculated: C71.17, H-5.12, N23.71.Obtained: 71.20, H-5.10, N-23.70.

10) N-(4-fluorobenzylidene)-1H-benzo[d]imidazol-2-amine (5i):

Orange red solid; yield-89%; m.p – 211^0c

^{1}HNMR (400MHz, $CDCl_3$) δ in ppm: 12.88(s,1H,NH), 9.51(s,1H,CH) & 8.10-7.20(m,8H,Ar-H). **^{13}CNMR (100MHz, $CDCl_3$)** δ in ppm: 165.2, 155.6, 137.9, 134.3, 131.8, 130.0, 122.6, 118.8 & 112.1.

LCMS (m/z):241.56(M+2). **Molecular formula**: $C_{14}H_{10}FN_3$.**Elemental analysis**: calculated: C-7.28, H-4.21, F-7.94, N-17.56. Obtained: C-70.32, H-4.20, F-7.92, N-17.55.

11) N-(4-chlorobenzylidene)-1H-benzo[d]imidazol-2-amine (5j):

Orange red solid; yield-89%; m.p – 250^0c

^{1}HNMR (400MHz, $CDCl_3$) δ in ppm: 12.82(S,1H,NH), 9.48(S,1H,CH) and 8.08-7.18(m,8H,Ar-H).**^{13}CNMR (100MHz, $CDCl_3$) δ** in ppm: 164.6, 155.7, 137.3, 133.9, 131.8, 129.4, 122.5, 117.9, & 112.1.**LCMS** (m/z): 255.39. **Molecular formula**: $C_{14}H_{10}ClN_3$ **. Elemental analysis**: calculated: C-65.76, H-3.94, Cl-13.86, N-16.43. Obtained: C-65.80, H-3.93, Cl-13.85,N-16.41.

12) N-(4-bromobenzylidene)-1H-benzo[d]imidazol-2-amine (5k):

Brick red solid; yield-92%; m.p – 252^0c

^{1}HNMR (400MHz, $CDCl_3$) δ in ppm: 12.56(s,1H,NH), 9.36(s,1H,CH), and 7.99-7.18(M,8H,Ar-H). **^{13}CNMR (100MHz, $CDCl_3$)** δ in ppm: 165.0, 155.3, 134.6, 132.1, 131.8, 126.8,122.7, 119.3, 112.0. **LCMS (m/z)**:298.95. **Molecular formula**: $C_{14}H_{10}BrN_3$. **Elemental analysis**: calculated: C-56.02,H-3.36,Br-26.62, N-14.00 . Obtained: C-56.05,H-3.35,Br-26.61, N-13.99

13) N-(4-cyanobenzylidene)-1H-benzo[d]imidazol-2-amine (5l):

Brick red solid; yield-90%; m.p – 215^0c

^{1}HNMR (400MHz, $CDCl_3$) δ in ppm: 12.6(s,1H,NH), 9.28(s,1H,CH), 8.08-7.05(m,8H,Ar-H).**^{13}CNMR (100MHz, $CDCl_3$)** δ in ppm: 160.0, 159.1, 140.7, 135.7, 132.3, 126.3, 123.0, 118.6, 114.9, 112.2. **LCMS** (m/z):246.50.**Molecular formula**: $C_{15}H_{10}N_4$**. Elemental analysis**: calculated: C-73.16, H-4.09, N-22.75. Obtained: C-73.20, H-4.07, N-22.73.

14) N-(4-carboxybenzylidene)-1H-benzo[d]imidazol-2-amine (5m):

Orange red solid; yield-90%; m.p – 270^0c

^{1}HNMR (400MHz, $CDCl_3$) δ in ppm: 12.44(s,1H,NH), 12.19(s,1H,COOH), 9.25(s,1H,CH), 8.38-8.04(m,4H, Ar-H), 7.64-7.22(m,4H,Ar-H). **^{13}CNMR (100MHz, $CDCl_3$)** δ in ppm: 168.5, 160.7, 159.0, 140.7, 135.7, 132.6, 129.9, 128.3, 123.5, 122.4. **LCMS** (m/z): 267.58. **Molecular formula**: $C_{15}H_{11}N_3O_2$. **Elemental analysis**: Calculated:C-67.92, 4.18, N-15.84, O-12.06. Obtained: C-67.95, H-4.17,N-15.83,O-12.05.

15) N-(4-carbaldehydebenzylidene)-1H-benzo[d]imidazol-2-amine (5n):

Brick red solid; yield-90%; m.p – 250^0c

^{1}HNMR (400MHz, $CDCl_3$) δ in ppm: 12.31(s,1H,NH), 9.80(s,1H,CHO), 9.29(s,1H,CH), 8.07-8.01(m,4H,Ar-H), 7.65-7.16(m,4H,Ar-H). **^{13}CNMR (100MHz, $CDCl_3$)** δ in ppm: 190.2, 159.2, 158.7, 139.5, 137.5, 134.5, 129.8, 129.1, 122.8, 11.6. **LCMS** (m/z): 249.17. **Molecular formula**:$C_{15}H_{11}N_3O$. **Elemental analysis**: Calculated:C-72.28,H-4.45,N-16.86,O-6.42. Obtained: C-72.32,H-4.44,N-16.85,O-6.40.

