Synthesis and characterized of new Cephalexin derivatives

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Abstract New Imidazole derivatives (5a - b) was synthesized by cyclization of hipuric acid derivatives (4a - b). The starting were readily obtained by reaction of Cephalexin with aromatic aldehyde then converted to Acid chloride (2a - b) which reaction with glycine (2-amino acetic acid) in basic medium. Compounds (5a - b) were converted into a variety of derivatives. All new compounds were characterized by FTIR and some of their by ^{1}H NMR and UV spectroscopy.

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Introduction

Cephalexin is in a group of drugs called cephalosporin antibiotics and is used to fight bacteria in the body. It works by interfering with the bacteria's cell wall formation, causing it to rupture, and killing the bacteria. Cefalexin is an antibiotic useful for the treatment of a number of bacterial infections. It is taken by mouth and is active against gram positive bacteria and some gram negative bacteria.In 2012, cefalexin was one of the top 100 most prescribed medications in the United States. In Australia it is one of the 15 most prescribed medications. It was developed in 1967 and first marketed in 1969 and 1970 by a number of companies [1]. In 2002, Cephalexin was synthesized in aqueous two-phase systems (ATPSs) by using penicillin G acylase (PGA) (penicillin amidohydrolase, EC3.5.1.11) as a catalyst and 7-amino deacetoxicephalosporanic acid (7-ADCA) and phenylglycine methyl ester (PGME) as substrates. In the ATPS composed of 20% (w/w) PEG 400 and 15% (w/w) magnesium sulfate, the partition coefficient of PGA (K_E) was less than 0.01, PGA biased to the magnesium sulfate-rich bottom phase [2] 1,3-Oxazole derivatives possess a broad spectrum of pharmacological activities such as antibacterial [3-5], herbicidal [6], anti-inflammatory[7], antitumor [8]. Imidazole is an organic compound with the formula C3H4N2. This aromatic heterocyclic is a "1, 3-diazole" and is classified as an alkaloid. Imidazole refers to the parent compound, whereas imidazoles are a class of heterocycles with similar ring structure, but varying substituents. This ring system is present in important biological building blocks, such as histidine, and the related hormone histamine. Imidazole can serve as a base and as a weak acid. Many drugs contain an imidazole ring, such as antifungal drugs and Nitroimidazole [9]. synthesis of imidazole have interest due to their various biological activities. Reported some of these activities were:antibacterial [10-12], Anticancer [13,14], Antifungal [15], Antimutagenicity [16], antitubercular[17].

2. material & Method

2. 1. General

Malting point were determine in open capillary tube on gallenkamp melting point apparatus and are uncorrected.

The FT-IR spectra were recorded by KBr disk using a perkin –Elmer 1600-series FT-IR spectrometer. 1HNMR spc. Were recorded onavariar –Mercury 200 μHZ spectrometer with using (DMSO) AS solvent in Jordan university.

The chemical material that we used from (fluka, BDH) combeny and cephalexin from samara factory).

2. 2. synthesis of compound (1a - b)

The corresponding aromatic aldehyde (0.01mol) was added to a stirred solution of Cephalexin (0.01mol) in (20 ml) ethanol absolute, than the mixture was reflexed for 7hrs. after cooling, the precipitate was filtered and recrystallized from ethanol to afford the desired compounds.

