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Research Article

SYNTHESIS OF NOVEL 5-AMINOSALICYLIC ACID SCHIFF BASES BY GRINDING METHOD: EVALUATION FOR *IN VITRO* ANTIOXIDANT AND ANTIBACTERIAL ACTIVITIES

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ABSTRACT

Grinding technique as a method employing green chemistry was selected for the synthesis of Schiff bases from 5-aminosalicylic acid and substituted benzaldehydes. Two known and eight novel 5-aminosalicylic acid Schiff bases were synthesized and recrystallized using methanol. All the compounds were characterized by their physical data and spectral studies such as IR, ^{1}H NMR, ^{13}C NMR and Mass. The synthesized compounds were evaluated for *in vitro* antioxidant activity by scavenging 1,1-diphenyl-2picrylhydrazyl (DPPH) and nitric oxide free radicals at 100µM concentration. The activity data revealed that the compounds with 4-hydroxy-3,5-dimethoxy substitution and 3,4-methylenedioxy substitution on N-benzylidene ring showed highest antioxidant activity in DPPH and nitric oxide scavenging models respectively. The activity of these compounds was found to be greater than 5-aminosalicylic acid and the standards employed. All the compounds were evaluated for antibacterial activity by agar well diffusion method using gram negative and gram positive bacteria such as *E. coli*, *P. aeruginosa*, *S. aureus* and *B. subtilis*. The results indicate that the evaluated compounds showed good to moderate antibacterial activity.

Keywords: 5-Aminosalicylic acid, Schiff bases, Green Chemistry, Grinding technique, Antioxidant, Antibacterial.

INTRODUCTION

The grinding technique as a method employing green chemistry has become an important tool in the synthetic chemistry. The first report for the synthesis of organic molecule using grinding method was made by Toda *et al*[1] in 1987. The reactions initiated by grinding causes the transfer of energy through friction and eliminate the use of hazardous solvents. Hence, it can be considered as environmentally benign method. Several organic transformations using grinding technique were reported, which include Aldol condensation[2-3], Knoevenagel condensation[4], Biginelli reaction[5], Cannizzaro reaction[6] and Schiff base synthesis[7].

The great interest in synthesis of Schiff bases was generated due to their significant biological activities like anticancer[8], anti-inflammatory[9-10], insecticidal[11], antibacterial[12], antituberculosis[13] and anticonvulsant[14] activities. They can be synthesized by conventional methods like stirring the reactants in a suitable solvent and refluxing the reaction mixtures. In addition, they can also be synthesized by green chemistry techniques such as microwave irradiation and grinding method. The synthesis of some Schiff bases from 5-aminosalicylic acid by conventional method and grinding technique was reported earlier[9-10]. They were found to possess good anti-inflammatory and analgesic activities. In view of better pharmacological activities of the reported 5-aminosalicylic acid Schiff bases and due to many beneficial aspects of green chemistry, the present study adopted grinding technique for the synthesis of new Schiff bases from 5-aminosalicylic acid and substituted benzaldehydes in a short period of time with high yields and purity. Further, it was found logical to evaluate them for *in vitro* antioxidant and antibacterial activities.

MATERIALS AND METHODS

All the chemicals used in the present study were purchased from Merck, Himedia and Sigma Aldrich. Melting points were determined in an open capillary tube in Tempo melting point apparatus and they were uncorrected. The IR spectra (cm^{-1}) were recorded on Bruker Alpha-T FT-IR spectrophotometer using KBr pellet technique. NMR spectra were recorded with Bruker NMR spectrometer at 400 MHz (^{1}H) and at 100 MHz (^{13}C) using DMSO as solvent. Chemical shifts were reported in parts per million (ppm) using tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on LC-MS, Agilent Technology 1200 infinity series, Apex chromatogram model.

