Prayogik Rasayan

Synthesis of 6-hydroxy-N-(6-methylpyridin-2-yl) naphthalene-2-carboxamide and its alkoxy analogues

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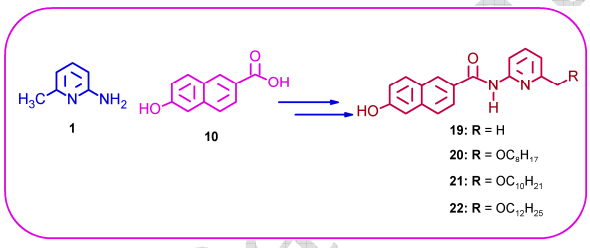
Received: April 15, 2017 | Accepted: May 21, 2017 | Published online: October 27, 2017

6-hydroxy-N-(6-methylpyridin-2-yl)naphthalene-2-carboxamide and its alkoxy analogues bearing long alkyl chains have been synthesized using 6-hydroxy-2-naphthoic acid and 2-amino-6-picoline. The facile synthetic scheme reported here using conventional laboratory reagents opens up a new strategy for the generation of libraries of such compounds in high yields. The H-bond donor acceptor groups along with the reactive 2-naphthol moiety present in the target compounds make them useful for their use in self-assembly and self-replication studies.



Keywords: binol, 2-hydroxy-2-naphthoic acid, 2-amino-6-picoline, hydrogenolysis.

1. Introduction

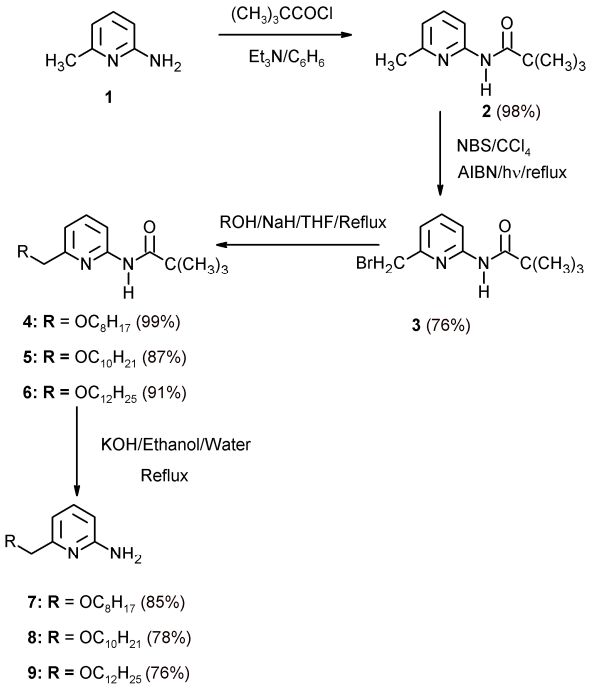
Binol (2,2'-dihydroxy-1,1'-binaphthyl) derivatives have been widely used in catalytic asymmetric transformations.[1,2,3,4,5,6,7] Since the report of aerobic oxidative coupling reaction of 2-hydroxynaphthalene to yield binols by the use of CuCl-amine complex by Koga and coworkers, there has been number of reports in the literature on the synthesis of binols and it analogues during the last two decades.[8] While designing self-replicating systems [9,10,11,12,13] based on binol derivatives, we required 6-hydroxy-N-(6-methylpyridin-2-yl) naphthalene-2-carboxamide and its alkoxy analogues as precursors. But there was no report in the literature on the synthesis of such precursors. Herein, we report the facile syntheses of four derivatives **19**, **20**, **21** and **22** starting from 6-hydroxy-2-naphthoic acid and 2-amino-6-picoline (scheme 1-3).

2. Experimental

Material and Methods

Commercial solvents were distilled and dried by the standard procedure prior to use.[14] 2-amino-6-picoline, pivaloyl chloride, NBS, AIBN, 6-hydroxy naphthanoic acid were purchased from SRL; triethyl amine (Et_3N), benzene, $CDCl_3$ were purchased from Spectrochem.

Synthesis of compound 2 : A solution of 2-amino-6-picoline **1** (1.01 g, 9.33 mmol) in dry benzene (10 mL) was treated with pivaloyl chloride (1.6 mL, 12.99 mmol) and the reaction mixture was stirred for 5 min. at room temperature and then



Scheme 1: Synthesis of 2-amino-6-picolin derivatives **7-9**

cooled in an ice bath and NEt_3 (2 mL, 14.34 mmol) was added. The reaction mixture was stirred at room temperature for 20 h. Then the reaction mixture diluted with ethyl acetate (30 mL) and washed with distilled water (15 mL) and brine solution (30 mL) and dried over anhydrous sodium sulfate. The volatiles were removed under reduced pressure and the crude product was purified by column chromatography (Si-gel, 100-200 mesh) using 15% ethyl acetate/petroleum ether as eluent to afford a brown solid **2** (1.77 g, yield: 98%), m.p. = 66 – 69 °C. FTIR (neat, cm^{-1}) ν_{max}: 3438, 3313, 3063, 2965, 2936, 2874, 1677, 1598, 1578, 1522. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 8.2 Hz, 1H), 7.57 (t, 1H), 6.87 (d, *J* = 7.4 Hz, 1H), 2.44 (s, 3H), 1.32 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.06, 156.55, 150.90, 138.76, 119.12, 110.74, 39.81, 27.51, 23.92 ppm.

