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REGULAR ARTICLE

One-pot synthesis of phenazines from 2-naphthols with 1, 2-diamines and its biological importance and binding studies

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Abstract. Synthesis of phenazine derivatives from the reaction of 2-naphthols with 1, 2-diamino benzenes in presence of $K_2S_2O_8$ in AcOH and water, through the intermediate formation of 1, 2-naphthoquinones from self-coupling of 2-naphthol and then followed by condensation of 1, 2-diamino benzenes in one pot. The present reaction was compatible with various substituted 2-naphthols as well as substituted 1, 2-diamino benzenes to obtain a variety of substituted phenazine derivatives in good to excellent yields. The reaction was highly regio-selective in the case of unsymmetrical substituted 1, 2-diamino benzenes for providing single regio isomeric phenazine compounds. Reaction conditions were also mild and metal-free and also used green solvents such as AcOH and water. Phenazine derivatives are an important class of heterocycles and occur both in natural and synthetic compounds which shows many biological activities and also present in many important dyestuffs. In meantime, we have also shown our interest in antibacterial, anti-inflammatory activities and molecular docking studies. It is important to note that the phenazine derivatives showed excellent anti-bacterial and anti-inflammatory activities.

Keywords. Phenazines; 2-Naphthols; 1,2-Diaminobenzene; Regio-selective condensation; Anti-bacterial activity; anti-inflammatory activity.

1. Introduction

Phenazine derivatives are an important class of heterocycles and occur both in natural and synthetic compounds which shows many biological activities. Phenazines also named as dibenzopyrazine, azo phenylene, dibenzo-*p*-diazine, and acridizine, are a dibenzo annulated pyrazine compounds.[1–4] In nature, phenazine core compounds are present in a wide range of microorganisms such as *Streptomyces, Pseudomonas, Methanosarcina, Pantoe* and *Pelagobacter.*[5–10] Also, phenazines are also important cores in dyes such as safranines,[11] toluylene red,[12] eurhodines and indulines and also important building blocks for the synthesis of organic semiconductors which are having chemically controllable switches.[13] Phenazine core structures attracted many synthetic chemists due to their biological importance and various methods have been developed for several years. In 1901 Wohl and Aue developed a method for the synthesis of phenazines and their derivatives by treating anilines with nitrobenzenes in the presence of a base. However, this reaction gave modest yields along with other by-products.[14] Bamberger and Ham also developed another method for the synthesis of phenazines derivatives in 1911, by self-coupling of 4-substituted nitrosobenzenes under acidic conditions. This reaction also gave moderate yields and restricted mostly for the electron-donating group containing substrates, especially for *para*-position.[15] Issidorides and Haddadin have developed another method for the synthesis of phenazine derivatives in 1960. However, this method offers phenazine derivatives with mono- or di-*N*-oxides that are easily deoxygenated under mild reducing conditions.[16] Synthesis of phenazine derivatives from 2-nitrodiphenylamine is one of the most widely used methods which undergoes intramolecular cyclization under reduction conditions. This method

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offers high-yields except for sterically hindered anilines and electron-withdrawing amines.[17] However, transition metal catalysts are the most expensive as well as moisture sensitive. Among all these methods, the *Condensation method* is one of the most useful alternative methods for the synthesis of phenazines which involves the condensation of substituted 1, 2-benzoquinones and 1, 2-diaminobenzenes.[18,19] This method has an advantage when compared to other methods because it is compatible with all types of substrates under mild and ambient temperature and metal-free conditions. Recently, Jeganmohan has also developed a method for the synthesis of phenazine derivatives with 2-Naphthols and 1, 2-diaminobenzenes.[20] However, this manuscript mainly focused on the synthesis of 1, 2-naphthaquinones which is our key intermediate. However, most of these methods have few limitations with respect to the reactants and starting material needs to be synthesized. So far, no efficient and general method has been reported and still, there is a need for a simple and efficient method for the synthesis of phenazines. Given this background, we focused our interest in the synthesis of phenazine derivatives using condensation method in one pot because one-pot synthesis also bears an advantage for minimizing the waste and time.

2. Experimental

2.1 *General procedure for the preparation of phenazine derivatives*

In a round bottom flask, a stirred solution of substituted 2-naphthols (**1a–c**) (100 mg) in CH_3COOH and H_2O (1:1 ratio, 2 mL) were added $K_2S_2O_8$ (2.0 equiv.). The reaction mixture was allowed to stir at 80 °C for 4 h under the atmospheric air. The reaction was monitored by TLC, after completion of the reaction, water was added to the reaction mixture and extracted in ethyl acetate with water and the organic layer was washed with brine solution and the combined organic layers were concentrated in a vacuum. The crude reaction mixture was directly used for further step without purification.

In a 25 mL round bottom flask, a crude reaction mixture of substituted quinones (**2a–c**) and 1, 2-diamino substituted benzenes (**3a–f**) (1.2 equiv.) were taken in AcOH (3 mL). Then, the reaction mixture was allowed to stir at room temperature for 12 h. After 12 h, the reaction mixture was diluted with CH_2Cl_2 and solvents were evaporated under vacuum. The crude residue was purified through a silica gel column using hexane and ethyl acetate as eluent to give pure phenazines (**4a–m**).

2.2 *Spectral data of compounds 4a–m and 2a–c*

1-(benzo[a]phenazin-5-yl)naphthalen-2-ol (**4a**): Yellow solid; Yield: 91%; eluent (15% ethyl acetate in hexanes). hexanes). **^{1}H NMR (500 MHz, DMSO):** δ 9.77 (s, 1H), 9.44 (d, J = 8.0 Hz, 1H), 8.37 (dd, J = 61.2, 7.6 Hz, 2H), 8.06–7.96 (m, 3H), 7.93 (d, J = 8.2 Hz, 1H), 7.90–7.81 (m, 2H), 7.68 (t, J = 7.5 Hz, 1H), 7.43 (d, J = 9.0 Hz, 1H), 7.36–7.27 (m, 2H), 7.24 (d, J = 3.4 Hz, 2H). **^{13}C NMR (126 MHz, DMSO)**: δ 152.66, 143.06, 142.54, 141.83, 141.30, 140.40, 133.62, 133.31, 130.72, 130.65, 130.52, 130.16, 129.88, 129.39, 128.97, 128.92, 128.12, 128.07, 127.90, 126.67, 125.00, 124.01, 122.84, 118.45, 117.28. **HRMS** (**ESI**): calc. for $[(C_{26}H_{16}N_2O)H]$ (M+H) 373.1341, measured 373.1352.

