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4-phenyldiazenyl 2-(phenylimino methyl) phenols; synthesis and *in-vitro* biological evaluation as potential antibacterial agents

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Abstract
A new series of 4-phenyldiazenyl 2-(phenylimino methyl) phenols were synthesized by the condensation of 5-[(2-chloro phenyl) diazenyl] 2-hydroxybenzaldehyde with different substituted aromatic amines and sulphonamides. All the synthesized compounds were screened *in-vitro* for their antibacterial activity against different human pathogens viz: *B. anthracis, E.coli, S. aureus, S. typhimurium,* and *P. aeruginosa* using disk diffusion assay. All the compounds exhibited considerable inhibition against the bacteria tested.

Keywords: *Antibacterial screening, imines, multidrug resistant, disc diffusion, 2-phenyldiazenyl 2-(phenylimino methyl) phenols*

Introduction

In all over the world, population is exposed to the burden of fatal microbial diseases. Due to acquire bacterial resistant and toxicity of drugs have highlighted the urgent need to discover new antibiotics, preferably those affordable to developing countries where infectious diseases are predominant. For the treatment of microbial infections an urgent need to develop new drugs either by synthesis of analogues, modifications in existing compounds or searching novel structure, that the concerned organisms has never been presented with before, [1].

It is evident that in azomethine derivatives the C═N linkage is an essential structural requirement for biological activity. These compounds are readily hydrolyzed under acidic conditions leading to active aldehydes which can act as alkylating agents [2]. Besides, several azomethines have been reported to possess remarkable antibacterial [3–9], antifungal [10–14], anticancer [15–19], antioxidant [20], antimycobacterial [21], antitumor [22–24], antiviral [25], antiHIV [26–28] herbicidal [29] and diuretic activities [30]. The azomethine derivatives and their complexes derived from *o*-formylphenoxyacetic acid with aminothiazoles, a number of aminobenzene derivatives, and some heterocyclic & aliphatic amines have revealed biological significance such as antimetabolites of pyridoxal phosphate [31], bacteriostatic activity [32] and chorismate synthase inhibition [33]. Many attempts have been made to synthesize, characterize and to study structure-activity relationship (SAR) of schiff bases [34–37]. In view of conclusions drawn from our previous work [38–42] and looking to the antimicrobial efficacy of $-SO_2NH_2$, $-SO_2NHC(NH)NH_2$, $-Cl$ and $-OCH_3$ moieties attached to aryl ring it seems logical and attractive to combine all these moieties together in a parent molecule. This study was aimed at exploring the potential antibacterial activity resulting from the combination of pharmacophores in one structure. The results of this study may be useful to researchers attempting to gain more insight into the antibacterial activity of azomethine derivatives. In present piece of research work we have selected substituted aromatic amines having above mentioned moieties, for the

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synthesis of azo salicylaldehyde and finally converted it into imine by condensing with appropriate substituted aromatic amines. Synthesized compounds were characterized by elemental analysis, IR, ^{1}H NMR & mass spectral analysis and evaluated for their antimicrobial efficacy.

Materials and methods

Chemistry

All the melting points were determined in open glass capillary and are uncorrected. The purity of compounds was ascertained by TLC on silica gel plates and spots were visualized using iodine vapors, purified by recrystallisation and column chromatography. Elemental analysis was carried out on Carlo Erba 1108 analyzer. The IR spectra were recorded on Perkin Elmer spectrophotometer, ^{1}H NMR spectra were recorded on Varian EM-390 MHz NMR spectrometer in DMSO d_6 using TMS as internal reference and chemical shift values were expressed in ppm δ Bruker DRX 300 (300 MHz, FT NMR); MS–FAB: Jeol–SX 102 Mass spectrometer.

