

FACILE REGIOSELECTIVE MONOBROMINATION OF ANILINES AND PHENOLS THROUGH GREEN PROTOCOL AND EVALUATION OF THEIR BIOACTIVITY

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ABSTRACT

Several bromoanilines and bromophenols were synthesized in good to nearly quantitative yields using a mixture of potassium bromide and potassium bromate in presence of dilute acid under mild conditions in a short time. Some of the prepared Bromo derivatives showed fairly strong antioxidant properties when screened for *in vitro* antioxidant activity using 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical and compared with standard natural antioxidant *L*-ascorbic acid. Most of the synthesized Bromo compounds displayed broad-spectrum activity against *Bacillus subtilis*, but except one, they were found to be inactive against *Escherichia coli*.

Keywords: Green Bromination, Bromoanilines, Bromophenols, DPPH Scavenging Activity, Antibacterial Activity
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INTRODUCTION

Methods for nuclear bromination of aromatic amines and phenols find attraction in the occurrence of brominated aromatic nuclei in a variety of naturally occurring and pharmaceutically important molecules. A wide range of biological activities like antibacterial, antifungal, antiparasitic, antiviral, antitumor, antioxidant, anti-inflammatory etc, are found in their properties. Several studies have also demonstrated that bromination can be an effective tool for enhancement of the potency of bioactive agents.¹⁻⁶ Commercially available organobromine pharmaceuticals include the vasodilator nicergoline, the sedative brotizolam, the anticancer agent pipobroman, and the antiseptic merbromin.⁷⁻¹⁰ Bromhexine and its metabolite ambroxol, acting as mucolytic agents, also possess brominated aniline nucleus.¹¹ Apart from being versatile pharmacophores, brominated aromatic nuclei are useful substrates in many important metals catalyzed cross-coupling reactions like Heck, Suzuki, Sonogashira, Stille, Buchwald – Hartwig etc.¹²⁻¹⁵

The conventional method of ring bromination involves the employment of elemental bromine along with a Lewis acid as the halogen carrier to generate the electrophile.¹⁶ However for activated nuclei like those of aromatic amines and phenols the halogen carrier may be omitted. This conventional method suffers from the disadvantage that elemental bromine is highly toxic, corrosive and causes several physiological distresses.¹⁷ So enormous amount of endeavor has been directed towards the achievement of ring bromination without elemental bromine since the last two decades. These so-called ‘Green Methods’ mainly rely on the generation of bromine *in situ* through oxidation of a suitable bromide.¹⁸⁻²² Ceric ammonium nitrate (CAN), orthoperiodic acid, hydrogen peroxide, sodium periodate, sodium bismuthate, sodium chlorite, benzyl triphenylphosphoniumperoxymonosulfate, oxone etc. are the common oxidizing agents used for this purpose.²³⁻⁴¹ These reagents suffer from the disadvantages that the reactions are mostly sluggish, often do not occur at room temperature and yields and regioselectivity of the products are not encouraging. A mixture of bromate and bromide in presence of acid can also release bromine *in situ* and was used for the bromination of alkenes, alkynes and carbonyls.⁴²⁻⁴⁶ However, to the best of our knowledge, when this methodology was employed in the bromination of aromatic amines and phenols, the reaction was lengthy, the omission of organic solvent was not possible, purification of the product required column chromatography and introduction of a single bromine atom in the nucleus was seldom

achieved.⁴⁶ Furthermore, neither of these papers dealt with the evaluation of bioactivity of the prepared bromo derivatives. Our objective, is, therefore, to achieve easy regioselective monobromination of anilines and phenols with potassium bromate and potassium bromide in the presence of dilute acid. The prepared bromo derivatives were screened for *in vitro* antioxidant activity using 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical and compared with standard natural antioxidant *L*-ascorbic acid. They were also evaluated for antibacterial activity against one Gram-positive (*Bacillus subtilis*) and one Gram-negative (*Escherichia coli*) strains using agar well diffusion method.

