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New Synthetic Routes to Acronycine, Noracronycine, and Their Analogues

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For a long time, acridone alkaloids have attracted much attention because of their broad spectrum of activity in several tumors, including sarcoma, myeloma, carcinoma, and melanoma.[1] Acridone alkaloids have been also used as photosensitizers for cancer treatment.[2] They are also have various biological properties, such as antiviral[3] and antimalarial properties,[4] induction of HL-60 cellular differentiation,[5] and inhibition of Epstein-Barr virus activities.[6] Among these alkaloids, acronycine (**1**) is isolated from the bark of *Acronychia baueri*[7] and exhibits strong antitumor and antiproliferative activities on several tumor models, including leukemia, sarcoma, myeloma, carcinoma, and melanoma.[8-9] Noracronycine (**2**) was isolated from *Medicosma subsessilis* (Figure 1).[10] Various analogues have been synthesized and studied, and their structure-activity relationships have shown that the pyranyl ring is essential for the cytotoxic and antitumor properties.[11] The attempts for improving the biological activity have been carried out by modifying the pyranyl ring through dihydroxylation[12] and epoxidation.[13] Its modified derivatives exhibited more potent antitumor activities than the original acronycine.[14] Although several synthetic approaches have been described for acronycine and its derivatives,[15] molecules with a long chain on the pyranyl ring have not been reported yet. A relationship between the activity and the presence of a long chain on the pyranyl ring has not been studied. Among known compounds, it was reported that the presence of the geranyl and prenyl groups leads to a remarkable increase in the corresponding bioactivities.[16]

Results and Discussion

Recently, biologically interesting natural products containing a pyranyl ring have been synthesized through a domino reaction in the presence of ethylenediamine diacetate (EDDA).[17] In a continuous effort to synthesize biologically active molecules, a new and facile synthesis technique was investigated for biologically interesting acronycine, noracronycine, and their derivatives. Thus, in this study a new synthetic route was reported for acronycine, noracronycine, and their derivatives with prenyl and geranyl groups.

First, a 65% yield of 1,3-dihydroxyacridone (**4**) was prepared as the starting material from phloroglucinol and anthranilic acid according to a known procedure (Scheme 1) in order to synthesize acronycine, noracronycine, and their derivatives.[18]

Acronycine, noracronycine, and their analogues were synthesized using the reaction in Scheme 2. Then **4** was reacted with 3-methyl-2-butenal in the presence of EDDA (20 mol %) in THF under reflux for 8 h to produce the cyclized compound **5** at a yield of 85%. Interestingly, in this reaction, the expected regioisomers were not detected. The assignment of **5** was confirmed through a comparison with the ^{1}H NMR data of the reported known compound.[19] Acronycine (**1**) and noracronycine (**2**) were produced through the methylation of **5**. The treatment of **5** with an excess of methyl iodide in the presence of K_2CO_3 under reflux for 12 h produced **1** at a yield of 85%, whereas the treatment with 1 equiv of methyl iodide at room temperature for 12 h provided **2** at a yield of 82%. Then a hydrogenation reaction was carried out to produce 1,2-dihydroacronycine (**6**) and 1,2-dihydronoracronycine (**7**). The catalytic hydrogenation of 1 over Pd/C (30 psi) in ethyl acetate for 1 h formed **6** at a yield of 80%, whereas the hydrogenation of **2** for 1 h afforded **7** at a yield of 82%.

Then **4** was further reacted with citral and *trans*,*trans*-farnesal in the presence of 20 mol % of EDDA in order to synthesize the various analogues (Scheme 3). The reaction of **4** with citral and *trans*,*trans*-farnesal in refluxing THF produced **8** and **9** at yields of 80 and 70 %, respectively. Compounds **8** and **9** were methylated and hydrogenated in order to obtain their derivates. The reaction of **8** and **9** with methyl iodide in the presence of potassium carbonate in refluxing acetone for 2 h produced **10** and **11** at yields of 86 and 70%, respectively. The catalytic