General procedure for synthesis of Schiff bases from 5-aminosalicylic acid (Scheme-I, IIIa-IIIj):

A mixture of different substituted benzaldehydes (0.01mol) and 5-aminosalicylic acid (0.01mol, 1.53g) was grinded vigorously for 20minutes in a clean and dry mortar using a pestle made of porcelain. The grinding process was continued till yellow or orange colour product appears and the completion of reaction was confirmed by TLC. The mixture was left overnight and the resultant product was recrystallized using methanol.

Using the above procedure ten compounds were prepared and characterized by their physical data and spectral studies such as IR, ^{1}H NMR, ^{13}C NMR and Mass.

IIIa: 2-hydroxy-5-{[(*E*)-(4-hydroxy-3,5-dimethoxyphenyl) methylidene]amino}benzoicacid:

IR (KBr) υ_{max}:3337(O-H str); 3077,2938(C-H str); 1670 (C=O str); 1631(C=N str); 1594,1508,1463(C=C str); 1240(Asym C-O-C str); 1117 (sym C-O-C str) cm^{-1}; ^{1}H NMR (DMSO) δ: 3.84

(s, 6H, OCH_3), 6.76 (s, 1H, OH), 6.98-7.68 (s, 5H, Ar), 8.53 (s, 1H, -CH=N), 9.8 (s, 1H, OH), 11.79 (s, H, -COOH) ppm; ^{13}C NMR (DMSO) δ:56.04, 56.11, 106.25, 117.27, 117.75, 121.61, 126.56, 128.72, 139.21, 142.68, 148.08, 158.92, 159.32, 171.59 ppm; Mass m/z: 318 (M+1)

IIIb: 2-hydroxy-5-{[(*E*)-(4-hydroxy-3-methoxyphenyl) methylidene]amino}benzoic acid:
IR (KBr) υ_{max}: 3068 (O-H str); 2934(C-H str); 1667(C=O str); 1584 (C=N str); 1501 (C=C str); 1212 (Asym C-O-C str); 1140 (sym C-O-C str) cm^{-1}; ^1H NMR (DMSO) δ: 3.85 (s, 3H, OCH_3), 6.72 (s, 1H, OH), 6.88-7.67 (m, 6H, Ar), 8.52 (s, 1H, -CH=N), 9.8(s, 1H, OH), 11.23 (s, 1H, -COOH) ppm; ^{13}C NMR (DMSO) δ: 55.50, 110.54, 115.30, 117.16, 117.63, 121.63, 123.75, 127.79, 128.49, 142.67, 147.89, 150.05, 158.66, 159.22, 171.50 ppm; Mass m/z: 288 (M+1).

IIIc: 2-hydroxy-5-{[(*E*)-(4-hydroxyphenyl) methylidene]amino}benzoic acid:
IR (KBr) υmax: 3077 (O-H str); 2923 (C-H str); 1659 (C=O str); 1599 (C=N str); 1500, 1454, 1415 (C=C str) cm-1; 1H NMR (DMSO) δ: 6.72 -7.79 (m, 7H, Ar), 8.53 (s, 1H, -CH=N), 9.79 (s, 1H, OH), 10.13 (s, 1H, OH), 11.12 (s, 1H, -COOH) ppm; Mass m/z: 258 (M+1)

IIId: 5-{[(*E*)-(3,4-dihydroxyphenyl)methylidene]amino}-2-hydroxybenzoic acid:
IR (KBr) υmax: 3433 (O-H str); 3063, 2980 (C-H str);); 1670 (C=O str); 1592 (C=N str); 1530,1497,1425 (C=C str) cm-1; 1H NMR (DMSO) δ: 6.71-7.64 (m, 6H, Ar), 8.44 (s, 1H, -CH=N), 9.28 (s, 1H, OH), 9.53 (s, 1H, OH), 9.70 (s, H, OH), 10.09 (s, 1H, -COOH) ppm

