

Synthesis of novel impurities in 2-(2-(4-fluorophenyl)-2-oxo-1-phenylethyl)-4-methyl-3-oxo-N-phenylpentanamide; an atorvastatin intermediate

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Abstract: (3R,5R)-7-(3-(phenylcarbamoyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-1H-pyrrol-1-yl)-3,5-dihydroxyheptanoic acid, calcium salt (2:1)trihydrate (**1**), a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, was demonstrated to be effective in reducing both triglyceride and cholesterol. In present communication, two novel impurities i.e., 2-acetyl-4-(4-fluorophenyl)-4-oxo-N,3-diphenylbutanamide (**18**) and 2-(2-(3-fluoro phenyl)-2-oxo-1-phenylethyl)-4-methyl-3-oxo-N-phenylpentanamide (**19**) of 2-(2-(4-fluorophenyl)-2-oxo-1-phenylethyl)-4-methyl-3-oxo-N-phenylpentanamide (**2**), were reported along with their identification and isolation. The compounds were characterized by spectral techniques such as IR, ¹HNMR, ¹³C NMR and mass.

Keywords: Atorvastatin; key intermediate; novel impurity synthesis. © 2017 ACG Publications. All rights reserved.

1. Introduction

(3R,5R)-7-(3-(phenylcarbamoyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-1H-pyrrol-1-yl)-3,5-dihydroxy heptanoic acid, calcium salt (2:1)trihydrate (**1**) is a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, which has been demonstrated to be effective in reducing both triglyceride and cholesterol¹. Almost all manufacturers of this drug use 2-(2-(4-fluorophenyl)-2-oxo-1-phenylethyl)-4-methyl-3-oxo-N-phenylpentanamide (**2**) as a key intermediate^{2,3}(Figure 1).

Even negligible quantity of impurities²⁻⁷ may have impact on the quality of bulk drug process. Thus, high standard principles and good manufacturing practices are required for reducing impurity level. Presence of impurity, even in small quantity, may influence the efficiency and safety of the pharmaceutical products.

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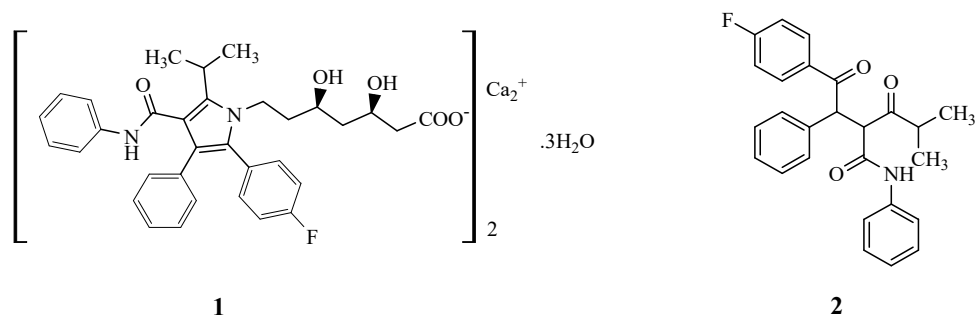


Figure 1. Structures of atorvastatin calcium and its key intermediate

During the manufacturing of 2-(2-(4-fluorophenyl)-2-oxo-1-phenylethyl)-4-methyl-3-oxo-*N*-phenylpentanamide, Raju et. al., reported number of impurities namely 4-methyl-3-oxo-2-(2-oxo-1,2-diphenylethyl)-*N*-phenylpentanamide, a desfluoro impurity (**3**), 2-(2-(3,4-difluorophenyl)-2-oxo-1-phenylethyl)-4-methyl-3-oxo-*N*-phenylpentanamide, a difluoro analog (**4**), 1,4-bis(4-fluorophenyl)-2,3-diphenylbutane-1,4-dione (**5**) and methyl 2-(2-(4-fluorophenyl)-2-oxo-1-phenylethyl)-4-methyl-3-oxopentanoate (**6**)²(Figure 2). Pai et. al., reported novel impurities of (*E*)-2-(2-(4-fluorophenyl)-2-oxo-1-phenylethyl)-3-hydroxy-4-methyl-*N*-phenylpent-2-enamide, a keto enol form (**7**)and (*Z*)-2-(2-(4-fluorophenyl)-2-oxo-1-phenylethoxy)-3-hydroxy-4-methyl-*N*-phenylpent-2-enamide, an O-alkylated impurity (**8**).³

