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DESIGNED A SYNTHESIS OF SCHIFF BASE CONTAINING ETHYL 2- AMINO BENZOATE MOIETY PROMOTED BY BRONSTED ACID

Y. Srilaxmi[1], K. D. Prabodh[1], B. Iswarya Lakshmi[1] and Dr. N. Krishnarao[1]*

[1]*Prism PG & DG College (Affiliated by Andhra University), Visakhapatnam, India.

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***Corresponding Author**
Dr. N. Krishnarao
Prism PG & DG College (Affiliated by Andhra University), Visakhapatnam, India.

ABSTRACT
The present study, to investigate the synthesis of bioactivity of an development method for the synthesis for series of Schiff bases from ethyl 2-aminobenzoate with substituted aromatic aldehydes using P-Toluene sulphonic acid in ethanol solvent at reflux. The intermediate moiety ethyl 2-aminobenzoate can be synthesized from 2-aminobenaoic acid and ethanol small amount of concentrated phosphoric acid which is obtained from pthalic anhydride with sodium hypo bromide. All the newly synthesized derivatives were evaluated by the advanced spectroscopic data (^{1}H-NMR, ^{13}C-NMR and LCMS) and also structural determination were calculated by elemental analysis. Besides to all compounds were screened by their biological activities.

KEYWORDS: Ethyl 2-aminobenzoate, methane sulfonic acid, P-Toluene sulphonic acid, Schiff bases, antibacterial.

1. INTRODUCTION
A Schiff base (or azomethine) is a functional group that contains a carbon nitrogen double bond with the nitrogen atom connected to an aryl or alkyl group but not hydrogen.[1] Schiff bases are usually synthesized from the condensation of primary amines and active carbonyl group.[2] Schiff bases are characterized by the −N=CH− (imines) group which is important for elucidating the mechanism of transamination and racemization reactions in biological systems.

The formation of carbon–nitrogen double bond plays an important role in organic synthesis. This can be achieved by the reaction of aldehydes and amines in acidic medium which leads to synthesis of Schiff bases (imines). Schiff bases have attracted considerable attention of organic chemists due to their significant biological properties.

Ethyl 2-aminobenzoate is an intermediate moiety which is being explored in the pharmaceutical industries and the substituted Ethyl 2-aminobenzoate derivatives have also been represents in the diverse therapeutic applications.[1] Because of the versatile core contained in several substances derivatives of titled moiety that was possess a broad spectrum of pharmacological activities in particular, it has been most important pharmacopoeia[2] and privileged structural moiety in medicinal chemistry[3], encompassing a diverse range of biological properties including antimicrobial and antiviral[4-10], anticancer[11-16], antiurease[17], antioxidant[18-20], anticonvulsant[21], antitube rculosis[22], Receptoanti gonism[23], antimalarial[24], anti-inflammatory.[25-29] In addition to benzimidazoles moiety showed anticancer activity against DNA topoisomerase and colon cancer cell lines.

In present investigation, we synthesized Schiff bases from ethyl 2-aminobenzoate with substituted aromatic aldehydes using methane sulfonic acid in free solvent at room temperature in the presence P-Toluene sulphonic acid as catalyst in ethanol as solvent condition. We aimed to synthesize new Schiff's bases using Bronsted acid catalyst due to easy to workup, improved better yield as well as completion of the minimum reaction time and also the intermediate of this reaction such as ethyl 2-aminobenzoate can be synthesized from phthalimide from sequential steps. In addition to studied the biologically potent activity of the titled derivatives. In the view of these facts as a continues search of antimicrobial activity of these Schiff base and its derivatives. (Scheme- 1).

2. EXPERIMENTAL METHODS
The synthetic grade chemicals, reagents, solvents and desired raw materials are parched from Fine chemical PVLTd and also used father without purification. The melting points of the synthesized derivatives were measured by Agarwal Thermo Scientific Fluke 51 II, melting point instrument and uncorrected was reported.

The newly synthesized derivatives were analyzed by advanced spectroscopic process such as ^{1}H NMR (400 MHz) and ^{13}C NMR (100MHz) spectra of the synthesized compounds were recorded values by an instrument Bruker Ultra Shield at room temperature Ultra Shield using tetramethylsilane (TMS) as the internal standard and deuterated chloroform ($CDCl_3$) as the solvent The molecular weights of the titled compounds were measured by LCMS instrument were run on a Shimadzu spectrometer instrument, which was operating at 70 eV in positive mode. The progress of the reactions was examined by thin layer chromatography (TLC) analyses using (Merck 60 F254 silica gel).