IIIe: 5-{[(*E*)-1, 3-benzodioxol-5-ylmethylidene]amino}-2-hydroxybenzoic acid:
IR (KBr) υ_{max}: 3056 (O-H str); 2984, 2910 (C-H str); 1670 (C=O str); 1576 (C=N str); 1457 (C=C str); 1259 (Asym C-O-C str); 1112 (sym C-O-C str) cm^{-1}; ^1H NMR (DMSO) δ: 6.12 (s, 2H, -O-CH_2-O-), 6.98-7.68 (m, 6H, Ar), 8.57 (s, 1H, -CH=N), 9.81(s, 1H, OH), 11.37 (s, 1H, -COOH) ppm; Mass m/z: 286 (M+1).

IIIf: 5-{[(*E*)-(3,4-dimethoxyphenyl)methylidene]amino}-2-hydroxybenzoic acid:
IR (KBr) υ_{max}: 3059 (O-H str); 3019, 2962 (C-H str); 1674 (C=O str); 1598 (C=N str); 1519, 1471, 1438 (C=C str); 1280 (Asym C-O-C str); 1148 (sym C-O-C str) cm^{-1}; ^1H NMR (DMSO) δ: 3.84 (s, 6H, OCH_3), 6.77-7.69 (m, 6H, Ar), 8.58 (s, 1H, -CH=N), 9.85 (s, 1H, OH), 11.55 (s, 1H, -COOH) ppm; ^{13}C NMR (DMSO) δ: 55.48, 55.66, 109.68, 111.43, 113.54, 117.76, 121.86, 123.66, 128.68, 129.14, 142.70, 149.04, 151.74, 158.61, 159.39, 171.60 ppm; Mass m/z: 302 (M+1).

IIIg: 2-hydroxy-5-{[(*E*)-(3,4,5-trimethoxyphenyl) methylidene]amino}benzoic acid:
IR (KBr) υ_{max}: 3072 (O-H str); 3008, 2941 (C-H str); 1676 (C=O str); 1629 (C=N str); 1586,1501,1461 (C=C str); 1261 (Asym C-O-C str); 1127 (sym C-O-C str) cm^{-1}; ^1H NMR (DMSO) δ: 3.74-3.86 (2s, 9H, OCH_3), 6.77-7.72 (m, 5H, Ar), 8.61 (s, 1H, -CH=N), 9.89 (s, 1H, OH), 11.98 (s, 1H, -COOH) ppm; ^{13}C NMR (DMSO) δ: 55.97, 56.10, 60.14, 105.88, 113.46, 117.84, 121.89, 128.91, 131.60, 140.33, 142.46, 153.13, 158.73, 159.55, 171.57 ppm; Mass m/z: 332 (M+1).

IIIh: 5-({(*E*)-[4-(dimethylamino) phenyl]methylidene}amino)-2-hydroxybenzoic acid:
IR (KBr) υ_{max}: 3077 (O-H str); 3037, 2920 (C-H str); 1661 (C=O str); 1661 (C=N str); 1497 (C=C str); cm^{-1}; ^1H NMR (DMSO) δ: 3.05-3.06 (2s, 6H, N-CH_3), 6.69-7.85 (m, 7H, Ar), 8.60 (s, 1H, -CH=N), 9.67 (s, 1H, OH) ppm; Mass m/z: 285 (M+1)

IIIi:5-{[(*E*)-(3-bromo-4-hydroxy-5-methoxyphenyl) methylidene]amino}-2-hydroxybenzoic acid:
IR (KBr) υ_{max}:3216 (O-H str); 2973 (C-H str); 1669 (C=O str); 1600 (C=N str); 1566, 1503, 1434 (C=C str); 1282 (Asym C-O-C str); 1192 (sym C-O-C str) cm^{-1}; ^1H NMR (DMSO) δ: 3.91 (s, 3H, OCH_3), 6.74-7.73 (m, 5H, Ar), 8.54 (s, 1H, -CH=N), 9.78 (s, 1H, OH), 10.17 (s, 1H, OH), 11.54 (s, 1H, -COOH)ppm; Mass m/z: 366, 368 (M+2)

