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REGULAR ARTICLE

Total synthesis of sannanine and analogues thereof

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Abstract. The first total synthesis of Sannanine has been accomplished with an overall 30% yield in a concise manner. The key strategies involve Friedländer quinoline synthesis, demethylation, *in situ* oxidation and amination process.

Keywords. Total synthesis; natural products; Friedländer synthesis; sannanine.

1. Introduction

Quinoline-5,8-dione is one of the most important cores, found in many natural products as well as in biologically potent molecules[1] (Figure 1). The potential of quinoline-5,8-dione has been proved in a variety of fields. In general, quinoline-5,8-dione shows the predominant biological activities such as anticancer, antimalarial, anti-inflammatory, and antifungal.[1a, 2] In addition, quinolone-5,8-dione has very good tenancy to form complexes with transition metals which result in dramatic changes in biological as well as photo-physical properties of quinoline-5,8-dione. Due to bathochromic shift of the metal complex of the quinolone-5,8-dione, quinoline-5,8-dione core has also revealed its potential in 'colour formers'.[3] Subsequently quinoline-5,8-dione is also used as a fundamental core in the synthesis of many natural products as well as biological efficient molecules. In short, quinoline-5,8-dione has a vital role in most of the fields such as synthetic, biological, and material chemistry.[4]

Sannanine (**1**) (Figure 1), an anticancer agent, was isolated from *Streptomyces sannanensis* in 2009 by Han and co-workers and it was found that sannanine exhibits anticancer activity against the four cancer cell lines, such as BGC823, PANC1, HepG2 and H460 with IC_{50} values of 6.6, 5.8, 3.1 and 1.8 μM, respectively.[5] Due to excellent biological activity of sannanine, there is an urgency for its synthesis. Till date, there is no synthetic report on sannanine natural product. Due to more efficacy of the quinoline-5,8-dione core, the natural product sannanine was chosen as an our target molecule, as a part of ongoing natural product synthesis.

2. Experimental

2.1 *General*

All the chemicals were used as purchased (Sigma Aldrich & Avra Synthesis P. Ltd., India) for the reaction without any purification. As per standard procedures, all solvents were dried for the reactions. In addition, highly moisture sensitive reactions were performed under nitrogen atmosphere. All the newly synthesized compounds were characterized by NMR in which $CDCl_3$ and DMSO-d_6 were used as solvents. In ^{1}H NMR, 7.26 ppm and 2.53 ppm peaks were fixed for $CDCl_3$ and DMSO-d_6 solvents, respectively. All the compounds were further characterized HRMS and IR spectral analysis. For all the newly synthesized by solid compounds, melting points were determined.

2.2 *Synthetic procedure for 5,8-dimethoxy-2,3-dimethylquinoline **(3)** and 2-ethyl-5,8-dimethoxyquinoline **(6)***

2-Amino-3,6-dimethoxybenzaldehyde (5 g, 0.0275 mol) was taken in EtOH (10 mL). Then, 10% ethanolic KOH (1.1 equiv.) was added to the reaction mixture and stirred for 12 h at 90 °C under N_2 atmosphere. The completion of reaction was monitored by thin layer chromatography (TLC). After completion of reaction, the reaction mixture was poured into water (100 mL) and extracted with EtOAc (4 × 50 mL). The crude product was purified by column chromatography using hexane/EtOAc solvent mixture. Finally, 5,8-dimethoxy-2,3-dimethylquinoline was obtained as a colourless solid in 62% yield. R_f = 0.23 (20% EtOAc/Hexane); M.p.: 126 °C; IR

