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AN EFFICIENT SYNTHESIS, CHARACTERIZATION AND BIOEVLUATION OF SCHIFF'S BASE CONTAINING BENZIMIDAZOLES MOIETY CATALYZED BY TFA

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ABSTRACT

Schiff's bases possessing a significant class of medicinally and pharmaceutical important moieties. An efficient process for the synthesis for a novel Schiff bases from 5-styryl-1, 3, 4-thiadiazol-2-amine with P-substituted aromatic aldehyde by using Trifluoroaceticacid in ethanol as solvent at reflux. The intermediate moiety 5-styryl-1, 3, 4-thiadiazol-2-amine can be synthesized from cinnamic acid with semithiocarbazide in the presence of ethanol with concentrated sulphuric 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: Cinnamic acid, semithiocarbazide, 5-styryl-1, 3, 4-thiadiazol-2-amine, P-substituted aromatic aldehydes, schiff bases, bioevluation.

1. INTRODUCTION

Schiff's base synthesized from the condemnation between the primary amines and substituted aldehyde which is also important class in organic, medicinally and pharmaceutical compounds. Mostly synthetic organic compounds are containing imines group and also very important significant 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 pharmacological activities. The compound containing five membered

heterocyclic rings. The 5-styryl-1, 3, 4-thiadiazol-2-amine is an important class of their significant biological properties against several virus like influenza, HIV, Herpus(HSV-1) and Epstein-barr.[1-3] and5-styryl-1, 3, 4-thiadiazol-2-amine moiety present in schiff bases which are show anti-cancer and anti-proliferate properties. 5-styryl-1, 3, 4-thiadiazol-2-amine is being explored intermediate in the pharmaceutical industries and the 5-styryl-1, 3, 4-thiadiazol-2-amine derivatives have also been found in the diverse therapeutic applications.[4,5] The versatile core contained in several substances of benzimidazoles derivatives are possess a broad spectrum of pharmacological activities[6-8] 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,[12-14] antioxidant,[15] anti viral,[16,14] antihypertensive,[18] antiprotozoal,[19] anti-inflammatory[20] and molluscicidal[21] agents. Further mode, benzimidazoles showed anticancer activity against DNA topoisomerase[22-23] and colon cancer cell lines.[24]

In this investigation, we synthesized Schiff base from 5-styryl-1, 3, 4-thiadiazol-2-amine and various P-substituted aryl aldehyde (Electron donating, a Electron withdrawing and halogen containing) using Trifluoroaceticacid as a acid catalyst. We aimed tothesynthesis of new Schiff's bases using organic acid (Trifluoroaceticacid) 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 can be synthesized from cinnamic acid with semithiocarbazide in the presence of ethanol with concentrated sulphuric acid medium 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.

2. METHODS AND MATERIALS

2.1. 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 Agarwal 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}CNMR 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 (singlet), 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.

2.2.1 General procedure of 5-styryl-1, 3, 4-thiadiazol-2-amine

Take dry and clean four necks RBF. The mixture of cinnamic acid and semithiocarbazide dissolved in the ethanol and few drops of concentrated sulphuric acid into RBF at room temperature which is also fitted on the magnetic stirrer containing hot plate. The reaction mixture continuous carried the reaction for 5 hrs. at 60^0C. The progress of the reaction checked by the TLC (EtOAc: n-hexane = 3:7). After completion of the consumed all reactants, cooled the reaction mixture at RT. The crude dissolved in ethyl acetate and washed with as saturated solution of sodium bicarbonate and separated the ethyl acetate layer and also washed with water separated the organic layer. The organic layer can be distilled off under vacuums and solid compound obtained.

Characterization of 5-styryl-1, 3, 4-thiadiazol-2-amine

Palepinksolid,yields-91%.1HNMR(400Mz,CDCl3)ppm:7.592-7.345(m,5H,Ar-H),6.525 (s,2H,2.=CH),5.825(s,2H,NH_2);13CNMR(100MHz,$CDCl_3$)ppm:160.67,155.72,136.33, 132.45,128.96,128.52,127.86,117.62;.LCMS(m/z):203.16(M+);Molecularformule: $C_{17}H_{13}N_3S$;.Elemental Analysis: Calculated C-59.07,H-4.46,N-20.67. Obtained: C-59.00, H-4.45, N-20.75.