EXPERIMENTAL

Materials and Methods

All reagents and solvents used were purchased from Spectrochem, India. Thin-layer chromatography (TLC) was used to monitor the reactions using silica gel GF254 plates. The spots were detected by iodine vapor staining. Melting points were determined on an electrical melting point apparatus (S.I.) and are uncorrected. IR spectra were run on KBr pellets on a Perkin-Elmer 1330 apparatus. The ¹H and ¹³C NMR spectra were recorded for solutions in CDCl₃ with TMS as internal standard on a Bruker 300 NMR spectrometer operating at 300.13 and 75.47 MHz, respectively. Chemical shifts were expressed in ppm (δ) downfield relative to internal reference TMS and the splitting pattern abbreviations in ¹H spectra are as follows: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet. Elemental analyses were carried out on a Perkin Elmer instrument 2400 Series II CHN analyzer. Results obtained were within ± 0.3% of the theoretical value.

General Procedure For the Synthesis of Bromoanilines and Bromophenols

0.015 moles of aromatic amine or phenol were dissolved in 5-10 mL of glacial acetic acid. 1 gm of potassium bromate and 3.5 gm of potassium bromide were dissolved in 10-15 mL of water. The dissolution process may be hastened by slight warming. The solution of potassium bromide and potassium bromate at room temperature was slowly added to the solution of the substrate in glacial acetic acid with continuous stirring. The mixture was then left at room temperature for 5 minutes. Then 8-10 mL of 6 (N) HCl was added to the reaction mixture. After thorough stirring, the reaction mixture was left at room temperature for 10 - 30 minutes. Completion of the reaction was monitored by thin-layer chromatography. The reaction mixture was added to ice-cold water with continuous stirring. The precipitated product was filtered, washed well with cold water and dried. They were crystallized from aqueous ethanol to get the titled compounds (1 -10).

Characterization Data for Bromo Derivatives

2,6-Dibromo-4-methylaniline (1)

Time 10 min; Yield 92%, mp. 74°C; IR (KBr) $\nu_{\max}$: 690, 1492, 1585, 2960, 3380, 3490 cm⁻¹; ¹H NMR (CDCl₃): δ 2.21 (3H, s), 4.61 (2H, s), 6.98 (2H, s); ¹³C NMR : 19.2, 118.5, 132.2, 134.1, 152.3; Anal. Calcd. For C₇H₇NBr₂; C, 31.73; H, 2.66; N, 5.29%. Found C, 31.82; H, 2.69; N, 5.41%.

4-Bromo-2-nitroaniline (2)

Time 30 min; Yield 94%, mp. 112°C; IR (KBr) $\nu_{\max}$: 680, 1360, 1490, 1600, 3080, 3385, 3495 cm⁻¹; ¹H NMR (CDCl₃): 4.27 (2H, s), 6.66 (1H, d, *J* 8.8 Hz), 7.59 (1H, d, *J* 8.8 Hz), 8.22 (1H, s); ¹³C NMR : 110.9, 118.6, 126.4, 138.3, 140.4, 145.6; Anal. Calcd. For C₆H₅N₂OBr; C, 33.21; H, 2.32; N, 12.91%. Found C, 33.13; H, 2.39; N, 12.78%.

2-Bromo-4-nitroaniline (3)

Time 25 min; Yield 97%, mp. 104°C; IR (KBr) $\nu_{\max}$: 667, 1370, 1498, 1602, 3370, 3475 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): 4.24 (2H, s), 6.59 (1H, d, *J* 8.8 Hz), 7.89 (1H, dd, *J* 8.8 Hz, 2.1 Hz), 8.19 (1H, d, *J* 2.1 Hz); ¹³C NMR : 118.4, 120.6, 125.4, 127.7, 139.3, 155.1; Anal. Calcd. For C₆H₅N₂OBr; C, 33.21; H, 2.32; N, 12.91%. Found C, 33.29; H, 2.45; N, 12.99%.

