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Synthesis of isoquinoline derivatives using multicomponent reaction of isocyanides

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Abstract: A simple and proficient method for the synthesis of isoquinoline derivatives *via* four component reaction of isocyanide, phthalaldehyde, ammonium acetate and 2-amino acetophenone in water at room temperatutre is reported.

Keywords: Isoquinoline derivatives, 2-Aminoacetophenone, Isocyanide, Four component reaction.

Introduction

Bridgehead nitrogen heterocycles are of interest because they constitute an important class of natural and unnatural products, many of which exhibit useful biological activity and are used in pharmaceutical preparations [1-4]. The isoquinoline skeleton is found in a large number of naturally occurring and synthetic biologically active heterocyclic compounds [5-9]. In particular, 1,2-dihydroisoquinolines act as delivery systems that transport drugs through the otherwise highly impermeable blood–brain barrier [10-13]. These compounds also exhibit sedative [14], antidepressant [15, 16], antitumour and antimicrobial activity [17-19]. Also, water is an ideal solvent and reagent for biochemical transformations. In addition carrying out synthesis of organic compounds in water media is very interesting because of water is cheap solvent, more available with high amounts. For the reactions that starting compounds aren't solved in water, the rate of reaction improves. Separation of products in these reactions is very easy because of products aren't solved in water and separated by employing filtration [20].

Also, the isoquinoline skeleton is found in a large number of naturally occurring and synthetic biologically active heterocyclic compounds. Continuing our efforts directed towards the simple preparation of biologically active target molecules through multi-component reactions and our interest in isocyanide-based multi-component reactions, we performed the synthesis of isoquinoline derivatives **5** *via* the reaction of 2-aminoacetophenone **1**, phthalaldehyde **2**, ammonium acetate **3** and isocyanide **4** in water at room temperature (Scheme **1**). Hence, we describe the reaction of isoquinoline with isocyanids in the presence 2-hydroxy acetophenone. The reaction of 2-amino acetophenone **1**, phthalaldehyde **2**, ammonium acetate **3** and isocyanides **4** produce isoquinoline derivatives **5** in good yield (Scheme **1**).

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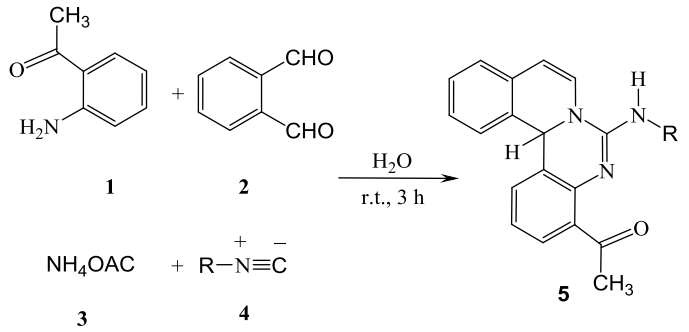
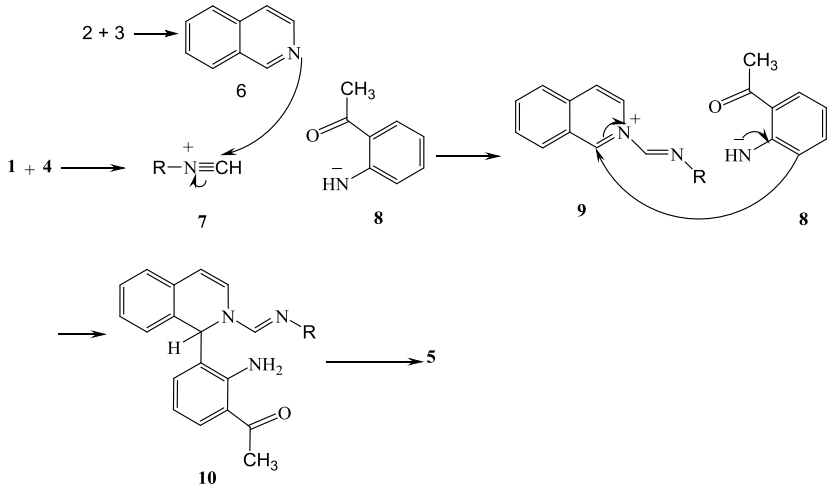


