

ATORVASTATIN, AN HMG-COA REDUCTASE INHIBITOR
AND EFFICIENT LIPID-REGULATING AGENT.
PART I. SYNTHESIS OF RING-LABELED [^{14}C]ATORVASTATIN.

Peter W. K. Woo,^{**} Jon Hartman,^a Yun Huang,^a
Thomas Nanninga,^b Kelvin Bauman,^b Donald E. Butler,^b
John R. Rubin,^c Helen T. Lee,^c and Che C. Huang.^a

Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company
Chemical Development Department,
^a2800 Plymouth Road, Ann Arbor, Michigan, 48105,
and ^bHolland, Michigan, 49424
^cChemistry Department, Ann Arbor, Michigan, 48105
U.S.A.

SUMMARY

Pyrrole-ring labeled [^{14}C]atorvastatin (Lipitor®, CI-981), [R-(R*,R*)]-2-(4-fluorophenyl)- β , γ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-[3- ^{14}C]pyrrole-1-heptanoic acid calcium salt (2:1) (**15**), was synthesized in a 5-step synthesis from [7- ^{14}C]benzaldehyde (**5**) with an overall yield of 6.9 to 9.6%. Thus, Knoevenagel condensation of **5** with isobutyryl-acetanilide (**6**) gave 4-methyl-3-oxo-N-phenyl-2-(phenyl[^{14}C]methylene)-pentamide (**7**). Stetter condensation of (**7**) with *p*-fluorobenzaldehyde (**8**), in the presence of the catalyst 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (**9**) and triethylamine, gave the key labeled intermediate diketone, 4-fluoro- α -(2-methyl-1-oxopropyl)- γ -oxo-N, β -diphenylbenzene[3- ^{14}C]butane-amide (**10**). Reaction of **10** with the protected chiral dihydroxyaminoheptanoic ester, [4R-cis]-1,1-dimethylethyl-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate (**11**), synthesized separately, gave atorvastatin in its protected form, [4R-cis]-1,1-dimethylethyl-6-[2[(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-[3- ^{14}C]pyrrol-1-yl]ethyl]-2,2-dimethyl-1,3-dioxane-4-acetate (**12**). Deprotection of **12** led to the sodium salt **13**. Subsequent calcium salt formation gave the ring-labeled atorvastatin **15**.

Keywords: carbon-14 synthesis, [^{14}C]pyrrole ring-labeled atorvastatin (Lipitor®), HMG-CoA reductase inhibitor, lipid-regulating agents.

INTRODUCTION

Lipid-regulating agents have been shown to be effective in the management of atherosclerosis, in arresting the progress of atherosclerotic lesions and reducing the risk of coronary heart disease and mortality.^{1,2a} Competitive inhibitors of the rate-limiting enzyme in cholesterol biosynthesis, 3-hydroxy-3-methyl-glutaryl coenzyme A reductase (HMG-CoA reductase; HMGR), known to reduce

total and LDL levels in the treatment of hypercholesterolemia, are thus important medicinal agents for this therapeutic strategy. Atorvastatin (Lipitor®, CI-981), [R-(R*,R*)]-2-(4-fluorophenyl)- β , γ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1), is a highly effective and one of the newest members of this class of medicinal agents. It has demonstrated enhanced effectiveness as well as other unique therapeutic properties.^{2,3} Thus it has been indicated as an adjunct to diet to reduce elevated total cholesterol, LDL-cholesterol, apo B, and triglycerides with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia, and as a possible agent to reduce total- and LDL-cholesterol in patients with homozygous familial hypercholesterolemia.⁵

During its development, two C-14 labeled forms of atorvastatin were synthesized for pharmacokinetics and metabolism studies. This paper presents the one in which the label is at the pyrrole nucleus (**15**), used more extensively in the studies, while an accompanying paper⁵ presents the one with the label at the carboxylic side chain.

DISCUSSION

The synthesis of the ^{14}C -pyrrole nucleus-labeled atorvastatin, vs. the side-chain labeled form, was prompted by concern over the possible metabolic loss of the side chain by N-dealkylation, which might then enter other endogenous metabolic pathways.

The reaction sequence, an adaptation of the methodology of Butler, et al.,⁶ is shown in Scheme 1. The label was introduced as [^{14}C]benzaldehyde (**5**). Sequential condensation of **5** with isobutyrylacetonilide (**6**), and of the product **7** with *p*-fluorobenzaldehyde (**8**), in the presence of ethyl thiazolium catalyst **9** and triethylamine,⁸ gave the key labeled intermediate diketone **10**. Reaction of **10** with the protected chiral dihydroxyaminoheptanoic ester **11**, synthesized separately,⁶ gave **12**. Deprotection of **12** led to the sodium salt **13**. Subsequent calcium salt formation gave the ring-labeled atorvastatin **15**.

