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AN EFFICIENT SYNTHESIS, CHARACTERIZATION AND BIOEVALUATION OF SCHIFFS BASE CONTAINING AMINOTHIAZOLE BY METHANE 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 thiazole with P-substituted aryl aldehyde by using methanesulphonic acid in organic solvent at room temperature. The intermediate moiety (2-amino thiazole) can be synthesized from 4-Chloro -2-bromo acetophenone with thiourea in the presence of sodium acetate and acetic 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.

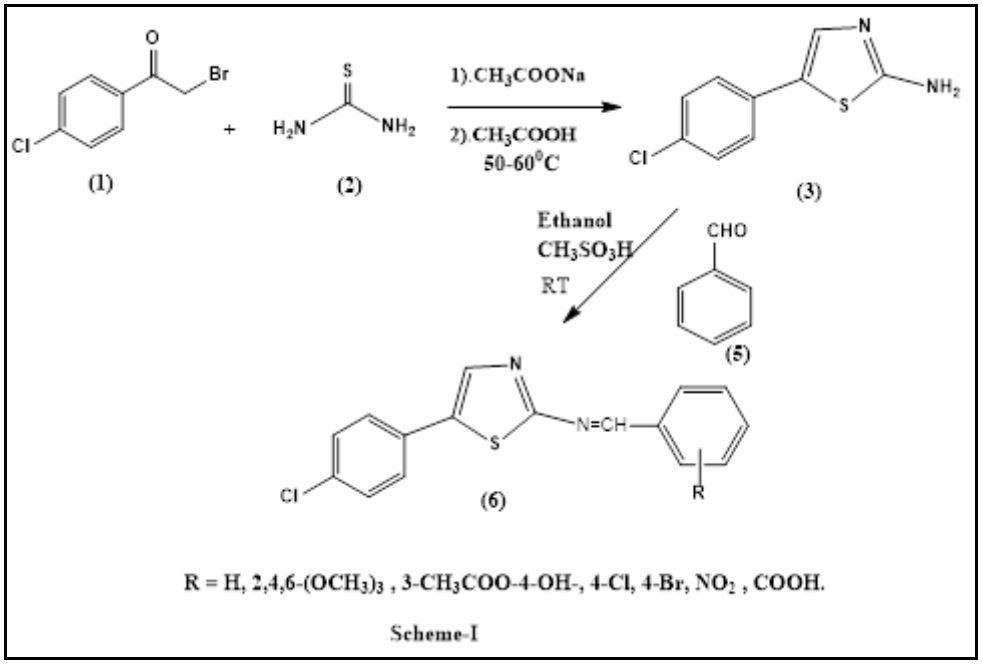
KEYWORDS: 4-chloro-2-bromo-acetophenone, thiourea, 5-(4-Chlorophenyl) thiazole-2-amine, Aromatic aldehyde, methane sulphonic acid, bioevluation.

INTRODUCTION

Schiff's base synthesized from the condensation between the substituted primary amines and substituted aromatic aldehyde which is also important class in organic, medicinally and pharmaceutical compounds. Most of the synthetic organic compounds having imines group and also very important significant class of organic synthesis due to their applications in various fields such as organic ,biological, inorganic and also analytical chemistry.

Compounds are having the combination of part of the heterocyclic moiety which is responsible for exhibited the different pharmacological properties. The compounds containing five membered heterocyclic rings. The substituted amino thiazole is an important types and their significant biological activities against several virus like influenza, HIV, Herpus(HSV-1) and Epstein-barr,[1-3] and Schiff bases possesses the substituted amino thiazole in present moiety which are showed anti-cancer and anti-proliferate properties. The substituted amino thiazole is being explored intermediate in the pharmaceutical industries and the derivatives of amino thiazole have also been found in the diverse therapeutic applications.[4-8] The versatile core contained in different substances of Schiff's bases derivatives are containing a broad spectrum of pharmacological activities.[4-9] in particular, it has been important pharmacopoeia and privileged 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,[10-21] antioxidant.[22-24] anti-inflammatory,[25,26] kinase (CDK-1, CDK-5 and GSK-3) inhibition activity,[27] cholinesterase inhibition,[28] antiproliferative activities,[29] antitubercular activity,[30,31] analgesic activity,[32] and cytotoxic activities agents.[32,34] Further mode, benzimidazoles showed anticancer activity against DNA topoisomerase and colon cancer cell lines.