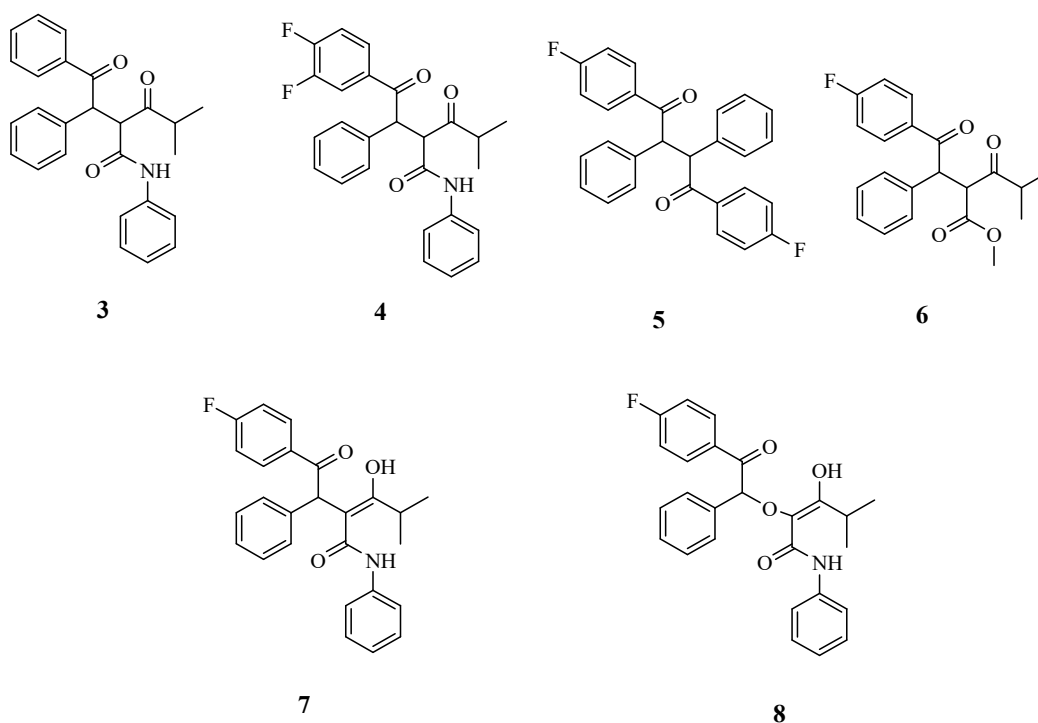


Figure 2. Structures of some earlier isolated impurities

In this present communication, we report identification, isolation and synthesis of some novel impurities, which are formed during the manufacturing of 2-(2-(4-fluorophenyl)-2-oxo-1-phenylethyl)-4-methyl-3-oxo-*N*-phenylpentanamide. They were characterized by spectroscopic techniques.

2. Experimental

2.1. General

All chemical reagents and solvents were procured from Acros, Fisher scientific Acros and Sigma-Aldrich etc., which are used without further purification. All the reactions were conducted under inert conditions. The products were purified applying column chromatography, crystallization and precipitation techniques. Silicagel (100-200 mesh) was used as a solid phase for column chromatography. Precoated silica aluminium sheets were used for TLC. The products were identified on TLC plate by using iodine or UV cabinet. NMR spectra were recorded on Bruker 400MHz by using CDCl₃ and DMSO-d₆ as solvents. Mass analyses were recorded on Apex. IR (KBr disc) spectra were obtained on Bruker.

2.2. Synthesis of 3-oxo-N-phenylbutanamide (22): A mixture of methyl acetoacetate (**20**) (10g, 86.21 mmol), aniline (**15**) (8.41g, 90.3 mmol) and triethylamine (1.85g, 18.3 mmol) was stirred at 80 – 85 °C for 1 h. Then the temperature was gradually raised to 120-125°C and stirred for 6 – 8 h, during which the liberated methanol was collected through distillation. The absence of starting material was monitored by TLC, using hexane/EtOAc mixture as a mobile phase (8:2). After completion of the reaction, it was cooled to room temperature. The reaction mixture was quenched with 2N HCl solution (20 mL) and extracted with CH₂Cl₂ (30 mL). The organic layer was sequentially washed with 1N HCl (5 mL), 5% NaHCO₃ (5 mL) and 5% NaCl (5 mL). The organic layer was concentrated under reduced pressure to give a brown product. (12.5g, 81.9% yield). ¹H-NMR (400 MHz, CDCl₃): δ 9.17 (s, 1H), 7.54 (d, *J*=8 Hz, 2H), 7.33 (t, *J*=8 Hz, 2H), 7.12 (t, *J*=8 Hz, 1H), 3.56 (s, 2H), 2.30 (s, 3H). ¹³C NMR (400 MHz, CDCl₃): δ 209.32, 164.74, 137.39, 128.35, 128.29, 123.95, 119.80, 51.69, 33.39. MS (EI): *m/z*: 178. Anal Calcd. for C₁₀H₁₁NO₂: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.05; H, 6.39; N, 7.68.