Synthesis of compound 3: Compound **2** (1.01 g, 5.25 mmol) was dissolved in dry CCl_4 (20 mL). Then AIBN (0.2432 g, 1.48 mmol) was added and the reaction mixture was refluxed for 30 min. by a 100 watt lamp and then crystalline NBS (1.08 g, 6.067 mmol) was added and the reaction mixture was refluxed for 6 h. Then the reaction mixture was filtered and washed with carbon tetrachloride, the filtrate on evaporation produced a deep brown crude product which was purified by column chromatography (Si-gel, 100-200 mesh) using 5% ethyl acetate/petroleum ether as eluent to afford a brown sticky mass **3** (0.62 g, yield: 55%); FTIR (neat, cm^{-1}) ν_{max}: 3433, 3340, 2965, 2909, 2872, 1689, 1595, 1578, 739, 701. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 8.4 Hz, 1H), 7.72 (t, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 4.44 (s, 2H), 1.54-1.21 (m, 9H) ppm; ^{13}C NMR(100 MHz, $CDCl_3$): δ = 177.36, 154.22, 151.19, 139.82, 119.09, 114.05, 39.87, 32.60, 27.43, 27.13, 23.43 ppm.

Synthesis of compound 4: n-Octanol (0.88 mL, 5.57 mmol) was diluted with dry THF (3 mL) and NaH (0.23 g, 5.632 mmol) was added and refluxed by a 100 watt lamp for 1 h. Then the mixture was cooled at 5 °C and THF solution (7 mL) of compound **3** was added during 10 minutes. The reaction mixture was allowed to stirred at room temperature over a period of 17 h then diluted with chloroform (70 mL) and washed with brine solution (30 mL) and dried over anhydrous sodium sulfate. The volatiles were removed under reduced pressure and the crude product was purified by column chromatography (Si-gel, 100-200 mesh) using 80% chloroform/petroleum ether as eluent to afford **4** as a brown sticky mass (0.88 g, yield: 99.3%). FTIR (neat, cm^{-1}) ν_{max}: 3437, 3356, 2955, 2927, 2857, 1691, 1638, 1623, 1601, 799. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 8.4 Hz, 1H), 7.71 (t, 1H), 7.15 (d, J = 7.2 Hz, 1H), 4.50 (s, 2H), 3.52 (t, 2H), 1.66 - 1.60 (m, 2H), 1.35 - 1.27 (m, 19H), 1.32 (s, 9H) 0.87 (t, 3H) ppm; HRMS (ESI): m/z calcd $C_{19}H_{33}N_2O_2$ [M + H^+] 321.2547; found 321.2531.

Synthesis of compound 5: n-decanol (1.3mL, 7.2mmol) was diluted with dry THF (5 mL). Then NaH (0.43 g, 10.83 mmol) was added and the reaction mixture was refluxed for 1 hr at 62 °C. Then the mixture was cooled upon ice bath and 2 ml dry THF added for dilution. Then 5 mL THF added to compound **3** and transfer to previous reaction mixture during 5 minutes (reaction mixture placed on ice- bath). The reaction mixture was allowed to stirred at room temperature over a period of 17 hours then diluted with ethyl acetate (60 mL) and washed with brine solution (30ml) and dried over anhydrous sodium sulfate. The volatiles were removed under reduced pressure and the crude product was purified by column chromatography (Si-gel, 100-200 mesh) using 5% ethylacetate/petroleum ether as eluent to afford **5** as a brown sticky mass (1.07 g, yield: 87%); FTIR (neat, cm^{-1}) ν_{max}: 3437, 3356, 2955, 2927, 2857, 1691, 1638, 1623, 1601, 799. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.2 (d, *J* = 8.4 Hz, 1H),7.71 (t, *J* = 8 Hz, 1H), 7.17 (d, *J* = 7.2 Hz, 1H), 4.5 (s, 2H), 3.54 (t, *J* = 6.4 Hz, 2H), 1.66 - 1.60 (m, 2H), 1.35 - 1.27 (m, 19H), 1.32 (s, 9H) 0.87 (t, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.24, 156.92, 151.11, 139.02, 117.23, 112.60, 76.60, 73.15, 71.30, 63.06, 39.83, 33.91, 32.80, 31.89, 29.70, 29.59, 29.56, 29.48, 29.43, 29.31, 29.13, 27.45, 27.10, 26.14, 25.74, 24.87, 23.44, 22.67 ppm; HRMS (ESI) m/z : calcd for $C_{21}H_{37}N_2O_2$ [M + H^+] 349.2849; found 349.2847.

