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Synthesis and Characterization of Aryl Alkanoic Acids as Potential Antimicrobial Agents

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Aryl alkanoic acid moieties are important because of its versatile biological actions. In the present study, aryl alkanoic acids (**IIIa-j**) have been synthesized by the condensation of 4-aminobenzoic acid (**I**) with various aromatic halides (**IIa-j**) in presence of glacial acetic acid. The structures of the newly synthesized compounds were characterized on the basis of elemental analysis, UV, IR and ^{1}H NMR spectral data. The synthesized compounds were screened for their *in vitro* growth inhibiting activity against different strains of bacteria and fungi *viz.*, *Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa, Candida albicans* and *Aspergillus niger* were compared with the standard antibiotics such as amikacin (30 µg/mL) and fluconazole (100 µg/mL) using well agar diffusion technique. Compounds (**IIIa**, **IIIe**, **IIIh** and **IIIi**) showed comparable antibacterial activity.

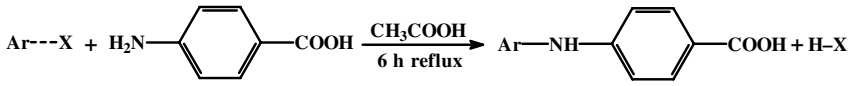
Key Words: Aryl alkanoic acids, 4-Aminobenzoic acid, Aromatic halides, Amikacin, Fluconazole, Antimicrobial evaluation.

INTRODUCTION

Aryl alkanoic acids provide one of the most fascinating class of compounds recognized for various pharmacological activities like antimicrobial[1], anticonvulsive[2] antipyretic, analgesic, antiinflammatory activity[3-5], used extensively in the treatment of rheumatic fever, arthritis (rheumatic, osteo and jaundice arthritis)[6-8], myocardial infarctions (disease associated with platelet aggregability, *e.g.*, coronary artery disease and post operative deep vein thrombosis), angiotensin-II receptor antagonist and management of primary dysmennorrhea[9]. Nalidixic acid is well known for its antibacterial activity against chronic urinary tract infections[10,11].

4-Aminobenzoic acid used as building block in the design of drugs and it exhibit wide range of therapeutic uses, such as antibacterial, antineoplastic, anticonvulsant, antiarrhythmic, antiemetic, local anesthetic, gastrokinetic, antipsychotic, sun-screening, neuroleptic and migraine prophylactic[12].

The good biological profile of aromatic acid derivatives prompted us to synthesize various aryl alkanoic acids by the condensation of 4-amino benzoic acid with various aromatic halides in the hope of getting potent biodynamic agents.



(I) **(IIa-j)** **(IIIa-j)**

Compd. Ar	Compd. Ar	Compd. Ar
IIIa : 2,4-$(NO_2)_2C_6H_3$	**IIIb** : 4-$COOHC_6H_4$	**IIIc** : C_6H_5CO
IIId : 4-$CH_3COC_6H_4$	**IIIe** : 4-$NH_2C_6H_4$	**IIIf** : 4-$COOHCH_2C_6H_4$
IIIg : 4-$CH_3CONHC_6H_4$	**IIIh** : 4-$CH_3COC_6H_4CO$	**IIIi** : 4-$CH_3C_6H_4SO_2$
IIIj : 4-$NO_2C_6H_4$		

Scheme-I: Synthetic route for the synthesis of aryl alkanoic acids (**III a-j**)

EXPERIMENTAL

The purity of all the compounds were checked by TLC on precoated Silica-60F_{254} plates (Merck, Mumbai) using iodine vapours and UV light as detecting agents with the solvent system of hexane:ethanol:acetic acid (65:30:5). The melting points of the synthesized compounds were recorded by open capillaries in a liquid paraffin bath and are uncorrected. The absorbance maxima (λ_{max}) of the synthesized compounds were determined on a Systronics UV-Visible double beam spectrophotometer (2201) in methanol. The IR Spectra of the synthesized compounds were recorded on a Perkin Elmer Spectrum RX I, FTIR spectrophotometer using potassium bromide (anhydrous IR grade) pellets. ^{1}H NMR spectra were recorded on AMX-400, NMR spectrometer using DMSO-d_6 as solvent and TMS as an internal standard (chemical shift in δ ppm). The structures of the newly synthesized compounds were assigned on the basis of elemental analysis and were recorded on a Carlo Erba 1108 Heraeus at Regional Sophisticated Instrumentation Centre, CDRI, Lucknow. All the chemicals used were of LR and AR grade and was procured from S.D. Fine Chem. Ltd., New Delhi, Merck, Mumbai and Central Drug House Pvt. Ltd., Delhi, India.