2-Bromo-4-chloroaniline (4)

Time 20 min; Yield 88%, mp. 66°C; IR (KBr) $\nu_{\max}$: 665, 735, 1500, 1590, 3390, 3485 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): 4.10 (2H, s), 6.62 (1H, d, *J* 8.8 Hz), 7.12 (1H, dd, *J* 8.8 Hz, 2.2 Hz), 7.42 (1H, d, *J* 2.2

Hz); ^{13}C NMR : 117.4, 120.6, 124.3, 127.9, 130.8, 146.7; Anal. Calcd. For $\text{C}_6\text{H}_6\text{NBrCl}$; C, 34.90; H, 2.44; N, 6.78%. Found C, 34.79; H, 2.55; N, 6.89%.

3-Bromo-4-aminobenzoic acid (5)

Time 20 min; Yield 76%, mp. 212°C; IR (KBr) ν_{max} : 670, 1496, 1720, 1605, 3380, 3490 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz): 4.76 (2H, s), 6.56 (1H, d, J 8.8 Hz), 7.62 (1H, d, J 8.8 Hz), 8.23 (1H, s), 11.1 (1H, s); ^{13}C NMR : 114.6, 116.5, 119.4, 128.7, 132.9, 154.2, 165.6; Anal. Calcd. For $\text{C}_7\text{H}_7\text{NBrO}_2$; C, 38.92; H, 2.80; N, 6.48. Found C, 38.76; H, 2.95; N, 6.59%.

2,4,6-Tribromophenol (6)

Time 15 min; Yield 98%, mp. 98°C; IR (KBr) ν_{max} : 645, 1495, 1520, 3100, 3510 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz): 6.76 (1H, s), 7.62 (2H, s); ^{13}C NMR: 116.8, 118.8, 136.4, 152.8; Anal. Calcd. For $\text{C}_6\text{H}_3\text{OBr}_3$; C, 21.78; H, 0.91%; Found C, 21.66; H, 0.85%.

4-Bromo-2-nitrophenol (7)

Time 25 min; Yield 88%, mp. 92°C; IR (KBr) ν_{max} : 635, 1330, 1424, 1510, 3338, cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz): 7.03 (1H, d, J 8.8 Hz), 7.75 (1H, dd, J 8.8 Hz, 2.1 Hz), 8.25 (1H, d, J 2.1 Hz), 11.02 (1H, s); ^{13}C NMR : 114.3, 122.7, 126.6, 136.3, 140.7, 153.7; Anal. Calcd. For $\text{C}_6\text{H}_4\text{NO}_3\text{Br}$; C, 33.06; H, 1.85; N, 6.42%. Found C, 32.93; H, 1.73; N, 6.49%.

2-Bromo-4-nitrophenol (8)

Time 20 min; Yield 82%, mp. 110°C; IR (KBr) ν_{max} : 625, 1320, 1410, 1502, 3350, cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz): 6.86 (1H, s), 7.23 (1H, d, J 8.8 Hz), 8.15 (1H, d, J 8.8 Hz), 8.32 (1H, s); ^{13}C NMR : 113.2, 118.2, 126.3, 127.5, 143.7, 163.1; Anal. Calcd. For $\text{C}_6\text{H}_4\text{NO}_3\text{Br}$; C, 33.06; H, 1.85; N, 6.42%. Found C, 33.13; H, 1.92; N, 6.52%.

5-Bromovanillin (9)

Time 15 min; Yield 95%, mp. 162°C; IR (KBr) ν_{max} : 680, 1110, 1580, 1715, 2760, 2850, 3100, 3290, cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz): 3.76 (3H, s), 6.69 (1H, s), 7.11 (1H, d, J 1.9 Hz), 7.58 (1H, d, J 1.9 Hz), 9.95 (1H, s); ^{13}C NMR : 55.2, 112.6, 116.3, 126.5, 130.8, 145.4, 156.1, 190.6; Anal. Calcd. For $\text{C}_8\text{H}_7\text{O}_3\text{Br}$; C, 41.59; H, 3.05%; Found C, 41.51; H, 2.97%.