IIIj: 2-hydroxy-5-{[(*E*)-(4-hydroxy-3-iodo-5-methoxyphenyl)methylidene]amino}benzoic acid:
IR (KBr) υ_{max}: 3084 (O-H str); 2967,2930 (C-H str); 1652 (C=O str); 1594 (C=N str); 1560, 1495,1428 (C=C str); 1184 (Asym C-O-C str); 1140 (sym C-O-C str) cm^{-1}; ^1H NMR (DMSO) δ: 3.90 (s, 3H, OCH_3), 6.73-7.84 (m, 5H, Ar), 8.52 (s, 1H, -CH=N), 9.76 (s, 1H, OH), 10.26 (s, 1H, OH), 11.15 (s, 1H, -COOH) ppm; Mass m/z: 414 (M+2)

***In Vitro* Antioxidant activity**

The title compounds were evaluated for *in vitro* antioxidant activity by assay of DPPH radical scavenging[15] and assay of nitric oxide radical scavenging[16].

Assay of DPPH radical scavenging

Solutions of various test compounds at 100 µM concentration were added to 100 µM DPPH in 95% ethanol. The test tubes were kept at ambient temperature for 20 minutes and the absorbance was measured at 517 nm. Control experiment was carried out with solvent only. Ascorbic acid and 5-amino salicylic acid were used as reference standards for comparison. All the measurements were run in triplicate. The percentage of scavenging activity was calculated as follows:

$$\text{Radical Scavenging Activity (\%)} = \frac{[\text{Absorbance of Control} - \text{Absorbance of Test}]}{\text{Absorbance of Control}} \times 100$$

Assay of nitric oxide radical scavenging

Sodium nitroprusside (10 µM) in phosphate buffer pH 7.4 was incubated with 100 µM concentration of drug dissolved in alcohol, the tubes were incubated at 25˚C for 120 minutes. Control experiment was kept without test compound but an equal amount of solvent was added in an identical manner. After incubation, 2 ml of incubation solution was removed and added to 2ml of Griess reagent. The absorbance of the chromophore formed during diazotization of nitrite with Sulphanilamide and subsequent coupling with N-(1-Naphthyl)ethylenediamine was measured at 546 nm. All the measurements were run in triplicate and the percentage of scavenging activity was calculated using the above formula.

Antibacterial activity[17-18]

The individual bacterial inoculums were uniformly spread using sterile cotton swab on solidified nutrient agar medium in different sterile petri plates. Three cups of 8 mm diameter were made in each petri plate using a sterile borer. Then 0.1 ml of each test solution containing 100 µg was added to the cups aseptically and the petri plates were labeled accordingly. Simultaneously, 0.1 ml of dimethylformamide was added in another petri plate to observe the solvent effect on antibacterial activity and a positive control was maintained by employing 0.1

ml of standard solution containing 100µg streptomycin. The plates were incubated for 24 h at 36ºC ± 1ºC, under aerobic conditions. After incubation, confluent bacterial growth was observed and the zones of inhibition of bacterial growth were measured in millimeters (mm).

RESULTS AND DISCUSSION

A series of 5-aminosalicylic acid Schiff bases (**IIIa-IIIj**) were synthesized in single step by adopting an eco-friendly grinding method[10], which is mainly concentrated on the formation of Schiff linkage between free amino group of 5-aminosalicylic acid and carbonyl group of various substituted benzaldehydes. The mixture consisting equimolar quantities of 5-aminosalicylic acid and substituted benzaldehyde was triturated vigorously in a clean and dry motar using pestle made of porcelain. The grinding process was continued till yellow or orange coloured product was obtained. The reactivity of carbonyl compounds towards 5-aminosalicylic acid differs with respect to reaction time. Among the series, two compounds **IIIb** and **IIIh** were synthesized previously by conventional method[9] and in the present study these compounds were synthesized by grinding technique. This green synthetic protocol is highly efficient as it avoids the use of hazardous solvents at any stage of the reaction. However, all the synthesized compounds were recrystallised using methanol. The purity of synthesized compounds was confirmed by TLC. The yield of the compounds was high and ranging from 75% to 98%. The percentage yields and the melting points were presented in Table 1. The structures of these compounds were established by means of their IR, ^{1}H NMR, ^{13}C NMR and Mass spectra.