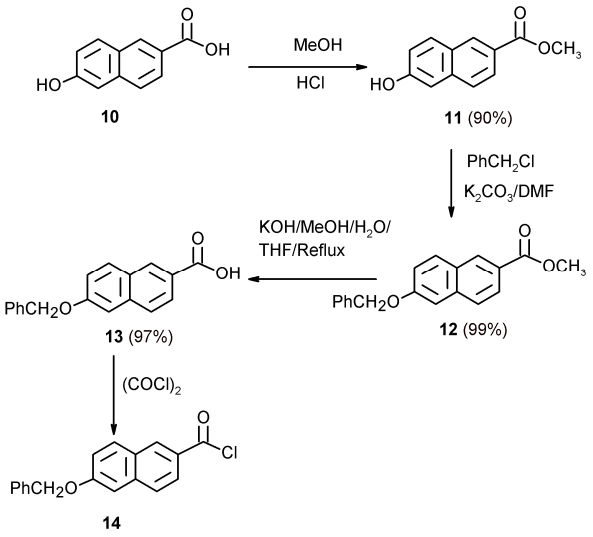
Synthesis of compound 6: n-Dodecanol (1.15 mL, 5.13 mmol) was diluted with dry THF (5 mL) and NaH (0.31g, 7.66 mmol) was added and the reaction mixture was refluxed for 1 h. Then the mixture was cooled and 2 ml THF added for dilution. Then 5 ml dry THF added to compound **3** and transferred to previous reaction mixture during 5 minutes (reaction mixture was placed on ice- bath). The reaction mixture was allowed to stirring at room temperature over a period of 17 h then diluted with ethyl acetate (40 mL) and washed with brine solution (30ml) and dried over anhydrous sodium sulfate. The volatiles were removed under reduced pressure and the crude product was purified by column chromatography (Si-gel 100-200 mesh) using 5% ethyl acetate/petroleum ether as eluent to afford **6** as a brown sticky mass (0.88 g, yield: 91%). FTIR (neat, cm^{-1}) ν_{max}: 3439, 3355, 2958, 2932, 2859, 1693, 1639, 1623, 1601,796. ^{1}H NMR (400 MHz, $CDCl_3$) : δ = 8.22 (s, broad, 1H), 8.17 (d, *J* = 8.4 Hz,1H), 7.72 (t, *J* = 8 Hz, 1H), 7.71 (d, *J* = 7.6 Hz, 1H), 4.51 (S, 2H), 3.55 (t, *J* = 6.4 Hz, 2H), 1.74-1.45 (m, 2H),1.34-1.28(m, 27H), 0.90 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.22, 156.94, 151.12, 138.99, 117.21, 112.60, 73.16, 71.30,63.05, 39.91, 33.91, 32.80, 31.90, 29.70, 29.65, 29.59, 29.47, 29.42, 29.33, 29.28, 29.13, 27.45, 27.10, 26.14, 25.74, 25.15, 24.87, 23.44, 22.67, 14.08 ppm. HRMS (ESI): m/z Calcd for $C_{23}H_{41}N_2O_2$ [M + H^+] 377.3163; found 377.3162.

Synthesis of Compound 7: Compound **4** (0.25 g, 0.78 mmol) was dissolved in (1:1) ethanol-water (16 mL) and 4(N) KOH and the solution was refluxed for 16 h. Then the solvent was removed and water was added to the residue and extracted with ethyl acetate (40 mL) and washed with brine solution (30 mL) and dried over anhydrous sodium sulfate. The volatiles were removed and the residue was purified by column chromatography (Si-gel, 100-200 mesh) using 25% ethyl acetate/chloroform as eluent to afford **7** (0.16g, yield: 85%) as a yellowish oily material. FTIR (neat, cm^{-1}) ν_{max}:

3465, 3347, 3192, 2926, 2855, 1662, 1619, 989. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (t, 3H), 6.76 (d, J = 7.6 Hz, 1H), 6.39 (d, J = 8.0 Hz, 1H), .43 (s, 2H), 3.52 (t, 2H), 1.66 - 1.59 (m, 2H), 1.36 - 1.27 (m, 10H), 0.87 (t, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.73, 156.77, 138.46, 111.23, 107.37, 73.31, 71.17, 31.76, 29.66, 29.39, 29.20, 26.09, 22.59, 14.04 ppm. HRMS (ESI): m/z calcd $C_{14}H_{24}N_2O$ [M + H^+] 237.1968; found 237.2685.