1-Bromo-2-naphthol (10)

Time 20 min; Yield 90%, mp. 80°C; IR (KBr) ν_{max} : 575, 1490, 3070, 3283 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz): 6.37 (1H, s), 6.69 (1H, d, J 8.6 Hz), 7.65 (1H, d, J 8.6 Hz), 7.45-8.12 (3H, m), 8.32 (1H, m); ^{13}C NMR : 104.4, 119.2, 123.3, 125.5, 126.8, 128.9, 130.5, 131.1, 132.5, 148.5; Anal. Calcd. For $\text{C}_{10}\text{H}_7\text{OBr}$; C, 53.84; H, 3.16%; Found C, 53.75; H, 3.09%.

Biological Assay

Determination of 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity

The DPPH radical scavenging ability of all the bromo derivatives was evaluated as previously delineated by Blois with some modifications.⁴⁷⁻⁴⁹ Briefly, the compounds were dissolved in a minimum volume of DMSO and diluted with PBS buffer. Different concentrations (1 - 100 μM) of the compounds under investigation were mixed with 0.1 mM methanolic solution of DPPH (SRL, India) and incubated in dark at 37°C for 30 minutes. The absorbance of the solution was measured with a digital colorimeter (Labtronics) at $\lambda = 517$ nm. *L*-ascorbic acid was taken as a standard positive control and DMSO as negative control. DPPH radical scavenging activity was calculated using the following equation:

$$\% \text{ of DPPH scavenging} = \frac{A(\text{control}) - A(\text{sample})}{A(\text{control})} \times 100$$

Where, A_{control} represents the absorbance of the control reaction (with all reagents except the test compound), and A_{sample} stands for the absorbance of the test sample. The concentration of the compound

showing 50% radical inhibitory activity (IC_{50}) was ascertained through Linear regression analysis. The experiment was carried out thrice and the data presented as the mean of three independent determinations.

Assessment of Antibacterial Activity

Bacterial Strains

One Gram-positive (*Bacillus subtilis*) and one Gram-negative (*Escherichia coli*) strains from American Type Culture Collection (ATCC) were used to examine the antimicrobial activity. The bacterial strains were maintained in Mueller-Hinton (M-H) agar medium (Hi Media, India) in slants at 4°C, and subcultured periodically.

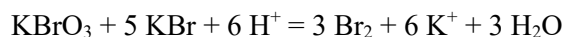
Determination of *In-vitro* Antibacterial Activity by Agar-well Diffusion Method

The antibacterial activity of the prepared bromo anilines and bromo phenols were carried out *in vitro* against the above two bacterial strains by agar-well diffusion assay.⁵⁰⁻⁵² Briefly, a number of colonies were picked up from the bacterial stock culture and transferred to 5 mL of sterile nutrient broth and incubated at 37°C for 18 hrs. Each bacterial culture was suspended in saline solution and adjusted to the final inoculum density of 1×10^7 CFU/mL (by 0.5 McFarland standard) on molten M-H agar plates. Once the agar was solidified, wells of uniform diameter (5 mm) were made with a sterile borer in the inoculated agar plates. 20 μ L solution containing different concentrations (0.05 – 0.5mg/mL) of prepared bromo derivatives was dispensed separately in each well under aseptic conditions. Ampicillin (Sigma-Aldrich, USA) was the standard drug used as a positive control at a concentration of 0.1 mg/mL, while DMSO was tested as vehicle control in this study. The plates were kept at room temperature for 2 hours to allow diffusion of the extracts into the agar and further incubated at 37°C for 24 hours. The diameters of inhibition zones around each well were measured. Each experiment was performed in duplicate to confirm the reproducibility and the best results were recorded.

RESULTS AND DISCUSSION

Chemistry

Potassium bromate and potassium bromide react in the presence of an acid to produce bromine according to the following equation.