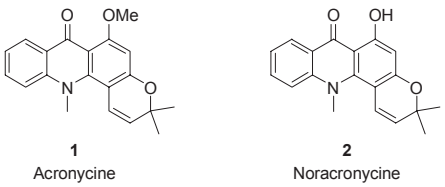
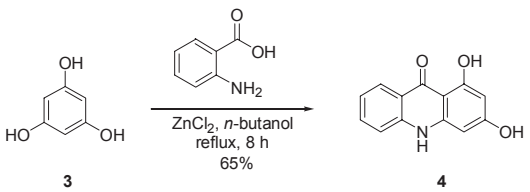
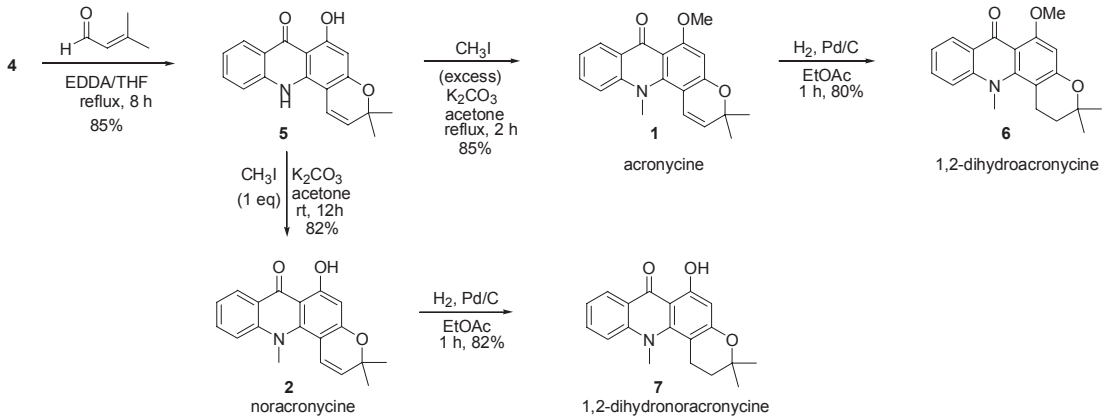


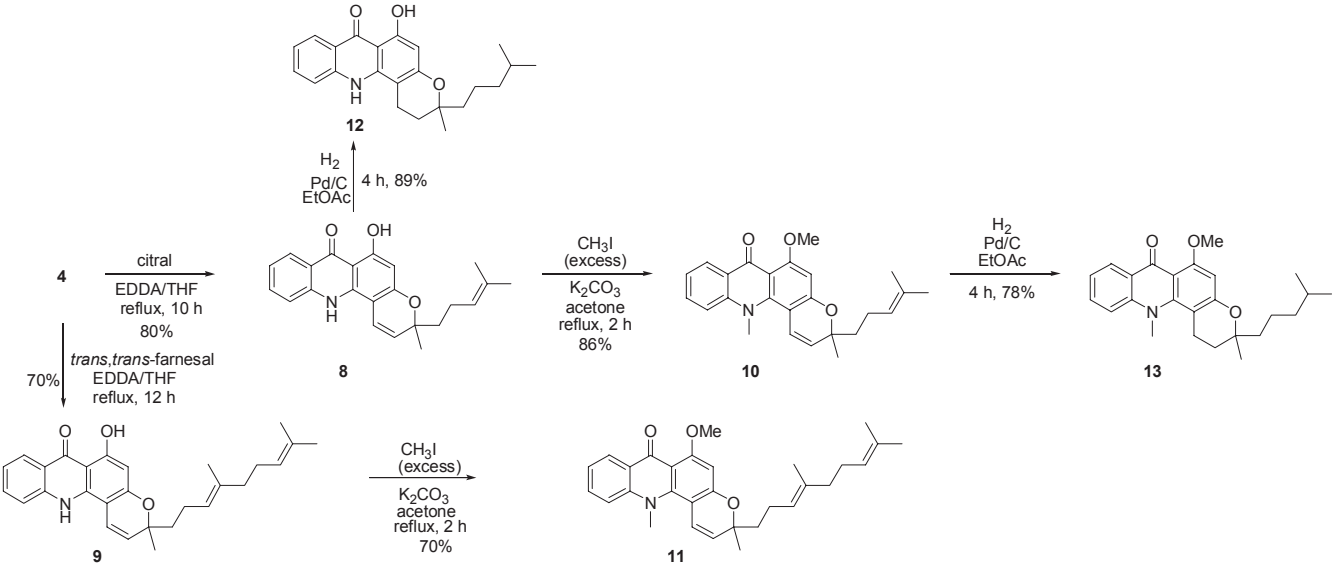
Figure 1. Naturally occurring acronycine (**1**) and noracronycine (**2**).