2.1).GENERAL PROCEDURE FOR THE SYNTHESIS OF ISOINDOLINE-1, 3-DIONE (2)

Take the mixture pthalicanahydride (1mol) and urea (1.125mol) in a dry and clean 50mL beaker. This mixture put on the sand bath and applies the heating at 100^0C. After completion of the reaction, the mixture dissolved in cold water filtrated and a solid can be separated. The solid was dried and recrystallized by ethanol. The compound can be characterized.

Yeild-95%; colourlesscompoud, M.P-231-233^{0}C;^{1}HNMR(400MHz,$CDCl_3$)δppm:7.786(d,J=8.8 Hzs,1H,Ar-H), 7.224-6.947(m,3H,Ar-H),6.146(s,2H,NH_2);^{13}CNMR(100MHz,$CDCl_3$)δppm. 168.56,147.76,131.37,128.77,128.12,126.76.LCMS(m/z) :138.54(M+H); Molecularformule. $C_7H_7NO_2$. Elementalanalysis:Calculated:C-61.31,H-5.15,N-10.21; Obtained:C-61.24, H-5.14,N-10.29.

2.2).GENERAL PROCEDURE OF SYNTHESIS OF 2-AMINOBENZOIC ACID (3)

The bromine liquid (1mol) dissolved in 5mL of 10% NaOH in conical flask at 010^0C. The phthalimide (1mol) is dissolved in 10% NaOH in a 50mL in RBF. The bromine liquid added in above solution and arranged on the magnetic stirrer and reaction was continued at 70^0C. As a observation, total amount of compounds consumed during the reaction and followed by TLC checked, the reaction mixture cooled under normal temperature, neutralised with 2N HCl and also finalised with few drops of glacial acetic acid. The crude is poured into ethylacetae and washed water in a twice and separated the organic layer and distilled off under vacuum. After, the desired product can be obtained by recrystlsation from ethanol.

Yeild-93%; Palebrownsolid; M.P-212-214^{0}C;^{1}HNMR(400MHz,$CDCl_3$)δppm:7.712(d,J=8.0 Hzs,1H,Ar-H),7.252-6.912(m,3H,Ar-H),6.235(s,2H,NH_2);^{13}CNMR(100MHz,$CDCl_3$)δppm :169.12,149.07,131.45,128.57,128.16,127.87.LCMS(m/z):138.78(M+H); Molecularformule. $C_7H_7NO_2$.Elementalanalysis:Calculated:C-61.31,H-5.15,N-10.21; Obtained:C-61.24,H-5.14,N-10.29.

2.3. GENERAL PROCEDURE OF SYNTHESIS OF ETHYL 2-AMINOBENZOATE (5)

The mixture of 2-aminobenzoic acid (1mol) and ethanol (1.5mol) taken in 50mL RBF. The H_3PO_4 catalyst (0.4mol) added in reaction mixture and continued the reaction at reflux. The reaction maintained appropriate time and cooled at RT. After the mixture distilled and collect the final product.

Yeild-92%;Broncopound;M.P-225-227^{0}C;^{1}HNMR(400MHz,$CDCl_3$)δppm:7.643(d,J=7.2Hz, 1H,Ar-H),7.114-6.896(m,3H,Ar-H),6.203(s,2H,NH_2),4.145-3.972(m,2H.CH_2),1.184(t,J=5.8 Hz,3H,CH_3);^{13}CNMR(100MHz,$CDCl_3$)δppm:166.87,147 .76,129.37,128.12,120.28,118.754. 112.31,58.40,12.37.LCMS(m/z):164.28(M-H);Moleculaformule:$C_9H_{11}NO_2$.Elemental analysis:Calculated:C-65.44,H-6.71,N-8.48;Obtained:C-65.37,H-6.69,N-8.55.

2.4. GENERAL PROCEDURE OF ETHYL (E)-2-(BENZYLIDENEAMINO) BENZOATE (7A-7G)

The mixture of ethyl 2-aminobenzoate (1mol) and substituted aromatic aldehydes (1mol) with ethanol (25 mL) taken in a four neck 50 mLRBF. The P-Toluene sulphonic acid catalyst (0.5mol) added gradually into 50 mLRBF. The total arrangement fitted on the magnetic stirrer and continues the reaction appropriate time. The progress of the reaction mixture checked by the TLC (as mobile system – n: hexane: EtOAc = 6:4). After completion of the reaction.