In this investigation, we synthesized Schiff base from 2-amino benzimidazoles and various P-substituted aryl aldehyde (Electron donating, a Electron withdrawing and halogen containing) using camphor sulphonic acid as a acid catalyst. We aimed to the synthesis 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 benzimidazoles 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 benzimidazoles are synthesized in the present work.



Scheme-1: synthetic protocol of the compounds

METHODS & MATERIALS

Experimental

All the synthetic grade reagents, solvents 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-n-hexane in different ratios as eluent. All the synthesized compounds find the molecular weight using LCMS.

Procedure for the synthesis of 5-(4-Chlorophenyl) thiazole-2-amine

A mixture of 4-chloro-2-bromo acetophenone (**1, 1 equiv**) and thiourea (**2, 1 equiv**) are introduced 100ml for neck RB flask and addition of an sodium acetate acetic acid to the above mixture. The reaction carried out on magnetic stirrer with reflux condition. After completion of the reaction, the progress of the reaction was checked by TLC as a mobile phase (EtOAc: n-hexane -5:5) and stop the reaction after decided the TLC observation. The mixture of the 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 (5:5, ethyl acetate: n-hexane).). The final compound obtained from recrystallizations.

Characterizations 5-(4-Chlorophenyl) thiazole-2-amine

Coloulesssolid;Yield-89%Rf-0.55(EtOAc:n-hexane-5:5):**^{1}HNMR(400MHz,$CDCl_3$)**δinppm:7.751 (s,1H, thiazole),7.448-7.394(m,4H,A-r),5.265(s,2H,NH_2).**^{13}CNMR(100MHz,$CDCl_3$)**δinppm:165.72,135.15, 132.49,130.03,128.96,128.22,121.66, **LCMS(m/z):212.07(M+2)**.**Molecularformula:**$C_9H_7ClN_2S$. **Elemental analysis**: Caliculated:C-51.31,H-3.35,N-13.30. Obtained: C-51.26, H-3.33, N-13.37.

General procedure for the synthesis of Schiff base

Taken dry and clean 50mL four neck RBF and was poured by 50mL ethanol .The mixture of 5-(4-Chlorophenyl) thiazole-2-amine (3, 1 equiv) and P-substituted aryl aldehyde (4, 1 equiv **)** introduced in 50 ml four neck RB flask in ethanol and methane sulphonic acid added to the RB flask. The reaction carried on magnetic stirrer at RT. The reaction was monitored by TLC as mobile phase (EtOAc : n-hexane) after all the reactants are consumed during the appropriate 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 recrystallized from ethanol.

1). N-(5-(4-chlorophenyl) thiazole-2-yl)-1-phenylmethamine: (6a)

Paleredsolid; yield-87%; m.p–210-212^{0}c;Rf-0.50 (EtOAc : n-hexane- 4:6), ^{1}HNMR (400MHz,$CDCl_3$) δinppm: 8.427(s,1H,N=CH),7.180(s,1H,thiazole),7.618 (d,J=8.8Hz,2H,Ar-H),7.576-7.362(m,7H,Ar-H);^{13}CNMR(100MHz,$CDCl_3$)δinppm:161.75,158.66,145 .08,133.43,131.27, 129.96,129.17,128.92,128.56,128.11; LCMS(m/z): 300.19(M+2).Molecularformula: $C_{16}H_{11}ClN_2S$. Elemental analysis: Caliculated:C-

64.32,H-3.71,N-9.38. Obtained: C-64.26, H-3.69, and N-9.458.

2). (E)-4-(((5-(4-chlorophenyl) thiazol-2-yl) methyl) phenol (6b)
Whitesolid;yield-91%;m.p–217-219^{0}c;Rf:0.40(4:5-EtOAc:n-hexane); ^{1}HNMR(400MHz,$CDCl_3$) δinppm:9.172(s,1H,-OH),8.232(s,1H,-N=CH-),7.814(s,1H,thiazole),7.614 (J=8.0Hz,2H,Ar-H),7.557(J=8.8Hz,2H,Ar-H),7.485 (J=8.8Hz,2H,Ar-H),7.266(J=6.8Hz,2H,Ar-H), ^{13}CNMR(100MHz,$CDCl_3$) δinppm:161.63,152.77,150.09,140.69,132.88, 131.44, 130.05,129.64,128.93, 128.44,127.36,126 .08.LCMS (m/z):314.17(M+). Molecular formula: C16H11ClN2OS. Elemental analysis: calculated: C-61.05, H-3.52, N-8.90. Obtained: C-61.00, H-3.50, and N-8.82.