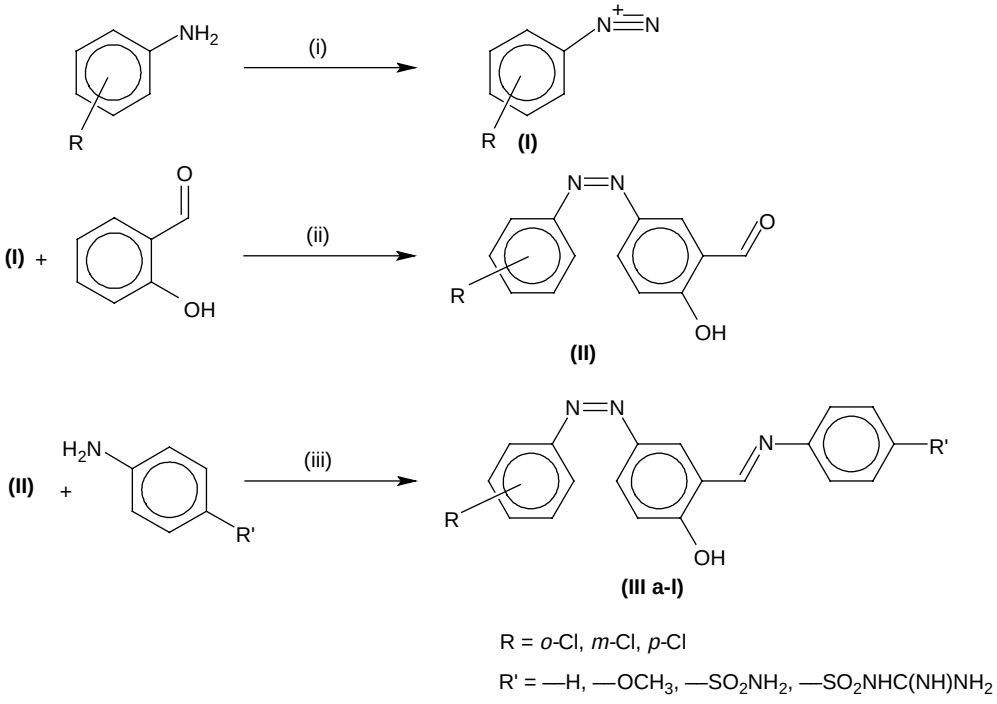
Our general synthetic route leading to new imines involved the preparation of suitably substituted aromatic azoaldehyde and subsequent coupling reaction with suitable aromatic amine resulting different aromatic imines is shown in Scheme 1.

General procedure for synthesis of compounds

*2-hydroxy-5-[phenyldiazenyl] benzaldehyde (**I**)*. Aniline (3.72 mL) was dissolved in aqueous hydrochloric acid (28 mL, 6 N) and mechanically stirred at 0–5°C. The cold solution of sodium nitrite (5 g in 10 mL water) was added to constantly stirred reaction mixture drop by drop.The diazotized solution was immediately added in small portions in salicylaldehyde (5 mL dissolved in 40 mL 6 N NaOH), during constant stirring at 0–5°C.The stirring was continued for 4h. The solid obtained was filtered under suction washed with cold water and recrystallised from glacial acetic acid.

*4- [(-2-chlorophenyl) diazenyl] -2-[(4-substituted phenyl)imino]methyl phenol (**III**)*. A mixture of appropriate, 2-hydroxy-5-[phenyldiazenyl] benzaldehyde (**I**) (1.30 g) and the suitable aniline (**II**) (0.46 g) were refluxed for 8 h in DMF (30 mL). The mixture was then cooled in ice bath and the product separated was repeatedly washed with water followed by ethanol and recrystallised from diethyl ether.

III(a). Recrystallization from diethyl ether: Yield 56.2.%; m.p. 208°C; IR (KBr) cm^1 3400 cm^{-1} (O—H), 3250 cm^{-1}(N—H),1620(CH═N), 1573(N═N) 1310, 1115(S—O), 745(C—Cl); ^{1}HNMR (DMSO d_6)δ, ppm: 9.3 (s, 1H, OH), 8.3 (s, 1H, CH═N), 7.3–7.6 (m, 11H, Ar—H), 6.8



Reagents and Conditions: (i) $NaNO_2$, HCl; 0-5°C **(ii)** NaOH; 0-5°C
(iii) EtOH; reflux for 8h

Scheme 1. General Synthetic Strategy for **III**(**a-l**).

(s, 1H, SO_2NH), 5.7(s, 2H, NH_2); Anal. Calcd. For $C_{20}H_{17}N_6O_3SCl$: C 52.57, H 3.75, N 18.39, Found C 52.53, H3.70, N18.33%; MS-FAB: (m/z) 456(M^+), 458(M + 2).

