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Synthesis and NMR characterization of Bile Acid Derivatives Bearing Ugi 4CR-Modified Side Chains

Josué Vazquez-Chavez, Brian A. Verdeja-Perdomo, Martin A. Iglesias-Arteaga*

Facultad de Química, Universidad Nacional Autónoma de México. CDMX, 04510, México

***Corresponding author:** Martin A. Iglesias-Arteaga, email: martin.iglesias@unam.mx

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Abstract. The application of the four-component Ugi reaction for the synthesis of five bile acid derivatives bearing modified side chains is described. The unambiguous structural characterization and assignment of the functional ^{1}H NMR signals and all ^{13}C{^{1}H} NMR chemical shifts are presented.
Keywords: Bile acids; Ugi 4CR; ^{1}H NMR; ^{13}C{^{1}H} NMR.

Resumen. Se describe la aplicación de la reacción de cuatro componentes de Ugi a la síntesis de cinco derivados de ácidos biliares que portan cadenas laterales modificadas. Se presenta la caracterización estructural inequívoca y la asignación de las señales funcionales de ^{1}H RMN y de todos los desplazamientos químicos de ^{13}C{^{1}H} RMN.
Palabras clave: Ácidos biliares; Ugi 4CR; ^{1}H RMN; ^{13}C{^{1}H} RMN.

Introduction

Bile acids (BA) are synthesized in the liver and play an important role in digestion and other physiological processes.[1] Their structure consists of a tetracyclic rigid framework, with a lipophilic β-side bearing methyl groups attached to positions C-10 and C-13, and a hydrophilic α-side that bears hydroxyl groups at different positions of the steroid core. A side chain that ends in a carboxylic group is attached to position C-17.

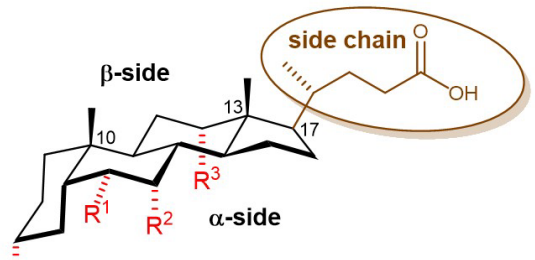

Fig. 1. Structure of some of most common bile acids.

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Regular Issue

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In addition to the wide variety of pharmacological applications of naturally occurring bile acids and their synthetic derivatives that have been described, multiple applications of this family of compounds have been developed based on their amphiphilic nature.[2] Thus, monomeric, dimeric and trimeric bile acid derivatives have been reported as molecular pockets,[3] anion receptors and transporters,[4] and gelators,[5] amongst others. In particular, the modification of the structure of BA has been found to produce dramatic changes in their aggregation properties [6] and crystal habits.[7]

Multicomponent Reactions (MCRs) allow the assemblage of three or more compounds into more complex structures bearing a wide range of functional groups and substituents. Excellent reviews and books have covered the development and application of these powerful diversity-oriented synthetic tools.[8] MCRs have been employed for the derivatization of the skeleton and the side chain of a wide spectrum of steroids triggering the generation of new physical, biological, and chemical properties.[9a] In particular, Rivera and Wessjohann described an interestin application of the four component Ugi reaction (Ugi 4CR) to synthesis of macrolactones derived from bile acids [9b].

The Ugi 4CR has revealed as a powerful and straightforward tool to develop structural diversity.[11] The simple exchange of components allows the rapid development of compound libraries useful for the systematic screening of properties.

As a part of our ongoing projects on the application of MCR to the generation of new steroid materials [10] we have decided to the setup procedures for the synthesis and characterization of side chain-modified bile acids derived from the four component Ugi reaction (Ugi 4CR) with formaldehyde, aniline and ethyl isocyanoacetate, that will serve as models for the construction and characterization of more complex structures.

Herein we report on the synthesis of five different bile acid derivatives bearing modified side chains (Scheme 1, *vide infra*). The unambiguous structural characterization and assignment of the functional ^{1}H NMR signals and all ^{13}C{^{1}H} NMR chemical shifts are presented.