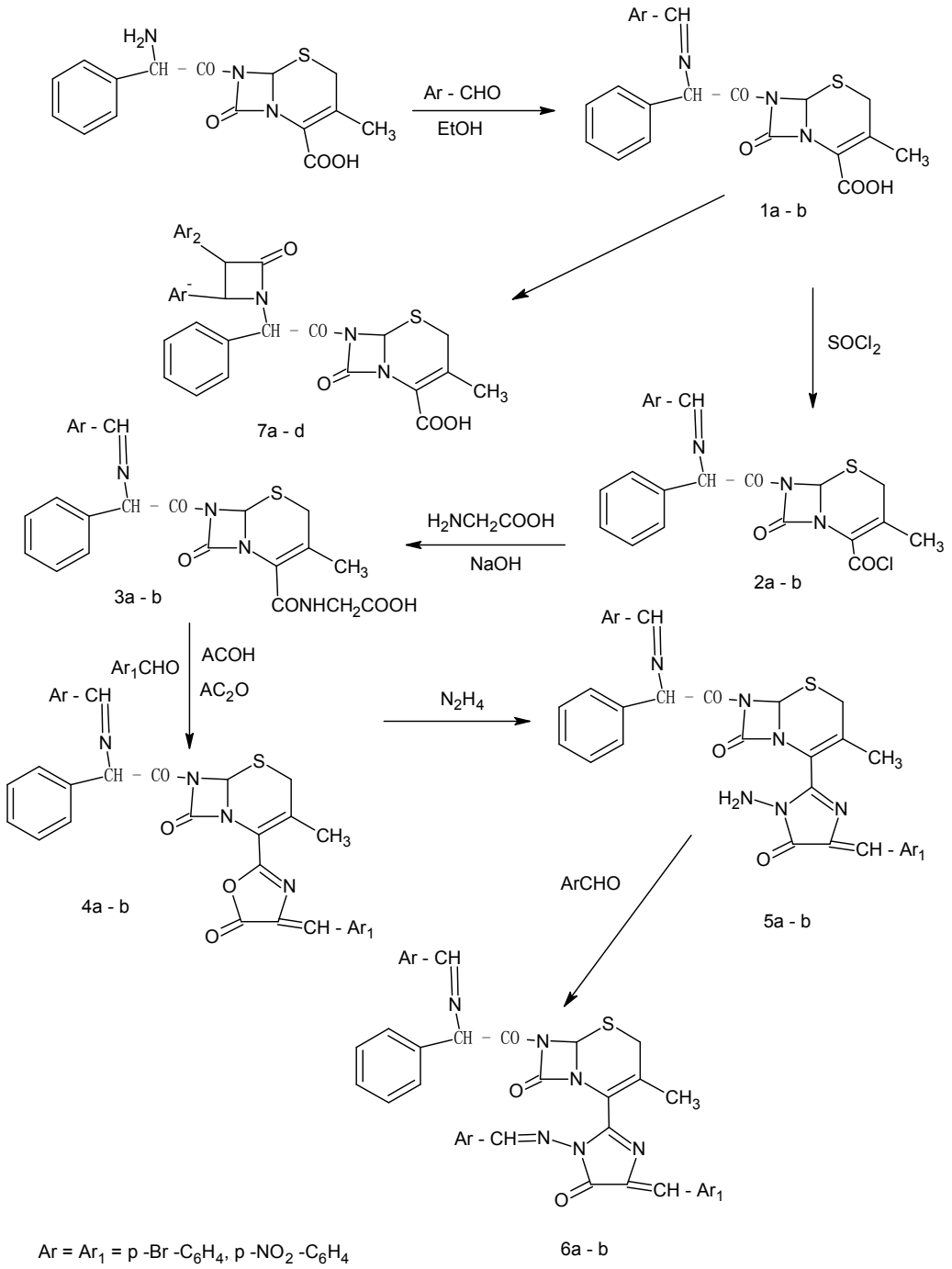
1a. (Yield 66 %), (m.p, 108 C°), IR. (KBr), (ν, Cm^{-1}), 3465- 2610 (OH acid) 3023 (CHar.), 2992-2889 (C-H, Asym. & sym.), 1708 (C=O beta-lactam) 1675(C=N), 1635 (C=O amide), UV. λ_{max} (MeOH) at (373 nm), (251nm).

1b. (Yield 78 %), (m.p, 95C°,), IR. (KBr), (ν, Cm^{-1}), 3433- 2543 (OH acid) 3067 (CHar.), 2987-2891 (C-H, Asym. & sym.), 1711 (C=O beta-lactam) 1665(C=N), 1641 (C=O amide), 1534, 1353 (NO2 Asym. & sym.), UV. λ_{max} (MeOH) at (357 nm), (232nm).