1-(2-hydroxybenzo[a]phenazin-5-yl)naphthalene-2,7-diol (**4b**): Yellow solid; Yield: 80%; eluent (30% ethyl acetate in hexanes). **^{1}H NMR (500 MHz, DMSO):** δ 10.33 (s, 1H), 9.53 (s, 1H), 9.34 (s, 1H), 8.80 (s, 1H), 8.41 (d, J = 9.7 Hz, 1H), 8.31 (d, J = 9.5 Hz, 1H), 8.04–7.98 (m, 2H), 7.81 (d, J = 8.9 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.61 (s, 1H), 7.17 (dt, J = 15.6, 8.8 Hz, 3H), 6.84 (d, J = 8.8 Hz, 1H), 6.48 (s, 1H). **^{13}C NMR** (**126 MHz**, **DMSO**): δ 174.53, 157.75, 155.95, 152.82, 143.74, 142.57, 141.50, 141.15, 140.91, 135.37, 132.65, 130.58, 130.15, 129.71, 129.38, 128.88, 128.62, 126.29, 125.04, 122.62, 119.67, 116.16, 115.25, 114.99, 109.28, 105.74. **HRMS (ESI):** calc. for $[(C_{26}H_{16}N_2O_3)H]$ (M+H) 405.1239, measured 405.1259.

7-bromo-1-(2-bromobenzo[a]phenazin-5-yl)-naphthalen-2-ol (**4c**): Yellow solid; Yield: 73%; eluent (20% ethyl acetate in hexanes). **^{1}H NMR** (**400 MHz, DMSO**): δ 10.08 (s, 1H), 9.35 (d, J = 8.7 Hz, 1H), 8.43 (s, 1H), 8.32 (d, J = 2.2 Hz, 1H), 8.24 (d, J = 2.1 Hz, 1H), 8.05 (ddd, J = 5.0, 3.2, 1.2 Hz, 4H), 7.95 (s, 1H), 7.48 (d, J = 9.0 Hz, 1H), 7.39 (dt, J = 4.0, 2.1 Hz, 2H), 7.24 (d, J = 9.1 Hz, 1H). **^{13}C NMR (75 MHz, DMSO)**: δ 153.20, 142.70, 141.45, 141.23, 138.32, 134.60, 132.08, 131.01, 130.59, 129.94, 129.67, 129.58, 129.34, 129.12, 129.03, 128.23, 127.31, 126.16, 123.97, 119.59, 116.65, 115.88. **HRMS** (**ESI**): calc. for $[(C_{26}H_{14}Br_2N_2O)H]$ (M+H) 528.9551, measured 528.9561.

1-(9-nitrobenzo[a]phenazin-5-yl)naphthalen-2-ol (**4d**): Brown solid; Yield: 78%; eluent (20% ethyl acetate in hexanes). **^{1}H NMR** (**500 MHz, DMSO**): δ 9.83 (d, J = 4.7 Hz, 1H), 9.38 (dd, J = 18.5, 7.9 Hz,

1H), 9.11 (dd, J = 86.1, 2.3 Hz, 1H), 8.61–8.56 (m, 1H), 8.00 (dd, J = 8.9, 2.8 Hz, 1H), 7.89 (ddd, J = 20.6, 16.7, 7.7 Hz, 3H), 7.73 (t, J = 7.5 Hz, 1H), 7.41 (d, J = 9.0 Hz, 1H), 7.37– 7.23 (m, 4H), 3.37 (s, 1H). **^{13}C NMR (126 MHz, DMSO)**: δ 153.09, 148.04, 145.07, 144.29, 143.57, 142.82, 141.24, 140.01, 134.36, 133.91, 131.77, 130.61, 130.53, 129.14, 128.98, 128.60, 128.32, 127.37, 127.18, 126.11, 125.63, 124.40, 123.65, 123.35, 118.87, 117.31. **HRMS (ESI)**: calc. for [($C_{26}H_{15}N_3O_3$)H] (M+H) 418.1192, measured 418.1182.

1-(9-chlorobenzo[a]phenazin-5-yl)naphthalen-2-ol (**4e**): Yellow solid; Yield: 68%; eluent (15% ethyl acetate in hexanes). **^{1}H NMR (500 MHz, DMSO)**: δ 9.79 (d, J = 3.0 Hz, 1H), 9.36 (dd, J = 7.9, 2.9 Hz, 1H), 8.42 (dd, J = 30.5, 5.6 Hz, 1H), 8.29 (dd, J = 21.1, 5.6 Hz, 1H), 7.96 (ddd, J = 20.4, 16.0, 8.7 Hz, 3H), 7.89–7.79 (m, 2H), 7.72–7.62 (m, 1H), 7.42 (d, J = 8.9 Hz, 1H), 7.37–7.19 (m, 4H). **^{13}C NMR (126 MHz, DMSO)**: δ 152.64, 143.53, 143.19, 142.51, 142.37, 141.96, 141.31, 141.03, 139.80, 135.02, 134.86, 133.56, 133.31, 131.19, 130.78, 130.51, 129.94, 128.76, 128.12, 127.88, 127.34, 126.67, 125.15, 124.00, 122.85, 118.44, 117.14. **HRMS (ESI)**: calc. for [($C_{26}H_{15}ClN_2O$)H] (M+H) 407.0951, measured 407.0962.

