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SYNTHESIS AND STUDY OF DERIVATIVES OF IMINES AND EXPLORED BIOEVALUATION

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ABSTRACT

A great deal of work has been done for the synthesis of some novel group of imines derivatives (Schiff base) from 2-aminobenzimidazole with heteroaromatic aldehydes by catalytic amount of methane sulfonic acid in ethanol. The intermediate moiety (benzimidazole) can be synthesized from o-phenyldiamine with cyanobromide in presence of acid medium all the titled compounds were evaluated based on advanced spectroscopic data (^{1}HNMR, ^{13}CNMR, LCMS) and Structural determination was calculated determined by elemental analysis. Besides, we examined biological properties about the synthesized compounds.

KEYWORDS

O-phenyldiamine, Cynobromide, 2-aminobenzimidazole, Heteroaromatic aldehydes, Schiff base, Methane sulfonic acid and Bioevaluation.

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INTRODUCTON

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.

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. 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 in the pharmaceutical industries and the substituted benzimidazole derivatives 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 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].

Several 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. Nowdays, they are used more importance such as their easy handling, low range 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]. Low cost and being environmental safe.

In this investigation, we synthesized Schiff base from 2-amino benzimidazole and various heteroaromatic aldehyde using methane sulphonic acid catalyst. We aimed to the synthesis of new schiffs bases using organicaci(methane 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.

METHODS ANDMATERIAL

Experimental

All the synthetic grade and analytical chemicals were purchased from merck chemicals. The melting point of the titled compounds were determined by with an electro thermal digital apparatus and uncorrected. The structure of the compound can be evaluated by advanced spectroscopic data(^{1}HNMR, ^{13}CNMR, LCMS) and Spectral data were recorded on Bruker spectrometer(400MHz, 100MHz). Chemical schifts (ppm) were reffered to the internal standard tetramethylsilanes (TMS). All the synthesized compounds determined the molecular weight using LCMS spectrometry and the reaction was monitored by TLC.

General procedure for the synthesis of 2-aminobenzimidazole

A mixture of o-phenyldiamine(1,1equiv) and cyanobromide (2,1equiv) are introduced 100 ml RB flask and addition of an (1:1), HCl:H_2O to the above mixture. The reaction done on the magnetic stirrer with reflux. The reaction mixture was checked by TLC(Ethylacetate:Hexane, 4:6). After completion of the reaction, the mixed product extracted with ethylacetate and washed with standard solution of anhydrous sodium bicarbonate. The intermediate compound can be separated by using column chromatography(4:6, ethylacetate: n-hexane). The final compound was obtained.

Synthesis of 2-aminobenzimidazole (3)

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

^{1}HNMR (400MHz, $CDCl_3$) δ in ppm:12.53 (s,1H,NH), 7.23-7.11(m,4H,A-r H), 6.48(s,2H,NH_2). ^{13}CNMR (100MHz, $CDCl_3$) δ in ppm:157.9, 137.3, 122.8, 115.5. 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 derivatives of imine group

2-aminobenzimidazole(3,1equiv) and heteroaromatic aldehydes (4, 1.2 equiv) dissolved in ethanol in RB flask. A catalytic amount of methane sulfonic acid was added to the solution present in RB flask. The reaction was carried on magnetic stirrer alonged with reflux. The reaction was monitored after all the reactants are consumed during the reaction time. After completion of the reaction, evaporate the ethanol from the reaction mixture. After the expel the ethanol, crude extracted with ethyl acetate and washed saturated brine solution, solid product separated out by using column chromatography and we desired compound recrystalized from ethanol.

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

Brickred solid; yield-91%; m.p – 215^0c

^{1}HNMR (400MHz, $CDCl_3$)δ in ppm:11.42 (s,1H,NH),8.212 (d,J=8.0Hz,1H,indoleAr-H),7.59 (s,1H,=CH),7.57-7.01m,8H,Ar-H),4.85(s,1H,NH). ^{13}CNMR (100MHz, $CDCl_3$) δ in ppm: 161.2,158.8,135.4,130.1,126.2,122.9,121.8,121.3,119.4,112.0,110.7,102.1.LCMS (m/z):260.10. Molecular formula:$C16_{14}H_{11}N_3$. Elemental analysis: Caliculated:C-73.83,H-4.65,N-21.52 Obtained: C-73.86, H-4.64,N-21.50

N-((Furan -2-yi) methylene)-1H-benzo[d]imidazol-2-amine (5b):