As points of interest in the reaction sequence, the configuration of **7-Z** was established by X-ray crystallography.⁷ The Stetter condensation of **7** with fluorobenzaldehyde⁸ is one of the most critical steps in the synthesis. The instability of **7** in the presence of trace amount of water led to the formation of desfluoro and difluoro derivatives (**10b**, **10c**), and the reaction had to be carried out under strictly controlled conditions. The sodium analog of **14** and, if necessary, intermediate **10**, could be effectively purified by preparative HPLC before conversion to the final product **15**.

Based on [^{14}C]benzaldehyde as reference, the synthesis consists of five steps with an overall radiochemical yield of 6.9 to 9.6%, depending on the yield of intermediate **10** from the Stetter reaction.

EXPERIMENTAL

General. Radiochemical counting was performed with a Packard Tri-Carb 4530 or 2300 TR liquid scintillation analyzer, using Beckman Ready-Gel or Packard Ultima Gold XR LSC-cocktail as the counting medium. The progress of various reactions was often monitored or estimated by radioactivity before the products were isolated in completely pure form. TLC was performed with Silica Gel 60 F₂₅₄ precoated plates by EM Science and were scanned on a Berthold LB2832 automatic TLC linear analyzer or a Bioscan System 200 imaging scanner. HPLC analyses of the final products were performed on a Water Associates 600E system with on-line Applied Biosystems 1000S diode array detector and either a β -RAM radioactivity detector or Radiomatic series A-200 radioactivity flow detector. HPLC was performed with Alltech Econosil C18-10 μ analytical columns, 4.6 mm x 250 mm, unless otherwise specified. HPLC analyses of atorvastatin (**15**) and the corresponding sodium salt (**13**) or acid (**14**) were performed with two systems: (1) Metachem Spherisorb ODS-2, 5 μ , 4.6 mm ID x 250 mm, 0.05 M NH₄H₂PO₄ (pH 5 with NH₄OH):CH₃CN:THF/66:22:12, 1.5 mL/min, 254 nm; (2) Phenomenex Ultramex C18 5 μ , 4.6 mm x 250 mm, 0.05 M citrate buffer:CH₃CN:THF/60:20:20, 1.5 mL/min, 254 nm.⁹ All labeled compounds synthesized were identified by TLC or HPLC comparison, or both, with the corresponding authentic unlabeled compounds. THF (tetrahydrofuran) was purified by distillation over sodium and benzophenone. Drying of non-hydroxylic solvents, if indicated, was generally accomplished with Molecular Sieves.

[7-¹⁴C]Benzaldehyde (5). Barium [¹⁴C]carbonate, 3676 mg (18.62 mmol, 1000 mCi), was treated with 50 mL of concentrated sulfuric acid in a vacuum-line apparatus, and the carbon dioxide was first collected in a trap cooled in liquid nitrogen and maintained under static vacuum (i.e., evacuated at liquid nitrogen temperature and then closed from the vacuum source). It was then warmed and sublimed into a flask containing 20.5 mmol of phenyl magnesium chloride (2 M solution in THF diluted with 30 mL of diethyl ether) under static vacuum at liquid nitrogen temperature. The stopper to the reaction flask was closed, the mixture was then stirred for 45 min at a bath temp of -20 °C, allowed to warm to about -10 °C, and finally quenched with 10 mL of 3 N HCl. The acidic aqueous layer was further washed three times with ether. The organic phases were combined, evaporated, and redissolved in 20 mL of ether. The ether layer was extracted with 21 mL of 2 M sodium carbonate, and the aqueous phase was washed with ether. The ether fractions were again extracted with sodium carbonate, and the extract washed with ether. The combined aqueous extract was acidified with conc. HCl to a pH of 1 to 2 and extracted with ether three times. The ether extracts were washed with saturated sodium chloride and evaporated to give 1.98 g (864 mCi) of crude [7-¹⁴C]benzoic acid (**3**). TLC (hexane:ether:88% formic acid:58:40:2) showed one component, R_f 0.45.

To a mixture of 849 mg (22.4 mmol) of lithium aluminum hydride in 50 mL of ether, stirred in an ice bath, was added a solution of 1.98 g of **3** in 60 mL of ether. After stirring at room temp overnight, 18 mL of 6 N sulfuric acid was added slowly with external cooling. The ether layer and additional ether extracts were combined and washed with saturated sodium bicarbonate (one 5-mL and two 2.5-mL portions), then twice with brine (5-mL portions), dried with anhydrous magnesium sulfate (3.9 g), filtered and evaporated to give 1.96 g (748 mCi) of crude [7-¹⁴C]benzyl alcohol (**4**) (13.8 mmol based on 54 mCi/mmol).