Scheme 1



Scheme 2



Scheme 3

hydrogenation of **8** and **10** over Pd/C (30 psi) provided **12** and **13** at yields of 89 and 78 %, respectively.

In conclusion, a concise and efficient synthetic route was described for biologically interesting acronycine, noracronycine, and their derivatives. These compounds were synthesized from acridone, which was prepared from commercially available phloroglucinol and anthranillic acid. Further work on the influence of the acronycine and noracronycine derivatives with a long chain is currently in progress for biological activities.

Experimental

All of the reactions were conducted under a nitrogen atmosphere. Merck precoated silica gel plates (Art. 5554) with a fluorescent indicator were used for the TLC analysis. Flash column chromatography was performed using silica gel 9385 (Merck, City, State, Country). The ^{1}H and ^{13}C NMR spectra were recorded using a Bruker Model ARX (300 and 75 MHz, respectively) spectrometer in $CDCl_3$, DMSO-d_6 and acetone-d_6 as the solvent for the chemical shift. The IR spectra were recorded using a Jasco FTIR 5300 spectrophotometer. The HRMS and MS spectra were carried out at the Korea Basic Science Institute.

Compound 4. A mixture of anthranilic acid (6.85 g, 50 mmol), phloroglucinol (**3**) (6.85 g, 50 mmol), anhydrous $ZnCl_2$ (7 g, 51 mmol) and *n*-butanol (150 mL) was refluxed for 8 h. The mixture was cooled, diluted with benzene-water (1:1, 100 mL), the organic layer was separated and dried over anhydrous Na_2SO_4. Removal of solvents under reduced pressure left an oily mass which was dissolved in hot and aqueous NaOH (5%, 500 mL) and filtered. The filtrate on acidification with dil. H_2SO_4 (5%) afforded product, which was purified by column chromatography on silica gel with hexane/EtOAc (2:1) to give **4** (7.4 g, 65%) as greenish yellow solid. mp 318 - 320 ^{o}C. ^{1}H NMR (300 MHz, Acetone-d_6) δ 10.70 (1H, s), 8.25 (1H, d, J = 8.1 Hz), 7.71-7.65 (1H, m) 7.46 (1H, d, J = 8.4 Hz), 7.28-7.22 (1H, m), 6.33 (1H, d, J = 2.1 Hz), 6.10 (1H, d, J = 2.1 Hz).

Compound 5. To a solution of **4** (567.5 mg, 2.5 mmol) in THF (10 mL) was added 3-methyl-2-butenal (630 mg, 7.5 mmol), EDDA (90 mg, 0.5 mmol) and the reaction mixture was refluxed under nitrogen atmosphere for 8 h. Removal of the solvent at reduced pressure left dark colored semi solid, which was then purified by column chromatography on silica gel with hexane/EtOAc (10:1) to give **5** (623 mg, 85%) as yellow solid. mp 248 -

249 °C. ^{1}H NMR (300 MHz, $CDCl_3$+ DMSO-d_6) δ 8.21 (1H, d, J = 7.8 Hz), 7.70 (1H, d, J = 8.4 Hz), 7.59 (1H, t, J = 7.5 Hz), 7.19 (1H, t, J = 7.5Hz), 7.01 (1H, d, J = 9.9 Hz), 6.05 (1H, s), 5.54 (1H, d, J = 10.2 Hz), 1.44 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$+ DMSO-d_6) δ 180.8, 163.9, 159.3, 140.7, 137.7, 133.1, 125.0, 124.7, 121.2, 119.1, 117.0, 116.0, 104.2, 97.8, 96.4, 76.6, 27.4. IR (KBr) 3331, 2942, 1645, 1540, 1475, 1428, 1331, 1154, 757 cm^{-1}. HRMS m/z $(M)^+$ calcd for $C_{18}H_{15}NO_3$: 293.1052. Found: 293.1050.