2. 3.Synthises of compound (2a - b)

To corresponding compound (1a - b) (0.01mol) thionyl chloride was added (15 ml), than the mixture

was reflexed for (7hrs). After that excess of thionyl chloride was removed under reduce pressure to get acid chloride (2a - b). **2a**. (Yield 71 %), (m.p, 80C°), IR. (KBr), (ν, Cm^{-1}), 3053 (CHar), 2986-2878 (C-H, Asym. & sym.), 1776 (C=O acid chloride), 1701 (C=O beta-lactam) 1648 (C=N), 1612 (C=O amide), **2b**. (Yield 78 %), (m.p, 91C°), IR. (KBr), (ν, Cm^{-1}), 3041 (CHar.), 2982-2884 (C-H, Asym. & sym.), 1782 (C=O acid chloride), 1705 (C=O beta-lactam) 1665 (C=N), 1623 (C=O amide), 1550, 1351 (NO2 Asym. &sym).



Ar = Ar_1 = p -Br -C_6H_4, p -NO_2 -C_6H_4

Ar_2 = C_6H_5 , Naphthyl

Scheme 1

2.4. Synthesis of compound (3a - b)

To astirring solution of glycine (0.75gm, 0.01mol) and sodium hydroxid (10ml, 10% solution), compounds (2a - b) (1.4gm) (0.01mol) was added. then,the reaction mixture was shacked vigorously for (1hur), afew grams of crash ice was added with stirring. After that, the solution was acidified with conc. hydrochloric acid, the precipitate was collected and recrystilized from appreciated solvent to afford the desired compound.

3a.. (Yield 84 %), (m.p, 150 C°), IR. (KBr), (ν, Cm^{-1}), 3414-2534 (OH acid),3203 (NH), 3023 (CHar.), 2985-2894 (C-H, aliph.Asym.& sym.),, 1743(C=O acid), 1668 (C=O amide), 1713 (C=O beta-lactam), 1641(C=N), 1219(C-N), 856 (Para substitution). UV.λ_{max} (EtOH) at (335 nm), (232nm).

3b.. (Yield 87 %), (m.p, 166C°,), IR. (KBr), (ν, Cm^{-1}), 3450-2512 (OH acid), 3167 (NH), 3063 (CHar.), 2993-2854 (C-H, aliph Asym & sym.), 1716(C=O acid), 1661 (C=O amide), 17012 (C=O beta-lactam), 1624 (C=N), 1545(Asym. NO2), 1338(sym. NO2), 1253(C-N), 835 (Para substitution). UV.λ_{max} (EtOH) at (382 nm), (227nm)

2.5.Synthesis of compound (4a - b)

To a stirring mixture of compounds (3a - b) (1.8g, 0.01mol), acetic acid (5ml) and acetic anhydride (20ml), aromatic aldehyde (0.01mol) was added. the temperature of reaction was arise to (70Ċ) for (10min), then the mixture reaction was poured in to crush ice and stirred for (30min) the product was collected and recrystallized from appreciated solvent to afford the desired compound

4a. (Yield 71 %), (m.p, 85 C°,), IR. (KBr), (ν, Cm^{-1}), 3068 (CHar.), 2990-2879(C-H, aliph.Asym.& sym.), 1757 (C=O lacton),1705 (C=O beta-lactam), 1614(C=N), 835 (Para substitution). UV.λ_{max} (EtOH) at (312 nm), (254).^{1}HNMR (DMSO-d6) ς (ppm), 2.03 (s, CH3 group), 2.78 (s, CH2 group), 4.21 (s, Ph-CH-N), 4.94 (s, S-CH-N). 6.21 (s, Ph-CH=C), 6.92– 8.44 (m, 13H, ArH), 8.92 (s, 1H, CH, Schiff's base group).

4b. (Yield 74 %), (m.p, 88 C°,), IR. (KBr), (ν, Cm^{-1}), 3047 (CHar.), 2914-2862 (C-H, aliph.Asym.& sym.), 1768(C=O lacton),1700 (C=O beta-lactam), 1678(C=N), 1550(Asym. NO2), 1338(sym. NO2), 835 (Para substitution). UV.λ_{max} (EtOH) at (325 nm), (223nm).