III(b). Recrystallization from diethyl ether: Yield 83.6%; m.p. 180°C; IR (KBr) cm^1 3420 cm^{-1}(O—H), 3310 cm^{-1} (N—H), 1630 (CH═N), 1560(N═N) 1300, 1105(S—O), 735(C—Cl). ^{1}HNMR (DMSO d_6)δ, ppm: 9.2(s, 1H, OH), 8.1 (s, 1H, CH═N), 7.2–7.7 (m, 11H, Ar—H), 6.3 (s, 1H, SO_2NH) Anal. Calcd. For $C_{19}H_{15}N_4O_3SCl$: C 55.01, H 3.64, N 13.50 Found C54.95, H3.60, N13.45%; MS-FAB: (m/z) 414(M^+), 416(M + 2).

III(c). Recrystallization from diethyl ether: Yield 71.4%; m.p. 184°C; IR (KBr) $cm^1$3410 cm^{-1} (O—H), 1617(CH═N), 1595(N═N), 715(C—Cl). ^{1}HNMR (DMSO d_6)δ, ppm: 9.4 (s, 1H, OH), 8.3 (s, 1H, CH═N), 7.0–7.6 (m, 11H, Ar—H), 3.5 (3H, m, OCH_3). Anal. Calcd. For $C_{20}H_{16}N_3O_2Cl$ C 65.67, H 4.41, N 11.49 Found C 64.61, H 4.36, N11.45%; MS-FAB: (m/z) 365(M^+), 367(M + 2).

III(d). Recrystallization from diethyl ether: Yield 89.8%; m.p. 202°C; IR (KBr) cm^1 3422 cm^{-1} (O—H), 1620 (CH═N), 1573 (N═N), 735(C—Cl). ^{1}H NMR (DMSOd_6)δ, ppm: 9.3 (s, 1H, OH), 8.5 (s, 1H, CH═N), 7.3–7.6 (m, 11H, Ar—H). Anal. Calcd. For $C_{19}H_{14}N_3OCl$: C 67.96, H 4.20, N 12.51 Found C67.90, H 4.15, N 12.46%; $C_{19}H_{14}N_3OCl$; MS-FAB: (m/z) 335(M^+), 337(M + 2).

III(e). Recrystallization from diethyl ether: Yield 57%; m.p. 206°C; IR (KBr) cm^1 3430 cm^{-1} (O—H), 3250 cm^{-1}(N—H), 1625(CH═N), 1570(N═N) 1315, 1115(S—O), 745(C—Cl); ^{1}HNMR (DMSO d_6)δ, ppm: 9.4 (s, 1H, OH), 8.2 (s, 1H, CH═N), 7.3–7.6 (m, 11H, Ar—H), 6.8 (s, 1H, SO_2NH), 5.7(s, 2H, NH_2); Anal. Calcd. For $C_{20}H_{17}N_6O_3SCl$: C 52.57, H 3.75, N 18.39, Found C 52.53, H3.70, N18.33%; MS-FAB: (m/z) 456(M^+), 458(M + 2).

III(f). Recrystallization from diethyl ether: Yield 80.6%; m.p. 201°C; IR (KBr) cm^1 3400 cm^{-1}(O—H), 3320 cm^{-1} (N—H), 1620 (CH═N), 1560(N═N) 1310, 1105(S—O), 735(C—Cl). ^{1}HNMR (DMSO d_6)δ, ppm: 9.2(s, 1H, OH), 8.1 (s, 1H, CH═N), 7.2–7.7 (m, 11H, Ar—H), 6.3 (s, 1H, SO_2NH) Anal. Calcd. For $C_{19}H_{15}N_4O_3SCl$: C 55.01, H 3.64, N 13.50 Found C54.95, H3.60, N13.45%; MS-FAB: (m/z) 414(M^+), 416(M + 2).

III(g). Recrystallization from diethyl ether: Yield 75.4%; m.p. 188°C; IR (KBr) $cm^1$3450 cm^{-1} (O—H), 1627(CH═N), 1595(N═N), 725(C—Cl). ^{1}HNMR (DMSO d_6)δ, ppm: 9.4 (s, 1H, OH), 8.3 (s, 1H, CH═N), 7.0–7.6 (m, 11H, Ar—H), 3.5 (3H, m, OCH_3). Anal. Calcd. For $C_{20}H_{16}N_3O_2Cl$ C 65.67, H 4.41, N 11.49 Found C 64.61, H 4.36, N11.45%; MS-FAB: (m/z) 365(M^+), 367(M + 2).