Experimental

Chemistry

General procedures. Reactions were monitored by TLC on ALUGRAM® SIL G/UV254 plates from MACHEREY-NAGEL. Chromatographic plates were sprayed with a 1 % solution of vanillin in 50 % $HClO_4$ and heated until color developed. Melting points were measured on a Melt-Temp II apparatus. Mass spectra were registered in a Thermo-Electron and Jeol- SX102A spectrometers. NMR spectra were registered in $CDCl_3$ solutions in a JEOL JNM-ECZ600R spectrometer using the solvent signal as reference. NMR signals assignments were carried out with the aid of a combination of 1D and 2D NMR techniques that included ^{1}H, ^{13}C, ^{1}H-^{1}H Correlated Spectroscopy (COSY), Nuclear Overhauser Effect Spectroscopy (NOESY), Heteronuclear Single Quantum Coherence (HSQC) and Heteronuclear Multiple Bond Correlation (HMBC). All 2D NMR spectra were recorded using the standard pulse sequences and parameters recommended by the manufacturer and were processed employing the MestreNova NMR processing program [See http://mestrelab.com/]. For copies of the NMR spectra see Supporting Information.

General procedure for Ugi 4CR

Aniline (100 µL, 1.1 mmol, 1.1 equiv) and 37 % aq. formaldehyde solution (96 µL, 1.18 mmol, 1.18 equiv.) were added to a suspension of the acetylated bile acid (1 mmol) in anhydrous CH_3OH (6 mL) and 1,2-dichloroethane (2 mL) and the mixture was stirred at room temperature for 15 min. Ethyl isocyanoacetate (120 µL, 1.1 mmol, 2.2 equiv.) was added and the mixture was stirred under reflux until the starting steroid was consumed (TLC). The solvent was evaporated in vacuo and the residue was submitted to a chromatographic column packed with silica gel (35 g), that was eluted with hexane/acetone mixture (85:15) to afford the desired adduct.

Ugi adduct 3a: Reaction time 29 h. Amorphous white solid (453 mg, 0.711 mmol, 71.3 % yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.42–7.24 (m, 5H, H-32, H-33, H-34, H-35, H-36), 6.91 (t, J = 5.5 Hz, NH), 4.68 (tt, J = 11.3, 4.8 Hz, 1H, H-3), 4.30 (d, J = 2.0 Hz, 1H, H-25), 4.19 (q, J = 7.1 Hz, 2H, H-29), 4.01 (d, J = 5.5 Hz, 1H, H-27), 2.16 (ddd, J = 14.8, 10.8, 4.6 Hz, 1H, H-23a), 1.99 (s, 3H. CH_3 acetyl), 1.26 (t, J = 7.2 Hz, 3H, H-30),

J. Mex. Chem. Soc. **2024**, *68*(2)
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ISSN-e 2594-0317

0.88 (s, 3H, H-19), 0.68 (d, *J* = 5.8 Hz, 3H, H-21), 0.55 (s, 3H, H-18). **^{13}C{^{1}H} NMR** (100.53 MHz, $CDCl_3$) δ: 35.0 C-1, 26.3 C-2, 74.3 C-3, 32.2 C-4, 41.8 C-5, 27.0 C-6, 26.6 C-7, 35.7 C-8, 40.3 C-9, 34.5 C-10, 20.8 C-11, 40.0 C-12, 42.6 C-13, 56.4 C-14, 24.1 C-15, 28.1 C-16, 56.0 C-17, 11.9 C-18, 23.3 C-19, 35.4 C-20, 18.2 C-21, 31.5 C-22, 31.0 C-23, 175.0 C-24, 53.9 C-25, 169.2 C-26, 41.2 C-27, 169.7 C-28, 61.4 C-29, 14.1 C-30, 142.8 C-31, 127.8 C-32 C36, 129.9 C-33 C-35, 128.4 C-34, 21.4 CH_3 acetyl, 170.6 C=O acetyl. **HRMS** (APCI) *m/z*: $[M+H]^+$ calcd for $C_{38}H_{57}N_2O_6$ 637.4211; found 637.42292.