2.6.Synthesis of compound (5a - b)

To mixture compounds (4a - b) (0.01mol) in dry pyridine (5ml) hydrazine hydrate (80%) (0.01 mol) was added, the reaction mixture was reflexed for (2hrs). than the reaction mixture was allowed to cool to room temperature, pyridine was removed under reduce pressure the product was recrystallized from benzene to afford the desired compound

5a. (Yield 70 %), (m.p, 130 C°), IR. (KBr), (ν, Cm^{-1}), 3402, 3302 (NH2, Asym. &sym.) 3099 (CHar.), 2989-2857 (C-H, Asym. & sym.), 1674(C=O lactam),1705 (C=O beta-lactam), 1614(C=N), 833 (Para substitution). UV.λ_{max} (EtOH) at (336 nm), (279).

5b. (Yield 63 %), (m.p, 155 C°), IR. (KBr), (ν, Cm^{-1}), 3402, 3379 (NH2, Asym. &sym.) 3097 (CHar.), 2958-2870 (C-H, aliph. Asym. & sym.), 1689(C=O lactam), 1709 (C=O beta-lactam), 1618 (C=N), 1550 (Asym. NO2), 1338(sym. NO2), 842 (Para substitution). UV.λ_{max} (EtOH) at (329 nm), (255). ^{1}HNMR (DMSO-d6) ς (ppm), 1.23 (s, CH3 group), 2.27 (s, CH2 group), 4..56 (s, Ph-CH-N),5.13 (s, S-CH-N). 5.53 (s, NH2) 6.11 (s, Ph-CH=C), 6.98 – 8.54 (m, 13H, ArH), 8.64 (s, 1H, CH, Schiff's base group).

2.7.Synthesis of compounds (6a - b)

The corresponding aryl aldehyde (0.01mol)was added to a stirred solution of compound (6)(0.01mol)in absolute ethanol (20ml) and the mixture was reflexed for 2hrs. After cooling,the reaction mixture was filtered and therecrystallized form ethanol to afford the desired compounds

6a. (Yield 65 %), (m.p, 195 C°), IR. (KBr), (ν, Cm^{-1}), 3084 (CHar.), 2914-2862 (C-H, Asym. & sym.), 1678 (C=O lactam),1699 (C=O beta-lactam), 1662(C=N), 1527 (Asym. NO2), 1371(sym. NO2),813 (Para substitution). UV.λ_{max} (MeOH) at (333 nm), (275nm) ^{1}HNMR (DMSO-d6) ς (ppm), 1.98 (s, CH3 group), 2.23 (s, CH2 group), 4.56 (s, Ph-CH-N),4.88 (s, S-CH-N). 6.29 (s, Ph-CH=C), 6.75– 8.49 (m, 17H, ArH), 8.26 (s, 1H, CH, Schiff's base group), 8.37 (s, 1H, CH, second Schiff's base group).

6b. (Yield 67 %), (m.p, 180 C°,), IR. (KBr), (ν, Cm^{-1}), 3065 (CHar.), 2992-2889 (C-H, Asym. & sym.), 1683 (C=O lactam),1657 (C=O beta-lactam), 1641(C=N), 1553 (Asym. NO2), 1346(sym. NO2), 827 (Para substitution). UV.λ_{max} (MeOH) at (360 nm), (232nm).

2.9. Synthesis of compound (7a - d)

To mixture of (0.01mol)phenyl acetic acid or (0.01mol) naphthayl acetic acid (2.02gm) triethylamin in (40ml) chloroform with compound (2a - b) are stirring in ice bath and added drop wise an the time amiture from thjonyl chloride (5ml), 20ml chloroform then the reaction was stirring for (10 hrs). after than the mixture was washed with (30ml,1N HCL) and (3x) with water, dried in Na2SO4 (5g), recrstallized from ethanol to afford the desired compounds.

7a. (Yield 70 %), (m.p, 123 C°), IR. (KBr), (ν, Cm^{-1}), 3064 (CHar.), 2982-2881 (C-H, Asym. & sym.), 1690 (C=O lactam),1710 (C=O anther beta-lactam), 1701 (C=O beta-lactam 1639(C=N), 1531(Asym. NO2), 1350 (sym. NO2),845 (Para substitution). UV.λ_{max} (MeOH) at (368 nm), (216nm).).^{1}HNMR (DMSO-d6) ς (ppm), 1.57 (s, CH3 group), 2.22 (s, CH2 group), 3.34 (s, CH =O new beta lactam), 3.67 (s, CH –N new beta lactam) 4..34 (s, Ph-CH-N),5.05 (s, S-CH-N), 6.65–8.31 (m, 14H, ArH), 12.43-13.97 (broad singlet, OH acid).

