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A facile synthesis of *N*-phenyl-6-hydroxy-3-bromo-4-arylazo quinolin-2-ones under phase transfer catalytic conditions and studies on their antimicrobial activities

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The synthesis and characterization of *N*-phenyl-6-hydroxy-3-bromo-4-arylazoquinolin-2-ones has been reported under phase transfer catalytic conditions in 70% yields. Interaction of *N*-phenyl-2,5-dihydroxy-3-arylazo indoles with dibromocarbene under phase transfer catalysis conditions at 50-60°C and 600 r.p.m. results in a cycloaddition of the *in situ* generated carbene to the C=C bond followed by skeletal rearrangement in the indole frame work to yield quinoline nuclei. The structure of the compounds are established on the basis of their elemental, IR and ^{1}H NMR and ^{13}C NMR data. All the synthesized compounds have been evaluated for their *in vitro* growth inhibitory activity against *Escherichia coli*, *Pseudomonas diminuta*, *Bascillus subtilis*, *Bacillus megaterium* and *Staphylococcus aureus*. All the compounds show significant antibacterial activity. A perusal of data reveals that molecular refractive index (M_R) is correlated linearly to the drug activity. The synthesized compounds have been subjected to acute toxicity studies to find out LD_{50} values. The compounds do not show any toxicity up to dose of 7.5 mg/kg body weights in rats.

Keywords: Arylazo quinoline, phase transfer catalysis, antimicrobial activities
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The development of a facile procedure for the preparation of heterocyclic compounds is a major challenge of modern heterocyclic chemistry in view of the environmental, practical and hence economic issue. Quinolines are important class of heterocyclic compounds. The quinoline unit is an essential feature of many natural products and there are a large number of reactions that prepare quinolines. Quinoline ring system[1] occurs naturally and was originally isolated from coaltar. The quinoline skeleton has since been used as the basis for the design of many synthetic antimalarial compounds of which chloroquine[1] is one example. The tetrahydroquinoline derivative oxamniquine[2] is used to eradicate blood flukes (*Schistosome mansoni*), which are a major cause of disease in tropical regions. Quinolines and their derivatives have been extensively explored for their applications in the field of biological[3-5], antifilarial[6], antibacterial[7-8], antimalarial activities[9-14]. Quinolium derivatives have been widely used as novel inhibitors i.e., DHA topo isomerase II inhibitor[15], topoisomerase inhibitor[16], lipoxygenase inhibitor[17], kinase inhibitor[18]. The derivatives of quinolines are also extensively used as receptor agonists[19-23]. Cardiovascular[24] and antineoplastic[25] activities of quinoline derivatives have also been studied. The synthesis of some quinoline derivatives have been carried out by Diels-Alder reactions[26-28], [4 +2] cycloaddition reactions[29], Pauson-Khand reactions[30], and other procedures[31-34].

Likewise, phase transfer catalysis (PTC) is a potent and versatile synthetic tool and has been employed not only in organic chemistry[35] but also in inorganic chemistry[36], electrochemistry[37-39], photo-chemistry[40-41], polymer chemistry[42].

The increasing interest in the chemistry of quinoline and its substituted derivatives result from the wide possibilities of their practical application, in particular, as intermediate in organic synthesis and for obtaining biologically active therapeutic agents. Reaction of carbene with compounds containing multiple bonds under phase transfer catalysis (PTC) conditions is an effective approach to form cyclopropane derivatives and, hence, quinolines after ring expansion.

In view of these and in continuation of our earlier work on the synthesis of heterocycles[43,44], azo compounds[45,46] and biological activity[47,48], we report herein a convenient and efficient method for the

preparation of *N*-phenyl-6-hydroxy-3-bromo-4-arylazoquinolin-2-ones under PTC conditions. All the synthesized compounds have been characterized by elemental, IR, ^{1}H NMR and ^{13}C NMR data. An attempt has been made to understand the antimicrobial behaviour of these compounds *in vitro*.