This reaction shows that potassium bromate and potassium bromide react with each other in (1:5) mole ratio. When considered in weight this ratio becomes (1:3.5). Weights of bromate and bromide are so adjusted that 1.2 moles of bromine are produced *in situ* for one mole of the substrate amine or phenol.

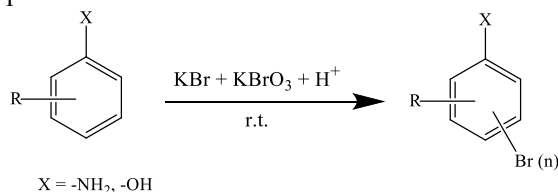
Amino and hydroxy functions activate the aromatic nuclei too strongly to arrest the reaction at monobromination. Simple aniline and phenol easily undergo tribromination on exposure to an even insufficient amount of bromine. However, if the nuclei contain any deactivating group the activation caused by mesomeric electron release of amino or hydroxy function may be expected to cut down so that introduction of a single bromine atom in the nucleus may be achieved. Among the amines we have used only *p*-toluidine contains two activating groups *viz.* amino and methyl. For other amines the groups (Cl, NO₂ and -COOH) are deactivating. So *p*-toluidine is expected to undergo bromination faster than the other amines. The result we have obtained is compatible with this speculation (Table-1). Furthermore, *p*-toluidine is found to undergo dibromination and when the amount of bromate and bromide is doubled only the dibrominated product is obtained. However, the other amines fail to produce any dibrominated product even when the amount of bromate and bromide is doubled at room temperature. It is noteworthy that aluminium bromide-catalysed aqueous phase bromination of 4-nitroaniline proceeds to dibromination when exposed to excess bromine.⁵³ Both ortho and para nitro anilines underwent exclusive dibromination in sufficiently higher time on bromination with (2:1) bromide-bromate reagent.⁴³ Monobromination of these compounds was accomplished in as many as 5 and 7 hours when benzyltriphenylphosphoniumperoxymonosulfate was used along with potassium bromide.⁴⁰

Among the phenols salicylic acid produces 2,4,6-tribromo phenol. Initial decarboxylative bromination (*Ipso* substitution) is thought to precede further brominations and incorporation of bromine atoms in the nucleus fails to suppress the activation caused by the hydroxy function. Very strong activation of the aromatic nucleus by the phenolic -OH leads to tribromination even when stoichiometric amount of

bromine (a mixture of potassium bromate and bromide) is used. None of the other phenols afforded di or polybrominated derivatives. Here also these phenols contain deactivating groups like $-\text{NO}_2$ and $-\text{CHO}$ which may partially cut down the activation conferred by the $-\text{OH}$ function.

However, ortho nitrophenol underwent exclusive dibromination when brominated with sodium bromide in presence of oxone.⁴¹ Both ortho and para nitro phenols furnished exclusively the dibrominated products in considerably higher time on bromination with (2:1) bromide-bromate reagent.⁴³ Bromination of para nitrophenol with KBr and ZnAl-BrO_3 -Layered Double Hydroxides, however, afforded the monobrominated product but the yield was not promising and the reaction did not take place at room temperature.⁴⁶

Table-1: Preparation of Bromo Derivatives of Aromatic Amines and Phenols



Entry	Substrate	Time (min)	Product	Yield (%) ^a	Observed M.P. (°C)	Literature M.P. (°C) ⁵⁴
1		10		92	74	74-76
2		30		94	112	110-113
3		25		97	104	104-108
4		20		88	66	64-68
5		20		76	212	211-215
6		15		98	98	96