Ugi adduct 3b: Reaction time 25 h. Amorphous white solid (558 mg, 0.802 mmol, 80.4 % yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.44–7.28 (m, 5H, H-32, H-33, H-34, H-35, H-36), 6.96 (t, *J* = 5.5 Hz, 1H, NH), 5.11 (dt, *J* = 12.3, 4.8 Hz, 1H, H-6), 4.67 (tt, *J* = 11.3, 4.7 Hz, 1H, H-3), 4.31 (d, *J* = 2.2 Hz, 2H, H-25), 4.20 (q, *J* = 7.2 Hz, 2H, H-29), 4.02 (d, *J* = 5.5 Hz, 2H, H-27), 2.17 (ddd, *J* =17.0, 10.5, 4.4 Hz, 1H, H-23a), 2.02 (s, 3H, CH_3 acetyl), 1.99 (s, 3H, CH_3 acetyl), 1.27 (t, *J* = 7.2 Hz, 3H, H-30), 0.93 (s, 3H, H-19), 0.69 (d, *J* = 5.7 Hz, H-21), 0.56 (s, 3H, H-18). **^{13}C{^{1}H} NMR** (100.53 MHz, $CDCl_3$) δ: 35.0 C-1, 26.4 C-2, 73.6 C-3, 26.2 C-4, 45.3 C-5, 70.9 C-6, 31.2 C-7, 34.5 C-8, 39.8 C-9, 36.0 C-10, 20.6 C-11, 39.8 C-12, 42.8 C-13, 56.0 C-14, 24.0 C-15, 27.9 C-16, 55.9 C-17, 11.9 C-18, 23.2 C-19, 35.3 C-20, 18.2 C-21, 31.5 C-22, 31.0 C-23, 175.0 C-24, 53.9 C-25, 169.1 C-26, 41.2 C-27, 169.8 C-28, 61.4 C-29, 14.1 C-30, 142.8 C-31, 127.8 C-32 C-36, 129.9 H-33 C-35, 128.4 H-34, 170.4 2xC=O acetyl, 21.3 2xCH_3 acetyl. **HRMS** (APCI) *m/z*: $[M+H]^+$ calcd for $C_{40}H_{59}N_2O_8$ 695.4266; found 695.42787.

Ugi adduct 3c: Reaction time 24 h. Amorphous white solid (612 mg, 0.880 mmol, 88.2 % yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.34-7.28 (m, 5H, H-32, H-33, H-34, H-35, H-36), 4.84 (q, *J* = 3.1 Hz, 1H, H-7), 4.56 (tt, *J* = 11.3, 4.5 Hz, 1H, H-3), 4.31 (d, *J* = 4.6 Hz, 2H, H-25), 4.20 (q, *J* = 7.2 Hz, 2H, H-29), 4.02 (d, *J* = 5.4 Hz, 2H, H-27), 2.03 (s, 3H, CH_3 acetyl), 2.01 (s, 3H, CH_3 acetyl), 1.27 (t, *J* = 7.2 Hz, 3H, H-30), 0.89 (s, 3H, H-19), 0.70 (d, *J* = 5.9 Hz, 3H, H-21), 0.56 (s, 3H, H-18). **^{13}C{^{1}H} NMR** (100.53 MHz, $CDCl_3$) δ: 34.6 C-1, 26.7 C-2, 74.1 C-3, 34.8 C-4, 40.9 C-5, 31.3 C-6, 71.2 C-7, 37.8 C-8, 34.0 C-9, 34.7 C-10, 20.6 C-11, 39.4 C-12, 42.6 C-13, 50.3 C-14, 23.5 C-15, 27.9 C-16, 55.8 C-17, 11.6 C-18, 22.6 C-19, 35.3 C-20, 18.2 C-21, 31.5 C-22, 31.0 C-23, 174.9 C-24, 53.9 C-25, 169.1 C-26, 41.2 C-27, 169.8 C-28, 61.4 C-29, 14.2 C-30, 142.8 C-31, 127.8 C-32 C-36, 129.8 C-33 C-35, 128.3 C-34, 21.5, 21.4 CH_3 acetyl, 170.5, 170.4 C=O acetyl. **HRMS** (APCI) *m/z*: $[M+H]^+$ calcd for $C_{40}H_{59}N_2O_8$ 695.4266; found 695.42884.