2.3. Synthesis of 2-acetyl-4-(4-fluorophenyl)-4-oxo-N,3-diphenylbutanamide (18): A mixture of 2-chloro-1-(4-fluorophenyl)-2-phenylethanone (**23**) (10g, 40.2mmol), K₂CO₃ (8g, 57.8 mmol) and 3-oxo-N-phenylbutanamide (**22**) (9.5g, 46.3 mmol) was refluxed in acetone (40 mL) for 8 – 10 h. The absence of starting material was monitored by TLC using hexane/EtOAc mixture as a mobile phase (8:2). Cool to 25-35°C. The mixture was cooled to room temperature, filtered and washed with acetone (20 mL). The solvent of the filtrate was removed under reduced pressure to obtain a crude solid product, to which isopropyl alcohol was added and the mixture was refluxed for 1 h. Then, the mixture was cooled to room temperature and the solid product was separated by filtration and washed with isopropyl alcohol (10 mL). It was dried at 70-80°C to obtain a white solid material which required no further purification (11.5g, 68.4% yield). m.p. 174-176°C. ¹H-NMR (400 MHz, CDCl₃): δ 8.02-7.98 (m, 2H), 7.58 (s, 1H), 7.33 (d, *J*=8 Hz, 2H), 7.26-7.21 (m, 5H), 7.16 (d, *J*=8 Hz, 2H), 7.10-7.01 (m, 3H), 5.41 (d, *J*=7 Hz, 1H), 4.52 (d, *J*=7 Hz, 1H), 2.36 (s, 3H). ¹³C NMR (400 MHz, DMSO-d₆): δ 202.00, 196.54, 166.24, 163.73, 138.13, 135.16, 132.25, 132.23, 131.71, 131.61, 128.81, 128.67, 127.52, 123.93, 119.69, 115.90, 115.68, 65.05, 51.71, 28.58. IR (KBr, cm⁻¹): 3151, 2955, 1705, 1650, 1612, 1442, 1164, 850. MS (EI): *m/z*: 390.2. Anal Calcd. for C₂₄H₂₀FNO₃: C, 74.02; H, 5.18; N, 3.60. Found: C, 74.35; H, 5.10; N, 3.65.

2.4. Synthesis of 1-(3-fluorophenyl)-2-phenylethanone (28): To a mixture of Deionised Mineral (DM) water (200 mL), cadmium chloride monohydrate (8.55g, 42.46 mmol), indium chloride (0.89g, 4.02 mmol), benzyl chloride (**26**) (10.3g, 80.1 mmol) and zinc dust (5.25g, 80.3 mmol) was added 3-fluoro benzaldehyde (**25**) (5g, 40.3 mmol), and the mixture was stirred at room temperature for 8-10h. Absence of starting material was monitored by TLC, using a mixture of hexane/EtOAc as a mobile phase (8:2). EtOAc (20 mL) was added to the reaction mixture, stirred for 15 min, filtered and washed, with EtOAc (20 mL). The filtrate was washed sequentially with 5% NaHCO₃ (2×20 mL) and 5% Na₂SO₃ (3×20 mL). The organic layer was concentrated under reduced pressure to give a yellow crude product. It was purified by column chromatography using silica gel (100-200 mesh) as a stationary phase, and the mixture of hexane/EtOAc as a mobile phase to obtain pure

1-(3-fluorophenyl)-2-phenylethanol (**27**)(5.5g). It was dissolved in 25 mL of acetone and slowly added to Jones reagent (Preparation: to 2.5g of CrO₃ was added 2.5 mL of H₂SO₄ to observe a clear solution. It was slowly added into DM water 7.5 mL) at room temperature. Absence of starting material was monitored by TLC using a mixture of hexane/EtOAc as a mobile phase (8:2). The mixture was slowly added into DM water (55 mL) and extracted with CH₂Cl₂ (55 mL). The organic layer was concentrated under reduced pressure to give a crude product, which was dissolved in n-hexane (50 mL) and sequentially washed with 5% NaHCO₃ (2×20 mL), 5% NaHSO₃ (3×20 mL) and DM water (20 mL). The organic layer was concentrated under reduced pressure to give a yellow semi solid (3.7g, 42.9% yield). ¹H-(400 MHz, CDCl₃): δ 7.80 (d, *J*=8 Hz, 1H), 7.70 (d, *J*=8 Hz, 1H), 7.48-7.40 (m, 2H), 7.34-7.28 (m, 2H), 7.27-7.25 (m, 3H), 4.27 (s, 2H). ¹³C NMR (400 MHz, CDCl₃): δ 195.66, 164.13, 134.19, 132.75, 132.72, 131.02, 130.92, 129.19, 128.42, 126.68, 119.50, 115.29, 45.08. MS (EI): *m/z*: 213.4. Anal Calcd. for C₁₄H₁₁FO: C, 78.49; H, 5.18. Found: C, 77.95; H, 5.30.