2.4.1). Ethyl (E)-2-(benzylideneamino) benzoate (7a)

Yeild-88%;Paleredsolid,M.P-214-216^{0}C;^{1}HNMR(400MHz,CDCl3)δppm: 8.179 (s,1H,=CH), 7.925-7.444(m,9H,Ar-H),4.202-3.912(m,2H,-CH2),1.112(t,J=7.2Hz,3H,-CH_3),^{13}CNMR(100MHz, $CDCl_3$) δppm:167.72,162.11,151.63,131.48,130.25,129.46,128.4 7,128.22,128.01, 127.56,126.12,119.45, 57.93,14.66.LCMS(m/z):253.57(M-H);Molecularformule:$C_{16}H_{15}NO_2$.Elementalanalysis: Calculated :C-75.87,H-5.97,N-5.53;Obtained:C-75.80,H-5.96,N-5.59.

2.4.2). Ethyl (E)-2-((4-hydroxybenzylidene) amino) benzoate (7b)

Yeild-94%;Paleredsolid,^{1}HNMR(400MHz,$CDCl_3$)δppm:8.914(s,1H,-OH), 8.154(s,1H,=CH), 7.885-7.512(m,6H,Ar-H),7.122-6.929(m,2H,Ar-H),4.205-3.856(m,2H,-CH_2),1.098(t,J=7.6Hz,3H,-CH_3), ^{13}CNMR(100MHz,CDCl3)δppm:166.74,158.16,150.22,1 30.41,129.18,128.94,128.55,128.39, 128.07,127.59,118.81,58.80,13.46.LCMS(m/z):270.58(M+H);Moleculerformule:$C_{16}H_{15}NO_3$ .Elementalanalysis:Calculated:C-71.36,H-5.61,N-5.20;Obtained:C-71. 29,H-5.60,N-5.29.3.

2.4.3). Ethyl (E)-2-((4-methoxybenzylidene) amino) benzoate (7c)

Yeild-90%Paleredsolid,M.P-239-241^{0}C,^{1}HNMR(400MHz,$CDCl_3$)δppm:8.369(s,1H,=CH), 7.884-7.504(m,6H,Ar-H),7.195-7.025(m,2H,Ar-H),4.214-3.843(m,2H,-CH_2),3.774(s,3H,-OMe),1.124 (t,J=8.0Hz,3H,-CH_3),^{13}CNMR(100MHz,$CDCl_3$)δppm:164.79,157.09,158.74, 150.87,130.31,129.59, 128.87,128.49,128.25,128.04,127.59,116.03,58.25,54.60, 13.69;.LCMS(m/z):282.58(M-H); Molecularformule:$C_{17}H_{17}NO_3$.Elemental Analaysis:Calculated:C-72.07, H-6.05,N-4.94; Obtained:C-72.00,H-6.04,N-5.04.

2.4.4). Ethyl (E)-2-((4-methylbenzylidene) amino) benzoate (7d)

Yeild-89%;Paleredsolid,^{1}HNMR(400MHz,$CDCl_3$)δppm:8.215(s,1H,=CH),7.884-7.516 (m,6H,Ar-H),7.215-7.116(m,2H,Ar-H),4.135-3.891(m,2H,-CH2),1.567(s,3H,CH_3),1.166 (t,J=8.0Hz,3H,-CH_3),^{13}CNMR(100MHz,$CDCl_3$)δppm:168.14,161.02,148.78,136.07,130.54,129.47,128.82, 128.11,127.54,126.62,124.32,11.72,58.73,22.08,12.55.LCMS (m/z):268.48(M+H); Molecularformule :$C_{17}H_{17}NO_2$.Elementalanalysis:Calculated:C-76.38,H-6.41,N-5.24;Obtained:C-76.30,H-6.40,N-5.31.