Pale yellow solid; yield-90%; m.p – 219^0c

^{1}HNMR (400MHz, $CDCl_3$) δ in ppm:7.76(d,J=8.4Hz,1H,furan), 7.59(s,1H,=CH),7.58-7.12(m,4H,Ar-H),6.88(d,J=7.6Hz,furan), 6.51(t,2H,furan), 4.92(s,1H,NH imidazol). ^{13}CNMR (100MHz, $CDCl_3$) δ in ppm: 159.3, 149.6, 145.4, 144.1, 135.3, 123.2, 118.5, 112.7, 111.9. LCMS (m/z):212.41. Molecular formula: $C_{12}H_9N_3O$. Elemental analysis: calculated: C-68.74, H-4.29, N-19.89, 0-7.57. Obtained:C-68.78, H-4.28, N-19.87, O-7.56.

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

Pale Orange solid; yield-88%;

^{1}HNMR (400MHz, $CDCl_3$) δ in ppm:11.27(s,1H,NH pyrrol), 7.62 (s,1H,=CH), 7.57-7.19(m,4H,Ar-H), 6.95(d,J=8.4,1H pyrrol), 6.55(d, J=8.4Hz,1H, pyrrol), 6.25(t, J=7.6, 2H pyrrol), 4.98(s,1H,NH imidazol). ^{13}CNMR (100MHz, $CDCl_3$) δ in ppm: 158.5, 152.4, 135.2, 128.7, 124.5, 123.1, 118.8, 112.4, 111.1. LCMS (m/z):210.39. Molecular formula: $C_{12}H_{10}N_4$. Elemental analysis: calculated: C-68.56, H-4.79, N-26.65. Obtained:C-68.60, H-4.78, N-26.62.

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

White solid; yield-85%;

^{1}HNMR (400MHz, $CDCl_3$) δ in ppm: 7.76(d,J=7.6Hz,1H,thiophene-H), 7.68(d,J=8.4Hz,1H,thiophene-H), 7.62(s,1H,=CH), 7.53-7.16(m,5H, Ar-H), 4.89(s,1H,imidazol ring). ^{13}CNMR (100MHz, $CDCl_3$) δ in ppm: 159.1, 150.9, 143.1, 129.3, 128.7, 127.4, 123.2, 112.3. LCMS (m/z):226.92. Molecular formula: $C_{12}H_9N_3S$. Elemental analysis: calculated: C-63.41, H-3.99, N-18.49, S-14.11. Obtained: C-63.45, H-3.98, N-18.47, S-14.10.

N-(P yridine-2-methylene)-1H-benzo[d]imidazol-2-amine (5e)

Brown solid; yield-87%;

^{1}HNMR (400MHz, $CDCl_3$) δ in ppm:8.65(s, J=8.Hz, 1H, pyridine-H) 7.85-7.74(m,3H,pyridine ring), 7.67(s,1H,=CH), 7.61-7.21(m,4H,Ar-H), 4.82(s,1H, imidazol ring). ^{13}CNMR (1000MHz, $CDCl_3$) δ in ppm: 158.6, 152.3, 148.7, 147.6, 140.2, 136.4, 126.1, 122.8, 112.7. LCMS (m/z):222.38. Molecular formula: $C_{13}H_{10}N_4$. Elemental analysis: calculated: C-70.26, H-4.54, N-25.21. Obtained: C-70.30, H-4.53, N-25.18.

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 microorganism.

Anti-Fungal Activity

Anti-fungal activity of new synthesized compounds were examined by disc diffusion method against the organism of *aspergillus niger* 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.

RESULTS AND DISCUSSION

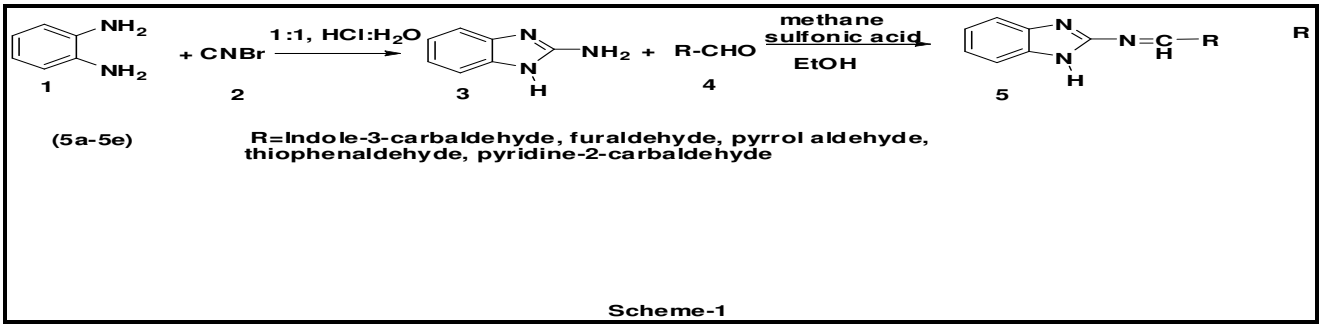
All newly synthesized compounds can be obtained at room temperature. These target compounds can be obtained, we used to organic acid catalyst is PTS. This organic catalyst can be used to develop the reaction conditions and reaction is completed maximum 3 hours.