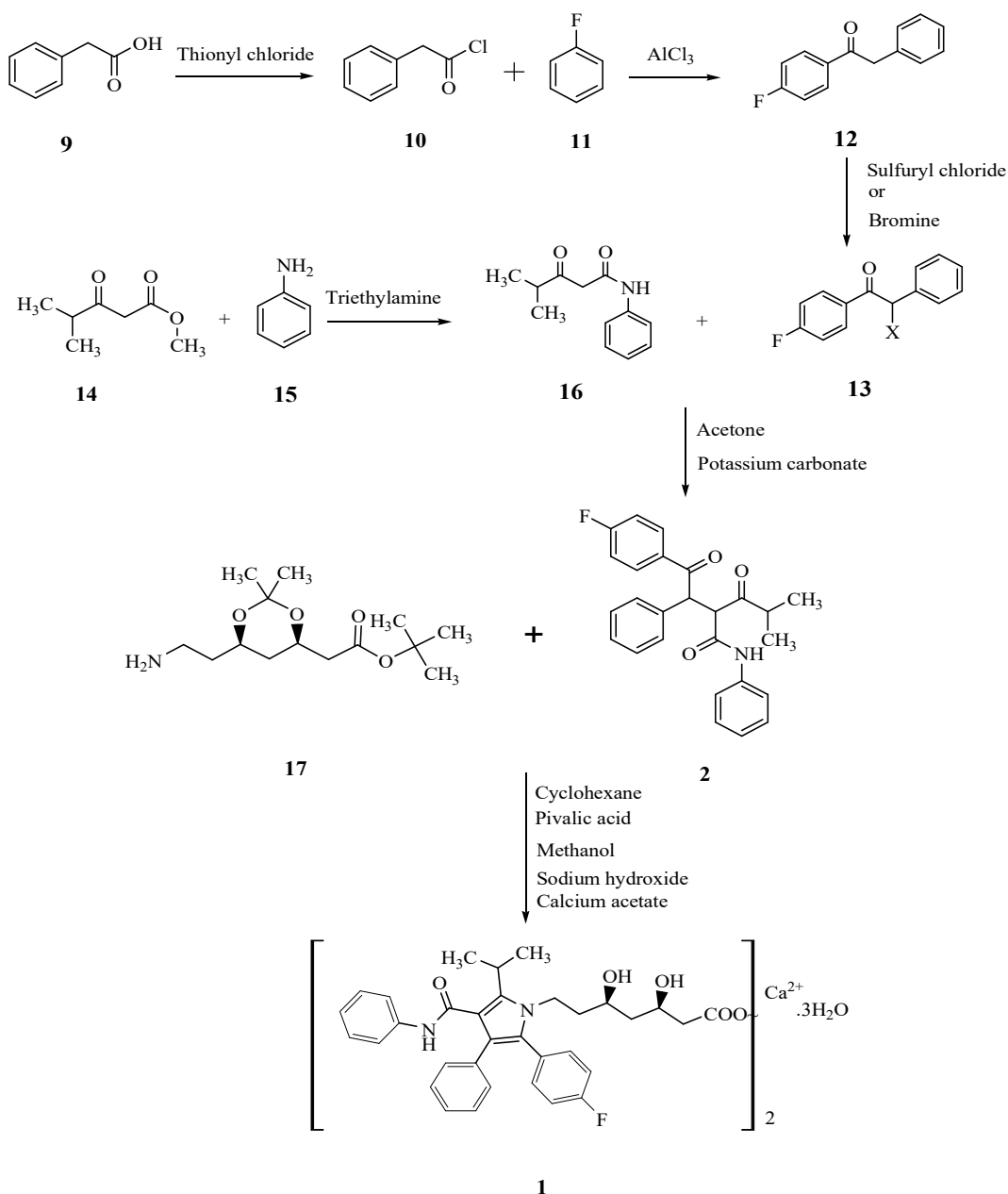
2.5. *Synthesis of 2-bromo-1-(3-fluorophenyl)-2-phenylethanone (29)*: To a mixture of 1-(3-fluorophenyl)-2-phenylethanone (**28**) (3.7g, 17.27 mmol) and CH₂Cl₂ (37 mL) was added 0.12 mL of 30% HBr in AcOH and then a cold solution of Br₂ (3.7g, 23.12 mmol) in 7.5 mL of CH₂Cl₂. The reaction progress was monitored by TLC using a mixture of hexane/CH₂Cl₂ as a mobile phase (1:1). After completion of the reaction, the organic layer was sequentially washed with 5% Na₂SO₃ (3×10 mL), 5% NaHCO₃ (10 mL) and 5% NaCl (10 mL). It was concentrated under reduced pressure to give a brown semi solid (5g, 98.8% yield). ¹H-NMR (400 MHz, CDCl₃): δ 7.76 (d, *J*=8 Hz, 1H), 7.66 (d, *J*=8 Hz, 1H), 7.53-7.50 (m, 2H), 7.40-7.29 (m, 4H), 7.29 (t, *J*=8 Hz, 1H), 6.31 (s, 1H). ¹³C NMR (400 MHz, CDCl₃): δ 189.70, 164.17, 135.44, 133.69, 131.60, 131.50, 130.27, 130.24, 129.67, 128.88, 128.80, 120.65, 115.67, 61.89. MS (EI): *m/z*: 292. Anal Calcd. for C₁₄H₁₀BrFO: C, 57.36; H, 3.44. Found: C, 57.33; H, 3.65.

