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An Improved Synthesis, Characterization and Bioevalution of Schiff Base Containing Benzimidazole Moiety Catalyzed by Methane Sulfonic Acid

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ABSTRACT

In present report an improved process for the synthesis for some novel Schiff bases from 2-amino benzimidazole with 5-substituted indole-3-carbaldehyde using methane sulfonic acid in free solvent at room temperature. The intermediate moiety (2-aminobenzimidazol) can be synthesized from o-phenyl diamine with cyanobromide in the presence of acid medium. All the newly synthesized compounds were confirmed by the advanced spectroscopic data (^{1}H-NMR, ^{13}C-NMR and LC-MS) and also structural determination were calculated by elemental analysis. In addition to all compounds were screened by their biological activities.

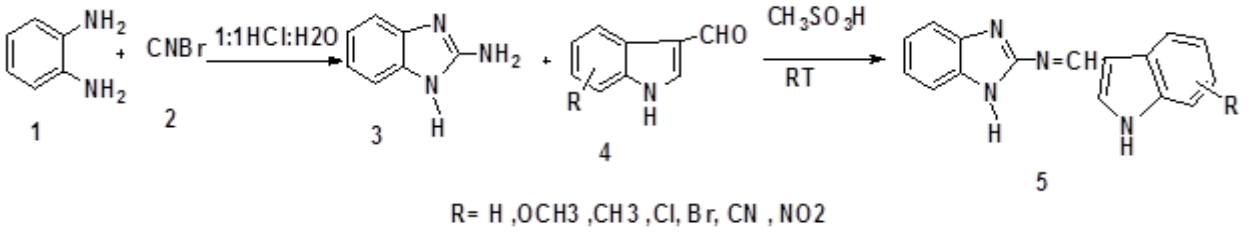
Keywords: O-phenyldiamine, CNBr, 2-Aminobenzimidazole, 5-Substituted indole-3-carbaldehydes, Methane sulfonic acid, Schiff bases, Bioevalution

INTRODUCTION

Schiff bases derived from aromatic primary amines and aldehydes which are also important class of organic compounds. Mostly, large area of synthetic organic compounds possess imines group and it also very important class of organic compounds because of their applications in various 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 biological properties. The compound possesses five membered heterocyclic ring with two nitrogen atoms. The benzimidazole is an important class of their significant biological properties against several virus like influenza, HIV, Herpus (HSV-1) and Epstein-Barr virus [1-3] and benzimidazole moiety present in Schiff bases which are show anticancer and antiproliferative properties. Benzimidazole is an intermediate moiety which is being explored in the pharmaceutical industries and the substituted benzimidazole dersivatives have also been found in the diverse therapeutic applications [4,5]. Because of 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 privileged structure in medicinal chemistry [9], encompassing a diverse range of biological activities including antimicrobial [10], antioxidant, antiviral, antihypertensive, antiprotozoal, anti-inflammatory and molluscicidal agents. In addition to benzimidazole moiety showed anticancer activity against DNA topoisomerase and colon cancer cell lines.

Many synthetic methods have been reported for the synthesis of Schiff bases. Now-a-days the numerous catalysts are used in the synthesis of Schiff bases like inorganic salts and zeolites. In organic synthesis has been attracted to condensed attention. Nowadays, they are used more importance such as their easy handling, low cost and being environmental safe. Schiff bases have been reported possess antimicrobial properties. Schiff bases are characterized by the –N=CH-(imines) group which is an important for elucidating and racemization reactions in biological systems and are known to have biological activities such as antimicrobial [11], antifungal [12], antitumor [13] and herbicidal [14] activities. Indole derivatives found to possess antibacterial, anticonvulsant [15] and antihypertensive activity. These observations led to the conception that Schiff bases of indole-3-aldehyde would possess antimicrobial properties.

In present investigation, we synthesized Schiff base from 2-amino benzimidazole and different 5-substituted indole -3-carbaldehydes in the presence methane sulphonic acid as catalyst in solvent free condition. We aimed to the synthesis of new Schiffs bases using Organicaci (methane sulphonic acid) catalyst due to easy to workup, 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).