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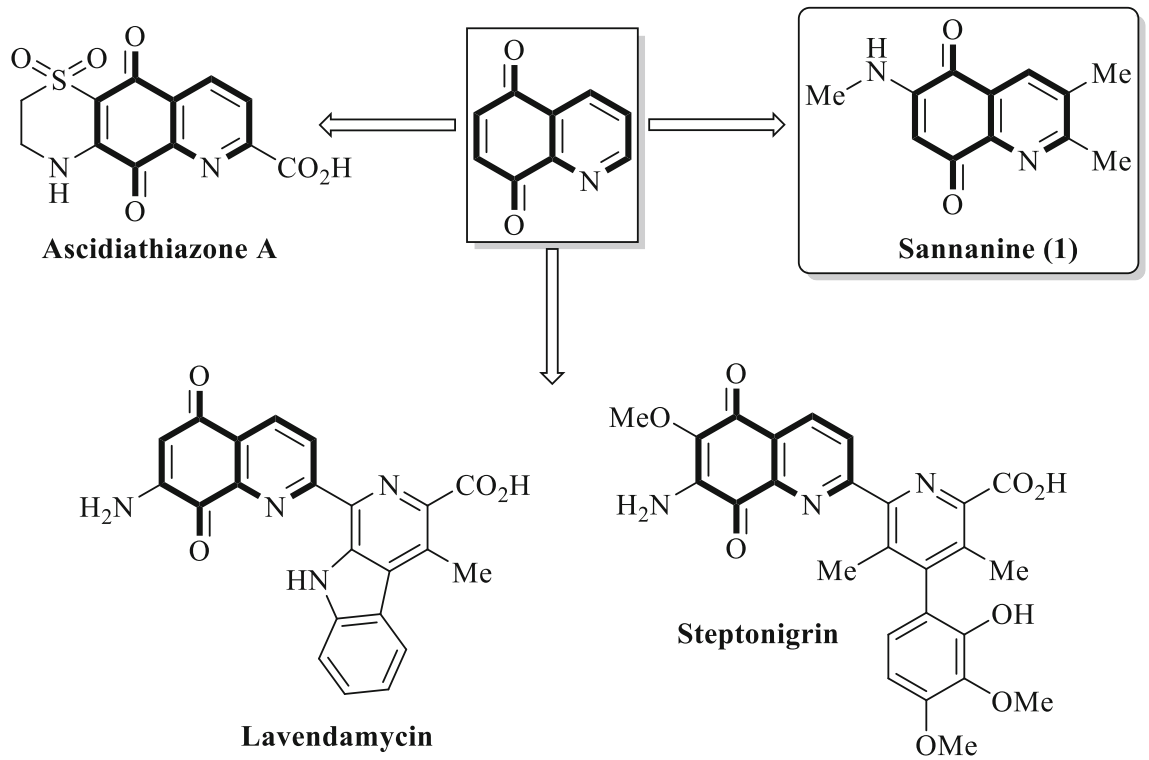


Figure 1. Structure of quinoline-5,8-dione, sannanine **1** and related natural products.

(KBr): υ_{max} 3586, 3484, 3004, 2941, 2915, 2815, 2835, 1621, 1609, 1482, 1467, 1454, 1426, 1404 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.16 (s, 1H), 6.77 (d, J = 8.4 Hz, 1H), 6.60 (d, J = 8.4 Hz, 1H), 3.96 (s, 3H), 3.86 (s, 3H), 2.68 (s, 3H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.3, 148.9, 148.2, 138.6, 130.1, 129.8, 120.6, 105.6, 102.8, 55.9, 55.6, 23.8, 19.6; HRMS (ESI): m/z calcd. for $C_{13}H_{15}NO_2$ $[M + H]^+$: 218.1182, found: 218.1185.

2.2a *2-Ethyl-5,8-dimethoxyquinoline **(6)***: Yield: 34%; brown coloured liquid; R_f = 0.28 (20% EtOAc/Hexane); IR (KBr): υ_{max} 3553, 3466, 3010, 2923, 2910, 2715, 2635, 1631, 1619, 1475, 1467, 1434, 1416, cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.47 (d, J = 8.6 Hz, 1H), 7.36 (d, J = 8.6 Hz, 1H), 6.91 (d, J = 8.5 Hz, 1H), 6.70 (d, J = 8.5 Hz, 1H), 4.03 (s, 3H), 3.94 (s, 3H), 3.08 (q, J = 7.5 Hz, 2H), 1.40 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.4, 148.9, 148.6, 139.9, 131.0, 120.1, 119.9, 106.8, 102.7, 55.9, 55.5, 32.3, 14.1; HRMS (ESI): m/z calcd. for $C_{13}H_{15}NO_2$ $[M + H]^+$: 218.1182, found: 218.1174.

2.3 *Synthetic procedure for 2,3-dimethylquinoline-5,8-dione **(2)***

5,8-Dimethoxy-2,3-dimethylquinoline (2 g, 0.0092 mol) was taken in CH_3CN (15 mL). This was followed by addition of aq. ceric ammonium nitrate (CAN) (0.0229 mol) to the reaction mixture at room temperature and allowed to stir for 1 h. The reaction was monitored by TLC. After completion of reaction, the reaction mixture was poured in water (50 mL) and extracted with EtOAc (5 × 20 mL). The crude product was further used for the next reaction without purification. Yield: 83% as a red coloured solid; R_f = 0.23 (50% EtOAc/Hexane); M.p.: 102 °C; IR (KBr): υ_{max} 1655, 1640, 1461, 1423, 1400, 1390, 1350 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.08 (s, 1H), 7.07 (d, J = 10.4 Hz, 1H), 6.98 (d, J = 10.3 Hz, 1H), 2.71 (s, 3H), 2.46 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 185.1, 183.6, 164.2, 144.8, 138.8, 137.6, 137.6, 134.4, 127.4, 23.4, 19.7; HRMS (ESI): m/z calcd. for $C_{11}H_9NO_2$ $[M + H]^+$: 188.0712, found: 188.0717.