1-(9,10-dimethylbenzo[a]phenazin-5-yl)naphthalen-2-ol (**4f**): Yellow solid; Yield: 79%; eluent (20% ethyl acetate in hexanes). **^{1}H NMR (400 MHz, DMSO):** δ 9.75 (s, 1H), 9.40 (d, J = 8.1 Hz, 1H), 8.11 (d, J = 54.4 Hz, 2H), 7.97 (dd, J = 25.2, 8.5 Hz, 2H), 7.89–7.78 (m, 2H), 7.66 (dd, J = 11.0, 4.1 Hz, 1H), 7.42 (d, J = 8.9 Hz, 1H), 7.36–7.28 (m, 2H), 7.24 (d, J = 4.5 Hz, 2H), 2.56 (d, J = 15.1 Hz, 6H). **^{13}C NMR (101 MHz, DMSO)**: δ 152.70, 142.35, 141.78, 141.60, 141.49, 141.06, 140.55, 139.37, 133.71, 133.09, 130.90, 129.84, 129.73, 129.02, 128.15, 127.92, 127.87, 127.41, 126.68, 126.57, 124.73, 124.09, 122.85, 118.48, 117.46, 21.12, 20.16. **HRMS (ESI)**: calc. for [($C_{28}H_{20}N_2O$)H] (M+H) 401.1654, measured 401.1644.

1-(9-chloro-2-hydroxybenzo[a]phenazin-5-yl)-naphthalene-2,7-diol (**4g**): Black solid; Yield: 65%; eluent (30% ethyl acetate in hexanes). **^{1}H NMR (400 MHz, DMSO)**: δ 10.43 (s, 1H), 9.47 (d, J = 80.1 Hz, 2H), 8.77 (s, 1H), 8.40 (ddd, J = 29.6, 22.1, 5.7 Hz, 2H), 7.99 (dd, J = 9.1, 2.2 Hz, 2H), 7.79 (dd, J = 26.2, 8.8 Hz, 2H), 7.61 (d, J = 4.3 Hz, 1H), 7.22 (dd, J = 8.5, 5.2 Hz, 2H), 6.93–6.80 (m, 1H), 6.48 (s, 1H). **^{13}C NMR (101 MHz, DMSO)**: δ 157.82, 155.92, 152.75, 143.84, 142.57, 141.63, 141.06, 139.40, 135.25, 134.94, 134.46, 132.30, 131.22, 130.73, 129.68, 128.67, 127.26, 126.44, 124.83, 122.55, 120.03, 115.95, 115.22, 114.92, 109.42, 105.64. **HRMS (ESI)**: calc. for [($C_{26}H_{15}ClN_2O_3$)H] (M+H) 439.0849, measured 439.0859.

1-(2-hydroxy-9,10-dimethylbenzo[a]phenazin-5-yl)naphthalene-2,7-diol (**4h**): Brown solid; Yield: 70%; eluent (30% ethyl acetate in hexanes). **^{1}H NMR (400 MHz, DMSO)**: δ 10.25 (s, 1H), 9.48 (d, J = 7.6 Hz, 1H), 8.74 (d, J = 2.5 Hz, 1H), 8.10 (d, J = 4.3 Hz, 2H), 7.78 (dd, J = 24.2, 8.8 Hz, 2H), 7.57 (s, 1H), 7.15 (dd, J = 11.2, 8.7 Hz, 3H), 6.84 (d, J = 4.3 Hz, 1H), 6.48 (d, J = 4.3 Hz, 1H), 2.60 (s, 3H), 2.56 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 162.73, 161.11, 158.02, 148.22, 146.97, 146.63, 146.21, 145.95, 145.35, 145.27, 140.64, 138.01, 134.91, 134.57, 133.65, 133.08, 132.57, 131.33, 130.35, 127.83, 124.51, 121.54, 120.44, 120.21, 114.14, 110.99, 25.36, 25.33. **HRMS (ESI)**: calc. for [($C_{28}H_{20}N_2O_3$)H] (M+H) 433.1552, measured 433.1542.

1-(benzo[f]pyrido[2,3-b]quinoxalin-5-yl)naphthalen-2-ol (**4i**): Golden yellow solid; Yield: 79%; eluent (20% ethyl acetate in hexanes). **^{1}H NMR (400 MHz, DMSO)**: δ 9.82 (s, 1H), 9.53–9.35 (m, 2H), 8.84–8.68 (m, 1H), 8.02 (dd, J = 7.2, 2.2 Hz, 2H), 7.93 (dd, J = 12.2, 9.1 Hz, 3H), 7.75 (t, J = 7.4 Hz, 1H), 7.43 (d, J = 8.9 Hz, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.34–7.29 (m, 1H), 7.25 (d, J = 3.5 Hz, 2H). **^{13}C NMR (101 MHz, DMSO)**: δ 172.55, 156.19, 153.11, 149.08, 144.23, 141.81, 138.68, 138.42, 134.04, 134.01, 131.30, 131.10, 130.47, 128.92, 128.85, 128.61, 128.34, 127.26, 127.20, 126.47, 126.05, 124.45, 123.35, 118.90, 117.52. **HRMS (ESI)**: calc. for [($C_{25}H_{15}N_3O$)H] (M+H) 374.1293, measured 374.1282.

1-(2-hydroxybenzo[f]pyrido[2,3-b]quinoxalin-5-yl)naphthalene-2,7-diol (**4j**): Brown solid; Yield: 75%; eluent (30% ethyl acetate in hexanes). **^{1}H NMR (400 MHz, DMSO)**: δ 10.44 (s, 1H), 9.55 (s, 1H), 9.48–9.27 (m, 2H), 8.91–8.67 (m, 2H), 8.01 (dd, J = 8.4, 3.9 Hz, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.76 (d, J = 8.8 Hz, 1H), 7.67 (s, 1H), 7.24 (s, 2H), 7.15 (d, J = 8.8 Hz, 1H), 6.85 (dd, J = 8.8, 2.0 Hz, 1H), 6.48 (s, 1H). **^{13}C NMR (101 MHz, DMSO)**: δ 158.41, 156.45, 155.81, 153.29, 148.80, 144.87, 143.77, 142.58, 138.68, 138.32, 135.75, 133.03, 130.21, 130.03, 129.25, 126.98, 126.41, 125.04, 123.06, 120.78, 116.41, 115.75, 115.44, 110.31, 106.15. **HRMS (ESI)**: calc. for [($C_{25}H_{15}N_3O_3$)H] (M+H) 406.1192, measured 406.1181.