Experimental Section

All the chemicals used were of AR grade. IR spectra (cm^{-1}) were scanned on a Shimadzu 460 IR spectrophotometer in KBr pellets. ^{1}H NMR and ^{13}C NMR spectra (δ, ppm) were recorded on a 300 MHz Bruker spectrometer with TMS as an internal standard. Melting points were determined in open capillary tubes using an electric melting point apparatus and are uncorrected. Purity of the compounds was checked by TLC using silica gel-G (E. Merk) in ethyl acetate : xylene (2:3 v/v) eluting system.

Preparation of N-phenyl-5-dihydroxy-3-arylazo indol-2-ones (1a-i). In a 250 mL R.B. flask, an equimolar quantity of pertinent 1-aminophenyl-2-arylhydrazono-butane-1,3-dione derivative (0.01 mole) and *p*-benzoquinone (1.8 gm, 0.01 mole) was taken together and allowed to undergo refluxation for a period of 4 hr in the presence of ethyl alcohol (25 mL) at reflux temperature. All the contents were cooled and kept overnight in refrigerator. A solid coloured mass thus appeared was filtered, washed with ether and recrystallized from a mixture of methanol and DMF (1:1,v/v) Physical features of all the compounds are given in **Table I** and they exhibit satisfactory elemental analysis and spectroanalytical data.

Preparation of N-phenyl-6-hydroxy-3-bromo-4-arylazo quinolin-2-ones (2a-i) *Method A.* A mixture of powdered potassium hydroxide (0.56 g, 0.01 mole), pertinent indole derivative **(1a-i)** (0.05 mole), bromoform (3.5 mL, 0.039 mole), tetrabutylammonium bromide (0.005 mole) and toluene (25 mL) were stirred at 600 r.p.m. for 3 hr in three necked glass reactor equipped with an air condenser, magnetic stirrer and a thermostat. The progress of the reaction was monitored by TLC. After the completion of the reaction the contents were diluted with water (100 mL) and the organic layer was separated, washed with water and brine and dried over anhydrous sodium sulphate. Evaporation of the solvent resulted in solidified product. The crude product on recrystallization from methanol gave a pure compound.

Method B. In a dry, 250 mL three-necked flask equipped with a dropping funnel and magnetic stirrer are placed a solution of sodium hydroxide (50%, 4 mL), 3-arylazo-5-hydroxy indole (0.05 mole) and cetyl triethylammonium bromide (0.006mole) in dry toluene (25 mL). To the ice-cooled solution, bromoform (10 mL) was added dropwise over about 30 min. The mixture was stirred at 20-30^{o}C for 48 hrs. The reaction mixture was poured into water (approx. 150 mL). The organic layer was separated, and dried over $MgSO_4$. The solvent was removed by distillation under reduced pressure and the residue was recrystallized from ethanol to give crystals of pure compound.

Results and Discussion

N-Phenyl-2,5-dihydroxy-3-arylazo indoles were synthesized under modified Neninzetsur conditions[49]. Dibromocarbene was used as the carbene component. It was generated by the usual method i.e., reaction of potassium hydroxide with bromoform in a two-phase system in the presence of tetrabutyl ammonium bromide (TBAB) as a phase transfer catalyst.

The starting indole derivative contains several reaction centers that can react with dibromocarbene. These are the C=C and N=N double bonds, C-H bonds and heteroatoms. It would be expected that the reaction products would be determined by competing formation of the possible alternate