2.4 *General synthetic procedure for the compounds **1** and **8-19***

2,3-Dimethylquinoline-5,8-dione (0.0004 mol) was taken in EtOH (2 mL). Subsequently, the amines (1.5 equiv.) were added to the reaction mixture and allowed to stir for 2 h at room temperature. After completion of reaction, the solvent was evaporated under reduced pressure and finally the crude products were purified by column chromatography using hexanes/EtOAc mixtures.

2.4a *2,3-Dimethyl-6-(methylamino)quinolone-5,8-dione **(1)***: Yield: 49% (in two steps) as a red colored solid; R_f = 0.44 (EtOAc/Hexane); M.p.: 198 °C; IR (KBr): υ_{max} 3288, 1683, 1627, 1596, 1550, 1505, 1453, 1414, 1372, 1333, 1290, 1234, 1200 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.99 (s, 1H), 5.97 (s, 1H), 5.80 (s, 1H), 2.90 (d, J = 4.5 Hz, 3H), 2.66 (s, 3H), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 181.81, 181.80, 164.4, 148.4, 146.8,

135.3, 134.3, 125.4, 101.1, 29.1, 23.4, 19.3; HRMS (ESI): m/z calcd. for $C_{12}H_{12}N_2O_2$ $[M + H]^+$: 217.0978, found: 217.0978.

2.4b *2,3-Dimethyl-7-(methylamino)quinolone-5,8-dione **(7)***: Yield: 27% (in two steps) as a red colored solid; R_f = 0.16 (50% EtOAc/Hexane); M.p.: 192 °C; IR (KBr): υ_{max} 3331, 1697, 1596, 1550, 1505, 1453, 1415, 1372, 1333, 1270, 1234, 1200, 1168 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.09 (s, 1H), 6.14 (s, 1H), 5.69 (s, 1H), 2.95 (d, J = 5.4 Hz, 3H), 2.65 (s, 3H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 182.2, 180.2, 161.8, 149.1, 144.0, 138.1, 134.4, 129.1, 99.5, 29.2, 23.0, 19.7; HRMS (ESI): m/z calcd. for $C_{12}H_{12}N_2O_2$ $[M + Na]^+$: 239.0795, found: 239.0795.

2.4c *6-(Benzylamino)-2,3-dimethylquinoline-5,8-dione **(8)***: Yield: 51% (in two steps) as a red colored solid; R_f = 0.16 (50% EtOAc/Hexane); M.p.: 180 °C; IR (KBr): υ_{max} 3289, 1673, 1624, 1599, 1585, 1552, 1498, 1445, 1381, 1332, 1280, 1228, 1211 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.02 (s, 1H), 7.34 (m, 5H), 6.18 (s, 1H), 5.89 (s, 1H), 4.37 (d, J = 5.5 Hz, 2H), 2.69 (s, 3H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 181.9, 181.8, 164.5, 147.1, 146.6, 135.6, 135.4, 134.3, 129.0, 128.2, 127.7, 125.5, 102.2, 46.8, 23.5, 19.4; HRMS (ESI): m/z calcd. for $C_{18}H_{16}N_2O_2$ $[M + H]^+$: 293.1291, found: 293.1288.

2.4d *7-(Benzylamino)-2,3-dimethylquinoline-5,8-dione **(9)***: Yield: 24% (in two steps) as a red colored solid; R_f = 0.40 (50% EtOAc/Hexane); M.p.: 168 °C; IR (KBr): υ_{max} 3245, 1694, 1598, 1550, 1454, 1440, 1415, 1378, 1353, 1335, 1273, 1233, 1202, 1192 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.10 (s, 1H), 7.32 (m, 5H), 6.38 (s, 1H), 5.77 (s, 1H), 4.41 (d, J = 5.8 Hz, 2H), 2.68 (s, 3H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 182.4, 180.3, 162.0, 147.9, 144.0, 138.2, 135.6, 134.4, 129.0, 128.2, 127.6, 100.7, 46.9, 23.0, 19.8; HRMS (ESI): m/z calcd. for $C_{18}H_{16}N_2O_2$ $[M + Na]^+$: 315.1109, found: 315.1107.