Synthesis of compound 8: Compound **5** (0.460 g, 1.32 mmol) was dissolved in (1:1) ethanol-water (4 mL) and 4(N) KOH and 2 mL dry THF was added to remove solubility problem. The reaction mixture was refluxed for 26 hr. Then ethanol in the mixture was removed by rotary evaporator then diluted with ethyl acetate (50 mL) and washed with brine solution (40 ml) and dried over anhydrous sodium sulfate. The volatiles were removed under reduced pressure and the crude product was purified by column chromatography (Si-gel, 100-200 mesh) using 25% ethyl acetate/petroleum ether as eluent to afford **8** (0.27 g, yield: 78%) as a yellowish oily material. FTIR (neat, cm^{-1}) ν_{max}: 3465, 3347, 3192, 2926, 2855, 1662, 1619, 989. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (t, 3H), 6.76 (d, J = 7.6 Hz, 1H), 6.39 (d, J = 8.0 Hz, 1H), 4.43 (s, 2H), 3.52 (t, 2H), 1.66 - 1.59 (m, 2H), 1.36 - 1.27 (m, 10H), 0.87 (t, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.73, 156.77, 138.46, 111.23, 107.37, 73.31, 71.17, 31.76, 29.66, 29.39, 29.20, 26.09, 22.59, 14.04 ppm. HRMS (ESI) m/z: calcd for $C_{16}H_{28}N_2O$ [M + H^+] 265.2274; found 265.2278.

Synthesis of compound 9: Compound **6** (0.80 g, 2.11 mmol) was dissolved in (1:1) ethanol-water (17.4 mL) and 4(N) KOH and 3 mL dry THF was added to remove solubility problem. The reaction mixture was refluxed for 24 hr. Then ethanol in the mixture was removed by rotary evaporator then diluted with ethyl acetate (50 mL) and washed with brine solution (30 ml) and dried over anhydrous sodium sulfate.



Scheme 2: Synthesis of precursor **14** from 6-hydroxy-2-naphthoic acid **10**

The volatiles were removed under reduced pressure and the crude product was purified by column chromatography (Si-gel, 100-200 mesh) using 25% ethyl acetate/petroleum ether as eluent to afford **9** (0.36 g, yield: 76 %) as a yellowish oily material. FTIR (neat, cm^{-1}) ν_{max}: 3471, 3346, 3191, 2925, 2854, 1616, 1466. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44-7.28 (t, 1H), 6.80 (d, J = 7.6 Hz, 1H), 6.41(d, J = 8.0 Hz, 1H), 4.49 (s, 2H), 4.45 (S, 2H), 3.55-3.52 (t, J = 6.8 Hz, 2H), 1.67-1.63 (t, 2H), 1.39-1.27 (m, 20H), 0.91-0.87 (t, J = 6.4 Hz, 3H) ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.93, 157.23, 138.32, 111.34, 107.25, 73.56, 71.20, 31.90, 29.74, 29.65, 29.62, 29.60,29.49,29.33, 26.16, 22.67, 14.08 ppm. HRMS (ESI): m/z Calcd for $C_{18}H_{32}N_2O$ [M + H^+] 293.2587; found 293.2580.

Synthesis of compound 11: 6-hydroxy-2-naphthoic acid **10** (0.52 g, 2.24 mmol) in methanol (5 mL) was treated with acetyl chloride (0.2 g, 2.75 mmol) at 0-5 ℃ and then the reaction mixture was stirred at room temperature for 24 h. The volatiles were removed under reduced pressure and the crude product was purified by column chromatography (Si-gel, 100-200 mesh) using 50% ethyl acetate/petroleum ether as the eluent to afford compound **11** (0.48 g, yield: 90%). m.p. = 168 -171 °C. FTIR (neat, cm^{-1}) ν_{max}: 3062, 3030, 2947, 2845, 1715, 1621, 1599, 823. ^{1}H NMR (400 MHz, CDCl3): δ = 8.53 (s, 1H), 8.04 (d, J = 9.2 Hz, 1H), 7.911 (m, 2H), 7.53-7.28 (m, 7H), 5.24 (s, 2H), 3.88 (s, 3H) ppm.

Synthesis of compound 12: A suspension of compound **11** (0.49 g, 2.42 mmol) in 4.8 mL of dry DMF was treated with solid K_2CO_3 (0.42 g, 2.97 mmol) and stirred for 10 min. Then $PhCH_2Cl$ (0.42 mL, 3.65 mmol) and a few pieces of molecular sieves were added and the reaction mixture was stirred magnetically for 48 hr at room temperature. The volatiles were removed under reduced pressure and the crude product was purified by column chromatography (Si-gel, 100-200 mesh) using 50% ethyl acetate/petroleum ether as the eluent to afford compound **12** (0.70 g, yield: 99%), m.p.= 151-153 °C. FTIR (neat, cm^{-1}) ν_{max}: 3062, 3030, 2947, 2845, 1715, 1621, 1599, 823. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53 (s, 1H), 8.04 (d, J=9.2 Hz, 1H), 7.911 (m, 2H), 7.53-7.28 (m, 7H), 5.24 (s, 2H), 3.88 (s, 3H) ppm.