16) N-(4-nitrobenzylidene)-1H-benzo[d]imidazol-2-amine (5O):

Brick red solid; yield-90%; m.p – 265^0c

^{1}HNMR (400MHz, $CDCl_3$) δ in ppm:12.83(s,1H,NH), 9.55(s,1H,CH), 8.35-8.16(m,4H,Ar-H) & 7.65-7.20(m,4H,Ar-H). **^{13}CNMR (100MHz, $CDCl_3$)** δ in ppm:164.01, 155.6, 149.9, 140.9, 130.5, 124.2, 118.9 & 112.0. **LCMS** (m/z):265.98. **Molecular formula**: $C_{14}H_{10}N_3O_2$. **Elemental analysis**: calculated: C-63.15, H-3.79, N-21.04, O-12.02. Obtained: C-63.18, H-3.78, N-21.03, O-12.01.

Biological Activity:

Anti Bacterial Activity:

The anti bacterial activities of newly synthesized compounds are examined against 5 pathogenic bacteria strains. The result of antibiotic activity studies for the compounds. The gram negative bacteria screened were Escerichia Coli NCCS 2065 and Pseudomonas aeruginosa NCS 2200. The gram positive bacteria screened were S-aureas NCCS 2079 and Bacillus NCCS 2106.

The target compounds were used at the concentration of 250 µglml and 500 µglml using DMSO as a solvent the amoxylin 10 µglml disc were used as a standard. The rest of the compounds were found to be moderate active against the tested micro organism.

Anti Fungal Activity:

Anti fungal activity of new synthesized compounds were examined by disc diffusion method against the organism of aspergillusniger NCCS 1196 and Candida ablicans NCCS 3471. Compared were treated at the concentrations of 500 µglml and 1000 µglml using DMSO as a solvent. The standard drug was used as ketoconazol 50 µglml against both organisms.

Result & Discussion:

All newly titled compounds can be synthesised at room temperature and also colored product. In this reaction, we got the percentage of the yeild 89-94%.These titled compounds can be obtained, we used to organic acid catalyst is camphor sulphonic acid. This organic catalyst can be used to develop the reaction conditions and reaction is completed maximum 3 hours.The rate of reaction enhanced by using this catalyst.The catalyst used due to emerging as a powerful nature, inexpensive, ecofriendly,readily available,econmical and water soluble compound.We used various P-substituted aromatic aldehydes such as electron donating group of aldehydes and electron withdrawing group of aldehydes.Hence ,electron donating group of aldehydes react with 2-aminobenzimidazole to give more yield and rate of reaction increases and completion of the reaction before 30 min compared to that of electron withdrawing group of aldehyde react with 2-aminobenzimidazole. We are using camphor sulphonic acid , the reaction workup is easily. (**Scheme-I).**

All the synthesized compounds were screened anti bacterial activity as well as antifungal. The electron withdrawing group of compounds (5o) didn't show any active potento. Other hand electron withdrawing group of compounds exhibited poor active potento compared with electron donating groups. All halogen compounds exhibit excellent potento activity. The compound which possess electron donating group shows moderate activity as shown in Table-I.

Compound Code	*Zone of inhibition in (mm)					
	Bacteria				Fungi	
	S.aureus	E.coli	S. typhi	B.substills	A. niger	C. albicans
5a	10	11	06	04	09	07
5b	21	18	12	21	06	08
5c	22	18	11	21	06	09
5d	18	20	09	20	17	21
5e	16	10	11	13	09	07
5f	21	18	12	19	11	09
5g	22	17	12	20	05	08
5h	16	17	10	12	10	09
5i	20	24	09	20	16	17
5j	23	20	14	16	15	12
5k	24	18	12	18	16	11
5l	15	19	07	10	15	10
5m	14	10	09	13	10	09
5n	15	11	09	12	08	05
5o	0	0	0	0	0	0
Amoxycilline	30	35	31	28	NA	NA
Ketoconazole	NA	NA	NA	NA	20	25
DMSO	---	----	---	---	---	---

Table-I Antimicrobial activity screening activity synthesized scaffold :

Conclusion :

The reaction condition carriedout at room temerature for all the newly synthesised compounds . The yield of the titled compounds obtained from 89-94%.The compound possesses electron donating group gives maximum yeild than that of the compound possesses electron withdrawing group. The rate of reaction developed by using camphor sulphonic acid catalyst.All the compounds tested by anti microbial activity against gram positive ,gram negitive and fungal.The compound having electron donating group showed excelent active potential .Other wise the compounds having halogens which showed better active potential than that of the electron with drwing group

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CONFLICT OF INTEREST:

We declare that we have no conflict of interest

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