2.4e *2,3-Dimethyl-6-(phenethylamino)quinolone-5,8-dione **(10)***: Yield: 66% (in two steps) as a red colored solid; R_f = 0.49 (EtOAc); M.p.: 206 °C; IR (KBr): υ_{max} 3345, 1688, 1614, 1559, 1538, 1460, 1375, 1342, 1292, 1235, 1200, 1156, 1120 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.99 (s, 1H), 7.33 (t, J = 7.4 Hz, 2H), 7.27 (d, J = 7.8 Hz, 1H), 7.22 (d, J = 7.2 Hz, 2H), 5.92 (s, 1H), 5.89 (s, 1H), 3.46 (q, J = 6.9 Hz, 2H), 2.98 (t, J = 6.9 Hz, 2H), 2.69 (s, 3H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 181.89, 181.80, 164.4, 147.1, 146.7, 137.6, 135.3, 134.3, 128.8, 128.6, 126.9, 125.4, 101.5, 43.6, 34.2, 23.5, 19.3; HRMS (ESI): m/z calcd. for $C_{19}H_{18}N_2O_2$ $[M + H]^+$: 307.1447, found: 307.1448.

2.4f *2,3-Dimethyl-7-(phenethylamino)quinolone-5,8-dione **(11)***: Yield: 30% (in two steps) as a red colored solid; R_f = 0.56 (EtOAc); M.p.: 148 °C; IR (KBr): υ_{max} 3331, 1698, 1604, 1552, 1508, 1449, 1370, 1332, 1272, 1235, 1202, 1146, 1106 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.11 (s, 1H), 7.34 (t, J = 7.2 Hz, 2H), 7.28 (d, J = 3.8 Hz, 1H), 7.23 (d, J = 7.1 Hz, 2H), 6.12 (s, 1H), 5.77 (s, 1H), 3.49 (q, J = 6.7 Hz, 2H), 3.00 (t, J = 7.4 Hz, 2H), 2.67 (s, 3H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 182.3, 180.2, 161.9, 147.9, 144.0, 138.1, 137.7, 134.4, 129.0, 128.8, 128.6, 126.9, 99.9, 43.9, 34.3, 23.0, 19.7; HRMS (ESI): m/z calcd. for $C_{19}H_{18}N_2O_2$ $[M + Na]^+$: 329.1265, found: 329.1265.

2.4g *6-((4-Methoxyphenethyl)amino)-2,3-dimethylquinoline-5,8-dione **(12)***: Yield: 47% (in two steps) as a red colored solid; R_f = 0.14 (50% EtOAc/Hexane); M.p.: 214 °C; IR (KBr): υ_{max} 3376, 1687, 1605, 1553, 1504, 1467, 1435, 1377, 1342, 1312, 1282, 1240, 1197, 1183 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.98 (s, 1H), 7.11 (d, J = 7.5 Hz, 2H), 6.85 (d, J = 7.4 Hz, 2H), 5.87 (s, 2H) (Including both -NH proton and -CH (7^{th} position) proton), 3.77 (s, 3H), 3.40 (q, J = 5.8 Hz, 2H), 2.90 (t, J = 6.3 Hz, 2H), 2.67 (s, 3H), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 181.9, 181.8, 164.4, 158.5, 147.1, 146.7, 135.3, 134.3, 134.2, 129.6, 125.4, 114.3, 101.4, 55.3, 43.8, 33.4, 23.5, 19.4; HRMS (ESI): m/z calcd. for $C_{20}H_{20}N_2O_3$ $[M + H]^+$: 337.1553, found: 337.1556.

2.4h *7-((4-Methoxyphenethyl)amino)-2,3-dimethylquinoline-5,8-dione **(13)***: Yield: 22% (in two steps) as a red colored solid; R_f = 0.21 (50% EtOAc/Hexane); M.p.: 198 °C; IR (KBr): υ_{max} 3366, 1677, 1615, 1573, 1500, 1477, 1425, 1370, 1345, 1315, 1282, 1251, 1187, 1180 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.12 (s, 1H), 7.14 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 6.11(s, 1H), 5.76 (s, 1H), 3.81 (s, 3H), 3.44 (q, J = 6.7 Hz, 2H), 2.94 (t, J = 7.3 Hz, 2H), 2.67 (s, 3H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 100MHz): δ 182.3, 180.2, 161.9, 158.5, 147.9, 144.0, 138.1, 134.4, 129.6, 129.6, 129.1, 114.3, 99.9, 55.2, 44.1, 33.4, 23.0, 19.7; HRMS (ESI): m/z calcd. for $C_{20}H_{20}N_2O_3$ $[M + H]^+$: 337.1553, found: 337.1554.