2.4.5). Ethyl (E)-2-((4-Chlorobenzylidene) amino) benzoate (7e)

Yeild-89%;Paleredyellowsolid,^{1}HNMR(400MHz,$CDCl_3$)δppm: 8.294(s,1H,=CH),7.907-7.454 (m,8H,Ar-H),4.147-3.894(m,2H,-CH_2),1.164(t,J=7.2Hz,3H,-CH_3),^{13}CNMR(100MHz,$CDCl_3$) δppm:169.07,158.81,151.54,132.25,130.39,129.27,128.83,128.42,128.05,126.98,118. 35,58.74, 12.65.LCMS(m/z):287.29(M+2);Molecularformule:$C_{16}H_{14}ClNO_2$.Elemental analysis: Calculated:C-66.78, H-4.90,N-4.88;Obtained:C-66.71,H-4.87,N-4.96

2.4.6). Ethyl (E)-2-((4-Bromobenzylidene) amino) benzoate (7f)

Yeild-89%;Browncompound;M.P-238-240^{0}C;^{1}HNMR(400MHz,$CDCl_3$)δppm:8.321(s,1H, =CH), 7.906-7.487(m,9H,Ar-H),4.116-3.914(m,2H,-CH_2),1.125(t,J=7.2Hz,3H,-CH_3), ^{13}CNMR(100MHz, $CDCl_3$)δppm:168.06,159.14,150.25,131.02,130.24,129.55, 128.54,128.27, 127.64,127.04,118.31, 58.45,12.35.LCMS(m/z):333.77(M+2);Molecularformule$C_{16}H_{15}BrNO_2$.Elementalanalysis :Calculated:C-57.85,H-4.25,N-4.22;Obtained:C-57.85,H-4.24,N-4.29.

2.4.7). Ethyl (E)-2-((4-nitrobenzylidene) amino) benzoate (7g)

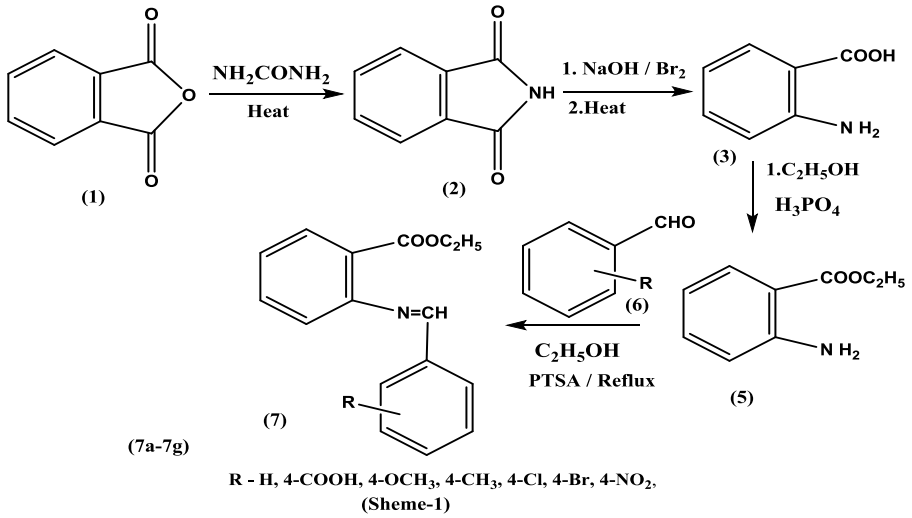
Yeild-87%;Brownsolid,M.P-245-247^{0}C;^{1}HNMR(400MHz,$CDCl_3$)δppm:8.558(s,1H,=CH), 8.350-8.125(m,4H,Ar-H),7.887-7.514(m,5H,Ar-H),4.226-3.908(m,2H,-CH_2),1.115(t,J=9.6Hz,3H,-CH_3),^{13}CNMR(100MHz,$CDCl_3$)δppm:169.47,164.14,150.55,138.59,136.37,129.48,128.44, 128.65,127.88,125.57,124.43,122.18,119.25,58.40,13.66. LCMS(m/z):299.87(M+H); Molecular formule:$C_{16}H_{14}N_2O_4$.Elementalanalysis:Calculated:C-64.42,H-4.73,N-9.39; Obtained:C-64.35,H-4.71,N-5.46.

3. RESULT AND DISCUSSION

3.1. Chemistry

All newly synthesized Schiff bases can be prepared at room temperature. These titled derivatives can be synthesized, we used to Bronsted acid catalyst methane sulfonic acid. The advantage of this s catalyst having accelerated the reaction, the appropriated time was required completion of the reaction, easy work up and commercially available. The advantage of this catalyst is used to improved and we also used for different substituted aromatic aldehydes such as electron donating group of aldehydes and electron withdrawing group of aldehydes. Therefore, electron donating group of aldehydes react with ethyl 2-aminobenzoate to obtained highest yield and rate as well as completion of the reaction increases before reaction time compared to that of electron withdrawing group of aldehyde.