2.2.2 The general procedure of 1-phenyl-N-(5-styryl-1,3,4-thiadiazol-2-yl)methamine analogous

In this project, to of 5-styryl-1, 3, 4-thiadiazol-2-amine (1mmol), trifluoroacetic acid (3mL) was added; the mixture was stirred for two hours in room temperature, then substituted aromatic aldehyde (1mmol) was added to a mixture and was stirred and heated under reflux in conditions an oil bath at 70^0C. The progress of reaction was monitored by thin layer chromatography (TLC). After the completion of reaction, cold water was added to the mixture. Then solid crystals were formed at the bottom of the beaker and after that, they were filtered. Finally, the solid product was washed with water, ethanol and n-hexane and dried in desiccator in R.T. The pure derivatives were obtained in good yields.

Characterization of1-phenyl-N-(5-styryl-1,3,4-thiadiazol-2-yl)methamine analogous (5a-5g)

2.2.2.1.1 phenyl-N-(5-styryl-1,3,4-thiadiazol-2-yl)methamine (5a)

Colourless,yields-87%.^{1}HNMR(400Mz,$CDCl_3$)ppm:8.654(s,1H,=CH)7.796-7.557(m,7H,Ar-H), 7.342-7.294(m,3H,Ar-H, 7.079(s,1H,=CH), 6.896(s,1H,=CH). ^{13}CNMR(100MHz, $CDCl_3$)ppm: 160.25, 154.65, 136.09, 130.72, 129.65, 128.97, 128.43, 128.23, 127.64, 127.35, 123.36, 114.79. LCMS (m/z): 292.42(M+H). Molecular formulae: $C_{17}H_{13}N_3S$, .Elemental Analysis: Calculated C- 70.08,H- 4.50,N-14.42. Obtained: C-70.00, H-4.48, N-14.50.

2.2.2.1 (4-methoxyphenyl)-N-(5-styryl-1,3,4-thiadiazol-2-yl)methanimine (5b)

Colourless,yields-77%.^{1}HNMR(400Mz,$CDCl_3$)ppm:9.676(s,1H,-N,=CH), 7.857-7.613 (m,4H,Ar-H), 7.412-7.294(m,5H,Ar-H), 6.945(s,1H,=CH), 6.816(s,1H,=CH), 3.724 (s,3H,OCH_3). ^{13}CNMR (100MHz, $CDCl_3$) ppm: 159.49, 155.62, 138.74, 132.16, 130.37, 129.64, 128.97, 128.44, 128.04, 126.72, 117.62, 54.68. .LCMS (m/z): 322.22(M+H). Molecular formulae: $C_{18}H_{15}N_3OS$, .Elemental Analysis: Calculated C- 67.27,H-4.70,N-13.07. Obtained: C-67.20, H-4.68, N- 13.15.

2.2.3 N-(5-styryl-1,3,4-thiadiazol-2-yl)-1-(3,4,5-trimethoxyphenyl)methanimine (5c)

Colourless,yields-92%.^{1}HNMR(400Mz,$CDCl_3$)ppm: 8.734(s,1H,=CH), 7.584(d,J=7.6Hz, 2H,Ar-H), 7.318-7.284(m,3H,Ar-H),7.148(s,2H,Ar-H), 7.089(s,1H,=CH), 6.846 (s,1H, =CH), 3.734(s,6H,-OCH_3), 3.0692(s,3H,-O CH_3) ^{13}CNMR(100MHz,$CDCl_3$)ppm:159.79, 156.62, 150.24, 138.35, 136.28, 134.09, 130.21, 128.92, 128.45, 128.76, 127.33, 117.82, 60.15, 55.27; LCMS(m/z): 384.03(M+). Molecular formulae: $C_{20}H_{19}N_3O_3S$, .Elemental Analysis: Calculated C- 62.98,H- 5.02,N-11.02. Obtained: C- 62.89, H- 5.01, N- 11.12.