1 2 3 4 5

Scheme 1: Synthetic protocol of the compounds

METHODS AND MATERIALS

Experimental

All the synthetic grade, analytical grade reagents as well as chemicals were procured from Meric and Sigma Aldrich chemicals. The melting point of the all newly synthesized compounds were find out using an electro thermal digital apparatus and uncorrected. ^{1}H-NMR, ^{13}C-NMR and spectral data were recorded on a Bruker (400 MHz, 100 MHz) spectrometer. Chemical shift (ppm) was referred to the internal standard Tetramethylsilane (TMS). All the synthesized compounds find out the molecular weight using LC-MS. The reaction was monitored by thin layer chromatography and the purity of the compound separated with using column chromatography.

General procedure for the synthesis of 2-aminobenzimidazole

A mixture of O-phenyl diamine (1, 1 equivalent) and cyanobromide (2, 1 equivalent) are introduced 100 ml RB flask and addition of 1:1 HCl: H_2O to the above mixture. The reaction carried out on magnetic stirrer with reflux condition in 5 h. The reaction was checked with using TLC (Ethyl acetate: Hexane). 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 final compound was obtained.

Synthesis of 2-aminobenzimidazole (3)

Orange red color, yield-91%: ^{1}H-NMR (400 MHz, $CDCl_3$) 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}C-NMR (100 MHz, $CDCl_3$) δ in ppm: 157.0, 135.92, 122.87, 115.1. LC-MS (m/z): 132.95. Molecular formula: $C_7H_7N_3$. Elemental analysis: Calculated: 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

2-aminobenimidazole (3, 1 equivalent) introduced in 100 ml RB flask and 5-substituted indole 3-carbaldehyde (4, 1 equivalent) added to the RB flask. A catalytic amount of methane sulfonic acid added to the above mixture. The reaction carried on magnetic stirrer at RT with solvent free conditions. The reaction was monitored with TLC after all the reactants are consumed during the reaction time and after completion of the reaction, cold water added to the product. The product can be washed with saturated anhydride sodium carbonate solution and solid product was separated out. We desired compound can be re-crystallized from ethanol.

N-((1-H-indole-3-yl)methylene)-1H-benzo[d]imidazol-2-amine (5a)

White solid; yield-85%: ^{1}H-NMR (400MHz, $CDCl_3$) δ in ppm: 11.22 (s, 1H, NH-indole), 8.81 (s, 1H, CH), 8.23 (d, j=8.4Hz, 1H), 7.61-7.07 (m, 8H, A-r H), 4.92 (s, 1H, imidazole-NH). ^{13}C-NMR (100MHz, $CDCl_3$) δ in ppm: 161.1, 158.9, 136.8, 135.1, 130.2, 126.4, 122.9, 122.6, 121.5, 120.7, 119.6, 112.0, 110.7, 101.7. LC-MS (m/z): 260.42. Molecular formula: $C_{16}H_{12}N_4$. Elemental analysis: Calculated: C-73.83, H-4.55, N-21.52. Obtained: C-73.85, H-4.54, N-21.51.

N-((5-methoxy-1H-indole-3-yl)methelene-1H-benzo[d]imidazol-2-amine (5b)

White solid; yield-87%: ^{1}H-NMR (400MHz, $CDCl_3$) δ in ppm: 11.14 (s, 1H, NH-indole), 8.53 (s, 1H, CH), 7.75 (s, 1H, -Ar-H), 7.59-7.12 (m, 6H, Ar-H), 6.72 (b, J=8.4 H, 1H), 4.82 (s, 1H, NH-imidazole), 3.77 (s, 3H, -OCH_3. ^{13}C-NMR (100MHz, $CDCl_3$) δ in ppm: 159.7, 158.8, 153.9, 135.3, 130.4, 129.5, 127.3, 123.2, 123.1, 12.0, 112.2, 112.1, 111.9, 104.2, 101.7, 55.9. LC-MS (m/z):290.10. Molecular formula: $C_{17}H_{14}N_4O$, Elemental analysis: calculated: C-70.33, H-4.86, N-19.30, 0-5.51. Obtained: C-70.37, H-4.85, N-19.28, O-5.50.