7b. (Yield 77 %), (m.p, 201C°), IR. (KBr), (ν, Cm^{-1}), 3063 (CHar.), 2980-2831 (C-H, Asym. & sym.), 1723 (C=O lactam),1715 (C=O anther beta-lactam), 1708 (C=O beta-lactam) 1660(C=N), 1529(Asym. NO2), 1371 (sym. NO2), 833 (Para substitution).UV.λ_{max} (MeOH) at (354 nm), (262nm)

7c. (Yield 73 %), (m.p, 165C°), IR. (KBr), (ν, Cm^{-1}), 3044 (CHar.), 2978-2881 (C-H, Asym. & sym.), 1725 (C=O lactam),1709(C=O anther beta-lactam), 1701 (C=O beta-lactam) 1676(C=N), 1534(Asym. NO2), 1353 (sym. NO2), 850 (Para substitution). UV.λ_{max}MetOH) at (331 nm), (225nm).

7d. (Yield 75%), (m.p, 173C°,), IR. (KBr), (ν, Cm^{-1}), 3091 (CHar.), 2989-2888 (C-H, Asym. & sym.), 1731 (C=O lactam), 1710 (C=O anther beta-lactam), 1703 (C=O beta-lactam) 1653(C=N), 1555(Asym. NO2), 1350 (sym. NO2), 821 (Para substitution). UV.λ_{max} (MeOH) at (371 nm), (232nm).