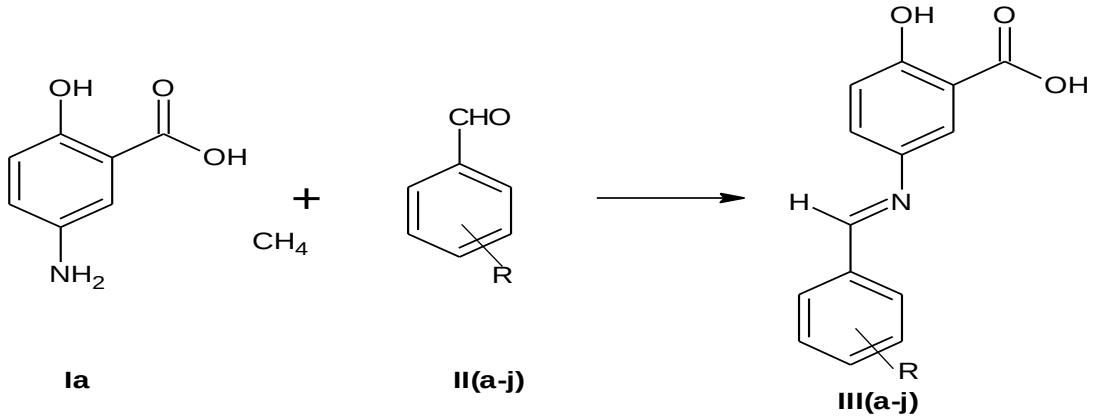
The IR spectra of all the compounds (**IIIa-IIIj**) showed the absence of bands at 3245 and 1745 cm^{-1} due to free amino group of 5-aminosalicylic acid and C=O of aldehyde, respectively. Instead, a new prominent band was observed in the range of 1661-1576 cm^{-1} due to azomethine C=N linkage in all the compounds indicating the nucleophilic addition of free amino group of 5-aminosalicylic acid to carbonyl group of substituted benzaldehyde. The IR spectra of all the compounds showed broad absorption bands at 3433-3056 cm^{-1}due to the O-H stretching, while the bands observed at 3077-2910cm^{-1} indicate aromatic and aliphatic C-H stretching. The bands observed in the range 1676-1652 cm^{-1} due to the C=O stretching of carboxylic acid. The absorption bands at 1594-1415cm^{-1} indicates the C=C stretching of aromatic ring. The IR spectra of compounds containing methoxy substitution revealed the presence of asymmetric and symmetric C-O-C stretching in the region of 1282-1184 cm^{-1}, 1192-1112 cm^{-1} respectively.

The IR spectral data was supported by ^{1}H NMR spectra which confirm the structure of synthesized compounds on the basis that the azomethine proton appearing as singlet resonated at δ values between 8.44-8.61. The spectra of all the compounds revealed the presence of singlet signals at δ value between 10.09 -11.98 due to the carboxylic acid proton and at δ value between 6.72 - 10.26 due to the phenolic OH proton. It should be noted that the phenolic protons appeared as singlet at high δ values due to intramolecular hydrogen bonding with the neighboring oxygen atom of carboxylic group in all the title compounds and nearness to the electron withdrawing halogen atoms as in compounds **IIIi** and **IIIj.** The aromatic protons of all the synthesized compounds were appeared as multiplets at δ value between 6.69 -7.85. The methoxy protons of **IIIa, IIIb, IIIf, IIIg, IIIi** and **IIIj** were appeared as singlet peaks between δ 3.74-3.91 and N-dimethyl protons of compound **IIIh** were observed in a range of δ 3.05-3.06 as singlet.