2.6. *Synthesis of 2-(2-(3-fluorophenyl)-2-oxo-1-phenylethyl)-4-methyl-3-oxo-N-phenyl pentanamide (19)*: To the mixture of K₂CO₃ (3.5g, 25.34 mmol) and 4-methyl-3-oxo-N-phenylpentanamide (**16**) (4.4g, 21.32 mmol) in acetone (15 mL) was added 2-bromo-1-(3-fluorophenyl)-2-phenylethanone (**29**) (5g, 17.05 mmol) in 5.5 mL of acetone. The mixture was stirred at room temperature for 6 – 8 h. Absence of the starting material was monitored by TLC using hexane/EtOAc as a mobile phase (8:2). After completion of the reaction, it was filtered and washed with acetone (10 mL). The filtrate was concentrated under reduced pressure. To the remaining residue was added 20 mL isopropyl alcohol and the solution was refluxed for 1h, after which the product was collected by filtration and wash with isopropyl alcohol (5 mL). The material was dried at 70-80°C to obtain a white solid. (4g, 56% yield). m.p. 207-209°C. ¹H-NMR (400 MHz, CDCl₃): δ 7.75 (s, 1H), 7.64-7.61 (m, 1H), 7.36-7.33 (m, 2H), 7.32-7.21 (m, 5H), 7.19-7.17 (m, 3H), 7.15-7.08 (m, 3H), 5.37 (d, *J*=7 Hz, 1H), 4.57 (d, *J*=7 Hz, 1H), 3.01-2.94 (m, 1H), 1.24 (d, *J*=7 Hz, 3H), 1.16 (d, *J*=7 Hz, 3H). ¹³C NMR (400 MHz, DMSO-d₆): δ 208.01, 196.84, 164.89, 160.96, 138.06, 137.85, 137.79, 134.78, 131.02, 130.94, 128.89, 128.69, 128.60, 127.59, 124.96, 124.93, 123.94, 120.33, 120.12, 119.73, 114.99, 63.02, 51.98, 38.86, 18.79, 17.88. IR (KBr, cm⁻¹): 3241, 2978, 1650, 1595, 1438, 1155, 692, 793. MS (EI): *m/z*: 418.1. Anal Calcd. for C₂₆H₂₄FNO₃: C, 74.80; H, 5.79; N, 3.36. Found: C, 74.55; H, 5.35; N, 3.69.

3. Results and Discussion

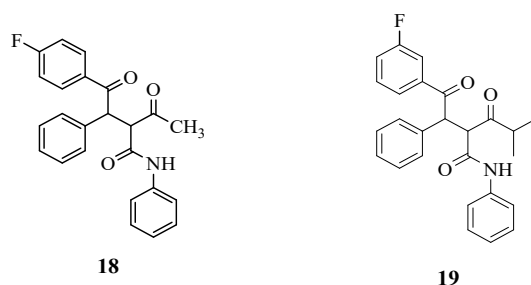
It is known that 2-(2-(4-fluorophenyl)-2-oxo-1-phenylethyl)-4-methyl-3-oxo-N-phenylpentanamide (**2**) is a key intermediate of Atorvastatin calcium (**1**) used for treatment of dyslipidemia and prevention of cardiovascular disease.