Acronycine (1). To a solution of **5** (293 mg, 1 mmol) in acetone (15 mL) was added iodomethane (1.42 g, 10 mmol), potassium carbonate (1.38 g, 10 mmol) and the reaction mixture was refluxed under nitrogen atmosphere for 2 h. The reaction mixture was filtered and removal of the solvent at reduced pressure left yellow colored solid, which was then purified by column chromatography on silica gel with hexane/EtOAc (1:1) to give **1** (273 mg, 85%) as yellow solid. mp 174 - 175 °C. ^{1}H NMR (300 MHz, Acetone-d_6) δ 8.16 (1H, d, J = 8.1 Hz), 7.62 (1H, m), 7.48 (1H, d, J = 8.7 Hz), 7.19 (1H, m), 6.69 (1H, d, J = 9.6 Hz), 6.29 (1H, s), 5.57 (1H, d, J = 9.6 Hz), 3.86 (3H, s), 3.84 (3H, s), 1.49 (6H, s). ^{13}C NMR (75 MHz, Acetone-d_6) δ 176.4, 163.7, 160.0, 147.7, 145.7, 133.2, 127.1, 126.4, 123.8, 122.8, 117.6, 111.2, 104.1, 95.0, 76.9, 56.3, 44.8, 27.0. IR (KBr) 2970, 1634, 1597, 1496, 1395, 1326, 1206, 1131, 1037, 778 cm^{-1}. HRMS m/z $(M)^+$ calcd for $C_{20}H_{19}NO_3$: 321.1365. Found: 321.1363.

Noracronycine (2). To a solution of **5** (293 mg, 1 mmol) in acetone (15 mL) was added iodomethane (142 mg, 1 mmol), potassium carbonate (138 mg, 1 mmol) and the reaction mixture was stirred at rt under nitrogen atmosphere for 12 h. The reaction mixture was filtered and removal of the solvent at reduced pressure left yellow colored solid, which was then purified by column chromatography on silica gel with hexane/EtOAc (15:1) to give **2** (252 mg, 82%) as yellow solid mp 214 - 215 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (1H, m), 7.61 (1H, m), 7.32 (1H, m), 7.20 (1H, m), 6.47 (1H, d, J = 9.9 Hz), 6.16 (1H, s), 5.44 (1H, d, J = 9.6 Hz), 3.81 (3H, s), 1.47 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.1, 165.2, 161.6, 144.8, 144.3, 134.0, 126.1, 122.9, 122.1, 121.8, 121.6, 116.2, 106.9, 101.0, 97.8, 76.4, 43.7, 27.0. IR (KBr) 3457, 2971, 1631, 1586, 1554, 1468, 1401, 1327, 1270, 1163, 762 cm^{-1}. EI-HRMS m/z $(M)^+$ calcd for $C_{19}H_{17}NO_3$: 307.1208. Found: 307.1210.