General procedure for the synthesis of aryl alkanoic acids (IIIa-j): A mixture of different aromatic halide(s) (0.01 mol) with 4-amino benzoic acid (1.3713 g, 0.01 mol) in glacial acetic acid (25 mL) was heated under reflux for 6 h. The progress of the reaction was monitored by TLC using hexane:acetic acid:ethanol (65:5:30) as eluent. The reaction mixture was poured onto crushed ice with continuous stirring. The solid that separated was collected by filtration, washed well with cold water, dried in vacuum and recrystallized from absolute ethanol. Yield and melting point of the product(s) were determined and presented. Adopting the above procedure 10 different aryl alkanoic acids (**IIIa-j**) were synthesized and their characterization data are presented in Table-1.

TABLE-1
CHARACTERIZATION DATA OF ARYL ALKANOIC ACIDS

Compd.	m.f. (m.w.)	Elemental analysis: Calcd. (Found) %		
		C	H	N
IIIa	$C_{13}H_9N_3O_6$ (303.330)	51.49 (51.47)	2.99 (2.96)	13.85 (13.83)
IIIb	$C_{14}H_{11}NO_4$ (257.240)	65.36 (65.32)	4.31 (4.27)	5.44 (5.39)
IIIc	$C_{14}H_{11}NO_3$ (241.240)	60.70 (60.68)	4.59 (4.57)	5.80 (5.76)
IIId	$C_{15}H_{13}NO_3$ (255.270)	70.57 (70.52)	5.13 (5.08)	5.48 (5.43)
IIIe	$C_{13}H_{12}N_2O_2$ (228.250)	68.40 (68.36)	5.29 (5.31)	12.27 (12.25)
IIIf	$C_{15}H_{13}NO_4$ (271.272)	66.41 (66.38)	4.83 (4.79)	5.16 (5.13)
IIIg	$C_{15}H_{14}N_2O_3$ (270.287)	66.65 (66.65)	5.22 (5.21)	10.36 (10.33)
IIIh	$C_{15}H_{13}NO_4$ (271.273)	66.4 (66.35)	4.83 (4.80)	5.16 (5.12)
IIIi	$C_{14}H_{13}NO_4$ (259.261)	64.85 (64.83)	5.05 (5.02)	5.40 (5.39)
IIIj	$C_{14}H_{10}N_2O_4$ (258.230)	60.46 (60.69)	3.88 (3.90)	10.84 (10.80)

4-[(2,4-Dinitrophenyl)amino]benzoic acid (IIIa): Yield: 82.66 % (2.5 g); m.p. 212 °C; R_f value: 0.82; UV (λ_{max}, nm): 342.0; IR (KBr, ν_{max}, cm^{-1}): 3321 (N-H, aromatic secondary amine), 3310 (carboxylic O-H), 3070 (aromatic C-H), 1526 (NO_2, asym), 1725 (carboxylic C=O), 1348 (NO_2, sym), 1298 (aromatic C-N); ^{1}H NMR (DMSO-d_6, δ ppm): 7.22-7.58 (7H, m, Ar-H); 2.06-2.49 (1H, s, NH), 10.22 (1H, s, COOH).

4,4'-Iminodibenzoic acid (IIIb): Yield: 76.56 % (1.96 g); m.p. 228 °C; R_f value: 0.72; UV (λ_{max}, nm): 352.0; IR (KBr, ν_{max}, cm^{-1}): 3360 (carboxylic O-H), 3330 (N-H), 3056 (aromatic C-H), 1760 (carboxylic C=O), 1595 (aromatic C=C), 1292 (aromatic C-N); ^{1}H NMR (DMSO-d_6, δ ppm): 7.28-7.52 (8H, m, Ar-H), 2.12-2.28 (1H, s, NH), 10.18 (1H, s, COOH).

4-(Benzoylamino)benzoic acid (IIIc): Yield: 87.20 % (2.1 g); m.p. 262 °C; R_f value: 0.69; UV (λ_{max}, nm): 346.0; IR (KBr, ν_{max}, cm^{-1}): 3440 (N-H secondary amide), 3350 (carboxylic O-H), 3325 (N-H), 3045 (aromatic C-H), 1756 (carboxylic C=O), 1638 (C=O, amide), 1599 (aromatic C=C), 1425 (C-N); ^{1}H NMR (DMSO-d_6, δ ppm): 7.32-7.58 (9H, m, Ar-H), 8.27 (1H, s, CONH), 10.12 (1H, s, COOH).