2.4i *6-((2-(1H-Indol-3-yl)ethyl)amino)-2,3-dimethylquinoline-5,8-dione **(14)***: Yield: 48% (in two steps) as a red colored solid; R_f = 0.25 (50% EtOAc/Hexane); M.p.: 144 °C; IR (KBr): υ_{max} 3341, 3273, 1685, 1633, 1609, 1588, 1557, 1504, 1462, 1443, 1370, 1329, 1229, 1271, 1233 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.17 (s, 1H), 8.12 (s, 1H), 7.63 (d, J = 7.9 Hz, 1H), 7.41 (d, J = 8.1 Hz, 1H), 7.24 (t, J = 7.7 Hz, 1H), 7.17 (t, J = 7.5 Hz, 1H), 7.10 (s, 1H), 6.18 (s, 1H), 5.78 (s, 1H), 3.55 (q, J = 6.0 Hz, 1H), 3.18 (t, J = 6.9 Hz, 1H), 2.67 (s, 3H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 182.2, 180.8, 163.8, 148.1, 146.5, 136.7, 135.5, 134.1, 127.5, 125.9, 123.5, 121.4, 118.7, 118.6, 111.8, 111.6, 100.5, 43.1, 23.7, 23.4, 19.0; HRMS (ESI): m/z calcd. for $C_{21}H_{19}N_3O_2$ $[M + H]^+$: 346.1556, found: 346.1557.

2.4j *7-((2-(1H-Indol-3-yl)ethyl)amino)-2,3-dimethylquinoline-5,8-dione **(15)***: Yield: 27% (in two steps) as a red colored solid; R_f = 0.32 (50% EtOAc/Hexane); M.p.: 150 °C; IR (KBr): υ_{max} 3229, 2927, 1682, 1630, 1601, 1584, 1557, 1511, 1460, 1443, 1381, 1337, 1301, 1272,

1244, 1226, 1175 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.43 (s, 1H), 8.12 (s, 1H), 7.62 (d, J = 7.7 Hz, 1H), 7.39 (d, J = 7.9 Hz, 1H), 7.23 (t, J = 6.8 Hz, 1H), 7.15 (d, J = 7.4 Hz, 1H), 7.10 (s, 1H), 6.19 (s, 1H), 5.78 (s, 1H), 3.53 (d, J = 6.2 Hz, 2H), 3.17 (t, J = 6.2 Hz, 2H), 2.66 (s, 3H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 182.3, 180.2, 161.8, 148.0, 144.0, 138.1, 136.4, 134.4, 129.1, 126.9, 122.3 (2 Ar-C), 119.6, 118.4, 111.8, 111.4, 99.8, 42.7, 24.1, 22.9, 19.7; HRMS (ESI): m/z calcd. for $C_{21}H_{19}N_3O_2$ $[M + H]^+$: 346.1556, found: 346.1552.

2.4k *6-(Allylamino)-2,3-dimethylquinoline-5,8-dione **(16)***: Yield: 59% (in two steps) as a red colored viscous liquid; R_f = 0.52 (50% EtOAc/Hexane); IR (KBr): υ_{max} 3281, 1673, 1637, 1566, 1550, 1495, 1451, 1434, 1382, 1334, 1293, 1236, 1203, 1172, 1102 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.99 (s, 1H), 5.97 (s, 1H), 5.82 (s, 1H), 5.30 (m, 2H), 3.81 (t, J = 5.5 Hz, 2H), 2.66 (s, 3H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 181.8, 181.8, 164.3, 147.1, 146.6, 135.3, 134.2, 131.4, 125.4, 118.3, 102.0, 44.8, 23.3, 19.2; HRMS (ESI): m/z calcd. for $C_{14}H_{14}N_2O_2$ $[M + Na]^+$: 265.0952, found: 265.0957.

[Note: Due to very low yield, compound **17** was only confirmed by HRMS (ESI): m/z calcd. for $C_{14}H_{14}N_2O_2$ $[M + H]^+$: 243.1134, found: 243.1134].

2.4l *2,3-Dimethyl-6-(prop-2-yn-1-ylamino)quinoline-5,8-dione **(18)***: Yield: 52% (in two steps) as a red colored solid; R_f = 0.30 (50% EtOAc/Hexane); M.p.: 156 °C; IR (KBr): υ_{max} 3291, 1676, 1647, 1568, 1555, 1505, 1454, 1424, 1380, 1344, 1292, 1246, 1205, 1177, 1112 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.00 (s, 1H), 7.77 (d, J = 5.5 Hz, 1H), 5.79 (s, 1H), 4.03 (t, J = 3.0 Hz, 2H), 3.26 (s, 1H), 2.55 (s, 3H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 182.0, 181.1, 163.8, 147.6, 146.1, 135.8, 134.1, 125.9, 102.4, 79.3, 75.0, 31.6, 23.4, 19.1; HRMS (ESI): m/z calcd. for $C_{14}H_{12}N_2O_2$ $[M + Na]^+$: 263.0796, found: 263.0796.