III(h). Recrystallization from diethyl ether: Yield 82.8%; m.p. 196°C; IR (KBr) cm^1 3422 cm^{-1} (O—H), 1620 (CH═N), 1573 (N═N), 730(C—Cl). ^{1}H NMR (DMSOd_6)δ, ppm: 9.3 (s, 1H, OH), 8.5 (s, 1H, CH═N), 7.3–7.6 (m, 11H, Ar—H). Anal. Calcd. For $C_{19}H_{14}N_3OCl$: C 67.96, H 4.20, N 12.51 Found C67.90, H 4.15, N 12.46%; $C_{19}H_{14}N_3OCl$; MS-FAB: (m/z) 335(M^+), 337(M + 2).

III(i). Recrystallization from diethyl ether: Yield 59.2.%; m.p. 217°C; IR (KBr) cm^1 3400 cm^{-1} (O—H), 3250 cm^{-1}(N—H), 1620(CH═N), 1583(N═N) 1310, 1115(S—O), 745(C—Cl); ^{1}HNMR (DMSO d_6)δ, ppm: 9.3 (s, 1H, OH), 8.3 (s, 1H, CH═N), 7.3–7.6 (m, 11H, Ar—H), 6.8 (s, 1H, SO_2NH), 5.7(s, 2H, NH_2); Anal. Calcd. For $C_{20}H_{17}N_6O_3SCl$: C 52.57, H 3.75, N 18.39, Found C 52.53, H3.70, N18.33%; MS-FAB: (m/z) 456(M^+), 458(M + 2).

III(j). Recrystallization from diethyl ether: Yield 81.6%; m.p. 213°C; IR (KBr) cm^1 3420 cm^{-1}(O—H), 3310 cm^{-1} (N—H), 1630 (CH═N), 1570(N═N) 1300, 1105(S—O), 738(C—Cl). ^{1}HNMR (DMSO d_6)δ, ppm: 9.2(s, 1H, OH), 8.1 (s, 1H, CH═N), 7.2–7.7 (m, 11H, Ar—H), 6.3 (s, 1H, SO_2NH) Anal. Calcd. For $C_{19}H_{15}N_4O_3SCl$: C 55.01, H 3.64, N 13.50 Found C54.95, H3.60, N13.45%; MS-FAB: (m/z) 414(M^+), 416(M + 2).

III(k). Recrystallization from diethyl ether: Yield 73.4%; m.p. 184°C; IR (KBr) $cm^1$3410 cm^{-1} (O—H), 1617(CH═N), 1590(N═N), 715(C—Cl). ^{1}HNMR (DMSO d_6)δ, ppm: 9.4 (s, 1H, OH), 8.3 (s, 1H, CH═N), 7.0–7.6 (m, 11H, Ar—H), 3.5 (3H, m, OCH_3). Anal. Calcd. For $C_{20}H_{16}N_3O_2Cl$ C 65.67, H 4.41, N 11.49 Found C 64.61, H 4.36, N11.45%; MS-FAB: (m/z) 365(M^+), 367(M + 2).

III(l). Recrystallization from diethyl ether: Yield 84.8%; m.p. 154°C; IR (KBr) cm^1 3422 cm^{-1} (O—H), 1620 (CH═N), 1583 (N═N), 735(C—Cl). ^{1}H NMR (DMSOd_6)δ, ppm: 9.3 (s, 1H, OH), 8.5 (s, 1H, CH═N), 7.3–7.6 (m, 11H, Ar—H). Anal. Calcd. For $C_{19}H_{14}N_3OCl$: C 67.96, H 4.20, N 12.51 Found C67.90, H 4.15, N 12.46%; $C_{19}H_{14}N_3OCl$; MS-FAB: (m/z) 335(M^+), 337(M + 2).

Microbiology

All the compounds were screened for their *in vitro* antimicrobial activity at Birla Institute of Medical Research and College of Life Sciences, Gwalior against 24 h old cultures of bacterial and fungal pathogens. Screening facilities (including pathogens, media and instruments) required, were provided by the same institute. Antimicrobial activity was determined against *Staphylococcus aureus, Escherichia coli, Salmonella typhimurium, Bacillus anthracis,* and *P.aeruginosa*, bacterial strains using disc diffusion assay. For this sterile filter

Table I. *In vitro* antibacterial activity of the newly synthesized compounds IIIa-l (1000μg /disc).