1-(dibenzo[a,i]phenazin-5-yl)naphthalen-2-ol (**4k**): Brown solid; Yield: 85%; eluent (10% ethyl acetate in hexanes). **^{1}H NMR (400 MHz, DMSO)**: δ 8.87 (s, 1H), 8.48 (d, J = 8.0 Hz, 1H), 8.12 (d, J = 52.7 Hz, 2H), 7.38 (dd, J = 21.7, 7.5 Hz, 2H), 7.03 (dd, J =

26.1, 8.4 Hz, 2H), 6.94–6.83 (m, 2H), 6.74–6.70 (m, 2H), 6.49 (d, J = 8.9 Hz, 1H), 6.41–6.32 (m, 4H), 4.82 (s, 1H). **^{13}C NMR (101 MHz, DMSO)**: δ 152.66, 144.40, 143.22, 141.23, 139.18, 138.05, 133.78, 133.70, 133.57, 133.48, 130.88, 130.72, 129.98, 129.25, 128.45, 128.37, 128.19, 127.93, 127.48, 127.00, 126.86, 126.76, 125.31, 124.09, 122.92, 118.49, 117.20. **HRMS (ESI)**: calc. for [($C_{30}H_{18}N_2O$)H] (M+H) 423.1497, measured 423.1486.

1-(2-hydroxydibenzo[a,i]phenazin-5-yl)naphthalene-2,7-diol (4l): Brown solid; Yield: 78%; eluent (20% ethyl acetate in hexanes). **^{1}H NMR (400 MHz, DMSO)**: δ 7.96 (s, 4H), 7.45–7.30 (m, 5H), 6.99 (dd, J = 5.9, 3.1 Hz, 3H), 6.82 (s, 3H), 2.58 (s, 3H). **^{13}C NMR (101 MHz, DMSO)**: δ 153.28, 143.99, 142.56, 139.25, 139.13, 138.10, 134.89, 133.98, 133.95, 132.11, 131.78, 131.29, 131.01, 130.06, 129.99, 129.80, 129.72, 129.40, 129.23, 128.51, 128.48, 128.46, 127.56, 127.21, 126.32, 124.55, 119.79, 119.70, 116.67, 116.02. **HRMS (ESI)**: calc. for [($C_{30}H_{18}N_2O_3$)H] (M+H) 455.1396, measured 455.13984.

7-bromo-1-(2-bromodibenzo[a,i]phenazin-5-yl)-naphthalen-2-ol (4m): Brown solid; Yield: 61%; eluent (20% ethyl acetate in hexanes). **^{1}H NMR (400 MHz, DMSO)**: δ 7.92 (dd, J = 10.7, 7.5 Hz, 4H), 7.57 (d, J = 3.1 Hz, 4H), 7.25 (s, 1H), 6.95 (d, J = 23.8 Hz, 2H), 6.39 (d, J = 36.6 Hz, 4H), 3.41 (s, 1H). **^{13}C NMR (101 MHz, DMSO)**: δ 153.17, 143.89, 142.45, 139.14, 139.02, 137.99, 134.78, 133.87, 133.85, 132.01, 131.68, 131.18, 130.90, 129.95, 129.88, 129.69, 129.61, 129.29, 129.13, 128.40, 128.37, 128.35, 127.45, 127.10, 126.21, 124.44, 119.68, 119.59, 116.56, 115.91. **HRMS (ESI):** calc. for [($C_{30}H_{16}Br_2N_2O$)H] (M+H) 578.9708, measured 578.9712.

2′-hydroxy-[1,1′-binaphthalene]-3,4-dione(2a): Brown solid; Yield: 91%; eluent (20% ethyl acetate in hexanes). **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 8.21 (d, J = 7.5 Hz, 1H), 7.88 (dd, J = 19.8, 7.8 Hz, 3H), 7.56–7.48 (m, 2H), 7.46–7.38 (m, 3H), 7.26 (t, J = 4.4 Hz, 2H), 6.89 (d, J = 7.7 Hz, 1H), 6.57 (s, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)**: δ 180.62, 179.63, 152.88, 150.21, 135.99, 135.23, 132.34, 131.84, 131.37, 131.28, 130.87, 130.52, 129.34, 128.98, 128.56, 127.67, 124.29, 124.23, 118.07, 115.75. **HRMS (ESI)**: calc. for [($C_{20}H_{12}O_3$)H] (M+H) 301.0865, measured 301.0854.

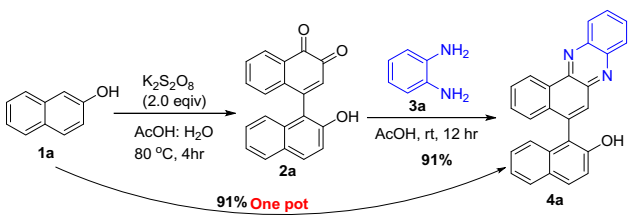
2′,6,7′-trihydroxy-[1,1′-binaphthalene]-3,4-dione (2b): Black solid; Yield: 80%; eluent (40% ethyl acetate in hexanes). **^{1}H NMR (400 MHz, DMSO)**: δ 10.54 (s, 1H), 9.61 (d, J = 34. 8 Hz, 2H), 7.72 (dd, J = 20.2, 9.1 Hz, 2H), 7.43 (d, J = 1.9 Hz, 1H), 7.03 (d, J = 8.8 Hz, 1H), 6.96–6.80 (m, 3H), 6.60 (d, J = 8.5 Hz, 1H), 6.13 (s, 1H). **^{13}C NMR (101 MHz, DMSO)**: δ 180.43, 179.51, 159.84, 156.20, 153.81, 151.87, 134.04, 133.44, 130.72, 130.04, 129.79, 126.89, 126.62, 122.45, 121.56, 115.95, 115.49, 114.86, 114.38, 105.71. **HRMS (ESI)**: calc. for [($C_{20}H_{12}O_5$)H] (M+H) 333.0763, measured 333.0752.