5	R	Yield (%) of 5
a	^{t}Bu	85
b	Cyclohexyl	80
c	1,1,3,3-tetramethylbutyl	80
d	CH_2CO_2Et	75
e	2,6-Dimethyl phenyl	83
f	Bn	78
g	2-nitrophenyl	65

Scheme 1: synthesis of isoquinoline derivatives **5**

Results and discussion

The data obtained from elemental analysis, IR, ^{1}H NMR and ^{13}C NMR spectra confirmed all of the proposed products. The ^{1}H NMR spectrum of **5a** displayed one singlet at 1.38 ppm for the *tert*-butyl group, two singlet at 2.10 and 2.54 ppm for methyl protons, two singlet at 5.30 and 5.85 for CH protons, one singlet at 8.74 ppm for NH proton and two set of doublet for vicinal methine protons at 4.78 and 5.73 ppm which appeared as with $^2J_{HH}$ of 3.5 Hz. One single resonance at δ = 196.2 ppm is observed in the ^{13}C NMR spectrum of **5a**, which is attributed to the carbonyl group. A proposed mechanism for the formation of compound **4** is shown in Scheme **2**. It is conceivable that the initial event is the formation of acid–base complex **7** from the isocyanide **4** and the 2-aminoacetophenone **1**. Complex **7** activates the isocyanide functional group sufficiently for further nucleophilic attack by isoquinoline **6** to produce intermediate **9**. Finally, nucleophilic attack of the conjugated base of the 2-aminoacetophenone **8** on **9** affords intermediate **10** that converted to **5** by cyclization.



Scheme 2: Proposed mechanism for the formation of **5**.

Conclusion

In conclusion, we have described a new and successful strategy for the convenient synthesis of isoquinoline derivatives *via* four component condensation reaction of a NH-acid, phthalaldehyde, ammonium acetate and an isocyanide in water at room temperature. The method offers few advantages including high yields of products and an easy experimental work-up procedure.

Experimental

General

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. ^{1}H, ^{13}C and ^{31}P NMR spectra were obtained with a Bruker FT-500 spectrometer in $CDCl_3$, and tetramethylsilane (TMS) was used as an internal standard or 85% H_3PO_4 as external standard. Mass spectra were recorded with a Finnigan Mat TSQ-70 spectrometer. Infrared (IR) spectra were acquired on a Nicolet Magna 550-FT spectrometer. Elemental analyses were carried out with a Perkin-Elmer model 240-C apparatus. The results of elemental analyses (C, H, N) were within ±0.4 % of the calculated values. Acetylenic ester, phenacyl bromide or its derivatives and triphenylphosphine were obtained from Fluka and were used without further purification.

General procedure for preparation of compounds 5

To a magnetically stirred solution of phthaldehyde **2** (2 mmol) and ammonium acetate **3** (2 mmol) in water (5 mL), after 30 min 2-aminoacetophenone **1** in water (5 mL) as the solvent was added isocyanide **4** (2 mmol). The reaction mixture was stirred for 5h. After completion of reaction (monitored by TLC), piperidine was added to the mixture of reaction and the reaction mixture was stirred for 30 min. Then, the reaction mixture was filtered and the solid residue was crystallized from ethyl acetate to afford **5**.

7-(tertbutylamino)-2-isopropenyl-14bH-furo[2,3-f]isoquino[2,1-c][1,3]benzoxazine-5-carboxylic acid (5a):