2.4m *2,3-Dimethyl-7-(prop-2-yn-1-ylamino) quinoline-5,8-dione **(19)***: Yield: 32% (in two steps) as a red coloured solid; R_f = 0.39 (50% EtOAc/Hexane); M.p.: 142 °C; IR (KBr): υ_{max} 3261, 1666, 1650, 1575, 1562, 1532, 1467, 1424, 1374, 1354, 1300, 1256, 1235, 1167, 1115, 1098 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.11 (s, 1H), 6.18 (s, 1H), 5.84 (s, 1H), 4.03 (d, J = 2.8 Hz, 2H), 2.67 (s, 3H), 2.44 (s, 3H), 2.37 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 182.5, 179.9, 162.2, 147.2, 143.9, 138.2, 134.4, 128.8, 101.5, 77.9, 73.5, 32.3, 23.0, 19.7; HRMS (ESI): m/z calcd. for $C_{14}H_{12}N_2O_2$ $[M + Na]^+$: 263.0796, found: 263.0801.

3. Results and Discussion

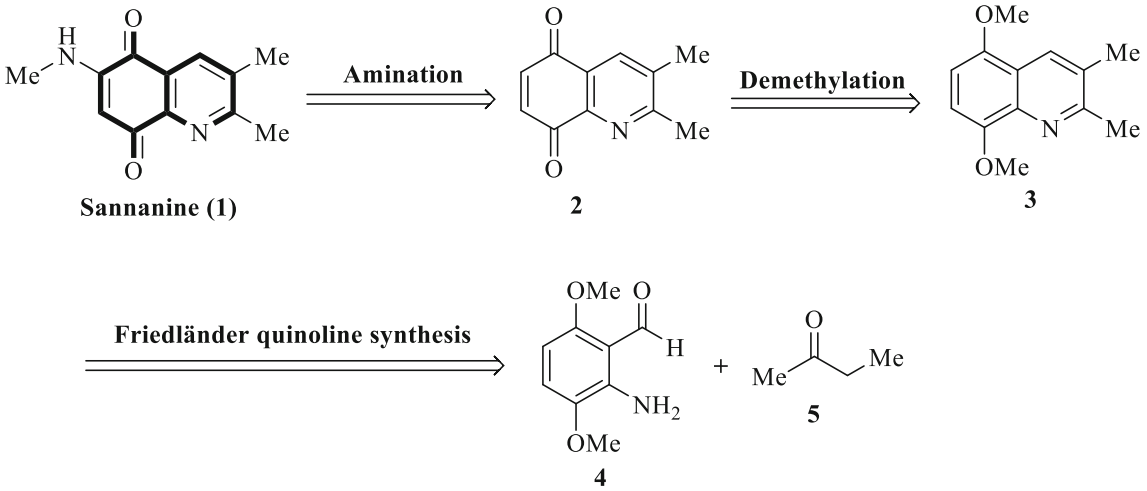
The proposed synthetic diagram for sannanine (**1**) is depicted in Scheme 1. Sannanine could be easily synthesized from quinoline-5,8-dione **2** by Michael addition of methylamine. Similarly, the 5,8-dione **2** could be obtained using demethylation of the quinoline compound **3**. At the initial stage, the quinoline compound **3** could be easily obtained by following the standard Friedländer quinoline synthesis.

The synthesis was commenced with the synthesis of starting precursor **4**. Using the standard literature procedure, *ortho*-amino aldehyde compound **4** was synthesized.[6] Having enough starting material **4** in hand, Friedländer quinoline synthesis[7] was carried out to synthesize 2,3-dimethyl-5,8-dimethoxy quinoline **3**. The compound **4** was treated with ethyl methyl ketone in the presence of 10% ethanolic KOH solution to afford the quinoline compound **3** in 62% yield and 2-ethyl quinoline **6** as a minor product in 34% yield (overall yield is 96%). Then, the compound **3** was subjected to demethylation and *in situ* oxidation to arrive at the dimethyl substituted quinoline-5,8-dione **2** which was treated with methylamine to obtain two regio isomers **1** and **7** with 46% and 27% yields (overall yield is 73%) in two steps, respectively. Out of the two regio isomers (**1** & **7**), 6-N-methylamine substituted quinoline-5,8-dione is our desired natural product **1**.