4-[(4-acetylphenyl)amino]benzoic acid (IIId): Yield: 82.41 % (2.1 g); m.p. 248 °C; R_f value: 0.79; UV (λ_{max}, nm): 286.0; IR (KBr, ν_{max}, cm^{-1}): 3340 (carboxylic O-H), 3325 (N-H), 3045 (aromatic C-H), 2962 (methyl C-H, γas CH_3), 2872 (γsy CH_3), 1750 (carboxylic C=O), 1685 (C=O aceto), 1590 (aromatic C=C), 1286 (aromatic C-N); ^{1}H NMR (DMSO-d_6, δ ppm): 7.22-7.58 (8H, m, Ar-H), 2.22-2.48 (1H, s, NH), 10.26 (1H, s, COOH); 2.51 (3H, s, $COCH_3$).

4-[(4-Aminophenyl)amino]benzoic acid (IIIe): Yield: 79.01 % (1.8 g); m.p. 210 °C; R_f value: 0.68; UV (λ_{max}, nm): 240.0; IR (KBr, ν_{max}, cm^{-1}):

3510 (N-H aromatic primary amine, asym), 3421 (N-H, sym), 3336 (N-H), 3030 (aromatic C-H), 1711 (carboxylic C=O), 3380 (O-H), 1595 (aromatic C=C), 1296 (aromatic C-N secondary amine), 1290 (aromatic C-N primary amine); ^{1}H NMR (DMSO-d_6, δ ppm): 7.18-7.71 (8H, m, Ar-H), 2.18-2.26 (1H, s, NH), 9.98 (1H, s, COOH), 4.40-4.62 (2H, s, NH_2).

4-{[4-(Carboxymethyl)phenyl]amino}benzoic acid (IIIf): Yield: 83.09 % (2.25 g); m.p. 202 °C; R_f value: 0.59; UV (λ_{max}, nm): 292.0; IR (KBr, ν_{max}, cm^{-1}): 3360 (carboxylic O-H), 3340 (N-H), 3338 (N-H secondary amine), 3065 (aromatic C-H), 2924 (methylene C-H, γasy CH_2), 2853 (γsy CH_2), 1710 (carboxylic C=O), 1600 (aromatic C=C), 1298 (aromatic C-N secondary amine); ^{1}H NMR (DMSO-d_6, δ ppm): 7.21-7.64 (8H, m, Ar-H), 2.26-2.68 (1H, s, NH), 10.24 (2H, s, 2COOH), 2.24 (2H, s, CH_2).

4-{[4-(Acetylamino)phenyl]amino}benzoic acid (IIIg): Yield: 74.34 % (2.0 g); m.p. 232 °C; R_f value: 0.62; UV (λ_{max}, nm): 234.0; IR (KBr, ν_{max}, cm^{-1}): 3430 (N-H secondary amide), 3338 (N-H secondary amine), 3310 (carboxylic O-H), 3070 (aromatic C-H), 2962 (methyl C-H stretch, γas CH_3), 2872 (γsy CH_3), 1720 (carboxylic C=O), 1680 (C=O, amide), 1605 (aromatic C=C), 1285 (aromatic C-N secondary amine); ^{1}H NMR (DMSO-d_6, δ ppm): 7.15-7.68 (8H, m, Ar-H), 2.12-2.42 (1H, s, NH), 10.44 (1H, s, COOH), 8.51 (1H, s, CONH), 2.75 (3H, s, $COCH_3$).

4-[(4-Acetylbenzoyl)amino]benzoic acid (IIIh): Yield: 79.40 % (2.15 g); m.p. 255 °C; R_f value: 0.78; UV (λ_{max}, nm): 295.0; IR (KBr, ν_{max}, cm^{-1}): 3310 (carboxylic O-H), 3300 (N-H), 3060 (aromatic C-H), 2954 (methyl C-H, γas CH_3), 2870 (methyl C-H, γsy CH_3), 1710 (carboxylic C=O), 1599 (aromatic C=C), 1290 (aromatic C-N), 1246 (asym C-O-C), 1040 (sym C-O-C); ^{1}H NMR (DMSO-d_6, δ ppm): 7.22-7.48 (8H, m, Ar-H), 8.53 (1H, s, CONH), 10.27 (1H, s, COOH), 3.85 (3H, s, OCH_3).