Synthesis of compound 13: A suspension of compound **12** (2.9 g, 9.92 mmol) in THF (20 mL) was treated with methanolic solution of KOH (4N, 35 mL) and H_2O (10 mL) and the reaction mixture was refluxed for 5 h. The volatiles were removed and the reaction mixture was diluted with ethyl acetate (10 mL) and acidified with 4(N) HCl. The precipitate was filtered through sintered glass funnel and washed with distilled water and dried under reduced pressure to afford a white solid **13** (2.68 g, yield: 97%), m.p. = 243-245 °C. FTIR (neat, cm^{-1}) ν_{max}: 3471, 3030, 2984, 2928, 1678, 1625. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, 1H), 7.87 (d, 1H), 7.78 (d, 1H), 7.65 (t, 2H), 7.51 (t, 3H), 7.42 (m, 3H), 3.72 (m, 2H) ppm.

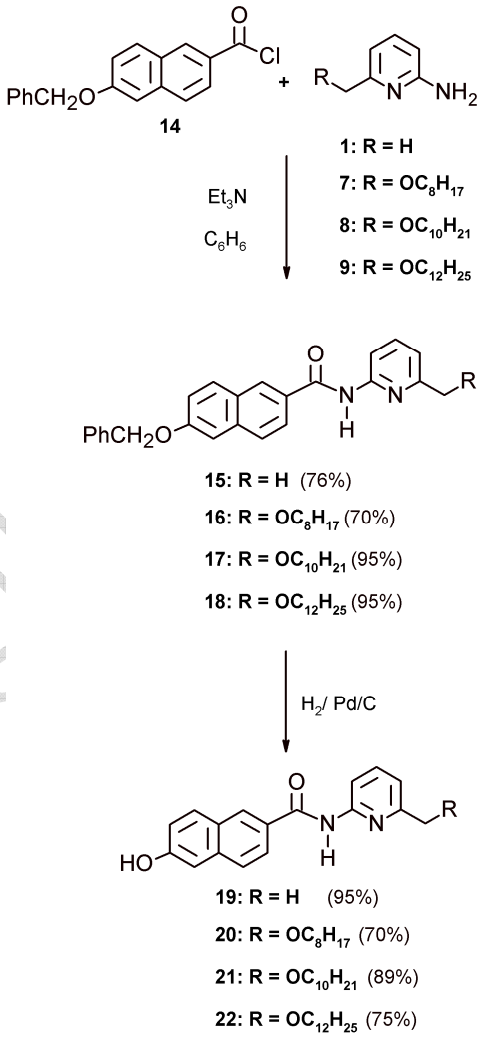
Synthesis of compound 14: Compound **13** (0.46 g, 1.65 mmol) was suspended in dry benzene (5 mL) and treated

with oxalyl chloride (1.5 mL, 17.19 mmol). The reaction was initiated by the addition of catalytic amount of dry DMF (5 µL) and the reaction mixture was stirred at room temperature for a period of 3 hr. The volatiles were removed under reduced pressure to afford the acid chloride **14** as a yellowish solid.

Synthesis of compound 15: The acid chloride **14,** obtained from corresponding acid derivative **13** (0.16 g, 0.57 mmol) by reaction with oxalyl chloride, was suspended in dry benzene (2.8 mL). Then **1** (0.122 g, 1.127 mmol) was added followed by addition of NEt_3 (0.24 mL, 1.69 mmol). The reaction mixture was stirred at room temperature for 12 h. The reaction mixture then diluted with chloroform (30 mL) and washed with brine solution (20 mL) and dried over anhydrous sodium sulfate. The volatiles were removed under reduced pressure and the crude product was purified by column chromatography (Si-gel, 100-200 mesh) using 20% ethyl acetate/petroleum ether as eluent to afford compound **15** as a white solid (0.152 g, yield: 76%).

Synthesis of compound 16: A solution of compound **7** (0.40 g, 1.69 mmol) in dry benzene (8 mL) was added to the dry acid chloride **14**, then NEt_3 (0.36 ml, 2.58 mmol) was added and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture then diluted with chloroform (40 mL) and washed with brine solution (20 mL) and dried over anhydrous sodium sulfate. The volatiles were removed and the crude product was purified by column chromatography (Si-gel, 100-200 mesh) using 20% ethyl acetate/petroleum ether as eluent to afford compound **16** (0.570 g, yield: 70 %) as a white solid. m.p. = 83 – 86 °C, FTIR (neat, cm^{-1}) ν_{max}: 3289, 3060, 3038, 2954, 2923, 2853, 1674, 1626, 1582. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.4 (t, 2H), 8.01 - 7.76 (m, 4H), 7.52 - 7.20 (m, 8H), 5.21 (s, 2H), 4.56 (s, 2H), 3.56 (t, 2H), 1.71 -1.60 (m, 2H), 1.42 - 1.28 (m, 10H), 0.88 (t, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.81, 158.53, 156.77, 151.05, 139.41, 136.59, 136.36, 130.74, 129.02, 128.65, 128.16, 128.01, 127.94, 127.55, 127.43, 124.25, 120.22, 117.40, 112.91, 106.91, 72.93, 71.33, 70.10, 31.78, 29.66, 29.40, 29.22, 26.10, 22.61, 14.07 ppm. $C_{32}H_{37}N_2O_3$ [M + H^+] 497.2795; found 497.2795.