Compound 6. To a solution of **1** (321 mg, 1 mmol) in ethyl acetate (10 mL) was added catalytic amount of Pd/C (10%) and hydrogenated (30 Psi) by using autoclave for 1 h. The reaction mixture was filtered through celite and removal of the solvent at reduced pressure left yellow colored solid, which was then purified by column chromatography on silica gel with hexane/EtOAc (1:1) to give **6** (259 mg, 80%) as pale yellow solid. mp 134 - 135 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (1H, m), 7.47 (1H, m), 7.21 (1H, m), 7.09 (1H, m), 6.21 (1H, s), 3.85 (3H, s), 3.66 (3H, s), 2.75 (2H, t, J = 6.3 Hz), 1.66 (2H, t, J = 6.3 Hz), 1.35 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9, 160.5, 159.6, 150.2, 145.9, 132.4, 126.9, 125.8, 121.6, 116.3, 110.9, 101.5, 95.5, 75.1, 56.1, 44.2, 33.2, 26.8, 22.9. IR (KBr) 2969, 1631, 1590, 1548, 1476, 1398, 1332, 1271, 1146, 754 cm^{-1}. HRMS m/z $(M)^+$ calcd for $C_{20}H_{21}NO_3$: 323.1521. Found: 323.1520.

Compound 7. To a solution of **2** (153.5 mg, 0.5 mmol) in ethyl acetate (7 mL) was added catalytic amount of Pd/C (10%) and hydrogenated (30 Psi) by using autoclave for 1 h. The reaction mixture was filtered through celite and removal of the solvent at reduced pressure left yellow colored solid, which was then purified by column chromatography on silica gel with hexane/EtOAc (10:1) to give **7** (127 mg, 82%) as yellow solid. mp 217 - 218 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (1H, d, J = 7.8 Hz), 7.59 (1H, t, J = 6.9 Hz), 7.32 (1H, d, J = 8.4 Hz), 7.16 (1H, t, J = 5.7 Hz), 6.11 (1H, s), 3.77 (s, 3H), 2.80 (2H, t, J = 6.0 Hz), 1.66 (2H, t, J = 6.3 Hz), 1.35 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.4, 162.5, 162.0, 148.0, 146.3, 133.8, 126.1, 122.2, 121.8, 116.6, 107.3, 99.4, 98.9, 75.2, 43.9, 33.3, 26.8, 23.1. IR (KBr) 3469, 2961, 1630, 1574, 1475, 1396, 1328, 1265, 1155, 757 cm^{-1}. EI-HRMS m/z $(M)^+$ calcd for $C_{19}H_{19}NO_3$: 309.1365. Found: 309.1363.

Compound 8. To a solution of **4** (567.5 mg, 2.5 mmol) in THF (10 mL) was added citral (1140 mg, 7.5 mmol), EDDA (90 mg, 0.5 mmol) and the reaction mixture was refluxed under nitrogen atmosphere for 10 h. Removal of the solvent at reduced pressure left dark colored semi solid, which was then purified by column chromatography on silica gel with hexane/EtOAc (10:1) to give **8** (722 mg, 80%) as yellow solid. mp 196 - 197 °C. ^{1}H NMR (300 MHz, Acetone-d_6) δ 10.24 (1H, s), 8.23-8.20 (1H, m), 7.68-7.61 (2H, m), 7.27-7.21 (1H, m), 6.96 (1H, d, J = 9.9 Hz), 6.02 (1H, s), 5.62 (1H, d, J = 10.2 Hz), 5.07 (1H, t, J = 5.7 Hz), 2.14-2.06 (2H, m), 1.75-1.66 (2H, m), 1.46 (3H, s), 1.39 (3H, s), 1.26 (3H, s). ^{13}C NMR (75 MHz, Acetone-d_6) δ 182.1 165.8, 161.0, 141.9, 138.8, 134.7, 132.1, 126.2, 125.8, 124.8, 122.6, 120.5, 118.1, 116.8, 105.2, 98.7, 97.3, 80.3, 41.7, 26.7, 25.8, 23.3, 17.7. IR (KBr) 3439, 2948, 1647, 1610, 1542, 1475, 1333, 1156, 758 cm^{-1}. HRMS m/z $(M)^+$ calcd for $C_{23}H_{23}NO_3$: 361.1678. Found: 361.1680.