Ugi adduct 3d: Reaction time 30 h. Amorphous white solid (592 mg, 0.851 mmol, 85.3 % yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.43-7.28 (m, 5H, H-32, H-33, H-34, H-35, H-36), 6.95-6.86 (m, 1H, NH), 5.01-4.94 (m, 1H, H-12), 4.67 (tt, *J* = 11.2, 4.6 Hz, 1H, H-3), 4.31 (d, *J* = 5.8 Hz, 2H, H-25), 4.20 (q, *J* = 7.1Hz, 2H, H-29), 4.03 (d, *J* = 5.3 Hz, 2H, H-27), 2.22-2.08 (m, 1H, H-23a), 2.01 (s, 3H, CH_3 acetyl), 2.00 (s, 3H, CH_3 acetyl), 1.27 (t, *J* = 7.1 Hz, 3H, H-30), 0.87 (s, 3H, H-19), 0.64 (s, 3H, H-18), 0.58 (d, *J* = 5.7 Hz, 3H, H-21). **^{13}C{^{1}H} NMR** (100.53 MHz, $CDCl_3$) δ: 34.7 C-1, 26.6 C-2, 71.2 C-3, 32.2 C-4, 41.8 C-5, 27.2 C-6, 25.8 C-7, 35.6 C-8, 34.3 C-9, 34.0 C-10, 26.8 C-11, 75.8 C-12, 44.9 C-13, 49.3 C-14, 23.4 C-15, 25.6 C-16, 47.5 C-17, 12.3 C-18, 23.0 C-19, 34.6 C-20, 17.4 C-21, 31.2 C-22, 30.9 C-23, 174.8 C-24, 53.9 C-25, 169.1 C-26, 41.2 C-27, 169.8 C-28, 61.5 C-29, 14.1 C-30, 142.7 C-31, 127.8 C-32 C-36, 129.9 C-33 C-35, 128.4 C-34, 21.4, 21.3 CH_3 acetyl, 170.5, 170.4 C=O acetyl. **HRMS** (APCI) *m/z*: $[M+H]^+$ calcd for $C_{40}H_{59}N_2O_8$ 695.4266; found 695.4278.

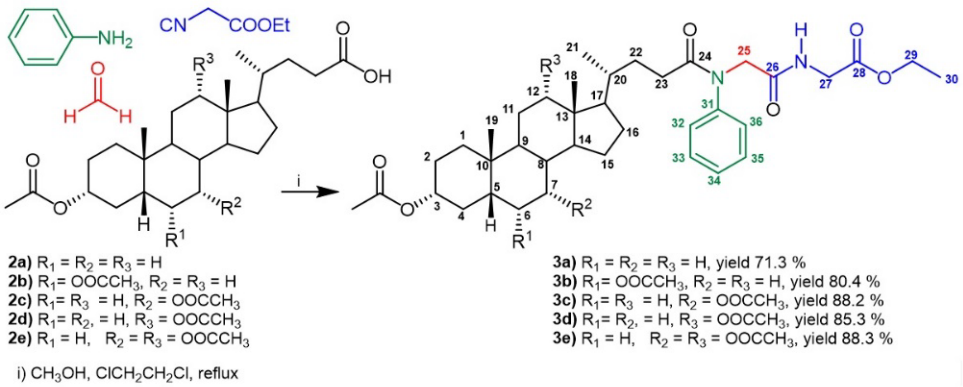
Ugi adduct 3e: Reaction time 30 h. Amorphous white solid (665 mg, 0.883 mmol, 88.3 % yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.43-7.27 (m, 5H, H-32, H-33, H-34, H-35, H-36), 6.87 (t, *J* = 5.5 Hz, NH), 5.00–4.97 (m, 1H, H-12), 4.87 (q, *J* = 3.1 Hz, 1H, H-7), 4.55 (tt, *J* = 11.4, 4.3 Hz, 1H, H-3), 4.30 (q, *J* = 15.3 Hz, 1H, H-25), 4.21 (q, *J* = 7.2 Hz, 2H, H-29), 4.03 (d, *J* = 5.0 Hz, 2H, H-27), 2.07 (s, 3H, CH_3 acetyl), 2.04 (s, 3H, CH_3 acetyl), 2.03 (s, 3H, CH_3 acetyl), 1.28 (t, *J* = 7.2 Hz, 3H, H-30), 0.88 (s, 3H, H-19), 0.65 (s, 3H. H-18), 0.59 (d, *J* = 5.7 Hz, 3H, H-21). **^{13}C{^{1}H} NMR** (100.53 MHz, $CDCl_3$) δ: 34.6 C-1, 27.1 C-2, 74.0 C-3, 34.6 C-4, 40.9 C-5, 31.2 C-6, 70.7 C-7, 37.8 C-8, 28.9 C-9, 34.3 C-10, 26.8 C-11, 75.3 C-12, 45.0 C-13, 43.3 C-14, 22.8 C-15, 25.5 C-16, 47.4 C-17, 12.1 C-18, 22.5 C-19, 34.5 C-20, 17.4 C-21, 31.2 C-22, 30.9 C-23, 174.7 C-24, 53.8 C-25, 169.02 C-26, 41.2 C-27, 169.8 C-28, 61.5 C-29, 14.1 C-30, 142.7 C-31, 127.8 H-32 C-36, 129.9 C-33 C-35, 128.4 C-34, 21.6, 21.4, 21.3 CH_3 acetyl, 170.5, 170.4, 170.3 C=O acetyl. **HRMS** (APCI) *m/z*: $[M]^+$ calcd for $C_{42}H_{60}N_2O_{10}$ 752.4242; found 752.4265.