Table I— Spectral data of some N-phenyl-2,5-dihydroxy-3-arylazo indoles

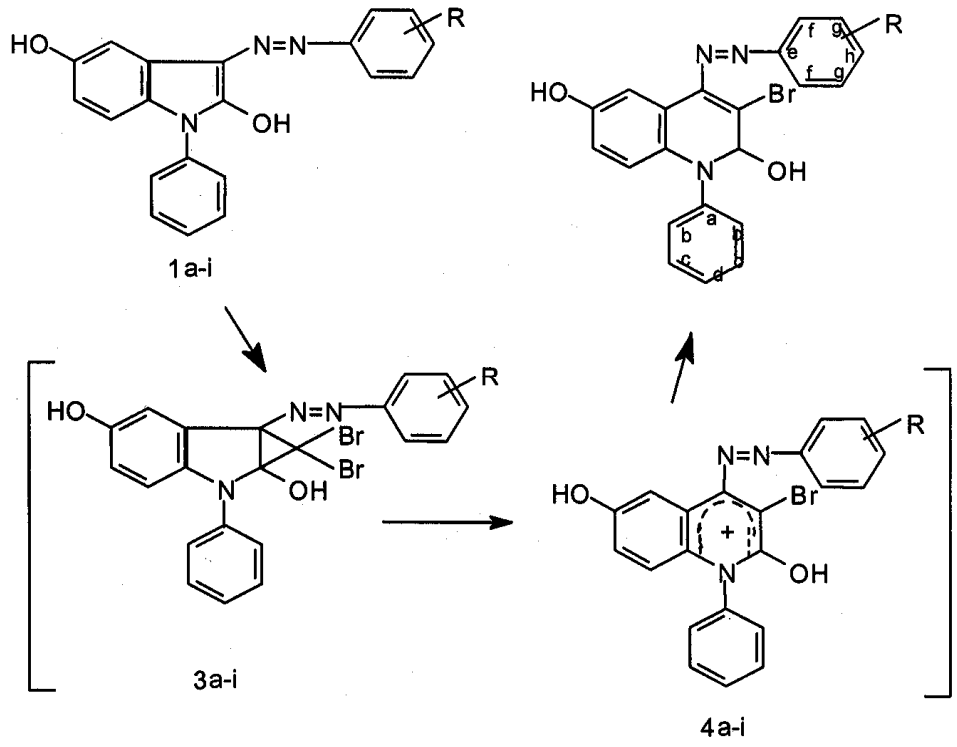
Compd. No.	R	IR (ν_{KBr}, cm^{-1})	^{1}H NMR (δ, ppm)
1a	H	3630 (OH); 3050 (C-H, Sp^2); 1660 (C=C); 1575 (N=N); 1600, 1500 (C⋯C, ring str.); 920, 740 (Sub. phenyl)	6.9 (d, 1H, H-8), 7.1 (d, 1H, H-7), 7.5 (S, 1H, H-5), 7.7-8.0 (S, 10H, Ar-H), 12.1 (bs, 2 × OH)
1b	4-CH_3	3550 (OH); 3080 (C-H, Sp^2); 2850 (C-H, Sp^3); 1630 (C=C); 1580 (N=N); 1590, 1490 (C⋯C, ring str.); 840, 720 (Sub. phenyl)	2.4 (S, 3H, CH_3), 6.8 (d, 1H, H-8), 7.0 (d, 1H, H-7), 7.2 (S, 1H, H-5), 7.4 (S, 5H, Ar-H), 7.9 (d, 2H, H_f × 2, *J* = 2Hz), 7.5 (d, 2H, Hg x 2, *J* = 2Hz)
1h	4-Cl	3660 (O-H); 3070 (C-H, Sp^2); 1640 (C=C); 1570 (N=N); 1600, 1490 (C⋯C, ring str.); 910, 840, 740 (Sub. phenyl)	6.9 (d, 1H, H-7), 7.0 (d, 1H, H-8), 7.2 (d, 1H, H-5), 7.5 (S, 5H, C_6H_5), 8.0 (d, 2H, H_f × 2, *J* = 2Hz), 7.7 (d, 2H, Hg x 2, *J* = 2Hz)

dibromocyclopropane structures namely the products of nucleophilic addition of the tribromomethylinium to the alkene or azo group. The introduction of the dibromocarbene into a C-H bond and the formation of ylide structures are due to carbene attack on the heteroatom free electron pair.

Under mild conditions (25–30°C), (1+2) cycloaddition at the C=C bonds of five membered fragment takes place to afford an intermediate dibromo species *N*-phenyl-2,6-dihydroxy-3,3-dibromo-4-arylazobenz-bicyclo[3.1.0]piperidine (**3a-i**). The formation of the products (**4a-i**) may occur through a skeletal rearrangement accompanied by expansion of the five membered ring and dehydrobromination. The overall result is hydrolysis of compounds (**4a-i**) and formation of N-phenyl-6-hydroxy-3-bromo-4-arylazo quinolin-2-ones **(2a-i)** (**Scheme I**). However, intermediate products *in situ* have not been isolated.