pale yellow powder, m.p. 145-147 °C, 0.73 g, yield 85%. IR (KBr) (ν_{max}/cm^{-1}): 1727, 1675, 1548, 1228 cm^{-1}. Anal. Calcd for $C_{27}H_{28}N_2O_3$ (428.53): C, 75.68; H, 6.59; N, 6.54%. Found: C, 75.54; H, 6.46; N, 6.47%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.38 (9 H, s, *Me*$_3$C), 2.10 (3 H, s, Me), 2.54 (3 H, s, Me), 4.78 (1 H, d, ^{2}J = 3.5 Hz, CH), 5.30 (1 H, s, CH), 5.73 (1 H, d, ^{2}J = 3.5 Hz, CH), 5.85 (1 H, s, CH), 6.42 (1 H, d, $^{3}J_{HH}$ = 5.8 Hz, CH), 7.54 (1 H, d, $^{3}J_{HH}$ = 7.6 Hz, CH), 7.69 (1 H, t, $^{3}J_{HH}$ = 7.2 Hz, CH), 7.73 (1 H, t, $^{3}J_{HH}$ = 7.2 Hz, CH), 7.82 (1 H, s, CH), 7.93 (1 H, d, $^{3}J_{HH}$ = 7.5 Hz, CH), 8.74 (1 H, s, NH), 8.69 (1 H, d, $^{3}J_{HH}$ = 7.5 Hz, CH), 9.31 (1 H, d, $^{3}J_{HH}$ = 7.6 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 18.6 (Me), 27.3 (Me), 29.5 (*Me*$_3$C), 48.7 (C), 52.7 (CH), 78.4 (CH), 107.8 (CH), 110.5 (C), 112.7 (CH), 114.3 (CH_2), 117.6 (C), 121.0 (C), 121.8 (C), 122.4 (CH), 124.9 (CH), 126.1 (CH), 128.4(CH), 129.5 (CH), 130.7 (CH), 136.8 (C), 138.2 (C), 154.5 (C), 157.6 (C), 159.4 (C), 196.2 (C=O). MS, *m/z* (%): 428 (M$^+$, 10), 371 (88), 299 (68), 129 (100), 57 (86).

7-(cyclohexylamino)-2-isopropenyl-14bH-furo[2,3-f]isoquino[2,1-c][1,3]benzoxazine-5-carboxylic acid (5b):

White powder, m.p.152-154 °C, 0.73 g, yield 80%. IR (KBr) (ν_{max}/cm^{-1}): 1728, 1685, 1487, 1348, 1257, 1129 cm^{-1}. Anal. Calcd for $C_{29}H_{30}N_2O_3$ (454.56): C, 76.63; H, 6.65; N, 6.16%. Found: C, 76.74; H, 6.72; N, 6.25%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.35 (2 H, m, CH_2), 1.43 (2 H, m, CH_2), 1.48 (2 H, m, CH_2), 1.65 (2 H, m, CH_2), 1.84 (2 H, m, CH_2), 2.14 (3 H, s, Me), 2.52 (3 H, s, Me), 3.80 (1 H, m, N-CH), 4.82 (1 H, d, ^{2}J = 3.0 Hz, CH), 5.25 (1 H, s, CH), 5.70 (1 H, d, ^{2}J = 3.0 Hz, CH), 5.82 (1 H, s, CH), 6.45 (1 H, d, $^{3}J_{HH}$ = 6.0 Hz, CH), 7.49 (1 H, d, $^{3}J_{HH}$ = 7.6 Hz, CH), 7.65 (1 H, t, $^{3}J_{HH}$ = 7.3 Hz, CH), 7.68 (1 H, t, $^{3}J_{HH}$ = 7.3 Hz, CH), 7.78 (1 H, s, CH), 7.86 (1 H, d, $^{3}J_{HH}$ = 7.5 Hz, CH), 8.65 (1 H, d, $^{3}J_{HH}$ = 7.5 Hz, CH), 8.78 (1 H, s, NH), 9.27 (1 H, d, $^{3}J_{HH}$ = 7.6 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 18.8 (Me), 24.5 (CH_2), 24.7 (CH_2), 25.6 (CH_2), 27.6 (Me), 33.4 (CH_2), 33.7 (CH_2), 48.7 (CH), 53.4 (CH), 80.2 (CH), 108.0 (CH), 112.2 (C), 113.4 (CH), 115.0 (CH_2), 118.5 (C), 121.4 (C), 122.0 (C), 122.8 (CH), 125.0 (CH), 126.7 (CH), 128.7 (CH), 130.4 (CH), 131.2 (CH), 137.4 (C), 139.0 (C), 155.0 (C), 158.3 (C), 160.2 (C), 194.0 (C=O). MS, *m/z* (%): 454 (M$^+$, 15), 371 (54), 325 (78), 129 (100), 81 (48).