Synthesis of compound 17: A solution of compound **8** (0.14 g, 0.38 mmol) in dry benzene (1.9 mL) was added to the solid acid chloride **14**. Then NEt_3 (0.08 ml, 0.57 mmol) was added and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture then diluted with ethyl acetate (40 mL) and washed with brine solution (30 mL) and dried over anhydrous sodium sulfate. The volatiles were removed and the crude product was purified by column chromatography (Si-gel, 100-200 mesh) using 20% ethyl acetate/petroleum ether as the eluent to afford compound **17** (0.20 g, yield: 95%) as a white solid. m.p.= 83-86 °C; FTIR (neat, cm^{-1}) ν_{max}: 3289, 3060, 3038, 2954, 2923, 2853, 1674, 1626, 1582. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.79 (s, 1H), 8.42 (d, J = 1.6 Hz, 1H), 8.37 (d, J = 8 Hz, 1H), 7.99 - 7.78 (m, 4H), 7.54-7.22 (m, 8H), 5.24 (s, 2H), 4.56 (s, 2H), 3.57 (t, 2H), 1.71-1.28 (m, 16H), 0.90 (t, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.69, 158.60, 157.22, 151.14, 139.07, 136.62, 136.47, 130.74, 129.27, 128.69, 128.13, 127.81, 127.57, 124.21, 120.28, 117.48, 112.73, 107.09, 73.33, 71.33, 70.20, 31.88, 29.72, 29.68, 29.59, 29.56, 29.48, 29.30, 26.15, 22.66, 14.08 ppm. HRMS (ESI) m/z: calcd for $C_{34}H_{41}N_2O_3$ [M + H^+] 525.311; found 525.3115.



Scheme 3: Synthesis of the target compounds **19 - 22**

Synthesis of compound 18: A solution of compound **9** (0.14 g, 0.38 mmol) in dry benzene (1.9 mL) was added to the solid acid chloride **14**, NEt_3 (0.08 ml, 0.57 mmol) was added and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture then diluted with ethyl acetate (40 mL) and washed with brine solution (30 mL) and dried over anhydrous sodium sulfate. The volatiles were removed and the crude product was purified by column chromatography (Si-gel, 100-200 mesh) using 20% ethyl acetate/petroleum ether as the eluent to afford compound **18** (200 mg, yield : 95%) as a white solid; m.p. = 85 - 88 °C. FTIR (neat, cm^{-1}) ν_{max}: 3285, 3060, 3038, 2954, 2918, 1647, 1628, 1533. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.82 (s, 1H), 8.42 (s, 1H), 8.37 (d, J = 8.4 Hz, 1H), 7.99-7.97 (dd, J_1 = 1.6 Hz, J_2 = 2 Hz, 1H),

7.98 – 7.96 (dd, J_1 = 1.6 Hz, J_2 = 8.6 Hz, 1H), 7.93 – 7.80 (m, 2H), 7.50 (d, J = 7.2 Hz, 2H), 7.44 – 7.41(t, 2H), 7.38 – 7.34 (dd, J_1 = 4.8 Hz, J_2 = 8.4 Hz, 1H), 7.33 – 7.20 (m, 2H), 5.22 (d, J = 7.2 Hz, 2H), 4.56 (s, 2H), 3.578 (t, J = 6.8, 2H), 1.72-1.65 (m, 2H), 1.44 – 1.31 (m, 17H), 0.88 (t, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.74, 158.59, 157.18, 151.15, 139.62, 136.45, 130.75, 129.24, 128.70, 128.20, 128.11, 127.84, 127.59, 127.50, 124.23, 120.28, 117.50, 112.77, 107.04,73.30, 71.34, 70.19, 31.91, 29.72, 29.69, 29.67, 29.67,29.61, 29.49, 29.35, 29.16, 26.16,22.68,14.11 ppm. HRMS (ESI): m/z Calcd for $C_{36}H_{45}N_2O_3$ [M + H^+] 553.3425, found 553.3427.

Synthesis of compound 19: Compound **15** (0.10 g, 0.27 mmol) was dissolved in ethyl acetate (5 mL). Then 10% Pd-C (0.05 g, 0.048 mmol) was mixed and the reaction mixture was stirred at room temperature under hydrogen atmosphere for 18 h. The reaction mixture was diluted with ethyl acetate (20 mL) and filtered by using fluted filter paper. The volatiles were removed under reduced pressure and the crude product was purified by column chromatography (Si-gel, 100-200 mesh) using 20% ethyl acetate/petroleum ether as eluent to afford compound **19** (0.073 g, yield: 94.4%) as a white solid. mp = 248 – 251 °C . FTIR (neat, cm^{-1}) ν_{max}: 3351, 2962, 1681, 1610, 1504, 877. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.39 (m, 2H), 7.98 (s, 1H), 7.63 (m, 1H), 7.46 - 7.19 (m, 3H), 6.67 (m, 2H), 6.45 (s, 1H), 1.99 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.9, 162.3, 161.5, 156.3, 143.3, 141.6, 135.7, 133.2, 133.0, 131.8, 131.3, 129.2, 124.5, 123.9, 116.2, 113.9, 28.8 ppm. HRMS (ESI): m/z calcd for $C_{17}H_{14}N_2O_2Na$ [M + Na^+] 278.3053; found 278.3051.