The reaction under phase transfer conditions is synthetically more viable and facile (method A with yield 65–74%) in comparison to method B with yield 43–62%. However, variation in the product yield can be accounted for the efficacy of catalytic ability of catalysts used in the study. The better catalysts seem to be those which have minimal lipophilicity and also have bulky groups surrounding the quaternary positively charged nitrogen atom. Tetrabutylammonium bromide is a much more efficient catalyst than cetyltriethylammonium bromide although the latter has six more carbon atoms than the former. The associated anion probably forms a tighter ion pair with the quaternary cation when the quat is less hindered than when the charge is buried. The structure of all the synthesized compounds were established on the basis of elemental, IR, ^{1}H NMR and ^{13}C NMR data.

2a: Yield: 65%, m.p. 170–71°C, Anal. Calcd for $C_{21}H_{16}BrN_3O_2$: C, 59.73, H, 3.82, N, 9.95. Found: C, 59.71, H, 3.80, N, 9.93. IR (cm^{-1}): 3550 (OH), 1660 (C=C), 1580 (N=N), 550 (C-Br); ^{1}H NMR (δ, ppm): 7.5 (S, 1H; H-5), 6.8 (S, 10H, Ar-H × 2) 7.0 (d, 1H, H-7, *J* = 6 Hz), 7.2 (d, 8-H, *J* = 6 Hz), 12.1 (bs, 2H, 2 × OH exchange); ^{13}C NMR (δ, ppm): 170.10 (C-2),



Where, R= (a) H (b) 4-CH_3 (c) 4-NO_2 (d) 2-NO_2 (e) 3-NO_2 (f) 2-Cl (g) 3-Cl (h) 4-Cl (i) 3-OH

Reagents & reaction conditions

Method A: $CHBr_3$/KOH/TBAB,stirring, 293K, 3hrs

Method B: $CHBr_3$/NaOH/CTEAB, stirring, 293K, 48 hrs

Scheme–I

132.5 (C-3), 117 (C-4), 115.1 (C-5), 155.6 (C-6), 114.3 (C-7), 128.6 (C-8), 140.2 (C-9), 162.1 (C-10), 145.87 (C_a), 143.5 (C_b), 124.8 (C_c), 120 (C_d), 113.6 (C_h), 132.0 (C_f), 129.1 (C_g), 132.6 (C_e).

2b: Yield: 68%, m.p.173–74°C; Anal. Calcd for $C_{22}H_{18}BrN_3O_2$: C, 60.56, H, 4.16, N, 9.63. Found: C, 60.52, H, 4.11, N, 9.60 IR (cm^{-1}); 3575 (OH), 1640 (C=C), 1590 (N=N), 575 (C-Br); ^{1}H NMR (δ, ppm): 2H (S, 3H; CH_3), 7.8 (S, 1H, H-3) 6.9 (d, 7-H, *J* = 5.5 Hz), 7.0 (d, 8-H, *J* = 5.5 Hz), 7.0 (d, 8-H, *J* = 5.5 Hz), 7.3 – 7.5 (m, 9H, Ar-H), 14.1 (S, OH); ^{13}C NMR (δ, ppm): 175.5 (C-2), 131.5 (C-3), 118 (C-4), 117.5 (C-5), 160.1 (C-6), 113.6 (C-7), 129.1 (C-8), 139.6 (C-9), 161.6 (C-10), 144.4 (C_a), 142.7 (C_b), 125.4 (C_c), 121.5 (C_d), 154.8 (C_h), 132.5 (C_f), 129.4 (C_g), 118.1 (C_h), 20.1 (-CH_3).

2c: Yield: 72%, m.p. 175–77°C; Anal. Calcd for $C_{21}H_{15}BrN_4O_4$: C, 53.98, H, 3.29, N, 11.99. Found: C, 53.95, H, 3.26, N, 11.97. IR (cm^{-1}): 3430 (OH), 1650 (C=C), 1575 (N=N), 555 (C-Br); ^{1}H NMR (δ, ppm): 7.6 (S, 1H; H-3), 7.0 (d, 7-H, *J* = 6.5 Hz), 7.3 (d, 8-H, *J* = 6.5 Hz), 7.4 – 5 (m, 5H, Ar-H), 11.1 (bs, OH); ^{13}C NMR (δ, ppm): 171.5 (C-2), 132.6 (C-3), 116.5 (C-4), 119.4 (C-5), 159.5 (C-6), 112.5 (C-7), 128.6 (C-8), 140.2 (C-9), 155.8 (C-10), 154.6 (C_a), 140.5 (C_b), 123.6 (C_c), 120.9 (C_d), 161.6 (C_e), 131.5 (C_f), 128.6 (C_g), 118.6 (C_h).