7-(1,1,3,3-tetramethylbutylamino)-2-isopropenyl-14bH-furo[2,3-f]isoquino[2,1-c][1,3]benzoxazine-5-carboxylic acid (5c):

Yellow crystals, m.p. 162-164 °C, 0.77 g, yield 80%. IR (KBr) (ν_{max}/cm^{-1}): 1735, 1674, 1528, 1457, 1364, 1229 cm^{-1}. Anal. Calcd for $C_{31}H_{36}N_2O_3$ (484.64): C, 76.83; H, 7.49; N, 5.78%. Found: C, 76.92; H, 7.56; N, 5.84%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.03 (9 H, s, C*Me*$_3$), 1.55 (3 H, s, Me), 1.62 (3 H, s, Me), 1.83 (2 H, s, CH_2), 2.17 (3 H, s, Me), 2.48 (3 H, s, Me), 4.75 (1 H, d, ^{2}J = 2.7 Hz, CH), 5.32 (1 H, s, CH), 5.74 (1 H, d, ^{2}J = 2.7 Hz, CH), 5.93 (1 H, s, CH), 6.57 (1 H, d, $^{3}J_{HH}$ =

5.5 Hz, CH), 7.53 (1 H, d, $^3J_{HH}$ = 7.4 Hz, CH), 7.72 (1 H, t, $^3J_{HH}$ = 7.2 Hz, CH), 7.78 (1 H, t, $^3J_{HH}$ = 7.3 Hz, CH), 7.82 (1 H, s, CH), 7.90 (1 H, d, $^3J_{HH}$ = 7.4 Hz, CH), 8.72 (1 H, d, $^3J_{HH}$ = 7.6 Hz, CH), 8.83 (1 H, s, NH), 9.28 (1H, d, $^3J_{HH}$ = 7.6 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 19.2 (Me), 28.3 (Me), 29.7 (C), 31.6 (C*Me*$_3$), 31.9 (2 Me), 50.4 (C), 51.2 (CH), 55.0 (CH_2), 81.4 (CH), 108.6 (CH), 112.5 (C), 113.7 (CH), 115.4 (CH_2), 119.2 (C), 121.8 (C), 122.5 (C), 123.0 (CH), 125.6 (CH), 127.2 (CH), 129.3 (CH), 130.8 (CH), 131.7 (CH), 137.6 (C), 139.4 (C), 155.3 (C), 159.2 (C), 160.6 (C), 196.7 (C=O). MS, *m/z* (%): 484 (M^+, 10), 371 (62), 129 (100), 113 (52).

7-(2-ethoxy-2-oxoethylamino)-2-isopropenyl-14bH-furo[2,3-f]isoquino[2,1-c][1,3]benzoxazine-5-carboxylic acid (5d):

Yellow powder, m.p. 158-160 °C, 0.69 g, yield 75%. IR (KBr) (ν_{max}/cm^{-1}): 1732, 1683, 1565, 1434, 1358, 1235 cm^{-1}. Anal. Calcd for $C_{27}H_{26}N_2O_3$ (458.51): C, 70.73; H, 5.72; N, 6.11%. Found: C, 70.65; H, 5.67; N, 6.02%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.31 (3 H, t, ^3J = 7.4 Hz, Me), 2.14 (3 H, s, Me), 2.50 (3 H, s, Me), 4.20 (2 H, s, CH_2), 4.25 (2 H, q, ^3J = 7.3 Hz, CH_2O), 4.75 (1 H, d, ^2J = 2.8 Hz, CH), 5.34 (1 H, s, CH), 5.75 (1 H, d, ^2J = 2.8 Hz, CH), 5.87 (1 H, s, CH), 6.62 (1 H, d, $^3J_{HH}$ = 5.6 Hz, CH), 7.58 (1 H, d, $^3J_{HH}$ = 7.5 Hz, CH), 7.74 (1 H, t, $^3J_{HH}$ = 7.4 Hz, CH), 7.82 (1 H, t, $^3J_{HH}$ = 7.5 Hz, CH), 7.87 (1 H, s, CH), 7.95 (1 H, d, $^3J_{HH}$ = 7.5 Hz, CH), 8.75 (1 H, d, $^3J_{HH}$ = 7.5 Hz, CH), 8.85 (1 H, s, NH), 9.24 (1H, d, $^3J_{HH}$ = 7.6 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 14.1 (Me), 18.5 (Me), 28.4 (Me), 50.2 (CH_2), 51.7 (CH), 60.7 (CH_2O), 81.6 (CH), 108.5 (CH), 112.7 (C), 114.0 (CH), 115.8 (CH_2), 119.6 (C), 122.4 (C), 122.8 (C), 123.7 (CH), 126.3 (CH), 127.8 (CH), 129.6 (CH), 131.2 (CH), 132.3 (CH), 138.0 (C), 139.7 (C), 155.6 (C), 159.8 (C), 159.4 (C), 167.2 (C=O), 195.2 (C=O). MS, *m/z* (%): 458 (M^+, 10), 329 (58), 129 (100), 43 (86).