The ^{13}C NMR spectra of compounds **IIIa, IIIb, IIIf** and **IIIg** showed absorption peaks at δ 171.56-171.60 and at δ 159.22-159.55 confirms the presence of COOH carbon and carbon attached to OH of 5-aminosalicylic acid respectively. The spectra also exhibited the absorption peaks in a range of δ 158.61-158.92 confirmed the presence of azomethine carbon. All aromatic carbons were observed in a range of δ 105.8-159.5 and the methoxy carbons were observed in a range of δ 55.48-60.14. The spectra of compounds **IIIa, IIIb** showed absorption peaks at δ 139.21 and 150.05 confirms the presence of carbons containing OH group of N-benzylidene moiety. The mass spectra of the compounds were recorded in positive ion mode and the peaks observed as M+1 or M+2 confirm their molecular formulae.

The *in vitro* antioxidant activity of all the synthesized compounds were evaluated by scavenging DPPH and nitric oxide free radicals and the data was given in table-2. Interestingly, all the evaluated compounds exhibited excellent antioxidant activity in DPPH radical scavenging and the reason for better activity may be due to the presence of salicylic acid moiety in all the compounds. It was evident from the activity data that the structural modification on N-benzylidene ring of the compounds (**IIIa-IIIj**) showed slight change in their antioxidant properties. A considerable increase in the percentage of DPPH radical scavenging activity was found with compounds **IIIa-IIIh**, this may be due to increase in the hydrogen donating properties. However, compound **IIIi** and **IIIj** were found to be less active when compared with the precursor 5-aminosalicylic acid and standard ascorbic acid. In nitric oxide scavenging activity all the compounds exhibited better antioxidant activity than the 5-aminosalicylic acid but they were found to be less active when compared with the standard tocopherol. Among the series, compounds **IIIe**, **IIId**, **IIIc** and **IIIh** showed prominent activity in decreasing order of percentage nitric oxide scavenging with values 52.5, 49.2, 46.5 and 46.1 respectively. Further, the results revealed that the modification of phenolic hydroxyl group to methoxy group and introduction of halogen atom on the N-benzylidene ring causes reduction in scavenging of nitric oxide free radical.

The antibacterial activities of the synthesized compounds were evaluated against gram negative and gram positive bacteria such as *E. coli*, *P. aeruginosa*, *S. aureus* and *B. subtilis* by agar well diffusion method. The antibacterial activity data of all the synthesized compounds was given in table-3. The activity data revealed that the compounds **IIIj** and **IIIg** showed good zone of inhibition towards all tested organisms. The activity of these compounds was found to be greater when compared with 5-aminosalicylic acid and was found to be less than the standard compound streptomycin. On observation of results, it can be concluded that the antibacterial activity depends on the nature of bacterial strain and chelating ability of the Schiff base.



Scheme-I: Synthesis of 5-aminosalicylic acid Schiff bases

(Ia): 5-aminosalicylic acid
(IIa-IIj): Substituted benzaldehydes
(IIIa-IIIj): Substituted Schiff bases of 5-aminosalicylic acid

Table 1: The Physical data of 5-aminosalicylic acid Schiff bases (IIIa-IIIj)