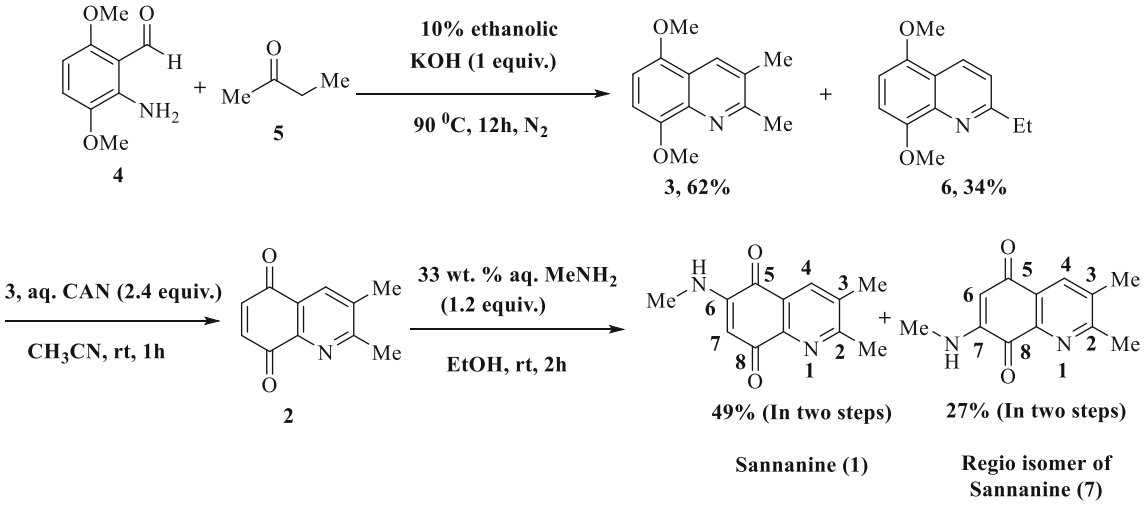
The spectral data of synthesized sannanine resembles with the reported values of **1** under fine shimming NMR. In ^1H NMR, the most important characteristic peak is that the methyl peak which should appear as a doublet with respect to NH proton (Table 1). In literature, the two carbonyl peaks for the natural product appeared in 181.78 & 181.75 ppm in ^{13}C NMR. Moreover, the difference between these two carbonyl peaks is 0.03 ppm. Similarly, for the synthesized product **1**, the peaks belonging to carbonyl groups appeared in 181.80 & 181.81 ppm and the difference is 0.01 ppm which are closer to reported values of reported ^{13}C NMR. Based on the above data, the synthesized product **1** was confirmed apart from its regio isomer **7**. As a result, the sannanine **1** was successfully synthesized in 30% overall yield for the first time using easily affordable starting materials in concise manner.

Subsequent to the synthesis of sannanine **1**, the analogues of the natural product **1** were synthesized (Scheme 3). To make a library of sannanine **1**, a variety of amines have been chosen as one of the starting materials. The synthesis of analogues of sannanine is outlined in Scheme 3. The quinoline-5,8-dione **2** was treated with different amines to obtained the two different regio isomers in moderate to good yields.

Among all the derivatives, phenyethylamine substituted analogues were obtained in good yields (**10** (66%) and **11** (30%)). However, in the case of allylamine, there is an isomer, which belongs to 6-substituted analogue **16**, achieved in 59% yield, whereas 7-substituted analogue **17** was found only in trace amount (yield 8%).