2-(2-(4-fluorophenyl)-2-oxo-1-phenylethyl)-4-methyl-3-oxo-N-phenylpentanamide (**2**) was prepared from phenylacetic acid (**9**), fluorobenzene (**11**) and methyl isobutyrylacetate (**14**). This intermediate was further reacted with *tert*-butyl 2-((4*R*,6*R*)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (**17**) to give (3*R*,5*R*)-7-(3-(phenylcarbamoyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-1H-pyrrol-1-yl)-3,5-dihydroxy heptanoic acid, calcium salt (2:1) trihydrate (Atorvastatin calcium) (**1**) (Scheme 1).

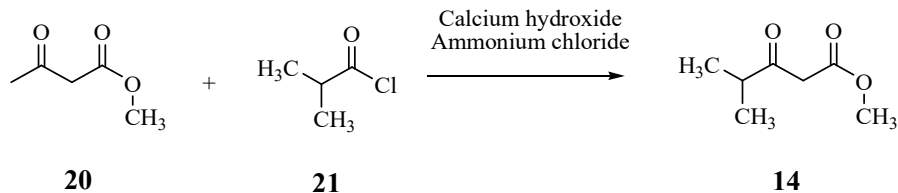


Scheme 1. Synthesis of (3*R*,5*R*)-7-(3-(phenylcarbamoyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-1*H*-pyrrol-1-yl)-3,5-dihydroxy heptanoic acid, calcium salt (2:1) trihydrate (Atorvastatin calcium)

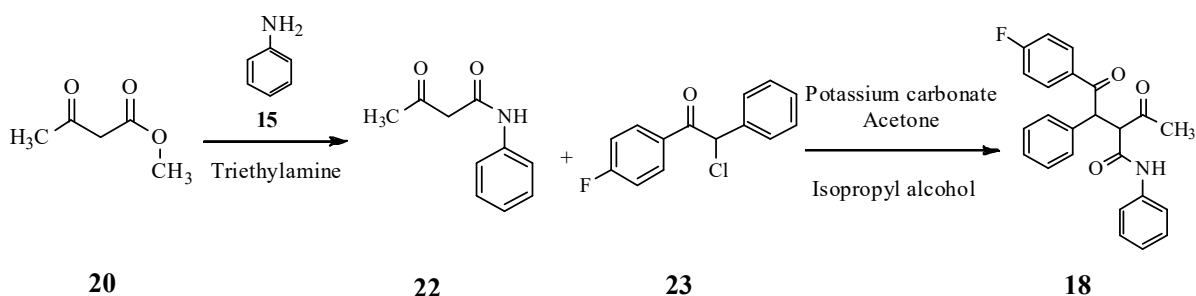
In this study, the possible impurities *i.e.*, 2-acetyl-4-(4-fluorophenyl)-4-oxo-*N*,3-diphenylbutanamide (**18**) and 2-(2-(3-fluorophenyl)-2-oxo-1-phenylethyl)-4-methyl-3-oxo-*N*-phenylpentanamide (**19**), formed during the synthesis of 2-(2-(4-fluorophenyl)-2-oxo-1-phenylethyl)-4-methyl-3-oxo-*N*-phenylpentanamide (**2**), were synthesized (Scheme 1 and Figure 3).

**Figure 3.** Structures of novel impurities

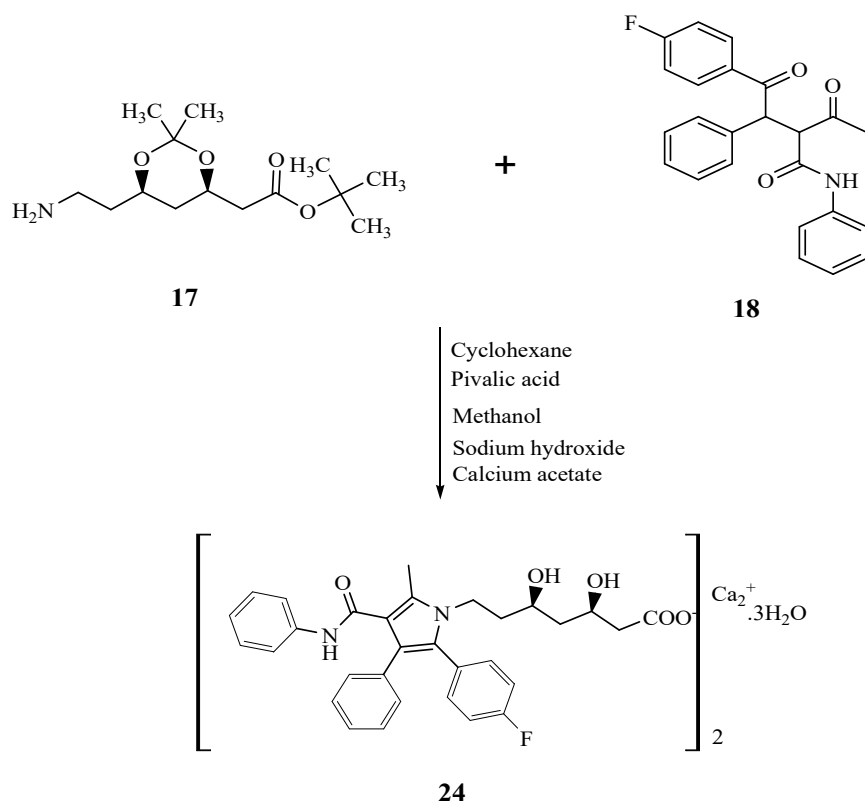
It is a general method that methyl isobutyrylacetate (**14**) is synthesized by the reaction of methyl acetoacetate (**20**) with isobutyryl chloride (**21**) in the presence of calcium hydroxide and ammonium chloride (Scheme 2).