Compound	R	Mol. Formula	M.P (ºC)	Yield (%)	R_f value*
IIIa	3,5-$(OCH_3)_2$, 4-OH	$C_{16}H_{15}NO_6$	279-281	98	0.43
IIIb	3-OCH_3 , 4-OH	$C_{15}H_{13}NO_5$	237-239 (241-242)	80	0.49
IIIc	4-OH	$C_{14}H_{11}NO_4$	289-291	84	0.44
IIId	3,4-$(OH)_2$	$C_{14}H_{11}NO_5$	248-250	99	0.52
IIIe	3,4-O-CH_2-O-	$C_{15}H_{10}NO_5$	255-257	77	0.46
IIIf	3,4-$(OCH_3)_2$	$C_{16}H_{15}NO_5$	243-245	86	0.43
IIIg	3,4,5-$(OCH_3)_3$	$C_{17}H_{17}NO_6$	255-257	83	0.58
IIIh	4-$N(CH_3)_2$	$C_{15}H_{16}N_2O_3$	256-258 (238-239)	76	0.51
IIIi	3-Br, 4-OH, 5-OCH_3	$C_{15}H_{12}NO_5Br$	254-256	90	0.55
IIIj	3-I, 4-OH, 5-OCH_3	$C_{15}H_{12}NO_5I$	231-233	75	0.52
Ia	5-aminosalicylic acid	$C_7H_7NO_3$	276-278 (282-284)	-	-

*Solvent system (Benzene : Ethyl acetate 1:2)

Table-2: The *in vitro* antioxidant activity data of 5-aminosalicylic acid Schiff bases (IIIa-IIIj)

Compounds	R	% inhibition at 100 µM	
		DPPH	NO
IIIa	3,5-$(OCH_3)_2$, 4-OH	76.9	39.9
IIIb	3-OCH_3 , 4-OH	73.7	37.6
IIIc	4-OH	74.9	46.5
IIId	3,4-$(OH)_2$	74.3	49.2
IIIe	3,4-O-CH_2-O-	76.6	52.5
IIIf	3,4-$(OCH_3)_2$	76.0	27.8
IIIg	3,4,5-$(OCH_3)_3$	75.2	36.1
IIIh	4-$N(CH_3)_2$	76.3	46.1
IIIi	3-Br, 4-OH, 5-OCH_3	71.7	36.1
IIIj	3-I, 4-OH, 5-OCH_3	68.3	27.2
Ia	5-aminosalicylic acid	72.0	21.6
Standard	Ascorbic acid	69.5	11.9

Table-3: The Antibacterial activity data of 5-aminosalicylic acid Schiff bases (IIIa-IIIj)

Compound	R	*Escherichia coli*	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	*Bacillus subtilis*
		Zone of inhibition (mm)			
IIIa	3,5-$(OCH_3)_2$, 4-OH	14	NA	14	12
IIIb	3-OCH_3 , 4-OH	20	NA	20	13
IIIc	4-OH	15	NA	18	17
IIId	3,4-$(OH)_2$	14	NA	15	18
IIIe	3,4-O-CH_2-O-	15	12	20	14
IIIf	3,4-$(OCH_3)_2$	14	17	15	18
IIIg	3,4,5-$(OCH_3)_3$	19	19	19	19

IIIh	4-N(CH_3)$_2$	NA	14	14	15
IIIi	3-Br, 4-OH, 5-OCH_3	NA	16	12	16
IIIj	3-I, 4-OH, 5-OCH_3	20	23	17	22
Ia	5-aminosalicylic acid	16	15	13	17
standard	streptomycin	28	30	26	29

NA = less than 10mm

CONCLUSION

The present study revealed the successful synthesis of various novel 5-aminosalicylic acid Schiff bases by adopting an eco-friendly grinding technique. Interestingly, all the compounds exhibited excellent *in vitro* antioxidant properties in both DPPH and nitric oxide scavenging assays when compared with 5-aminosalicylic acid indicates the structural importance of azomethine. The difference in response of studied Schiff bases was due to the different substitution on the N-benzylidene ring. The antibacterial activity of the evaluated compounds showed good to moderate antibacterial activity. Since the 5-aminosalicylic acid Schiff bases possess better *in vitro* antioxidant properties than 5-aminosalicylic acid, they may further be evaluated against diseases associated with oxidative stress such as cancer, inflammation and also against inflammatory bowel disease.

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