2.2.4.1 (4-chlorophenyl)-N-(5-styryl-1,3,4-thiadiazol-2-yl)methamine(5d)

Pale pink solid, yields-89%.^{1}HNMR(400Mz,$CDCl_3$)ppm: 8.462(s,1H,=CH), 7.763-7.346 (m,9H,Ar-H), 6.426(s,1H,=CH), 6.316(s,1H,=CH), ^{13}CNMR(100MHz,$CDCl_3$)ppm: 163.62,156.89,135.53,133.04,132.11,130.02,129.74,128.96,128.63,128.31,127.81,117.96. LCMS (m/z): 327.21(M+2). Molecular formulae: $C_{17}H_{12}N_2ClS$; .Elemental Analysis: Calculated C- 62.67, H- 3.71, N- 12.90. Obtained: C- 62.60, H- 3.70, N- 12.98.

2.2.5.1 (4-bromophenyl)-N-(5-styryl-1,3,4-thiadiazol-2-yl)methamine(5e)

Palered;yields-89%.1HNMR(400Mz,$CDCl_3$)ppm: 8.567(s,1H,-N=CH), 7.693-7.346 (m,9H,Ar-H), 6.494(s,1H,=CH), 6.316(s,1H,=CH), 13CNMR (100MHz, $CDCl_3$)ppm:

163.67,156.09,138.52,133.04,131.25,128.87,128.53,128.12,127.96,127.44,126.15,117.69. LCMS(m/z): 370.33(M+2). Molecular formulae: $C_{17}H_{12}BrN_3S$, Elemental Analysis: Calculated C- 55.15.,H- 3.27,N- 11.35. Obtained: C- 55.04, H-3.25,N-11.43.,

2.2.6.1 (4-nitrophenyl)-N-(5-styryl-1,3,4-thiadiazol-2-yl)methamine (5f)

Pale-yellow solid; yields-87%.1HNMR(400Mz,$CDCl_3$)ppm: 8.574(s,1H,-N=CH),8.214-7.894(m,4H,Ar-H), 7.583-7.356(m,5H,Ar-H), 6.454(s,1H,=CH), 6.396(s,1H,=CH); ^{13}CNMR(100MHz,CDCl3)ppm: 164.76,156.94,146.52,140.75,136.36, 133.46, 128.54, 128.13,127.96,127.55,124.16,117.91.LCMS(m/z): 337.26(M+H). Molecular formulae: $C_{17}H_{12}N_4O_2S$, .Elemental Analysis: Calculated C- 60.70,H-3.60,N- 16.66. Obtained: C-60.61, H-3.58,N-16.24.

3. Biological activity

3.1. Anti-Bacterial activity

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

The tested 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.

3.2. Anti-Fungal activity

Anti-fungal activity of new synthesized derivatives was examined by disc diffusion method against the organism of A. NCCS 1196 and C. albicans 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 ketoconazole 50 µglml against both organisms.