The rate of reaction increased by using this catalyst. We used various heteroaromatic carb aldehydes such as indole-3-carbaldehyde,furan aldehyde, pyrrole aldehyde, thiophenal, pyridine -2-carbaldehyde. Consequently nitrogen containing five member heterocyclic compound such as furan and pyrrole 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 thiophene aldehyde and pyridine -2-carbaldehydereact with 2-aminobenzimidazole. We are using methane sulfonic acid, the reaction workup is easily. (Scheme No.1).

All the synthesized compounds were examined anti-bacterial activity as well as antifungal. Indole -3-carbaldehyd showed poor activity. Furan 2-carbaldehyde and pyrrole aldehyde showed good activity whereas thophenal and pyridine -2-carbaldehyde showed moderate activity as shown in Table No.1.

Table No.1: Antimicrobial activity screening activity synthesized scaffold

S.No	Compound Code	*Zone of inhibition in (mm)					
		Bacteria				Fungi	
		S.aureus	*E.coli*	*S. typhi*	*B.substills*	*A. niger*	*C. albicans*
1	5a	10	11	06	04	09	07
2	5b	21	18	12	21	06	08
3	5c	22	18	11	21	06	09
4	5d	18	20	09	20	17	21
5	5e	16	10	11	13	09	07
6	Amoxicillin	30	35	31	28	NA	NA
7	Ketoconazole	NA	NA	NA	NA	20	25
8	DMSO	---	----	---	---	---	---



Scheme No.1: Synthetic protocol of the compounds

CONCLUSION

A great deal of work has been done for the synthesis of some novel group of imines derivatives (Schiff base) from 2-aminobenzimidazole with heteroaromatic aldehydes by catalytic amount of methane sulfonic acid in ethanol. 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.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

BIBLIOGRAPHY

1. Tamm I, Seghal P B.Halobenzimidazole Ribosides and RNA Synthesis of Cells and Viruses,*Adv. Virus*. Res,22, 1978,187-258.
2. Tamm I.Inhibition of Influenza and Mumps Virus Multiplication by 4,5,6- (or 5,6,7-) Trichloro-1-β-D-Ribofuranosylbenzimidazole, *Science,* 120(3125), 1954, 847-848.
3. Ramla M M, Omar A M, Tokudo H, El-Diwoni I H.Synthesis and inhibitory activity of new benzimidazole derivatives against Burkitt's lymphoma promotion, *Bioorg. Med. Chem*, 15(19), 2007 6489-6496.
4. Lu J, Yangf B and Bai Y. Microwave irradiation synthesis of 2-substituted benzimidazoles using ppa as a catalyst under solvent-free conditions, *Synthetic. Communm,* 32(24), 2002, 3703-3709.
5. Velyk J, Baliharova V, Fink-Gremmels J, Bull S, Lamka J and Skalova L.Benzimidazole drugs and modulation of biotransformation enzynesm Res*, Veter. Sci*, 76(2), 2004, 95-108.
6. Liu JF, Lee J, Dalton AM, Bi G, Yu L, Baldino CM,McElory E and Brown M. Microwave-assisted one-pot synthesis of 2,3-disubstituted 3H-quinazolin-4-ones, *Tet. Lett,* 46(8), 2005, 1241-1244.
7. Liu JF, Wilson CFJ, Ye P, Sprague K, Sargent K, Si Y, Beletski G, Yohannes D and Ng S C. Privileged structure-based quinazolinone natural product-templated libraries; Identification of novel tubulin polymerization inhibitors*, Blorg. Med. Chem. Lett*, 16(3), 2006, 686-690.
8. Liu JF, Kaselj M, Isome Y, Ye P, Sargent K, Sprague K, Cherrak D, Wilson CJ, Si Y, Yohannes D and Ng S C. Design and Synthesis of a Quinazolinone Natural Product-Templated Library with Cytotoxic Activity, *J, Comb. Chem*, 8(1), 2006, 7-10.
9. Evans BE, Rittle KE, Bock M G, Dipardo RM, Freidinger RM, Whittel WL, Lundell GF, Veber DF, Anderson PS, Chang RSL, Lotti VJ, Cerino DJ, Chen TV, Kling P J and Hirshfield J.Methods for drug discovery: development of potent, selective, orally effective cholecystokinin antagonists, *J. Med. Chem*, 31(12), 1988, 2235-2246.
10. Gker H, Kus C, Boykin D W, Yildiz S and Altanlar N. Synthesis of some new 2-substituted 1H-benzimidazole-5-carbonitrile and their potent activity against candida species, *Bioorg. Med. Chem*, 10(8), 2002, 2589-2596.
11. Ozden S, Tabey D, Yildiz S and Goker H. Synthesis and potent anti-microbial activity of some methyl or ethyl 1H-benzimidazole-5-carboxylate derivatives carrying amide or amidine groups, *Bioorg. Med. Chem*, 13(5), 2005, 1587-1597.
12. Nofal ZM, Fahmy HH and Mohamed H S. Synthesis and antimicrobial activity of new substituted anilinobenzimidazoles, *Arch. Pharm. Res*, 25(3), 2002, 250-257.
13. Kus, Ayhan-Kilcigil G, Eke B C and Iscan M. Synthesis and antioxidant activities of some novel benzimidazole derivatives on lipid