J. Mex. Chem. Soc. **2024**, *68*(2)
Regular Issue

ISSN-e 2594-0317

Results and discussion

Treatment of the acetylated lithocholic acid **2a** with 1.1 equivalents of aniline, formaldehyde and ethyl isocyanoacetate in methanol at room temperature afforded the desired Ugi adduct **3a** in poor yield (less than 50 %) after more than 24 hours. The same reaction in refluxing methanol afforded **3a** in 67.5 %. Refluxing **2a** in 3/1 anhydrous methanol/dichloroethane mixture increased the yield to 71.3 %. Thus, treatment of the parent acetylated bile acids **2b-e** un such conditions afforded the corresponding Ugi adducts **3b-e** in good yields (Scheme 1). This suggest that the low solubility of the staring material **2a**, hindered the reaction.



Scheme 1. Synthesis of modified side chain bile acid by Ugi 4CR reaction.

Combined 1D and 2D NMR techniques allowed the assignment of the observed chemicals shifts and the corroboration of the structures of the obtained Ugi adducts **3a-e**. In addition to the NMR signals associated to the functionality present in the steroid core of each bile acid, the most salient characteristics are the signals of the enlarged and highly functionalized side chain. Tables 1 and 2 respectively show ^{1}H and ^{13}C NMR signals of the side chain of the obtained compounds.

The signals of H-20, H-21 and H-23a,b corroborate the integrity of the fragment corresponding to the side chain of the starting bile acid. The addition of the new fragment is evinced by the signals of the protons of three new methylenes (H-25, H-27 and H-29) as well as that of the methyl group (H-30). Additionally, the chemical shifts of the NH group and the aromatic protons characterize the introduced fragment (Table 1).

Table 1. Selected ^{1}H NMR signals of the obtained compounds (δ ppm; *J* Hz).

	3a	**3b**	**3c**	**3d**	**3e**
H-21	0.68(δ, *J* = 5.8)	0.69(δ, *J* = 5.7)	0.70(δ, *J* = 5.9)	0.58(δ, *J* = 5.7)	0.59(δ, *J* = 5.7)
H-23a	2.16(δ, *J* = 14.8, 10.8, 4.6)	2.17(δ, *J* = 17.0, 10.5, 4.4)	2.18 (δ, *J* = 14.8, 11.5, 4.4)	2.15 (δ, *J*= 15.1, 11.2, 4.3)	2.15 (m)
H-23b	2.03 (m)	2.01 (m)	2.02 (m)	2.01 (m)	2.01 (m)
H-25	4.30(δ, *J* = 2.0)	4.31(δ, *J* = 2.2)	4.31(δ, *J* = 4.6)	4.31(δ, *J* = 5.8)	4.30(δ, *J* = 15.3)
H-27	4.01(δ, *J* = 5.5)	4.02(δ, *J* = 5.5)	4.02(δ, *J* = 5.4)	4.03(δ, *J* = 5.3)	4.03(δ, *J* = 5.0)
H-29	4.19(δ, *J* = 7.1)	4.20(δ, *J* = 7.2)	4.20(δ, *J* = 7.2)	4.20(δ, *J* = 7.1)	4.21(δ, *J* = 7.2)