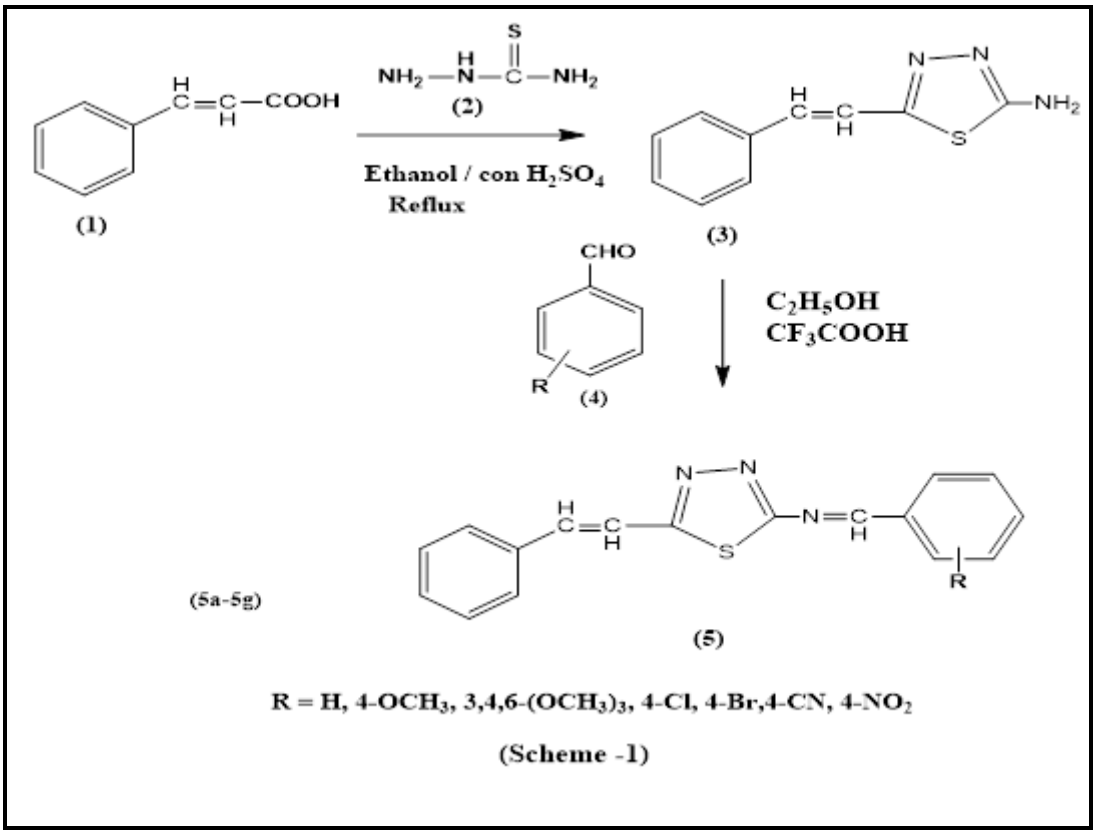
4. RESULT AND DISCUSSION

4.1. Chemistry

All newly titled derivatives can be synthesised 70^0C and also cooler product. In this reaction, we acquired the percentage of the yield 85-92%. These titled derivatives can be obtained, we used to Bronsted acid catalyst is trifluoro acetic acid. This acid catalyst can be used to

improve the reaction conditions and reaction is completed maximum 3 hours. The rate of reaction increased by using this catalyst. The catalyst used due to emerging as a powerful nature, inexpensive, eco-friendly, readily available, economical and water soluble compound. We used various P-substituted aromatic aldehydes having electron donating group of aldehydes and electron withdrawing group of aldehydes. Hence ,electron donating group of aldehydes react with 5-styryl-1, 3, 4-thiadiazol-2-amine: to give more yield and rate of reaction increases and completion of the reaction before 60 min compared to that of electron withdrawing group of aldehyde react with5-styryl-1, 3, 4-thiadiazol-2-amine:. 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 (5f) show poor active potent. Other hand electron withdrawing group of compounds exhibited poor active potent compared with electron donating groups. All halogen compounds exhibit excellent potent activity. The compound which possess electron donating group shows moderate activity as shown in Table-I.



(Scheme -1)

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	08	10	06	04	09	07
5b	21	18	12	21	06	08
5c	22	18	11	21	06	09
5d	24	24	23	22	17	21
5e	25	24	23	22	09	07
5f	07	08	05	05	09	07
Amoxicillin	30	30	28	28	NA	NA
Ketoconazole	NA	NA	NA	NA	20	25
DMSO	---	----	---	---	---	---

5. CONCLUSION

The reaction condition carried at room temperature for all the newly synthesised compounds. The yield of the titled compounds obtained from 85-92%. The compound possesses electron donating group gives maximum yield than that of the compound possesses electron withdrawing group. The rate of reaction developed by using trifluoroacetic acid catalyst. All the compounds tested by anti-microbial activity against gram positive, gram negative and fungal. The compound having electron donating group showed excellent active potential. Otherwise the compounds having halogens which showed better active potential than that of the electron with drawing group.

6. Acknowledgement

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7. Conflict of interest

We declare that we have no conflict of interest.

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