peroxidation on the rat liver, *Arch. Pharm.* Res, 27(2), 2004, 156-163.

14. Porcari AR, Devivar RV, Kucera LS, Drach JC and Townsend L B. Design, synthesis, and antiviral evaluations of 1-(substituted benzyl)-2-substituted-5, 6-dichlorobensimidazoles as nonnucleoside analogues of 2,5,6-trichloro-1-(beta-Dribofuranosyl)benzimidazole*, J. Med. Chem*, 41(8), 1998, 1252-1262.
15. Tewari A K and Mishra A. Synthesis and antiviral activities of N-substituted-2-substituted-benzimidazole derivatives*, Ind. J. Chem.* Sect, 45B, 2006, 489-493.
16. Achar KS, Hosamani KM and Seetharam H R.*In-vivo* analgesic and anti-inflammatory activities of newly synthesized benzimidazole derivatives, *Eur. J. Med. Chem,* 45(5), 2010, 2048-2054.
17. Nofal ZM, Fahmy HH and Mohamed H S. Synthe3sis, antimicrobial and moluscicidal activities of new benzimidazole derivatives, *Arch. Pharm.* Res, 25(1), 2001,28-38.
18. Selcen AA, Sevil Z, Istvan Z, Gunes C, Borbala R, Semih GH and Zeki T.Biological activity of bis-benzimidazole derivatives on DNA topoisomerase I and Hela, MCF7 and A431 cells*, J. Enz. Inhib. Med. Chem*, 24(3), 2009, 844-849.
19. Alper S, Arpaci OT, Aki E S and Yalcin I. Some new bi-and ter-benzimidazole derivatives as topoisomerase Inhibitors, *Farmac*o, 58(7), 2003, 497-507.
20. Abdel-Aziz HA, Tamer S, Saleh TS and El-Zahabi H A. Facile Synthesis and *InVitro* Antitumor Activity of Some Pyrazolo[3,4-b] pyridines and Pyrazolo[1,5-a] pyrimidines Linked to a Thiazolo[3,2-a] benzimidazole Moiety, *Arch. Pharm. Chem. Life Sci*, 343(1), 2010, 24-30.
21. Thompson RL, Price ML and Miaton S A. Protection of mice against vaccinia virus by administration of benzyldehyde thiosemicarbazone, *Proc. Soc. Exptl. Bio. M*ed, 78(1), 1951, 11-13.
22. Furniss BS, Hannaford A, Jm Smith PWG and Patchel I R. Vogel's Textbook of practical Organic Chemistryl. *Singapore: Pearson Education Pvt. Ltd.*1996,
23. Preston PN.In the Chemistry of Heterocyclic Compounds, Benzimidazoles and Congeneric Tricyclic Compounds*, John Wiley and Son*, New York, 40(pt1), 1980,
24. Kumar J R, Jawahar J L and Pathak D P. Synthesis and pharmacological evaluation of benzimidazole derivatives, *Eur. J.Chem*, 3(2), 2006, 278.

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