7		25		88	92	90-94
8		20		82	110	111-115
9		15		95	162	164
10		20		90	80	78-81

^ayields refer to the crude yields after workup

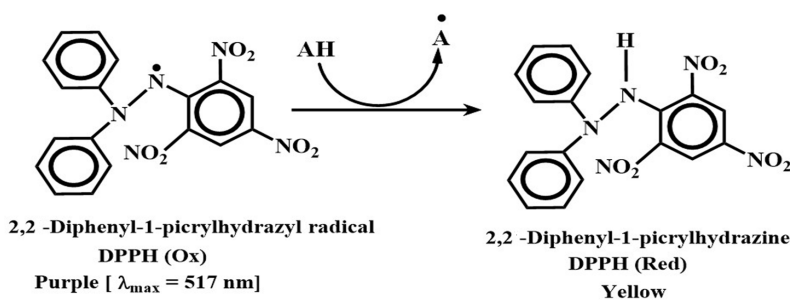
Biology

In-vitro DPPH Radical Scavenging Activity

The mechanism of DPPH radical scavenging activity is based on electron or hydrogen transfer capacity to the DPPH radical from the compound to form DPPH-H as shown in Scheme -1.

The data in terms of the respective IC_{50} values presented in Table-2 establishes the moderate to strong antioxidant property of most of the bromo derivatives, which indicates their radical scavenging as well as reducing abilities. However, compound **10** showed very poor activity and compound **1** could not scavenge 50% of the DPPH radicals even at the highest tested concentration (100 μ M) [Fig.-1].

Some compounds *viz.*, **3**, **5** and **8** exhibited potent activities suggesting that the substituents present in the respective aromatic ring may enhance the antioxidant activity by increasing their hydrogen transferability.



Scheme-1: Reaction of DPPH Radical with Antioxidant

Table-2: DPPH Radical Scavenging Activity of Bromo Derivatives

Compounds	IC_{50} (μ M) $\pm$ S.E.
1	> 100
2	30.59 ± 1.63
3	22.28 ± 0.63
4	76.28 ± 1.63
5	18.56 ± 1.27

6	30.64 ± 1.07
7	38.98 ± 0.51
8	26.27 ± 1.29
9	63.51 ± 1.35
10	88.17 ± 1.29
L- Ascorbic acid	8.44 ± 0.78

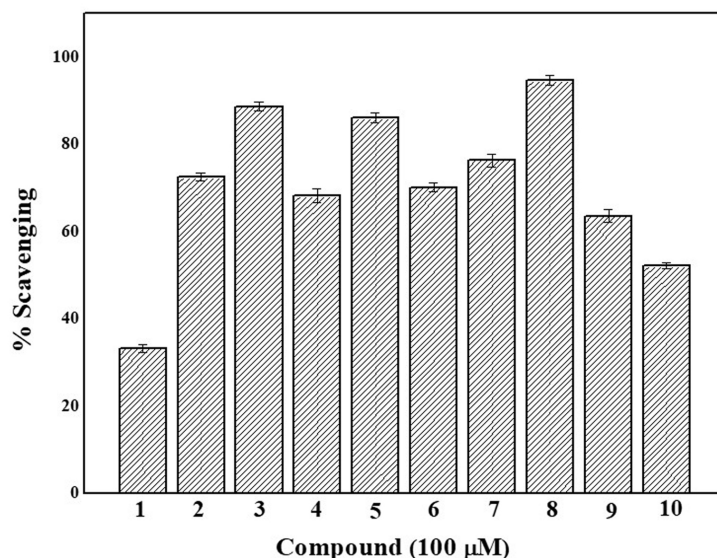


Fig.-1: *In vitro* DPPH Radical Scavenging Activity of Bromo Derivatives (100 μ M) of Aromatic Amines and Phenols. Error Bars represent the Standard Error in each Compound of three Separate Determinations

Antibacterial Activity

The antibacterial activity of prepared bromo derivatives against two bacterial strains was evaluated by agar-well diffusion method and expressed as the diameter of the inhibition zones in mm (Table-3 and Fig.-2).