Synthesis of compound 20: Compound **16** (0.10 g, 0.20 mmol) was dissolved in ethyl acetate (4 mL). Then 10 % Pd/C (0.04 g, 0.04 mmol) was mixed and the reaction mixture was stirred at room temperature under elevated pressure of hydrogen gas atmosphere for 20 h. The reaction mixture was diluted with ethyl acetate (20 mL) and filtered by using fluted filter paper. The volatiles were removed under reduced pressure and the crude product was purified by column chromatography (Si-gel, 100-200 mesh) using 20 % ethyl acetate/petroleum ether as eluent to afford compound **20** as a white solid (0.04 g, yield: 70%). m.p. = 99 - 102 °C; FTIR (neat, cm^{-1}) ν_{max}: 3394, 3265, 2920, 2852, 1680, 1550. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.71 (broad , 1H), 8.35 (d, J = 8 Hz, 1H), 8.14 (s, 1H), 7.83 - 7.73 (m, 3H), 7.62 (d, J = 8.4 Hz, 1H), 7.27 - 7.20 (m, 4H), 4.59 (d, J = 12.8 Hz, 2H), 3.59 (t, 2H), 1.67 - 1.25 (m, 12H), 0.86 (t, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ =166.0, 155.9, 151.2, 139.5, 136.7, 131.3, 128.8, 127.9, 127.5, 126.9, 124.2, 119.4, 117.7, 113.1, 109.6, 103.0, 73.1, 71.5, 31.8, 29.7, 29.4, 29.3, 26.2, 22.7, 14.1 ppm. HRMS (ESI): m/z calcd for $C_{25}H_{30}N_2O_3Na$ [M + Na^+] 429.2154; found 429.2152.

Synthesis of compound 21: A solution of compound **17** (0.18 g, 0.34 mmol) in ethyl acetate (5 mL) was treated with 10% Pd-C (0.07 g, 0.07 mmol) and the reaction mixture was stirred at room temperature under elevated pressure of hydrogen gas atmosphere for 18 hr. Then the reaction mixture was diluted with ethyl acetate (30 mL) and filtered by using fluted filter paper. The volatiles were removed under reduced pressure and the crude product was purified by column chromatography (Si-gel, 100-200 mesh) using 20 % ethyl acetate/petroleum ether as eluent to afford compound **21** (0.13 g, yield : 89%) as a light yellow solid. m.p. = 88–90 °C; FTIR (neat, cm^{-1}) ν_{max}: 3346, 2949, 2922, 2851, 1684, 1629, 1549, 874. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.77 (s, 1H), 8.35 (d, J = 8.4 Hz, 1H), 8.09 (s, 1H), 7.85-7.81(t, 1H), 7.79-7.68 (dd, J_1 = J_2 = 8.4 Hz, 2H), 7.59 (d, J = 8.4 Hz, 2H), 7.28-7.21 (m, 3H), 4.64 (s, 2H), 3.63 - 3.60 (t, 2H), 1.82 - 1.65 (m, 2H), 1.39 - 1.37 (m, 3H), 1.27 - 1.085 (m, 13H), 0.89 (t, 3H) ppm. ^{13}C NMR(100 MHz, $CDCl_3$): δ = 166.03, 156.79, 156.01, 151.17, 139.46, 136.66, 131.29, 128.72, 127.54, 126.90, 124.15, 119.39, 117.68, 113.18, 109.59, 73.04, 71.51, 31.88, 29.63, 29.58, 29.55, 29.46, 29.30, 26.13, 22.66, 14.09 ppm. HRMS (ESI) m/z: calcd for $C_{27}H_{34}N_2O_3Na$ [M + Na^+] 457.2462; found 457.2467.