7-(2,6-dimethylphenylamino)-2-isopropenyl-14bH-furo[2,3-f]isoquino[2,1-c][1,3]benzoxazine-5-carboxylic acid (5e):

Yellow powder, m.p. 164-166 °C, 0.79 g, yield 83%. IR (KBr) (ν_{max}/cm^{-1}): 1734, 1684, 1576, 1425 1374, 1247, 1129 cm^{-1}. Anal. Calcd for $C_{31}H_{28}N_2O_3$ (476.57): C, 78.13; H, 5.92; N, 5.88%. Found: C, 78.24; H, 6.04; N, 5.94%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.10 (3 H, s, Me), 2.24 (3 H, s, CH_3), 2.27 (3 H, s, CH_3), 2.52 (3 H, s, Me), 4.80 (1 H, d, ^2J = 2.6 Hz, CH), 5.28 (1 H, s, CH), 5.78 (1 H, d, ^2J = 2.6 Hz, CH), 5.83 (1 H, s, CH), 6.48 (1 H, d, $^3J_{HH}$ = 5.5 Hz, CH), 7.43 (1 H, d, $^3J_{HH}$ = 7.4 Hz, CH), 7.46 (1 H, d, $^3J_{HH}$ = 7.5 Hz, CH), 7.57 (1 H, t, $^3J_{HH}$ = 7.3 Hz, CH), 7.64 (1 H, t, $^3J_{HH}$ = 7.2 Hz, CH), 7.66 (2 H, d, $^3J_{HH}$ = 7.4 Hz, 2 CH), 7.78 (1 H, s, CH), 7.82 (1 H, d, $^3J_{HH}$ = 7.4 Hz, CH), 8.82 (1 H, s, NH), 8.92 (1 H, d, $^3J_{HH}$ = 7.6 Hz, CH), 9.27 (1 H, d, $^3J_{HH}$ = 7.6 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 18.3 (Me), 18.5 (Me), 18.7 (Me), 27.5 (Me), 53.0 (CH), 78.6 (CH), 108.2 (CH), 110.7 (C), 113.4 (CH), 114.8 (CH_2), 118.4 (C), 121.5 (C), 122.3 (C), 122.7 (CH), 125.4 (CH), 126.6 (CH), 127.3 (2 C), 128.5 (CH), 129.2 (2 CH), 130.2 (CH), 130.7 (CH), 134.0 (CH), 137.2 (C), 138.4 (C), 154.6 (C), 155.2 (C), 157.8 (C), 159.8 (C), 196.5 (C=O). MS, *m/z* (%): 476 (M^+, 15), 347 (68), 129 (100), 43 (86).

7-(benzylamino)-2-isopropenyl-14bH-furo[2,3-f]isoquino[2,1-c][1,3]benzoxazine-5-carboxylic acid (5f):