Table- 3: Antibacterial Activity (Diameter of Inhibition Zone* in mm) of Bromo Derivatives of Aromatic Amines and Phenols

Compound ↓ Concentration → (in mg/ mL)	Gram-positive Bacteria (<i>Bacillus subtilis</i>)						Gram-negative Bacteria (<i>Escherichia coli</i>)					
	0.05	0.1	0.2	0.3	0.4	0.5	0.05	0.1	0.2	0.3	0.4	0.5
1	10	12	14	14	17	17	-	-	-	-	-	-
2	8	9	9	12	14	17	-	-	-	-	-	-
3	12	12	15	16	18	20	-	-	-	-	-	-
4	-	-	-	8	10	13	-	-	-	-	-	-
5	10	12	12	14	16	19	-	-	-	-	8	8
6	14	16	20	24	25	28	-	-	-	-	-	-
7	8	8	10	11	16	19	-	-	-	-	-	-
8	-	10	10	11	14	18	-	-	-	-	-	-
9	12	11	15	17	21	24	-	-	-	-	-	-
10	-	-	8	13	16	16	-	-	-	-	-	-
Ampicillin (0.1 mg/mL) [Positive control]	24						20					
DMSO [Vehicle control]	Not detected						Not detected					

* Including the diameter of well (5 mm); - No activity (diameter of the inhibition zone less than 7 mm).

The solvent vehicle DMSO, was found to be inactive against all the tested bacteria. At 0.1 mg/mL concentration, the positive control ampicillin showed a significant level of bacterial inhibition against both of these Gram-positive and Gram-negative strains. All of the bromo derivatives exhibited strong to moderate bactericidal activities against the Gram-positive organism (*Bacillus subtilis*) in a dose-dependent manner. The maximum zone of inhibition (24 mm) observed by 0.5 mg/mL concentration of compound **9** was nearly equivalent to that exhibited by 0.1 mg/mL of ampicillin, while only 0.3 mg/mL of compound **6** produced the same effect. However, except 3-bromo-4-aminobenzoic acid (**5**), all of these compounds did not show any activity against Gram-negative bacteria viz., *Escherichia coli* at any of the applied concentrations (0.05 - 2 mM). In fact, compound (**5**), exhibited moderate activity at higher doses (0.4 and 0.5 mg/mL) of concentrations.

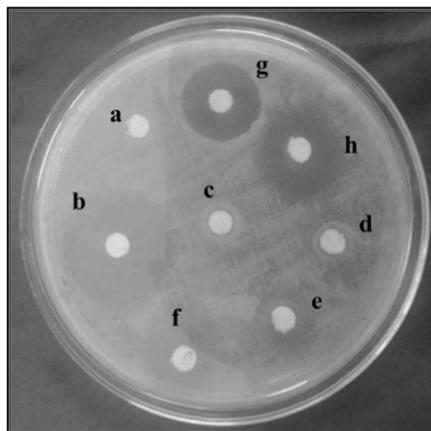


Fig.- 2: Antibacterial Activity of Compound **3** against *Bacillus subtilis*
a: DMSO; b: Ampicillin (0.1 mg/mL); c: 0.05; d: 0.1 mg/mL; e: 0.2 mg/mL;
f: 0.3 mg/mL; g: 0.4 mg/mL; h: 0.5 mg/mL of compound **3**

CONCLUSION

We have synthesized a few bromo anilines and bromophenols in good to excellent yields utilizing the green method *sans* elemental bromine. Except for two cases, regioselective monobromination was achieved. Operational simplicity coupled with easy isolation and purification of products renders this process an expedient and eco-friendly avenue to bromoanilines and bromophenols. These reactions occurred in a reasonably shorter time than those reported recently through the green protocol with no loss in yield of the product. Some of the bromo compounds showed a fairly strong antioxidant property. Most of them exhibited broad spectrum activity against *Bacillus subtilis*, but except one, they were found to be inactive against *Escherichia coli*. Promising radical scavenging and antimicrobial activity of the bromo derivatives prompt our attention towards undertaking a study on the synthesis of more bromo analogs, especially of heterocyclic origin as the latter presents a wide variety of versatile pharmacophore in future.

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