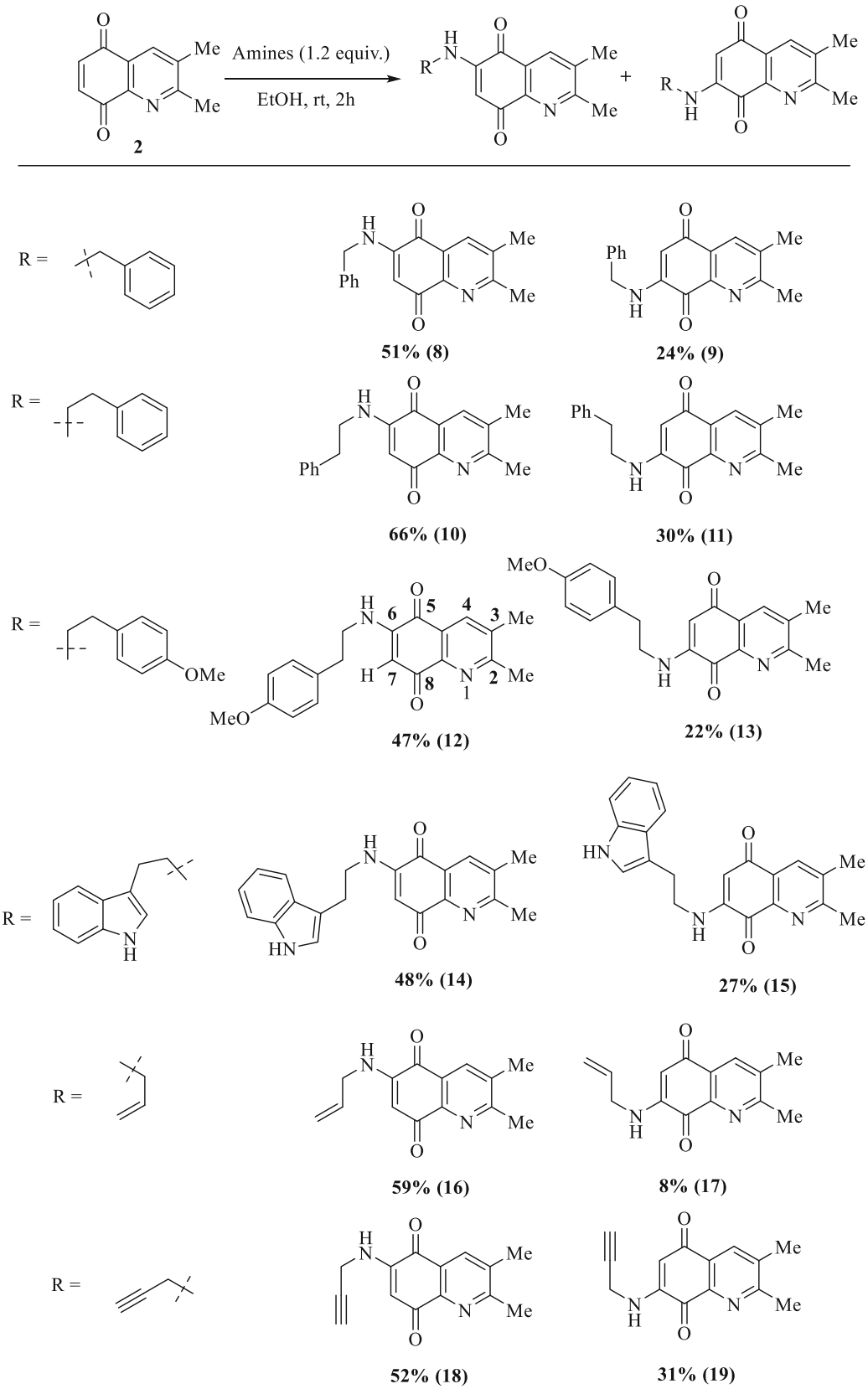
Scheme 1. Retrosynthetic analysis of sannanine (**1**).



Scheme 2. Synthesis of sannanine **1** and its regio isomer **7**.

Table 1. ^{1}H (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) data of reported and synthesized compound **1**.

Sl. No	δ_H (Reported) ppm	δ_H (Synthesized)	δ_C (Reported) ppm	δ_C (Synthesized)
NH	5.91 (1H, brs)	5.98 (1H, brs)	-	-
2	-	-	164.4	164.4
3	-	-	135.3	135.3
4	8.01 (1H, s)	7.99 (1H, s)	134.2	134.3
4a	-	-	125.3	125.4
5	-	-	181.78	181.80
6	-	-	148.3	148.4
7	5.83 (1H, s)	5.80 (1H, s)	101.1	101.1
8	-	-	181.75	181.81
8a	-	-	146.7	146.8
9	2.69 (3H, s)	2.66 (3H, s)	23.8	23.4
10	2.40 (3H, s)	2.39 (3H, s)	19.3	19.3
11	2.93 (d, $J = 5.4$ Hz, 3H)	2.92 (d, $J = 5.6$ Hz, 3H)	29.1	29.1



Scheme 3. Synthesis of analogues **8**-**19** of sannanine **1**.

While considering the biological potent of indole containing compounds, tryptamine core was used in the analogues of **14** and **15**. Gratifyingly, all other analogues have reached in moderate to good yields. The major intention of choosing the substitution in the quinoline-5,8-dione core was to develop the method to construct many natural products as well as core structure of the biologically potent molecules using the quinoline-5,8-dione as the main core.

4. Conclusions

In summary, the synthesis of sannanine and its analogues have been accomplished for the first time. The overall yield of the sannanine of 30% was achieved using easily affordable starting materials in a concise manner.

Supplementary Information (SI)

For newly synthesized compounds, $^{1}H/^{13}C/^{13}C$ DEPT NMR spectral data are depicted in Supplementary Information. Supplementary Information is available at www.ias.ac.in/chemsci.

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