Results and discussion

Schemes (1) were summarized the synthesis of different derivatives of Cephalexin Schiff's base (1a – b) was synthesized by treatment of Cephalexinwith aromatic aldehyde. The reaction is followed by shows disappearance of the NH2 group and the appearance of the new (C=N) band at (1665-1675 Cm^{-1}) and bands at (3465-2610 Cm^{-1})(1a.) and at (3433-2543 Cm^{-1}) (1b.) for stretching vibration of (OH carboxylic group) and bands). 3023 (CHar.), 2992-2889 (C-H, Asym. & sym.), 1708 (C=O beta-lactam) 1675(C=N), 1635 (C=O amide)λ_{max} (MeOH) at (1a.)373) and (1b.)(357 nm) responsible for (n → π*) transition of (N and O) atoms and (1a.) at (251) and (1b.)at (232 nm) due to(π → π). When thecarboxylic group was treated thionyl chloride, derivative (2a - b) was obtained in good yield the reaction take place by tetrahedral mechanism. The IR spectra indicated by disappearance band of OH of carboxylic acid at (3465-2610 Cm^{-1}) (1a.) and at (3433-2543 Cm^{-1}) (1b), and increase band of (C=O) of acid chloride to (1776Cm^{-1})(1a.) and (1782Cm^{-1}) (1b.), in additional the bands at 3053 (CHar.), 2986-2878 (C-H, Asym. & sym.), 1701 (C=O beta-lactam) 1648 (C=N), 1612 (C=O amide), 1550, 1351 (NO2 Asym. &sym). Hipuric acid derivative (3a - b) have been obtained by reaction of compounds (2a - b) with glycine (amino acid) in basic medium, mechanism of this reaction has been showed the lone pair of electron of amino group has been attacked carbon of carbonyl group and then loos HCl. The FTIR spectra of compound (7) show band at (3414-2534) (3a) for OH acid, three bands at 1743 (C=O acid),1713 (C=O beta-lactam), and at 1668 (C=O) amide for (3a.), and 1716 (C=O acid),1712 (C=O beta-lactam), and at 1661 (C=O) amide for (3b.). The U.V spectra of these compounds showed the λ_{max} (MeOH) at (335 nm) (3a.) and (382 nm) (3b.), responsible for(n → π*) transition of (N and O) atoms and at (232 nm) (3a.), (227nm) (3b) due to (π → π*). The Acetic acid and acetic anhydride has been used as cyclizing agent for cyclization of hipuric acid derivative (3a – b) to produce 1,3-oxazole derivative (4a – b). The FTIR spectra of compound (4a - b) shows disappearance broad band at (3465-2610 Cm^{-1}) (1a.) and at (3433-2543 Cm^{-1}) (1b), for stretching vibration of (O-H) of carboxylic acid, and increase band of (C=O) to (1757Cm^{-1})(1a.) and (1768)Cm^{-1}) (1b.)**4a**. for 1,3-oxazole (Yield 71 %), (m.p, C°,), IR. (KBr), (ν, Cm^{-1}), 3068 (CHar.), 2990-2879 (C-H, aliph.Asym.& sym.), 1757.λ_{max} (EtOH) at The U.V spectra of these compounds showed the λ_{max} (MeOH) at (312 nm) (3a.) and (325 nm) (3b.), responsible for(n → π*) transition of (N and O) atoms and at (254 nm) (3a.), (223nm) (3b) due to (π → π *).The ^{1}H-NMR spectrum of compound (4a.) shows the following signals a singlet at (2.03 ppm) due to (CH_3) group, a singlet at (2.78 ppm) due to (CH_2) group, and at4.21 (s, Ph-CH-N), 4.94 (s, S-CH-N), 6.21 (s, Ph-CH=C), multiplet at (6.92 – 8.44), due to aromatic protons and singlet at Refluxing compound (4a - b) with hydrazine hydrate (99%) for 20 hrs offered good yields of compound (5a - b). The IR spectra of compounds (5a - b) shows appearance of the two bands (asymmetric & symmetric at (3402 & 3302 Cm^{-1}) (5a.)and at (3402, 3379) (5b.) for NH_2 group, at (3099 Cm^{-1}) (5a.), (3097Cm^{-1}) (5b) for stretching vibration of (C-Har), and decrease stretching vibration of (C=O) to (1674 Cm^{-1}) (5a) and (1689) (5b.). The U.V spectrum of compounds (5a.) and (5b.) has λ_{max} (EtOH) at (336, 329 nm) respectively responsible for (n → π*) transition of (N and O) atoms and at (279nm, 255 nm) due to (π → π*). The ^{1}H-NMR spectrum of compound (5b.) shows the following signals, a singlet at (1.23 ppm) due to (CH_3) group.a singlet at (2.27 ppm) due to (CH_2) group, a multiplet at (6.98 – 8.54 ppm) due to aromatic protons, a singlet at (5.53 ppm) due to (NH_2) group and singlet at8.64 for Schiff's base group). Compounds (6a – b) have been synthesized by the reaction of compound (5a - b) with aryl aldehyde the reaction proceeds by elimination of H_2O molecule. The reaction is followed by appearance of the new (C=N) band at (1662 and 1641 Cm^{-1}) for (6a.) and (6b.). The ^{1}HNMR spectrum shows (ppm), 1.98 (s, CH3 group), 2.23 (s, CH2 group), 4.56 (s, Ph-CH-N),4.88 (s, S-CH-N). 6.29 (s, Ph-CH=C), 6.75 – 8.49 (m, 17H, ArH), 8.26 (s, 1H, CH, Schiff's base group), 8.37 (s, 1H, CH, second Schiff's base group).A number of new bata lactam derivatives**(7a - d)** ware prepared by treatment of compounds (1a - b) with phenyl acetic acid and naphthyl acetic acid. The formation of new beta lactam were confirmed byappearance bands of C=O at (1715-1709 Cm^{-1}), and appearance ather band at (1690-1731 Cm^{-1}) for (C=O) imidazole. ^{1}HNMR of compound (7a) shows the new signals observed at 1.57 (s, CH3 group), 2.22 (s, CH2 group), 3.34 (s, CH =O

new beta lactam), 3.67 (s, CH –N new beta lactam) 4..34 (s, Ph-CH-N),5.05 (s, S-CH-N), 6.65 – 8.31 (m, 14H, ArH), 12.43-13.97 (broad singlet, OH acid).

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