Compound 9. To a solution of **4** (567.5 mg, 2.5 mmol) in THF (10 mL) was added farnesal (1650 mg, 7.5 mmol), EDDA (90 mg, 0.5 mmol) and the reaction mixture was refluxed under nitrogen atmosphere for 12 h. Removal of the solvent at reduced pressure left dark colored semi solid, which was then purified by column chromatography on silica gel with hexane/EtOAc (10:1) to give **9** (751 mg, 70%) as yellow solid. mp 170 - 171 °C. ^{1}H NMR (300 MHz, Acetone-d_6) δ 10.28 (1H, s), 8.26 (1H, m), 7.71-7.69 (2H, m), 7.29 (1H, m), 7.01 (1H, d, J = 10.2 Hz), 6.07 (1H, s), 5.88 (1H, d, J = 10.5 Hz), 5.15 (1H, t, J = 7.5Hz), 5.07 (1H, t, J = 7.8 Hz), 2.19-2.11 (2H, m), 2.08-2.03 (2H, m), 1.97-1.92 (2H, m), 1.80-1.74 (2H, m), 1.62 (3H, s), 1.57 (3H, s), 1.56 (3H, s), 1.44 (3H, s). ^{13}C NMR (75 MHz, Acetone-d_6) δ 182.2, 165.8, 161.1, 142.0, 138.9, 135.9, 134.7, 131.7, 126.3, 125.9, 125.1, 124.8, 122.7, 120.6, 118.1, 116.8, 105.3, 98.8, 97.4, 80.4, 41.8, 40.4, 27.4, 26.7, 25.8, 23.3, 17.7, 16.1. IR (KBr) 3321, 2920, 1646, 1600, 1539, 1479, 1370, 1275, 1160, 753 cm^{-1}. EI-HRMS m/z $(M)^+$ calcd for $C_{28}H_{31}NO_3$: 429.2304. Found: 429.2303.

Compound 10. To a solution of **8** (361 mg, 1 mmol) in acetone (15 mL) was added iodomethane (1.42 g, 10 mmol), potassium carbonate (1.38 g, 10 mmol) and the reaction mixture was refluxed under nitrogen atmosphere for 2 h. The reaction mixture was filtered and removal of the solvent at reduced pressure left yellow colored solid, which was then purified by column chromatography on silica gel with hexane/EtOAc (1:1)

to give **10** (335 mg, 86%) as yellow solid. mp 79 - 80 °C. ^{1}H NMR (300 MHz, Acetone-d_6) δ 8.18 (1H, m), 7.64 (1H, m), 7.50 (1H, m), 7.21 (1H, m), 6.75 (1H, d, J = 9.6 Hz), 6.34 (1H, s), 5.61 (1H, d, J = 9.6 Hz), 5.13 (1H, t, J = 5.7 Hz), 3.89 (3H, s), 3.87 (3H, s), 2.20-2.11 (2H, m), 1.87-1.82 (2H, m), 1.64 (3H, s), 1.58 (3H, s), 1.50 (3H, s). ^{13}C NMR (75 MHz, Acetone-d_6) δ 176.4, 163.8, 160.1, 147.4, 145.7, 133.3, 132.2, 127.1, 126.4, 124.9, 123.1, 122.3, 117.6, 111.3, 104.1, 95.0, 79.3, 56.4, 44.8, 40.5, 25.8, 25.2, 23.4, 17.7. IR (KBr) 2966, 2919,1649, 1600, 1540, 1477, 1429, 1381, 1282, 1159, 753 cm^{-1}. HRMS m/z (M)$^+$ calcd for $C_{25}H_{27}NO_3$: 389.1991. Found: 389.1993.