The *in vitro* antibacterial activity of all the newly synthesized compounds was evaluated by bacterial strains. In the present investigation both of electron withdrawing group of moiety as well as electron donating group of moiety and we also find the potent activity of these compounds. The activity potential of electro withdrawing group of derivatives lower than that of electron donating group of compounds but halogen substituted compounds (7e and 7f) exhibit excellent activity potential. Electron withdrawing group of compounds (7e-7g 6g) exhibit low activity potential. Electron donating group of compounds (6b and 6d) showed moderate activity.



Scheme-1 - The total synthetic route of the titled moiety.

The structure of titled compounds was characterized by the advanced spectroscopic data. The 1H- and ^{13}C-NMR spectra of all newly synthesized Schiff bases are consistent with their structures. The ^{1}H-NMR spectra of these derivatives are simple and consist of the aromatic protons appears at 8.386 respectively. The aromatic protons resonate as a multiple signal at 6.869-8.854 ppm depending on the Ar group. and hydroxyl proton showed 8.986.The methoxy proton appeared at 3.676.

Initially we sought a mild and convenient method for the synthesis of titled Schiff bases at room temperature. For optimization of the amount of catalyst, the reaction of ethyl 2-aminobenzoate with 4-hydroxybenzaldehyde at ambient temperature was carried out as a model reaction and different amounts of catalyst were evaluated under the similar. The use of 5 mol% of methane sulfonic acid in ethanol for 20 min afforded the corresponding Schiff base in 96% yield (Table 1, entry 1). The optimization of the other reaction conditions was considered to develop the yield employing various catalyst loadings in different solvents. The results are expressed in Table 1. The yield of reaction in the presence of 3 mol% of methanesulphonic acid and using ethanol a solvent was increased up to 94%.

To study the improved this process, the optimized procedure was extended for synthesis of other Schiff bases. The reaction was carried out at room temperature by taking a 1:1 mol ratio mixture of ethyl 2-aminobenzoate with corresponding aromatic aldehyde 4-hyroxyenzaldehyde the presence of 3 mol% of P-toluene sulphonic acid in ethanol to give Schiff bases **(7a-7g)** (Scheme-1).

Table 1: Schiff bases derived from the reaction ethyl 2-aminobenzoate and 4-hyroxyenzaldehyde using different catalysts and solvents for 20 min at room temperature.

Entry	Brønstedacids catalyst	Catalyst loading (mol %)	Solvent	Yield (%) [a]
1	Sulphanilic acid	3mmol	Ethanol	70
2	P-toluene sulphonic acid	3mmol	Ethanol	94
3	Methanesulphonic acid	3mmol	Ethanol	81
4	Silicasulfuric acid	3mmol	Ethanol	69

a) Isolated yields

3.2. Biological Activity

All the titled compounds were evaluated by anti-bacterial activity as well as antifungal. Potent activity. The electron withdrawing group of derivatives and electron releasing group compounds showed a various potent activities against bacterial as well as fungal strains. Therefore, electron withdrawing group of compounds showed low biological potent activity compared with electron releasing groups. All halogen compounds exhibit well to excellent activity. The compound which possess electron donating group showed moderate activity as shown in Table-II.

Table II: Antimicrobial activity screening activity Titled compounds scaffold.

Compound Code	*Zone of inhibition in (mm)					
	Bacteria				Fungi	
	S.aureus	E.coli	S. typhi	B.substill	A. Niger	C. albicans
7a	09	08	10	08	07	08
7b	13	12	14	16	09	08
7c	21	19	19	20	12	13

7d	19	20	20	19	15	14
7e	14	14	15	14	17	17
7f	10	14	13	17	16	17
7g	08	09	07	07	10	12
streptomycin	25	25	22	22	NA	NA
Ketoconazole	NA	NA	NA	NA	20	20
DMSO	---	----	---	---	---	---

4. CONCLUSION

The reaction condition carried at RT condition for all the desired synthesized compounds. The development of the titled analogous was prepared from 85-92%. The electron releasing group derivatives group acquired excellent yield than that of the derivatives possesses electron withdrawing group. The rates of the reaction of the desired compounds were enhanced by catalyst such as P-Toluene sulphonic acid. All the prepared compounds are examined by anti- microbial activity against gram (+ve), gram (+ve) and fungal. The compound possess halogens exhibited an excellent potent active. Otherwise the compounds having electron releasing group which showed better potent active than that of the electron attracting group.

5. AKOWNLDEMENT

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