**Scheme 2.** Synthesis of methyl isobutyrylacetate

Unreacted methyl acetoacetate (**20**) in methyl isobutyrylacetate (**14**) was reacted with aniline (**15**) in the presence of trimethylamine to give 3-oxo-*N*-phenylbutanamide (**22**). Condensation of **22** with 2-chloro-4-(4-fluorophenyl)-2-phenylethanone (**23**) in presence of potassium carbonate in acetone produced 2-acetyl-4-(4-fluorophenyl)-4-oxo-*N*,3-diphenylbutanamide (**18**) (Scheme 3).

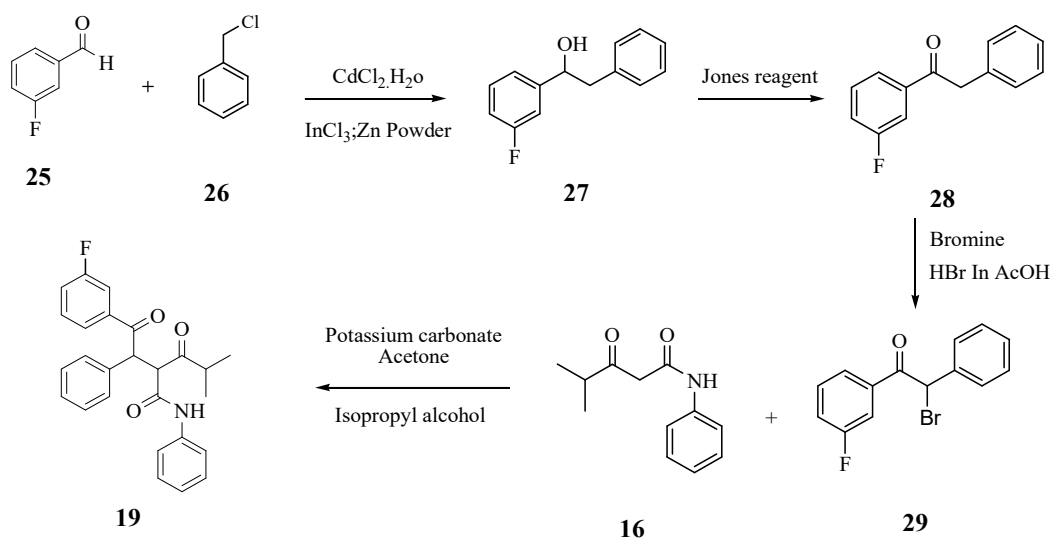
**Scheme 3.** Synthesis of 2-acetyl-4-(4-fluorophenyl)-4-oxo-*N*,3-diphenylbutanamide

2-Acetyl-4-(4-fluorophenyl)-4-oxo-*N*,3-diphenylbutanamide (**18**), formed due to the presence of methyl acetoacetate (**20**), was further reacted with *tert*-butyl 2-((4*R*,6*R*)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (**17**) to yield (3*R*,5*R*)-7-(3-(phenylcarbamoyl)-5-(4-fluorophenyl)-2-methyl-4-phenyl-1H-pyrrol-1-yl)-3,5-dihydroxyheptanoic acid, calcium salt (2:1) trihydrate (a methyl analog of atorvastatin calcium) (**24**) (Scheme 4).