J. Mex. Chem. Soc. **2024**, *68*(2)
Regular Issue

ISSN-e 2594-0317

H-30	1.26(δ, *J* = 7.2)	1.27(δ, *J*=7.2)	1.27(δ, *J* = 7.2)	1.27(δ, *J* = 7.1)	1.28(δ, *J* = 7.2)
H (Ar)	7.42–7.24(m)	7.44–7.28(m)	7.34-7.28(m)	7.43-7.28(m)	7.43-7.27(m)
NH	6.91(δ, *J* = 5.5)	6.96(δ, *J* = 5.5)	6.93(δ, *J* = 5.5)	6.91(δ, *J* = 5.5)	6.87(δ, *J* = 5.5)

The connectivity in the enlarged side chain can verified by HMBC correlations. The combined HSQC and NOE correlations also corroborate the signal assignment and the connectivity (Fig. 2).

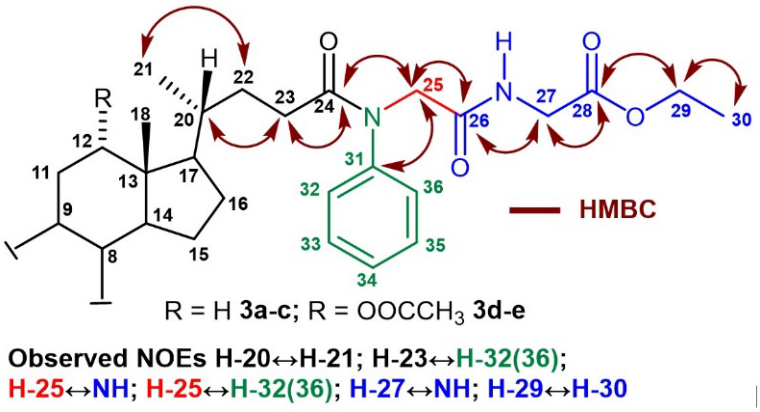


Fig. 2. Structure and 2D NMR correlations in the side chain of the obtained Ugi adducts.

The signals of carbons C-20 to C-24 account for the integrity of the fragment of the side chain coming for the bile acid. The acetylated hydroxyl group at position C-12α in compounds **3d** and **3e**, exert minor shielding effects on the signals of C-20 and C-21, compared to those in compounds **3a-c** (*vide supra*, Figure 2). The introduced fragment is characterized by the signals of the C=O groups of the amide and ester moieties installed at positions C-26 and C-28 respectively. In addition to the signals of the carbons of the ethyl group (C-29 and C-30) of the ester at C-28, the chemical shifts of the methylenes C-25 and C-27 respectively attached to the nitrogen atoms, also characterize the enlarged side chain. Additionally, the NMR signals associated to the aromatic ring corroborate the introduction of the aniline fragment (Table 2).

Table 2. $^{13}C\{^{1}H\}$ signals of the obtained compounds (δ ppm).

	3a	**3b**	**3c**	**3d**	**3e**
C-20	35.4	35.3	35.3	34.6	34.5
C-21	18.2	18.2	18.2	17.4	17.4
C-22	31.5	31.5	31.5	31.2	31.2
C-23	31.0	31.0	31.0	30.9	30.9
C-24	175.0	175.0	174.9	174.8	174.7
C-25	53.9	53.9	53.9	53.9	53.8

J. Mex. Chem. Soc. **2024**, *68*(2)
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C-26	169.2	169.1	169.1	169.1	169.0
C-27	41.2	41.2	41.2	41.2	41.2
C-28	169.7	169.8	169.8	169.8	169.8
C-29	61.4	61.4	61.4	61.5	61.5
C-30	14.1	14.1	14.2	14.1	14.1
C-31	142.8	142.8	142.8	142.7	142.7
C-32, C-36	127.8	127.8	127.8	127.8	127.8
C-33, C-35	129.9	129.9	129.8	129.9	129.9
C-34	128.4	128.4	128.3	128.4	128.4

Conclusions

We have set up optimal conditions for the four-component Ugi Reaction involving five different acetylated bile acids, formaldehyde, aniline and ethyl isocyanoacetate that affords the corresponding adducts in 71 to 88 % yield. Combined 1D and 2D NMR techniques allowed the unambiguous structural characterization and assignment of the functional ^{1}H NMR signals and all ^{13}C{^{1}H} NMR chemical shifts.

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J. Mex. Chem. Soc. **2024**, *68*(2)
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