N-((5-methyl-1H-indole-3-yl)methylene)-1H-benzo[d]imidazol-2-amine (5c)

Pale red solid; yield-89: ^{1}H-NMR (400MHz, $CDCl_3$) δ in ppm: 1122 (s, 1H, NH-indole), 8.75 (s, 1H, CH) (s, 1H, CH), 7.98 (s, 1H, Ar-H), 7.61-7.17 (m, 6H, Ar-H), 7.10 (d, J=7.6Hz, 1H), 4.49 (s, 1H, NH-imidazole), 2.32 (s, 3H, OCH_3). ^{13}C-NMR (100MHz, $CDCl_3$) δ in ppm: 160.2, 158.7, 134.8, 133.9, 130.3, 128.8, 126.3, 123.2, 123.1, 120.7, 120.2, 112.5, 112.3, 110.3, 101.9, 21.9. LC-MS (m/z): 274.33. Molecular formula: $C_{17}H_{14}N_4$. Elemental analysis: calculated: C-74.43, H-5.14, N-20.43. Obtained: C-74.46, H-5.13, N-20.41.

N-((5-chloro-1H-indole-3-yl)methylene)-1H-benzo[d]imidazol-2-amine (5d)

Pale Orange colour solid; yield-88%: ^{1}H-NMR (400MHz, $CDCl_3$) δ in ppm: 11.31 (s, 1H, NH indole), 8.77 (s, 1H, CH), 7.61-7.21 (m, 8H, Ar-H), 4.92(s, 1H, imidazole-NH). ^{13}C-NMR (100MHz, $CDCl_3$) δ in ppm: 160.1, 158.9, 135.6, 135.1, 130.8, 127.8, 125.3, 123.4, 123.2, 122.5, 121.6, 114.2, 112.3, 112.1, 101.9. LC-MS (m/z): 294.74. Molecular formula: $C_{16}H_{11}ClN_4$. Elemental analysis: calculated: C-65.20, H-3.76, Cl-12.03, N-19.01. Obtained: C-65.25, H-3.75, Cl-12.00, N-19.00.

N-((5-bromo-1H-imidazol-3-yl)methylene)-1H-benzo[d]imidazol-2-amine (5e)

Orange red solid; yield-86%: ^{1}H-NMR (400MHz, $CDCl_3$) δ in ppm: 11.39 (s, 1H, NH-indole), 8.67 (s, 1H.CH), 7.69 (s, 1H, Ar-H), 7.61-7.13 (m, 7H, Ar-H), 5.09 (s, 1H, NH-imidazol). ^{13}C-NMR (100MHz, $CDCl_3$) δ in ppm: 160.2, 158.8, 136.3, 135.5, 129.9, 128.3, 126.8, 124.8, 123.2, 123.1, 113.6, 113.1, 112.2, 101.7. LCMS (m/z): 339.20. Molecular formula: $C_{16}H_{11}BrN_4$. Elemental analysis: calculated: C-56.56, H-3.27, Br-23.56, N-16.52. Obtained: C-56.60, H-3.26, Br-23.54, N-16.51.

3-((1H-benzo[d]imidazol-2-ylimino) methylene) -1H-indole-5-carbonitrile (5f)

pale red solid; yield-87%: ^{1}H-NMR (400MHz, $CDCl_3$) δ in ppm: 11.35 (s, 1H, NH-indole), 8.81 (s, 1H, CH), 7.92 (s, 1H, Ar-H), 7.73-7.21 (m, 7H, Ar-H), 5.18 (s, 1H, NH-imidazole. ^{13}C-NMR (100MHz, $CDCl_3$) δ in ppm: 160.1, 158.5, 14.1, 135.8, 130.9, 126.8, 125.7, 123.6, 123.2, 122.9, 118.4, 112.3, 102.5, 101.8. LC-MS (m/z): 285.30. Molecular formula: $C_{17}H_{11}N_5$. Elemental analysis: Calculated: C-71.57, H-3.84, N-24.55. Obtained: C-71.60, H-3.83, N-24.53.