3). N-(5-(4-chlorophenyl) thiazole-2-yl)-1-(2,4,6-trimethoxyphenyl) meth amine(6c):
Pale yellow solid; yield-92%; m.p – 255-257^{0}c : Rf-0.55 (5:5-EtOAc:n-hexane),
^{1}HNMR(400MHz,$CDCl_3$)δinppm:8.708(s,1H,N=CH),7.674((s,1H,thiazol),7.613-7.509(m,4H,Ar-H),6.932 (J=8.0Hz,1H,Ar-H)3.692(s,3H,-OCH3),3.601(s,6H,2.OCH3).**^{13}CNMR(100MHz,$CDCl_3$)** δinppm:161.72, 157.33,153.64,145.66,141.28,133.36,131.47,130.08,129.14,128.47,109.77,98.44,55.09.**LCMS**(m/z): 389.29(M+H),. **Molecular formula**: C19H17ClN2O3S. **Elemental analysis**: calculated: C-58.69, H-4.41, N-7.20. Obtained: C-58.62, H-4.40, N-7.14.

4).(E)-1-(4-bromophenyl)-N-(5-(4-chlorophenyl) thiazole-2-yl)methamine (6d):
Pale yellow; yield-89%; m.p – 241-242^{0}c ,Rf-0,45 (4:6-EtOAc : n-hexane);
^{1}HNMR(400MHz,$CDCl_3$)δinppm: 8.694(s,1H,-N=CH),7.821(J=8.4Hz,2H,Ar-H),7.676(J=8.0Hz,2H,Ar-H),7.647(s,1H,Ar-H),7.577(d,J=6.4Hz,2H,Ar-H),7.485(d,J=8.0Hz,2H,Ar-H).**^{13}CNMR(100MHz, $CDCl_3$)**δinppm:161.79,153.34,142.28,133.63,132.17,130.38,129.67,128.96,128.56,128.09,127.75, 126.17;LCMS(m/z):377.94(M+2).**Molecularformula**:$C_{16}H_{10}BrN2S$.**Elementalanalysis**: calculated: C-50.88, H-2.67, N-7.42, Obtained: C-750.81, H-2.65, N-7.50.

5).(E)-N-(5-(4-chlorophenyl) thiazole-2-yl)-1-(4-nitrophenyl) methamine(6e):
White solid; yield-91%; m.p – 223-225^{0}C, Rf: 0.45 (4:6-EtOAc: n-hexane)
^{1}HNMR(400MHz,$CDCl_3$)δinppm:8.673(s,1H,-N=CH-),8.236(d,J=4.8Hz,2H,Ar-H)7.934(d,J=8.0Hz, 2H,Ar-H),7.656 (s,1H,thiazole),7.637-7.536(m,2H,Ar-H);**^{13}CNMR(100MHz,$CDCl_3$)**δinppm:162.74, 158.09147.27,141.64,135.78,133.33,131.88,130.02,129.44,128.73,128.04,127.32.**LCMS**(m/z): 345.18(M+).**Molecularformula**:C16H10ClN2O3S.**Elemental analysis**: calculated: C-55.90, H-2.93, N-12.22. Obtained: C-55.83, H-2.91, N-12.31.

Biological Activity
Anti Bacterial Activity
The anti-bacterial activities of newly synthesized derivatives were is examined against 5 pathogenic bacteria strains. The result of antibiotic activity studies for the compounds. The gram negative bacteria screened were *Escherichia Coli* and *Pseudomonas aeruginosa*. The gram positive bacteria screened were *S-aureas* and *Bacillus.*

The tested compounds were used at the concentration of 150 µglml and 250 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 screened by disc diffusion method against the organism of *AspergillusNiger* and *Candida albicans*. Compared were treated at the concentrations of 150 µglml and 250 µglml using DMSO as a solvent. The standard drug was used as ketoconazol 50 µglml against both organisms.