2h: Yield: 64%, m.p. 169–71°C, Anal. Calcd for $C_{21}H_{15}BrClN_3O_2$: C, 55.23, H, 3.31, N, 9.20. Found: C, 55.20, H, 3.29, N, 9.18. IR (cm^{-1}): 3600 (OH), 1630 (N=N), 880 (C-Cl), 550 (C-Br); ^{1}H NMR (δ, ppm): 7.9 (S, 11H; H-3), 6.9 (d, 7-H, *J* = 6.2 Hz), 7.1 (d, 8-H, *J* = 6.2 Hz), 7.3-7.6 (m, 9H, Ar-H); 12.5 (bs, 2H, 2 × OH), ^{13}C NMR (δ, ppm) : 165.6 (C-2), 131.9 (C-3), 118.4 (C-4), 114.6 (C-5), 158.7 (C-6), 113.6 (C-7), 129.6 (C-8), 142.3 (C-9), 165.1 (C-10), 156.5 (C_a), 142.1 (C_b), 126.6 (C_c), 120.5 (C_d), 142.1 (C_e), 132.9 (C_f), 128.5 (C_g), 111.5 (C_h).

2i: Yield: 65%, m.p. 171–73°C, Anal. Calcd for $C_{21}H_{16}BrN_3O_2$: C, 57.55, H 3.68, N, 9.59, Found: C, 57.51, H, 3.64, N, 9.58. IR (cm^{-1}): 3450 (OH), 1595 (N=N), 560 (C-Br); ^{1}H NMR (δ, ppm): 7.8 (S, 1H; H-3), 7.0 (d, 7-H, *J* = 6.6 Hz), 7.1 (d, 8-H, *J* = 6.6 Hz), 7.3 – 7.5 (m, Ar, 9H, Ar-H), 12.5 (S, 3H, 3 × OH); ^{13}C NMR (δ, ppm): 172.6 (C-2), 131.6 (C-3), 116.6 (C-4), 112.5 (C-5), 162.6 (C-6), 116.6 (C-7), 128.5 (C-8), 140.1 (C-9), 168.5 (C-10), 154 (C_a), 143.2 (C_b), 128.1 (C_c), 122.4 (C_d), 142.5 (C_e), 135.5 (C_f), 129.1 ($C_{f'}$), 162.5 (C_g), 138.0 ($C_{g'}$), 132.0 (C_h).

Antimicrobial Activity

Nutrient agar media of the requisite composition viz., peptone (2.5 g), beef extract (0.5 g), agar-agar (10 g) and distilled water (500 mL), was prepared and *p*H of the medium was adjusted to 6.6. For the preparation of media all the above ingredients (except agar-agar) were weighed and dissolved in distilled water (250 mL) by application of gentle heating. After dissolving the ingredients completely, more distilled water and weighed quantity of agar-agar were added. Then, it was filtered through cotton to obtain a clear solution. The mixture was autoclaved for 30 min at a pressure of 1.5 kg/cm^2. All the glass apparatus were cleaned with chromic acid and then sterilized by keeping in oven. Medium was cooled to 37.1°C and homogeneous suspension was prepared by transferring aseptically a loopful of all the corresponding microorganism from fresh subculture into agar medium followed by vigorous shaking. 20 mL of this medium was poured into each sterilized petri dish under aseptic conditions and allowed to set.

After preparing the medium, the paper disc (6 mm) was immersed in seeded agar containing petri dishes. The solution (500 μg/mL) was dropped into the filter paper disc. The inhibition zone for each test solution was measured in mm.