Synthesis of compound 22: Compound **18** (0.14 g, 0.26 mmol) was dissolved in ethyl acetate (4mL). Then 10 % Pd/C (0.06 g, 0.23 mmol) was mixed and the reaction mixture was stirred at room temperature under elevated pressure of hydrogen gas atmosphere for 18 h. Then reaction mixture was diluted with ethyl acetate (20 mL) and filtered by using fluted filter paper. The volatiles were removed under reduced pressure and the crude product was purified by column chromatography (Si-gel, 100-200 mesh) using 20% ethyl acetate/petroleum ether as eluent to afford compound **22** as a white solid (0.08g, yield: 75%). m.p. = 85-88 °C; FTIR (neat, cm^{-1}) ν_{max}: 3285, 3060, 3038, 2954, 2918, 1647, 1628, 1533 ; ^{1}HNMR (400 MHz, $CDCl_3$): δ = 8.792 (s, 1H), 8.375 (d, J = 8.4 Hz, 1H), 8.172 (S, 1H), 7.823 (t, J_1 = 4.8 Hz, J_2 = 8.8 Hz, 1H), 7.98 – 7.96 (dd, J_1 = 1.6 Hz, J_2 = 8.6 Hz, 1H), 7.93 – 7.80 (m, 2H), 7.50 (d, J = 7.2 Hz, 2H), 7.44 – 7.41(t, 2H), 7.38 – 7.34 (dd, J_1 = 4.8 Hz, J_2 = 2 Hz, 2H), 7.77 (d, J = 8.4 Hz, 1H), 7.65 (d, J = 8 Hz, 1H), 7.24 - 7.02 (m, 3H), 4.62 (s, 2H), 3.61(t, J = 6.8, 2H), 1.96-1.71 (m, 2H), 1.69 - 1.60 (m, 2H) 1.44 - 1.26 (m, 16H), 0.88 (t, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.94, 156.92, 155.79, 151.17, 139.36, 136.64, 131.28, 128.90, 127.68, 127.63, 126.93, 124.22, 119.24, 117.60, 113.10, 109.57, 73.07, 71.46, 31.90, 30.29, 29.65, 29.56, 29.46, 29.33, 29.14, 28.95, 26.14,22.67,14.08 ppm. HRMS (ESI): m/z Calcd for $C_{29}H_{39}N_2O_3Na$ [M + Na^+] 463.2955; found 463.2957.

3. Results and Discussion

The amino group of 2-amino-6-picoline **1** was reacted with pivaloyl chloride in the presence of triethyl amine as a base to produce **2** in 98% yield (Scheme 1). Reaction of **2** with NBS in CCl_4 in the presence of AIBN produced compound **3** in 76% isolated yield.[15,16] Reaction of **3** with n-octaol, n-decanol and n-dodecanol in the presence of NaH in THF produced the corresponding alkoxy derivatives **4**, **5** and **6** in 99%, 88% and 91% yields respectively. Removal of the pivaloyl protecting group of **4**, **5** and **6** was carried out by

refluxing with KOH in ethanol/water to produce **7**, **8** and **9** in 85%, 78%, 76% yield respectively. Suffice to mention, when the molarity of the starting material during the alkaline hydrolysis was 0.1 M, then the reaction was not complete even after refluxing for 3 days. However, on increasing the concentration of starting material was 0.2 M or more, then the reaction complete within one day of refluxing.

6-hydroxy-2-naphthoic acid **10** was converted to its methyl ester **11** by stirring with dry methanol at room temperature in the presence of HCl as a catalyst in 90% yield. The OH group of **11** was protected by benzylation with benzyl chloride in the presence of K_2CO_3 in dry DMF to afford **12** in 99% yield. The methyl ester **12** was hydrolyzed by refluxing in a mixture of water-THF-methanol to yield **13** in 97% yield. The carboxylic acid **13** was transformed to the corresponding acid chloride **14** by stirring with $(COCl)_2$ in dry benzene at room temperature for 12 hour.

The acid chloride **14** was reacted with 2-amino-6-picoline **1** and its alkoxy derivatives **7**, **8** and **9** in dry benzene in the presence of triethyl amine as a base to afford the amides **15**, **16**, **17** and **18** in 76%, 70%, 95%, and 95% yields respectively. Reductive debenzylation of **15**-**18** with H_2/Pd/C afforded the target compounds **19**, **20**, **21** and **22** in 95%, 70%, 90% and 75% yields respectively.[17]

4. Conclusion

In conclusion, syntheses of four 6-hydroxy-N-(6-methylpyridin-2-yl) naphthalene-2-carboxamide and its alkoxy analogues bearing long alkyl chains have been reported starting from 6-hydroxy-2-naphthoic acid and 2-amino-6-picoline in high yields. The straight forward methods reported here for the synthesis of the carboxamide derivatives opens up a new strategy for the synthesis of such derivatives. The presence of the H-bond donor-acceptor groups and the reactive 2-naphthol moiety in the caroxyamide derivatives opens up its use in studying self-assembly and self-replication. Studies along these lines are in progress and the results will be reported in due course.

5. Acknowledgement

BGB thanks Science and Engineering Research Board (SERB), India (ref. EMR/2016/001123), Indo-Srilanka project (DST/INT/SL/P25/2016), DST Fast-Track (SR/FTP/CS-42/2001), UGC-SAP and DST-FIST New Delhi and Vidyasagar University for financial support and infrastructural facilities. SKD, KP, SG thank CSIR and SG, SKP thank UGC-BSR for providing research fellowships.

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