Yellow powder, m.p. 174-176 °C, 0.72 g, yield 78%. IR (KBr) (ν_{max}/cm^{-1}): 1735, 1678, 1556, 1367 1284 cm^{-1}. Anal. Calcd for $C_{30}H_{26}N_2O_3$ (462.55): C, 77.90; H, 5.67; N, 6.06%. Found: C, 77.84; H, 5.73; N, 6.14%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.15 (3 H, s, Me), 2.58 (3 H, s, Me), 4.71 (2 H, s, CH_2), 4.83 (1 H, d, ^2J = 2.8 Hz, CH), 5.32 (1 H, s, CH), 5.76 (1 H, d, ^2J = 2.8 Hz, CH), 5.87 (1 H, s, CH), 6.52 (1 H, d, $^3J_{HH}$ = 5.4 Hz, CH), 7.25 (2 H, t, $^3J_{HH}$ = 7.8 Hz, 2 CH), 7.45 (1 H, t, $^3J_{HH}$ = 7.4 Hz, CH), 7.58 (1 H, d, $^3J_{HH}$ = 7.5 Hz, CH), 7.64 (2 H, d, $^3J_{HH}$ = 7.6 Hz, 2 CH), 7.74 (1 H, t, $^3J_{HH}$ = 7.4 Hz, CH), 7.75 (1 H, t, $^3J_{HH}$ = 7.6 Hz, CH), 7.80 (1 H, s, CH), 7.95 (1 H, d, $^3J_{HH}$ = 7.5 Hz, CH), 8.78 (1 H, s, NH), 8.94 (1 H, d, $^3J_{HH}$ = 7.5 Hz, CH), 9.35 (1 H, d, $^3J_{HH}$ = 7.5 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 19.2 (Me), 28.4 (Me), 51.9 (CH_2), 53.4 (CH), 79.0 (CH), 108.4 (CH), 111.2 (C), 112.8 (CH), 114.7 (CH_2), 118.3 (C), 122.0 (C), 122.7 (C), 123.4 (CH), 125.4 (CH), 126.7 (CH), 128.2 (2 CH), 128.6 (CH), 129.1 (2 CH), 130.4 (CH), 131.2 (CH), 134.0 (CH), 137.0 (C), 138.5 (C), 139.3 (C), 154.6 (C), 158.3 (C), 158.8 (C), 197.3 (C=O).

7-(2-nitrophenylamino)-2-isopropenyl-14bH-furo[2,3-f]isoquino[2,1-c][1,3]benzoxazine-5-carboxylic acid (5g):

Yellow powder, m.p. 158-160 °C, 0.32 g, yield 65%. IR (KBr) (ν_{max}/cm^{-1}): 1738, 1656, 1587, 1447 1364, 1337, 1295 cm^{-1}. Anal. Calcd for $C_{29}H_{23}N_3O_5$ (493.51): C, 70.58; H, 4.70; N, 8.51%. Found: C, 70.62; H, 7.76; N, 8.57%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.12 (3 H, s, Me), 2.54 (3 H, s, Me), 4.78 (1 H, d, ^2J = 3.2 Hz, CH), 5.17 (1 H, s, CH), 5.72 (1 H, d, ^2J = 3.2 Hz, CH), 5.76 (1 H, s, CH), 6.52 (1 H, d, $^3J_{HH}$ = 6.2 Hz, CH), 7.45 (2

H, d, $^3J_{HH}$ = 7.5 Hz, 2 CH), 7.48 (1 H, d, $^3J_{HH}$ = 7.5 Hz, CH), 7.62 (1 H, t, $^3J_{HH}$ = 7.4 Hz, CH), 7.65 (1 H, t, $^3J_{HH}$ = 7.5 Hz, CH), 7.72 (2 H, d, $^3J_{HH}$ = 7.4 Hz, 2 CH), 7.75 (1 H, s, CH), 7.82 (1 H, d, $^3J_{HH}$ = 7.4 Hz, CH), 8.75 (1 H, s, NH), 8.87 (1 H, d, $^3J_{HH}$ = 7.5 Hz, CH), 9.25 (1 H, d, $^3J_{HH}$ = 7.8 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 18.5 (Me), 27.8 (Me), 52.6 (CH), 78.7 (CH), 108.6 (CH), 111.2 (C), 113.6 (CH), 115.2 (CH_2), 118.7 (C), 122.0 (C), 123.4 (C), 123.6 (CH), 125.7 (CH), 127.2 (CH), 127.8 (2 C), 128.6 (CH), 129.5 (2 CH), 130.4 (CH), 131.2 (CH), 133.8 (CH), 137.5 (C), 139.2 (C), 154.7 (C), 155.6 (C), 158.2 (C), 160.0 (C), 195.7 (C=O).

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