4-{[(4-Methylphenyl)sulfonyl]amino}benzoic acid (IIIi): Yield: 73.42 % (1.90 g); m.p. 199 °C; R_f value: 0.68; UV (λ_{max}, nm): 259.0; IR (KBr, ν_{max}, cm^{-1}): 3330 (carboxylic O-H), 3262 (N-H secondary sulfonamide), 3060 (aromatic C-H), 2962 (methyl C-H, γas CH_3), 2872 (methyl C-H, γsy CH_3), 1710 (carboxylic C=O), 1355 (asym $S(=O)_2$), 1177 (sym $S(=O)_2$); ^{1}H NMR (DMSO-d_6, δ ppm): 7.13-7.52 (8H, m, Ar-H), 10.6 (1H, s, SO_2NH), 10.12 (1H, s, COOH), 2.37 (3H, s, CH_3).

4-[(4-Nitrophenyl)amino]benzoic acid (IIIj): Yield: 83.41 % (2.15 g); m.p. 258 °C; R_f value: 0.71; UV (λ_{max}, nm): 330.0; IR (KBr, ν_{max}, cm^{-1}): 3348 (N-H), 3310 (carboxylic O-H), 3070 (aromatic C-H), 1725 (carboxylic C=O), 1525 (asym, NO_2), 1349 (sym, NO_2), 1306 (C-N, aromatic secondary amine), 854 (C-N, $ArNO_2$); ^{1}H NMR (DMSO-d_6, δ ppm): 7.12-7.58 (8H, m, Ar-H), 2.17-2.32 (1H, s, NH), 9.96 (1H, s, COOH).

Screening of antimicrobial activity: The antimicrobial activity of all the newly synthesized compounds were determined by well plate method[13,14]

in nutrient agar (Hi-Media) was used for antibacterial activity and Sabouraud dextrose agar (Hi-Media) was used for antifungal activity. The bacterial strains used were *Bacillus subtilis* (ATCC 6633) and *Staphylococcus aureus* (ATCC 25923) for gram positive and *Escherichia coli* (ATCC 25922) and *Pseudomonas aeruginosa* (ATCC 27853) for gram negative and for fungal strain *viz.*, *Candida albicans* (ATCC 10231) and *Aspergillus niger* (ATCC 16404). The petridishes used for antibacterial screening were incubated at 37 ± 1 ºC for 24 h, while those used for antifungal activity were incubated at 28 ºC for 48-72 h. The diameters of zone of inhibition (mm) surrounding each of the wells were recorded.The results were compared to Amikacin (30 µg/mL) for antibacterial activity and fluconazole (100 µg/mL) for antifungal activity by measuring zone of inhibition in mm at 100 µg/mL concentration using well plate method. The results for the antimicrobial screening are presented in Table-2.

TABLE-2
ANTIBACTERIAL AND ANTIFUNGAL SCREENING RESULTS OF ARYL ALKANOIC ACIDS

Compd.	Antibacterial activity				Antifungal activity	
	Zone of inhibition (mm)				Zone of inhibition (mm)	
	S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. niger*
IIIa	24	21	23	21	12	10
IIIb	21	19	20	18	11	9
IIIc	20	18	21	17	10	8
IIId	18	15	17	16	9	7
IIIe	22	20	22	21	10	9
IIIf	19	16	18	17	8	6
IIIg	20	16	20	17	9	8
IIIh	23	20	22	21	12	10
IIIi	22	22	22	21	13	11
IIIj	19	18	15	17	10	9
Amikacin	24	21	23	22	-	-
Fluconazole	-	-	-	-	24	19

RESULTS AND DISCUSSION

All the compounds were active against all the four bacteria tested at 100 µg/mL concentrations. Compounds (**IIIa**, **IIIe**, **IIIh** and **IIIi**) showed comparable activity against *Staphylococcus aureus, Bacillus subtilis, Escherichia coli* and *Pseudomonas aeruginosa* at 100 µg/mL concentration using amikacin (30 µg/mL) as standard. But the other compounds (**IIIb**,

IIIc and **IIIg**) showed moderate activity and compounds (**IIId**, **IIIf** and **IIIj**) showed mild antibacterial activity against both gram positive and gram negative organisms. All the synthesized compounds (**IIIa-j**) showed mild antifungal activity at 100 µg/mL concentration. Compound **IIIa** and **IIIi** showed better antifungal activity against *Candida albicans* using fluconazole (100 µg) as standard.

The activity of the compounds depends upon the nature and position of the substituents at aryl alkanoic acid moiety. It can be concluded from antimicrobial activity that aryl alkanoic acids were substituted with 2,4-dinitro phenyl, 4-aminophenyl and *p*-toluene sulphonyl groups the antimicrobial activity is altered to appreciable extent.

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