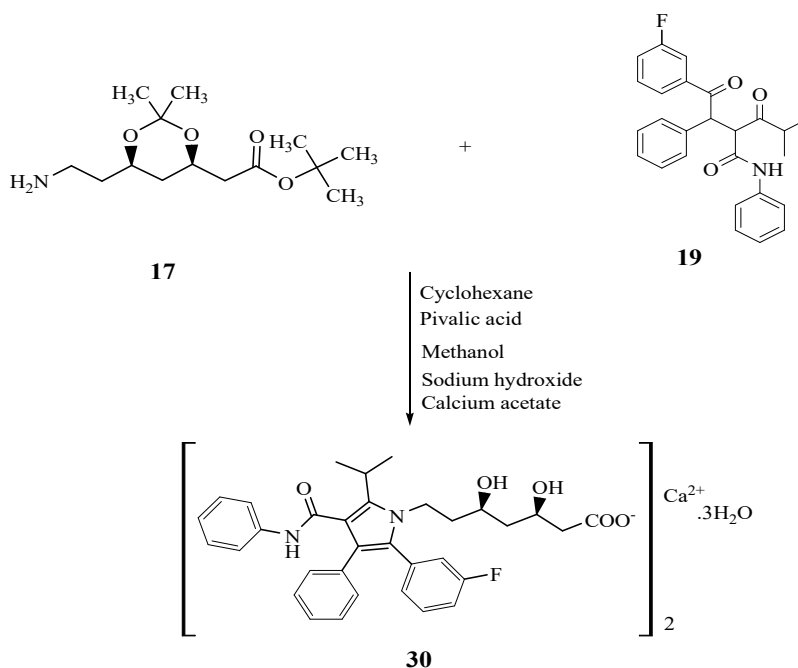
Scheme 4. Synthesis of (3*R*,5*R*)-7-(3-(phenylcarbamoyl)-5-(4-fluorophenyl)-2-methyl-4-phenyl-1*H*-pyrrol-1-yl)-3,5-dihydroxyheptanoic acid, calcium salt (2:1)trihydrate (methyl analog of atorvastatin calcium)

2-(2-(3-Fluorophenyl)-2-oxo-1-phenylethyl)-4-methyl-3-oxo-*N*-phenylpentanamide (**19**), which was synthesized similarly, may form due to the reaction temperature during Friedel crafts acetylation of phenyl acetyl chloride with fluoro benzene in the presence of aluminum chloride. Formation of this impurity is very low, (less than 0.05%), hence, it is difficult to isolate through column chromatography. Thus, it was prepared by reacting a mixture of cadmium chloride monohydrate, indium chloride, benzyl chloride (**26**) and zinc dust with 3-fluoro benzaldehyde (**25**) in water at room temperature to give 1-(3-fluorophenyl)-2-phenylethanol (**27**). It was undergone oxidation in the presence of Jones reagent in acetone to obtain 1-(3-fluorophenyl)-2-phenylethanone (**28**), which, upon bromination, yielded 2-bromo-1-(3-fluorophenyl)-2-phenylethanone (**29**). It was further reacted with 4-methyl-3-oxo-*N*-phenylpentanamide (**16**) in the presence of potassium carbonate in acetone to gives 2-(2-(3-fluorophenyl)-2-oxo-1-phenylethyl)-4-methyl-3-oxo-*N*-phenylpentanamide (**19**) (Scheme 5).



Scheme 5. Synthesis of 2-(2-(3-fluorophenyl)-2-oxo-1-phenylethyl)-4-methyl-3-oxo-*N*-phenylpentanamide

2-(2-(3-Fluorophenyl)-2-oxo-1-phenylethyl)-4-methyl-3-oxo-*N*-phenylpentanamide (**19**) was reacted with *tert*-butyl 2-((4*R*,6*R*)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxan-4-yl) acetate (**17**) to obtain (3*R*,5*R*)-7-(3-(phenylcarbamoyl)-5-(3-fluorophenyl)-2-isopropyl-4-phenyl-1*H*-pyrrol-1-yl)-3,5-dihydroxy heptanoic acid, calcium salt (2:1) trihydrate (a 3-fluoro analog of atorvastatin calcium) (**30**) (Scheme 6).



Scheme 6. Synthesis of (3*R*,5*R*)-7-(3-(phenylcarbamoyl)-5-(3-fluorophenyl)-2-isopropyl-4-phenyl-1*H*-pyrrol-1-yl)-3,5-dihydroxy heptanoic acid, calcium salt (2:1) trihydrate (3-fluoro analog of atorvastatin calcium)

4. Conclusion

To summarize, we have identified and synthesized novel impurities *i.e.*, 2-acetyl-4-(4-fluorophenyl)-4-oxo-N,3-diphenylbutanamide (**18**) and 2-(2-(3-fluorophenyl)-2-oxo-1-phenylethyl)-4-methyl-3-oxo-N-phenylpentanamide (**19**), which form during manufacturing of 2-(2-(4-fluorophenyl)-2-oxo-1-phenylethyl)-4-methyl-3-oxo-N-phenylpentanamide (**2**). Those impurities are well characterized by spectroscopic techniques. We will further study the impact of these impurities on Atorvastatin calcium (**1**).

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