6,7′-dibromo-2′-hydroxy-[1,1′-binaphthalene]-3,4-dione (2c): Brown solid; Yield: 73%; eluent (20% ethyl acetate in hexanes). **^{1}H NMR (400 MHz, DMSO)**: δ 10.20 (s, 1H), 8.20 (s, 1H), 7.99 (t, J = 8.6 Hz, 2H), 7.78 (dd, J = 12.5, 9.0 Hz, 2H), 7.52 (d, J = 8.9 Hz, 1H), 7.38 (d, J = 8.9 Hz, 1H), 6.76 (s, 1H), 6.43 (s, 1H). **^{13}C NMR (101 MHz, DMSO)**: δ 179.28, 177.90, 152.32, 149.05, 137.05, 133.18, 131.93, 131.27, 131.12, 130.65, 130.06, 129.99, 129.96, 129.84, 129.07, 128.92, 126.43, 119.53, 116.27, 115.05. **HRMS (ESI)**: calc. for [($C_{20}H_{10}Br_2O_3$)H] (M+H) 456.9075, measured 456.9066.

3. Results and Discussions

We have developed a method for synthesis of phenazine derivatives through oxidation of 2-naphthol into self-coupled 1, 2-naphthaquinone in presence of $K_2S_2O_8$ and followed by condensation reaction with 1, 2-diaminobenzene to produce phenazine derivatives in one pot. We have initially studied the reaction of 2-naphthol (**1a**) with 1, 2-diaminobenzene (**3a**) to synthesize phenazine derivatives in the presence of $K_2S_2O_8$ in a mixture of acetic acid and water solvent under air atmosphere at 80 °C for 4 h. The reaction occurred rapidly through the intermediate of 2′-hydroxy-[1, 1′-binaphthalene]-3, 4-dione (**2a**) to give 1-(benzo[*a*]phenazin-5-yl) naphthalen-2-ol (**4a**) in excellent yield in one pot (Scheme 1).

Herein, our aim was to synthesize phenazine derivatives from reaction of 2-naphthol (**1a**) with 1, 2-diaminobenzene (**3a**) in one pot through the formation of 1, 2-naphthaquinone. For this strategy we have started our optimization studies for the reaction of 2-naphthol (**1a**) with 1, 2-diaminobenzene (**3a**) in the presence of $K_2S_2O_8$ (2.0 equiv) in AcOH at 80 °C for 4 h. However, in the reaction, cyclization product only



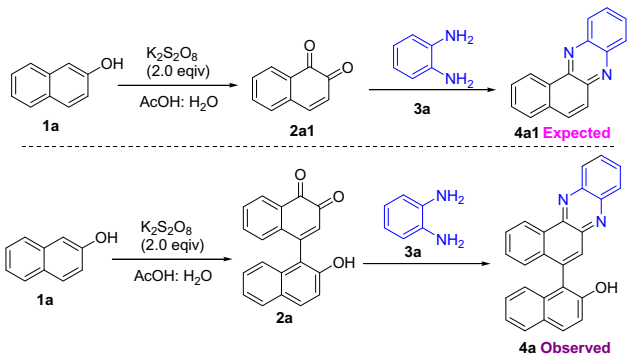
Scheme 1. Synthesis of phenazine 4a in one pot.

with 2-naphthol self-coupled followed by cyclization compound **4a** was observed in 50% yield.

The catalytic reaction was also tested with various solvents such as TFA and TfOH to obtain expected compound **4a1** (Scheme 2) but in all these conditions observed only **4a** in 40% and 23% yields, respectively. In order to increase the yield of **2a**, the initial reaction was studied with different types of solvents such as AcOH, TfOH and TFA in presence of $K_2S_2O_8$ at 80 °C (Table 1, entry 1–3).

Among these, AcOH solvent provides compound **2a** in 50% yield (Table 1, entry 1) and TFA and TfOH solvents were less effective and giving compound **2a** in 35% and 23% yields, respectively (Table 1, entry 2–3). The catalytic reaction was also tested with various oxidants such as $Na_2S_2O_8$, $PhI(OAc)_2$ and Oxone which were less effective giving **2a** in 30%, 10%, 5% yields, respectively (entry 4–6). The reaction was tested without $K_2S_2O_8$ and just only in the presence of AcOH but in the reaction no product **2a** was observed (entry 7). When the catalytic reaction were tested in present $K_2S_2O_8$ and reaction were carried out with a mixture of CH_3CN+H_2O, $PEG+H_2O$ and water, CH_3CN were less effective giving **2a** in 78%, 55%, 5%, 43% yields, respectively (entry 9–12). Among them, the reaction was carried out with a mixture of AcOH and water for providing the compound **2a** in an excellent 91% yield (entry 8). The yield of products **2a** and **4a** were determined by the ^1H NMR integration methods using mesitylene as an internal standard. Thus, the one-pot condensation reaction of 2-naphthol with 1, 2-diaminobenzene (**3a**) for the synthesis of phenazine derivatives under the same optimized reaction conditions through the formation of intermediate **2a**, in the reaction cyclization compound **4a** was observed in excellent yield (Table 2).

Under similar reaction conditions, the reaction was examined with various substituted 2-naphthols **1a–c**. Thus, 7-hydroxy **1b** and 7-bromo **1c** in the presence of optimized conditions with $K_2S_2O_8$ yield the corresponding **2a–c** in good to excellent **2a**, **2b** and **2c** 91%, 78% and 73% yields, respectively (Scheme 3).



Scheme 2. Synthesis of phenazine.

Table 1. Optimization studies.

Entry	Oxidant	Solvent	Yield (%)[a]
1	$K_2S_2O_8$	AcOH	50
2	$K_2S_2O_8$	TfOH	23
3	$K_2S_2O_8$	TFA	35
4	$Na_2S_2O_8$	AcOH	30
5	$Ph(OAc)_2$	AcOH	12
6	Oxone	AcOH	10
7	–	AcOH	Nr
8	$K_2S_2O_8$	$AcOH+H_2O(1:1)$	91
9	$K_2S_2O_8$	$CH_3CN+H_2O(1:1)$	78
10	$K_2S_2O_8$	$PEG+H_2O(1:1)$	55
11	$K_2S_2O_8$	H_2O	5
12	$K_2S_2O_8$	CH_3CN	43

All reactions were carried out using **1a** (1.0 mmol) and oxidant (2 mmol) in solvent (2.0 mL) at 80 °C for 4 h

[a]Yields were determined by the ^1H NMR integration method, using mesitylene as an internal standard

The scope of the one-pot condensation reaction of substituted 2-naphthols was examined under the optimized reaction conditions (Scheme 4, Table 2). Initially, when the reaction was tested with 2-naphthol **1a**, 7-hydroxy-2-naphthol **1b** and 7-bromo-2-naphthol **1c** with 1, 2-diaminobenzene **3a**, phenazine derivatives **4a–c** were observed in 91%, 80% and 73% yields, respectively (Table 2).