Compound 11. To a solution of **9** (429 mg, 1 mmol) in acetone (15 mL) was added iodomethane (1.42 g, 10 mmol), potassium carbonate (1.38 g, 10 mmol) and the reaction mixture was refluxed under nitrogen atmosphere for 2 h. The reaction mixture was filtered and removal of the solvent at reduced pressure left yellow colored solid, which was then purified by column chromatography on silica gel with hexane/EtOAc (1:1) to give **11** (320 mg, 70%) as yellow semi solid. ^{1}H NMR (300 MHz, Acetone-d_6) δ 8.11 (1H, m), 7.55 (1H, m), 7.38 (1H, m), 7.10 (1H, m), 6.64 (1H, d, J = 9.6 Hz), 6.25 (1H, s), 5.51 (1H, d, J = 9.6 Hz), 5.08 (1H, t, J = 6.9 Hz), 4.99 (1H, t, J = 6.3 Hz), 3.80 (3H, s), 3.75 (3H, s), 2.12-2.05 (2H, m), 1.97-1.93 (2H, m), 1.90-1.85 (2H, m), 1.79-1.74 (2H, m), 1.54 (3H, s), 1.51 (3H, s), 1.48 (3H, s), 1.40 (3H, s). ^{13}C NMR (75 MHz, Acetone-d_6) δ 176.4, 163.7, 160.0, 147.6, 145.7, 135.9, 133.2, 131.7, 127.1, 126.4, 125.1, 124.8, 123.1, 123.0, 122.2, 117.5, 111.2, 104.0, 95.0, 79.2, 56.3, 44.8, 40.5, 40.4, 27.4, 25.9, 25.2, 23.3, 17.8, 16.1. IR (KBr) 2956, 2923, 1618, 1490, 1388, 1208, 1140, 757 cm^{-1}. EI-HRMS m/z (M)$^+$ calcd for $C_{30}H_{35}NO_3$: 457.2617. Found: 457.2614.

Compound 12. To a solution of **8** (361 mg, 1 mmol) in ethyl acetate (10 mL) was added catalytic amount of Pd/C (10%) and hydrogenated (30 Psi) by using autoclave for 4 h. The reaction mixture was filtered through celite and removal of the solvent at reduced pressure left yellow colored solid, which was then purified by column chromatography on silica gel with hexane/EtOAc (2:1) to give **12** (325 mg, 89%) as yellow solid mp 189 - 190 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (1H, m), 7.52 (1H, m), 7.22-7.12 (2H, m), 6.06 (1H, s), 2.59-2.55 (2H, m), 1.95-1.80 (2H, m), 1.60-1.43 (4H, m), 1.34 (1H, m), 1.24 (3H, s), 1.14-.106 (2H, m),0.80 (6H, d, J = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.3, 162.3, 160.5, 140.1, 140.0, 133.6, 126.3, 122.2, 120.4, 116.4, 104.7, 97.8, 94.8, 77.5, 39.7, 39.4, 30.2, 28.0, 24.0, 22.7, 21.5, 16.8. IR (KBr) 3429, 2929, 1629, 1598, 1493, 1394, 1205, 1105, 1034, 759 cm^{-1}. HRMS m/z (M)$^+$ calcd for $C_{23}H_{27}NO_3$: 365.1991. Found: 365.1993.

Compound 13. To a solution of **10** (194.5 mg, 0.5 mmol) in ethyl acetate (10 mL) was added catalytic amount of Pd/C (10%) and hydrogenated (30 Psi) by using autoclave for 4 h. The reaction mixture was filtered through celite and removal of the solvent at reduced pressure left yellow colored solid, which was then purified by column chromatography on silica gel with hexane/EtOAc (1:1) to give **13** (153.3 mg, 78%) as pale yellow semi solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (1H, m), 7.47 (1H, m), 7.22 (1H, m), 7.08 (1H, m), 6.16 (1H, s), 3.85 (3H, s), 3.66 (3H, s), 2.75-2.70 (2H, m), 1.68-1.48 (5H, m), 1.31 (3H, s), 1.61-1.10 (4H, m), 0.81 (6H, d, J = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9, 160.5, 159.7, 150.1, 145.9, 132.4, 126.9, 125.8, 121.5, 116.3, 110.8, 101.8, 95.6, 77.2, 56.1, 44.2, 40.1, 39.4, 31.3, 27.9, 23.9, 22.8, 22.7, 22.6, 21.4. IR (KBr) 2944, 1595, 1479, 1388, 1325, 1138, 753 cm^{-1}. HRMS m/z (M)$^+$ calcd for $C_{25}H_{31}NO_3$: 393.2304. Found: 393.2303.

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