N-((5-nitro-1H-indole-3-yl)methylene)-1H-benzo[d]imidazol-2-amine (5g)

Brick red solid; yield-87: ^{1}H-NMR (400MHz, $CDCl_3$) δ in ppm: 11.35 (s, 1H, NH), 8.89 (s, 1H, CH), 8.60 (s, 1H, Ar-H), 8.06 (d, J=8.4Hz, 1H), 7.79-7.22 (m, 6H, Ar-H), 5.10 (s, 1H, NH-imidazole). ^{13}C-NMR (100MHz, $CDCl_3$) δ in ppm: 160.2, 159.5, 143.3, 135.4, 132.4, 130.1, 127.4, 126.8, 123.2, 123.1, 112.3, 112.2, 111.8, 101.2. LC-MS (m/z): 309.30. Molecular formula: $C_{16}H_{11}N_5O_2$. Elemental analysis: Calculated: C-62.95, H-3.63, N-22.94, O-10.48. Obtained: C-62.98, H-3.62, N-22.93, O-10.47.

Biological activity

Antibacterial activity

Preliminary investigation of anti-microbial activity of newly synthesized compounds (5a-5g) were examined by cup plate drugs biological method, various pathogenic strains Viz. *Staphylococcus aureus*, *Bacillus substills* (Gram-positive), *Salmonella typhi* and *Escherichia coli* (Gram-negative) were employed using standard drug gentamycin for antibacterial growth respectively.

Nutrient Agar Medium (NAM) is used to test for the antibacterial activity of newly synthesized compound; NAM was prepared with beef extract (4 g), peptone (7 g), NaCl (5 g), agar-agar (20 g) 1000 ml distilled water and pH was maintained to 7.0. NMA was sterilized in an auto clave at 121°C, 15 lbs pressure for 30 min. After sterilization 20 ml of NAM was poured into petro dish as in a laminar air flow and allowed to solidify. After solidification of NMA was in osculated with 100 µl of derived bacteria. Compounds was dissolved in Dimethyl Sulfoxide (DMSO) with a concentration of 100 ppm, 250 pm and Whatman No.1 filter paper disks were placed in the solution and kept for 1 min. After drying the disks were placed as NAM inoculated with bacteria and NAM plates were incubated at 37°C. Zones of inhibition were measured after 24 h compared with ciprofloxacin.

The antibacterial activities of newly synthesized compounds are examined against 4 pathogenic bacteria strains. The result of antibiotic activity studies for the compounds. The gram bacteria screened were *E. coli, S. aureus, S. typhi* and *B. subtilis.* The target compounds were used at the concentration of 250 µg/ml and 500 µg/ml using DMSO as a solvent the gentamycin 22 µg/ml disc were used as a standard. Each test carried out three times and taken average value.

RESULTS AND DISCUSSION

All newly synthesized Schiff bases can be obtained at room temperature. These target compounds can be obtained, we used to organic acid catalyst methane sulfonic acid. This organic catalyst can be used to develop the reaction conditions and reaction is completed maximum 3 h. The rate of reaction increased by using this catalyst and we used various 5-substituted indole-3-carbaldehydes such as electron donating group of aldehydes and electron withdrawing group of aldehydes. Consequently electron donating group of aldehydes react with 2-aminobenzimidazole to obtained 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 were used methane sulfonic acid because the easy to work up of the compound, improved the yield and the reaction time can be decreased and enhanced by reaction conditions.

All the newly synthesized compounds were screened by antibacterial activity. In the present study both electron withdrawing group of compounds as well as electron donating group of compounds and we observe activity potential of compounds. The activity potential of electro withdrawing group of compounds less than that of electron donating group of compounds but halogen substituted compounds (5d and 5e) exhibit high activity potential. Electron withdrawing group of compounds (5f and 5g) exhibit low activity potential. Electron donating group of compounds (5b and 5c) exhibit moderate activity. The inhibition zone of all the synthesized compounds summarized in Table 1.

Table 1: Antimicrobial activity screening activity synthesized scaffold

Compound code	Bacteria			
	Staphylococcus aureus	***Escheriea coli***	***Salmonella typhi***	***Bacillus subtilis***
5a	15	11	9	12
5b	16	10	11	13
5c	15	11	12	13
5d	16	17	10	14
5e	15	17	10	12
5f	14	10	9	11
5g	10	9	6	4
5h	16	17	10	12
Gentamycin	22	22	22	22
DMSO	-	-	-	-

CONCLUSION

Primarily based of the high-quality yields, short reaction time, easy work-up, solvent-free facile and environment greener reaction, it can be concluded that methane sulfonic acid is a very useful catalyst for the synthesis of Schiff bases.

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