The cyclization reaction was also tested with 2-naphthol **1a** and 1,2-diamino benzenes of 4-nitro **3b**, 4-chloro **3c** and 4, 5-dimethyl **3d** under similar reaction conditions afforded phenazine derivatives **4d–f** in 78%, 68% and 79% yields. The reaction was also studied with 7-hydroxy-2-naphthol **1b** with 4-chloro-1,2-diamino benzene **3c** and 4, 5-dimethyl-1,2-diamino benzene **3d** under the optimized reaction conditions providing **4g** and **4h** in 65% and 70% yields. The condensation reaction of 2-naphthol **1a** and 7-hydroxy-2-naphthol with 2,3-diaminopyridine **3e**, providing **4i** and **4j** in 79% and 75% yields. Interestingly, this reaction was also tested with 2-naphthol **1a**, 7-hydroxy-2-naphthol **1b** and 7-bromo-2-naphthol **1c** with naphthalene-1,2-diamine **3f** giving phenazine derivatives **4k–m**, in 85%, 78% and 61% yields (Table 2). The reaction was carried out with 2-naphthol **1a** and pyrazine-2,3-diamine **3g** in presence of optimized conditions, but reaction yield was very low. However, a similar reaction was performed with 2-naphthol **1a** and 2, 3-diaminophenazine **3h**, no desired product was obtained.

Table 2. Synthesis of phenazines.

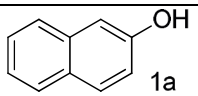
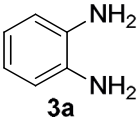
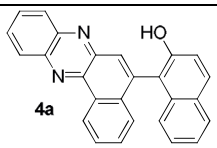
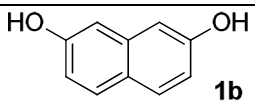
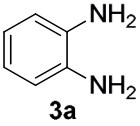
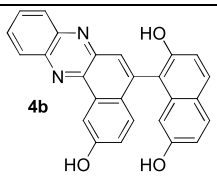
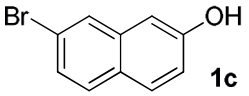
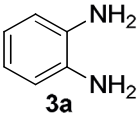
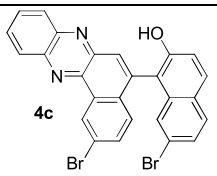
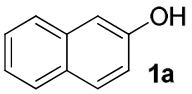
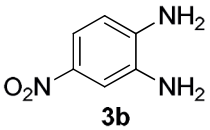
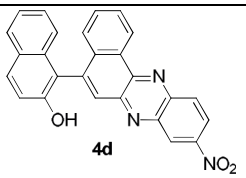
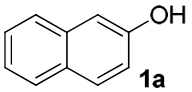
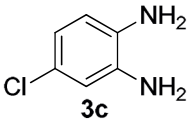
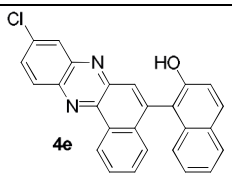
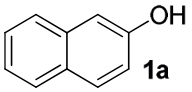
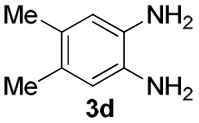
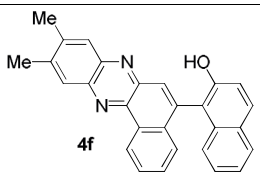
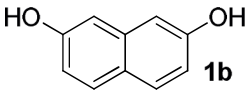
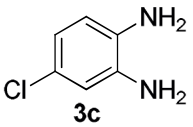
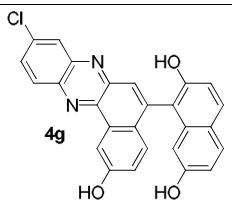
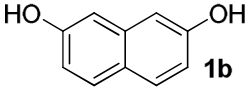
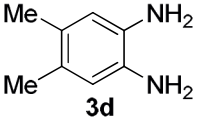
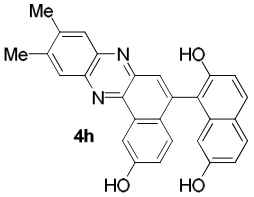
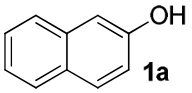
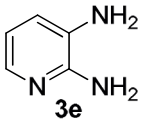
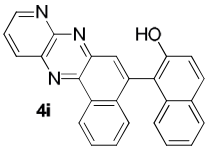
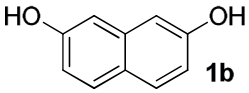
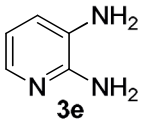
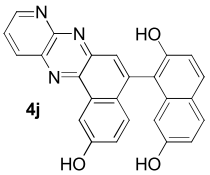
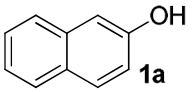
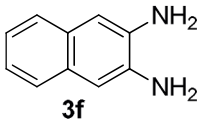
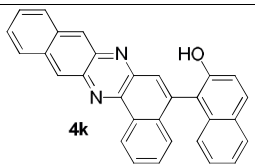
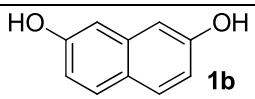
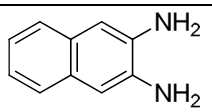
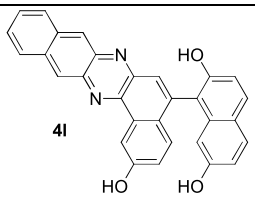
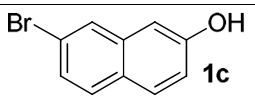
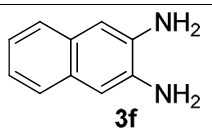
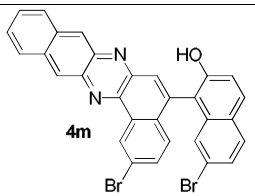
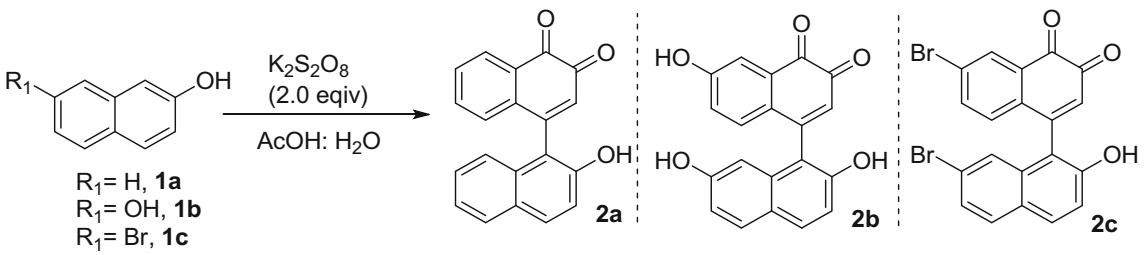
S. no.	Reactant	Reactant	Product	Yield[a] (%)
1	 **1a**	 **3a**	 **4a**	91
2	 **1b**	 **3a**	 **4b**	80
3	 **1c**	 **3a**	 **4c**	73
4	 **1a**	 **3b**	 **4d**	78
5	 **1a**	 **3c**	 **4e**	68
6	 **1a**	 **3d**	 **4f**	79
7	 **1b**	 **3c**	 **4g**	65
8	 **1b**	 **3d**	 **4h**	70