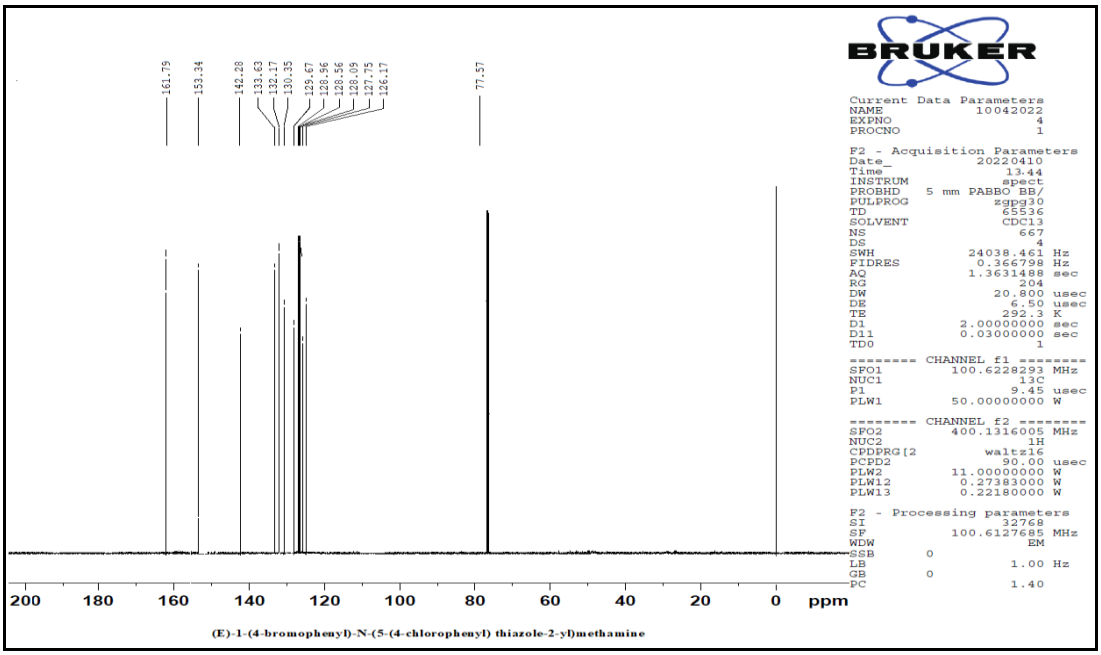
RESULT AND DISCUSSION

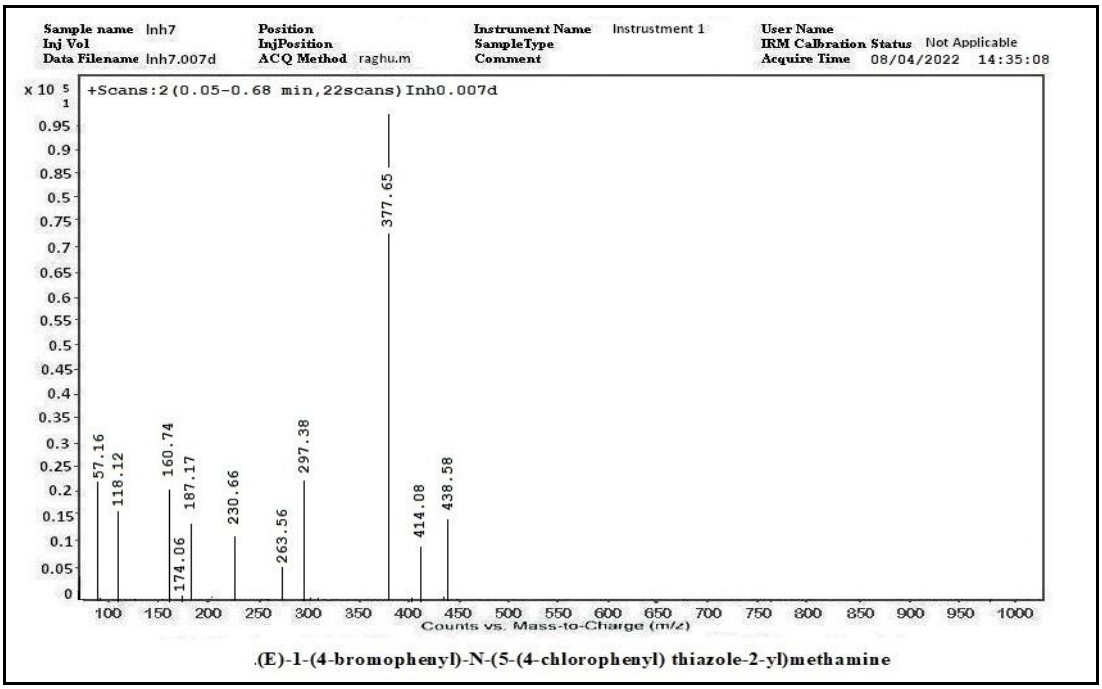
All newly titled compounds can be synthesized reflux temperature and also colored product. In this reaction, we obtained the percentage of the yield 89-92%. These titled derivatives can be obtained, we used to organic acid catalyst is methane sulphonic acid. This organic catalyst can be used to improve the reaction conditions and also reaction was completed maximum 3 hours. The rate of reaction increased by this catalyst effect. The catalyst used due to emerging as a powerful nature, inexpensive, ecofriendly, readily available, economical and easy handling. We used various P-substituted aromatic aldehydes such as electron donating group of aromatic aldehydes and electron withdrawing group of aromatic aldehydes. Hence ,electron donating group of aldehydes react with 2-aminothiazole 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 are using camphor sulphonic acid, the reaction workup is easily. (**Scheme-I).**