			B.anthrasis		*S.aureus*		*E.coli*		*S.typhimurium*		*P.aeruginosa*	
Comp	R	R′	*Z I*	*% I*	*Z I*	*% I*	*Z I*	*% I*	*Z I*	*% I*	*Z I*	*% I*
IIIa	*o*-Cl	$SO_2NHC(NH)NH_2$	27	69.23	31	77.50	25	71.42	25	65.78	23	65.71
IIIb	*o*-Cl	SO_2NH_2	25	64.10	27	67.50	23	65.71	23	60.52	20	57.14
IIIc	*o*-Cl	OCH_3	23	58.97	24	60.00	20	57.14	20	52.63	18	51.42
IIId	*o*-Cl	H	16	41.02	19	47.50	15	42.85	17	44.73	16	45.71
IIIe	*m*-Cl	$SO_2NHC(NH)NH_2$	25	64.10	26	65.00	23	65.71	22	57.89	21	60.00
IIIf	*m*-Cl	SO_2NH_2	23	58.97	21	52.50	20	57.14	18	47.36	17	48.57
IIIg	*m*-Cl	OCH_3	17	43.59	17	42.50	14	40.00	14	36.84	10	28.57
IIIh	*m*-Cl	H	13	33.33	15	37.50	12	34.28	11	31.42	–	0.00
IIIi	*p*-Cl	$SO_2NHC(NH)NH_2$	17	43.59	21	52.50	19	54.28	17	44.73	15	42.85
IIIj	*p*-Cl	SO_2NH_2	16	41.02	19	47.50	17	48.57	12	31.57	10	28.57
IIIk	*p*-Cl	OCH_3	14	35.89	15	37.50	15	42.85	07	18.42	–	0.00
IIIl	*p*-Cl	H	10	25.64	11	27.50	09	25.71	–	0.00	–	0.00
Std.			**39**	**100**	**40**	**100**	**37**	**100**	**38**	**100**	**35**	**100**

ZI, Zone of inhibition in mm; % I, Inhibition percentage; Std., Tetracycline; Control (DMF) = No activity.

paper disc (6 mm) impregnated with fixed doses (250, 500, 1000 μg/mL) of synthesized compounds under investigation were placed upon the seeded petri dishes. Similar disc were prepared for the standard drugs, tetracycline and solvent control, dimethyl formamide.The plates were allowed to stay for 24 h at 37°C for bacterial strains. The zone of inhibition, observed around the disc after incubation was measured. The compounds exhibited promising activities at 1000μg/disc concentration, are presented in Table I.

Results and discussion

In the present work, 12 new compounds were synthesized. The synthetic route for the compounds is outlined in Scheme 1. For the synthesis of the title compounds, azosalicylaldehyde required as starting material, was prepared for the first time by the diazotization of aniline and coupling with salicylaldehyde. The reaction of equimolar quantities of these azosalicylaldehyde (**I**) with respective aromatic amines in ethanol resulted in the formation of the title compounds (**IIIa-l**). The structures of the obtained compounds were elucidated by spectral data. In the IR spectra, some significant stretching bands due (CH═N) and (N═N) were at 1615 $cm^{-1}$and 1580 cm^{-1} respectively. In the ^{1}H-NMR spectra, all compounds (**IIIa-l**) were characterized by the presence of the imino protons (CH═N) at 8.1–8.5 ppm as a singlet. Mass spectra MS (FAB) of compounds showed M + and M + 2 peaks in agreement with their molecular formula. All compounds gave satisfactory elemental analysis.

The antibacterial activities of the synthesized compounds were screened *in-vitro* using *B.anthracis, S.aureus, E.coli, S.typhimurium* and *P.aeruginosa* at three different concentrations i.e., 250, 500 and 1000 μg/disc. The results of the biological evaluation, expressed as a zone of inhibition and percentage inhibition of the growth pathogens, are summarized in Table I, and compare with standard drug tetracycline. Inspite of all the tested compounds proved to be moderate active against bacterial pathogens, can be used as lead compounds. The activity was affected by substituents on the rings. Thus, compound **IIIa** which including *p*- Cl and —SO_2NHC(NH)NH2 groups showed the highest inhibition (77.50%). Other compounds showed varying degrees of inhibition between 00.00–67%. The MIC values against the test bacterial pathogens were determined at different concentration i.e. from 1000μg/mL to 15.62 μg/mL by serial dilution tube technique. For the most potent compounds **IIIa**, **IIIb**, **IIIe** and tetracycline control the MIC values are 250, 500, 500 and 125μg/mL respectively against the most inhibited bacterial pathogen *S.aureus.*

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