Table 2. continued

9	 **1a**	 **3e**	 **4i**	79
10	 **1b**	 **3e**	 **4j**	75
11	 **1a**	 **3f**	 **4k**	85
12	 **1b**	 **3f**	 **4l**	78
13	 **1c**	 **3f**	 **4m**	61

All reactions were carried out using **1a-c** (1.0 mmol), oxidant (2.0 mmol in AcOH: H_2O (1:1) (2.0 mL) at 80 °C for 4 h; then 1, 2-diaminobenzenes **3a-f** (1.2.mmol), AcOH, rt for 12 h.

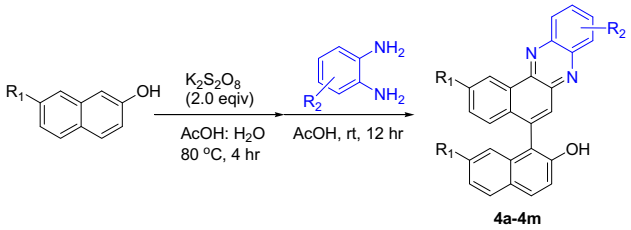
[a]Yields were determined by the ^{1}H NMR integration method, using mesitylene as an internal standard.



Scheme 3. Synthesis of intermediate of 2′-hydroxy-[1, 1′-binaphthalene]-3, 4-diones.

3.1 *Biological importance*

3.1a *Anti-bacterial activity*: The *in vitro* studies of antibacterial activity was performed against a series of Gram-positive bacteria Bacillus subtilis, Staphylococcus aureus and Gram-negative bacteria Escherichia coli, Pseudomonas putida and Klebsiella pneumonia using standard reference drug Ampicillin by using agar well diffusion technique.[21] Among all, **4b**, **4d**, **4e**, **4l** and **4m** have shown good inhibition activity, with all types of stains as shown in (Table 3 and Figure 1).



Scheme 4. Synthesis of phenazines.

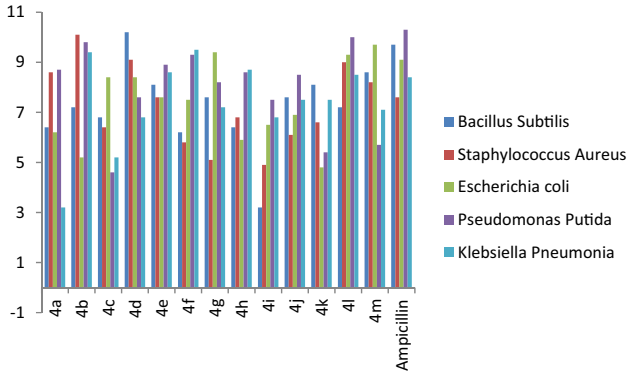


Figure 1. Anti-bacterial evaluation graph of the phenazine compounds.

3.1b *Anti-inflammatory activity*: The *in vivo* studies of the anti-inflammatory activity of phenazine compounds were evaluated on Male Swiss albino rats at (10 mg/kg) by carrageenan-induced paw edema model Male Swiss albino rats. Among the anti-inflammatory activities of phenazines, few of them showed excellent anti-inflammatory activity. These are listed every three hours and potency increases with time. The results were expressed as the increase in paw volume at various time intervals in comparison to the initial values.[22]

The anti-inflammatory activity was tested for phenazine derivatives, among these, **4h** and **4i** showed significant activity and the remaining was shown moderate to good activity after 12 h. In the present investigation, the activity of **4i**, **4f**, **4k**, **4j**, **4h** and **4g** compounds is higher than standard drugs; it may be attributed to the presence of indomethacin group which has been playing an important role in the activity. It is also found that the compounds were having more polar binding sites at 9 h and at 12 h and compound **4i** was shown excellent activity. However, the compounds **4a**–**m** exhibited good to moderate anti-inflammatory activity (Table 4). The % of anti-inflammatory inhibition activity of phenazine derivatives is greater than standard drugs, after 3 h, 6 h, 9 h and 12 h. The increasing order of degree of anti-inflammatory activity and percentage of inhibition is (**4e**) <(**4l**) <(**4m**) <(**4a**) <(**4b**) <(**4i**) <(**4c**) <(**4k**) <(**4h**) <(**4f**) <(**4j**) with standard drug indomethacin by the inhibition of carrageenan-induced paw edema. After 12 h, studies show a normal activity in the entire right paw but it was observed (disease control) carrageenan paw with some inflammatory and also normal paw. The paw edema rat's feet after the injection of carrageenan drug in 3 h was considered as 0 h (Table 4).

3.2 *Molecular docking studies*

The molecular docking studies were performed using the LigandFit module and obtained results were scrutinized based on the highest dock score and number of

Table 3. Anti-bacterial studies of compounds (**4a**–**m**) (bold letters indicate the highest activity).