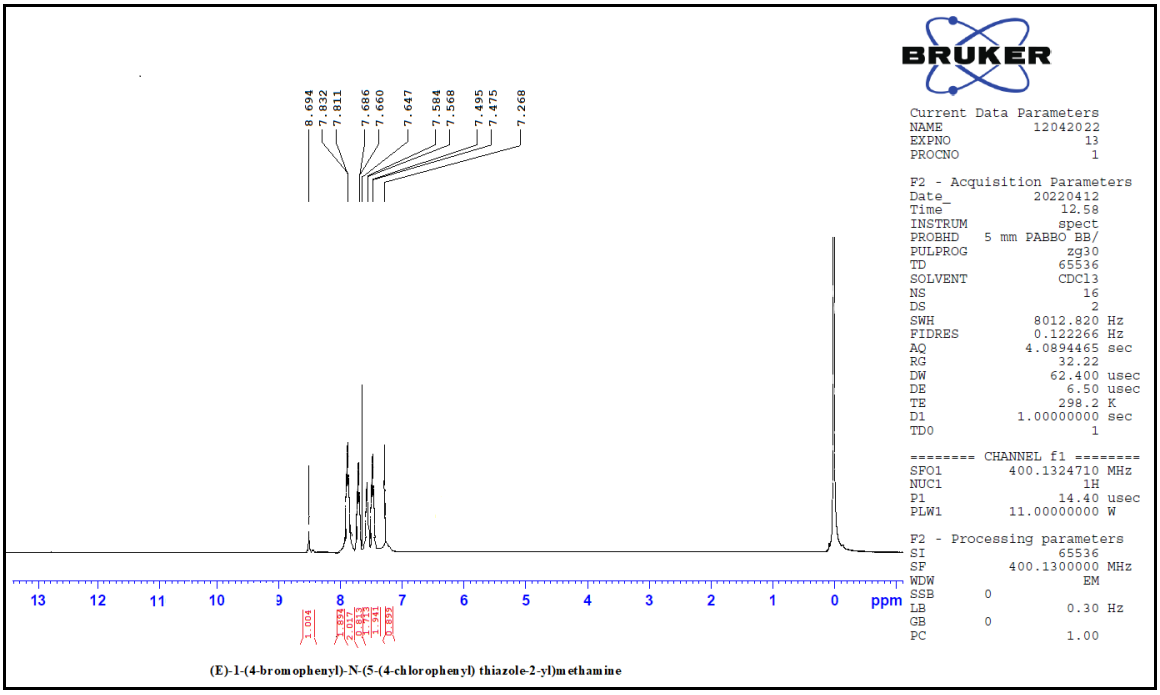
All the synthesized derivatives were screened anti-bacterial activity as well as antifungal. The electron withdrawing group of compounds showed poor active potent whereas electron withdrawing group of compounds exhibited poor active potento compared with electron donating groups. All halogen compounds exhibit excellent potent activity due to lipophilic nature. The compound which possess electron donating group shows moderate activity as shown in Table-I.

Table-I: Antimicrobial activity screening activity synthesized scaffold.

Compound Code	*Zone of inhibition in (mm)					
	Bacteria				Fungi	
	S.aureus	E.coli	S. typhi	B.substills	A. niger	C. albicans
5a	09	10	06	04	08	06
5b	24	23	18	22	09	11
5c	25	21	23	21	06	09
5d	18	20	09	20	17	21
5e	16	10	11	13	09	07
Amoxicillin	30	30	28	28	NA	NA
Ketoconazole	NA	NA	NA	NA	25	25
DMSO	---	----	---	---	---	---







CONCLUSION

The reaction condition carried out at 50-60^{0}C temperature for all the newly synthesised derivatives. The yield of the titled compounds obtained from 85-92%.The compound containing electron donating group aquired maximum yeild than that of the compound possesses electron withdrawing group. The rate of reaction developed by using methane sulphonic acid catalyst.All the compounds tested by anti microbial activity against gram positive,gramnegitive and fungal.The compound containg 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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