The synthesized compounds were tested for their antimicrobial activity against *E. coli*, *P. diminuta*, *B. subtilis*, *B. megaterium* and *S. aureus* using standard ampicilin as control drug. The biological activity of these compounds have been evaluated by filter paper disc method[50] at 500 ppm. Inhibition (%) = $[(\alpha - \beta)/\alpha] \times 100$ was calculated[47] and presented in **Table II**, where α and β stand for inhibition zone of control drug and quinoline derivatives, respectively.

A perusal of the data presented in **Table II** reveals that compound *N*-phenyl-2,6-dihydroxy-3-bromo-4-(2-nitro) phenyl azo quinoline was found to be more active against *P. diminuta* in the series. Most of the compounds of series were found to be highly active against *P. diminuta* while least against *B. megaterium*. It is also observed that compounds having aryl group substituted by 3-NO_2, 2-Cl associated with quinoline moiety also show good antibacterial activity. The data exhibited in table reveals that the activity shown by synthesized quinoline derivatives follows the pattern *P. diminuta* > *E. coli* > *B. substilus* > *S. auresis* > *B. magaterium*.

Table II— Antimicrobial activity of N-phenyl-6-hydroxyl-3-bromo-4-arylazo quinolin-2-ones

			% inhibition $(\alpha - \beta)/\alpha \times 100$				
Compd	M_R	LD_{50}	*E.coli*	*P.diminuta*	*B.subtilis*	*B.megaterium*	*S.aureus*
2a	54.43	3.42	-14.29	-18.18	-10.00	10.00	4.76
2b	59.32	3.78	-20.83	-25.00	-17.39	-9.09	-13.04
2c	60.73	6.25	-21.55	-9.09	4.34	10.00	9.09
2d	60.73	4.05	-31.04	-34.48	-28.57	-23.08	-25.93
2e	60.73	6.42	-28.57	-31.04	-25.00	-20.00	-23.08
2f	59.40	5.75	-25.93	-28.57	-23.08	-17.39	-20.83
2g	59.40	5.80	-24.00	-26.92	-20.00	-12.50	-16.67
2h	59.40	7.50	-4.06	-9.52	4.44	22.72	9.52
2i	56.06	6.85	-19.05	-21.74	-17.39	4.76	-10.00

To study quantitative structure-activity relationship (QSAR), molecular refractive index (M_R) has been calculated by the method of Dreishach[51] and reported in **Table II**. It is observed from the data that with the increase of M_R, the biological activity increases. The compounds having electron-attracting group i.e., NO_2, Cl are more active. However, these electron-attracting groups at *para* position decrease the activity. Introduction of hydroxyl group also increases the activity of the synthesized compounds. In general, it has been observed that antimicrobial results follow the pattern **2d** > **2e** > **2f** > **2g** > **2b** > **2i** > **2a** > **2h** > **2c**.

Likewise, hydrophobic properties has also been quantized for correlation of structure with biological activity[52]. Hydrophobic compounds have high P value, whereas, hydrophilic compound will have a low P value. It is deduced from the data exhibited that the halogen derivatives have high value of logP [$\log P = \log P_{Benzene} + \pi$] i.e. 2.84 and the hydroxyl group containing compound has lowest value of logP i.e. 1.96. Thus, compounds having aryl group substituted by NO_2 associated with quinoline moiety has more antimicrobial activity than compounds containing hydroxyl group.

Determination of LD_{50}

The substituted quinoline derivatives were subjected to acute toxicity studies to find out LD_{50} values. The results of screening are presented in **Table II**. All the synthesized compounds did not show any toxicity upto the dose of 8.0 mg kg^{-1} in rats.

Conclusion

The reaction of phase transfer generated dibromocarbene with *N*-phenyl-2,5-dihydroxy-3-arylazoindoles **1a-i** proceed through the addition – rearrangement sequence. The initial carbene adduct is unstable under reaction condition and undergoes rearrangement and dehydrobromination. The indole derivative rearrange and aromatize to form *N*-phenyl-2,6-dihydroxy-4-arylazo quinolines **2a-i**. All the compounds have been tested *in vitro* for their antimicrobial activity against *E. coli*, *P. diminuta, B. subtilis*, *B. megaterium* and *S. auresus*. The synthesized compounds exhibit moderate to good antibacterial activity.

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