		Anti-bacterial data in mm(μg/mL)				
Entry	Compound	Bacillus Subtilis	Staphylococcus Aureus	Escherichia coli	Pseudomonas Putida	Klebsiella Pneumonia
Standard	Ampicillin	**9.7**	**7.6**	**9.1**	**10.3**	**8.4**
1	**4a**	6.4	**8.6**	6.2	8.7	3.2
2	**4b**	7.2	**10.1**	5.2	**9.8**	**9.4**
3	**4c**	6.8	6.4	8.4	4.6	5.2
4	**4d**	**10.2**	**9.1**	8.4	7.6	6.8
5	**4e**	8.1	**7.6**	7.6	8.9	**8.6**
6	**4f**	6.2	5.8	7.5	9.3	**9.5**
7	**4g**	7.6	5.1	**9.4**	8.2	7.2
8	**4h**	6.4	6.8	5.9	8.6	**8.7**
9	**4i**	3.2	4.9	6.5	7.5	6.8
10	**4j**	7.6	6.1	6.9	8.5	7.5
11	**4k**	8.1	6.6	4.8	5.4	7.5
12	**4l**	7.2	**9.0**	**9.3**	**10.0**	**8.5**
13	**4m**	8.6	**8.2**	**9.7**	5.7	7.1

Table 4. The anti-inflammatory activities of (**4a–m**) with standard drugs (values are expressed in % of inhibition).

Compounds	1 h % of inhibition	3 h % of inhibition	6 h % of inhibition	9 h % of inhibition	12 h % of inhibition
4a	73.12	51.063	48.77	30.874	12.529
4b	84.94	82.978	40.33	38.132	14.089
4c	86.997	73.829	48.0614	36.713	21.985
4d	62.316	48.463	43.971	38.676	− 0.165
4e	70.047	52.1513	22.364	7.47	0.236
4f	75.413	66.028	57.825	40.094	30.732
4g	70.449	58.297	51.134	39.148	8.51
4h	90.226	71.702	54.751	47.754	28.368
4i	90.685	69.5744	55.224	43.971	21.276
4j	87.234	68.628	56.973	42.789	31.347
4k	82.033	51.219	52.387	50.591	23.073
4l	49.243	40.094	21.749	1.0165	1.418
4m	89.598	81.229	54.349	24.113	1.796
Carrageenan	96.595	70.685	60.756	25.13	14.089
Diseases control	163.356	206.382	202.364	162.884	105.981
Indomethacin	93.924	88.7943	72.104	62.789	26.784

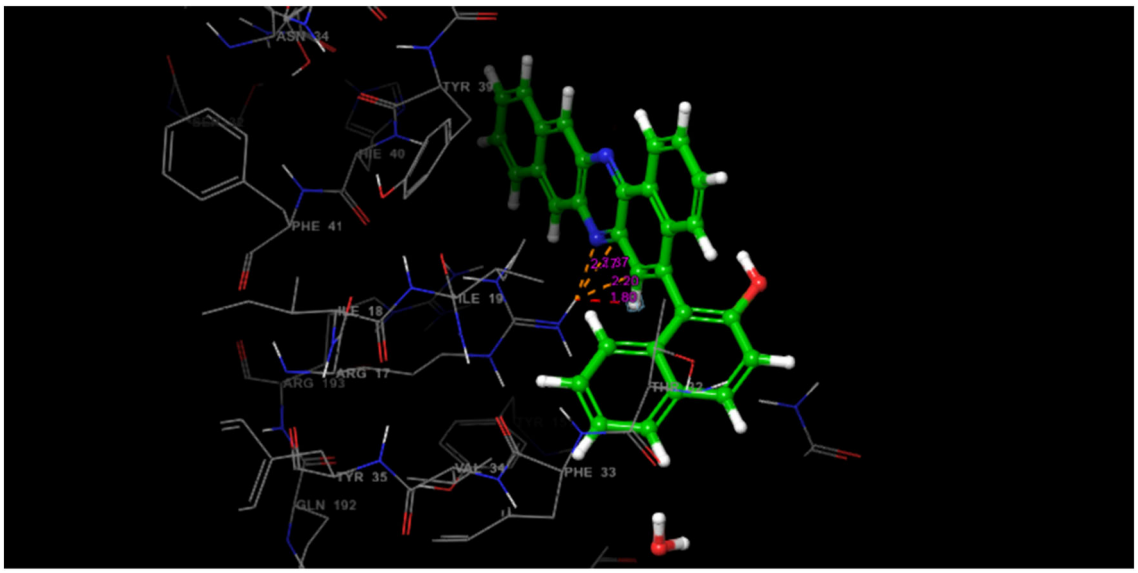


Figure 2. Dock position diagram of **4j**.

H-bonds by SSViewer.[23] The docking studies revealed that all the phenazine derivatives **4a–m** exhibited excellent binding energies towards the receptor active sites.

Molecular docking results were measured based on the ideal interaction of ligand. The ligand-binding interaction primarily depends on binding energy, docking score, number of H-bonds, hydrophobic interactions at receptor site. The compounds **4a–g** strongly binds with the receptor because phenazine compounds were having both donor and acceptor sites in each molecule. The binding interaction of compound 4j was shown in Figure 2. The compound **4j** has both acceptor and donor sites so that it can bind strongly with ligand acceptor and donor sites.

4. Conclusions

In conclusion, we have developed a method for the synthesis of phenazine derivatives from the reaction of substituted 2-naphthols with 1, 2-diamines. The present reaction is performed in one pot with the

formation of 1, 2 keto compounds with 2-naphthols in presence of $K_2S_2O_8$ followed by condensation with substituted 1, 2-diamins to afford highly regioselective phenazine derivatives in good to excellent yields. In the reaction, substituted 2-naphthol compounds, self-coupling takes place very selectively at the position of 1, 2-diketo compound 4th position with 1st position of 2-naphthol (4–1 connectivity) bond and also in the reaction 2-naphthol moiety is converting into the 1, 2-diketo naphthalene compound. Further, the substituted 1, 2-diketo naphthalene compound was converted into phenazine derivatives in the presence of $K_2S_2O_8$ in a mixture of AcOH and water. In the meanwhile, we have also studied the biological importance of phenazine derivatives and it shows good to excellent anti-bacterial and anti-inflammatory activities.

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