To a solution of 1.96 g of **4** in 20 mL of dried dichloromethane was added 5.16 g (13.5 mmol) of 98% pyridinium dichromate (PDC), and the mixture was stirred in the dark for 12 h. TLC showed the presence of benzaldehyde (85%, R_f 0.73), starting benzyl alcohol (12.3%, R_f 0.4), and benzoic acid (1.08%, R_f 0.5). Additional PDC, 727 mg (1.9 mmol), was added. After stirring for 18.5 h, TLC showed the absence of starting material but 4.8% of benzoic acid and 95% benzaldehyde. The reaction mixture was passed over a column containing 12 g of silica gel packed in pentane and eluted with 50-mL and 25-mL portions of dichloromethane to give 650 and 10 mCi of [7-¹⁴C]benzaldehyde **5** in the eluates, respectively. The first fraction, 650 mCi (12 mmol) was stored at -30 °C as a stock solution for the next reaction.

4-Methyl-3-oxo-N-phenyl-2-(phenyl[¹⁴C]methylene)pentamide (7) (benzylideneisobutyrylacetanilide; BIBEA). A dichloromethane solution containing 1.64 g (8.0 mmol) of isobutyrylacetanilide (**6**) and 325 mCi [7-¹⁴C]benzaldehyde (**5**) in a 50-mL Kjeldahl flask was cautiously evaporated in vacuo to 4 g of an inhomogeneous liquid. (Overevaporation was avoided to prevent loss of benzaldehyde). The flask was then charged with 21 mL of hexane (previously aerated with nitrogen), 206 mg (1.94 mmol) of unlabeled benzaldehyde, 182 mg (2.04 mmol) of β-alanine, and 305 mg (5.08 mmol) of glacial acetic acid. The flask was fitted with a Dean-Stark trap and condenser, and the content was heated under reflux under a nitrogen atmosphere for 21 h. The first 4 mL of distillate, containing dichloromethane, was discarded. The supernatant, 7 mL, was withdrawn and found to contain 77 mCi of radioactivity, 60% of which was [¹⁴C]benzaldehyde. TLC (hexane:ether:2:1) showed the presence of *Z*-benzylidene at R_f 0.15 and *E*-benzylidene at R_f 0.34, in addition to benzaldehyde at R_f 0.47. The solid product was also analyzed and found to contain much less benzaldehyde. Another run using the remaining 325 mCi of [¹⁴C]benzaldehyde (**5**) was carried out similarly.

The solid products from the two runs (about 500 mCi) were combined and partitioned between about 25 mL of dichloromethane and 3 mL of water, and the dichloromethane layer was added to a column containing 50 g of silica gel packed in pentane. After further washing with 25 mL of dichloromethane, the column was developed with 3% ethyl acetate in dichloromethane while 5-mL fractions were collected. Fractions 20 to 62, apparently containing *E*- and *Z*-isomers only (TLC, hexane/dichloromethane/ethyl acetate: 2/2/1; radiochemical purity based on total of the two isomers >99%), were combined to four fractions totaling 450 mCi. Each fraction, however, was found to contain considerable amount of various impurities using another TLC system (ether:pentane/1:2; R_f, *E*-isomer 0.27, *Z*-isomer 0.63). They were purified by repeated fractional crystallization from dichloromethane/hexane (approx. 1.5 mL/5.0 mL per gram of *E/Z* mixture) to give pure **7** as the *Z*-isomer (2276 mg., 282 mCi). The mother liquor was rechromatographed and the best fractions were combined and subjected to repeated fractional recrystallizations to give an additional 462 mg (57 mCi) of product. Total yield was thus 337 mCi of **7Z**.⁵

4-Fluoro- α -(2-methyl-1-oxopropyl)- γ -oxo-N, β -diphenylbenzene[3- ^{14}C]butaneamide (10). A mixture of 506 mg (1.72 mmol, 63 mCi) of **7** and 93 mg (0.368 mmol) of 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (**9**) was placed in a 15-mL flask having a side arm with Teflon-lined septum, a magnetic stirrer, and a condenser through which either vacuum or argon atmosphere could be maintained with a Firestone valve. The content was subjected to vacuum for 1 h, then filled with argon. Dry ethanol (0.165 mL), triethylamine (196 mg, 1.93 mmol), and *p*-fluorobenzaldehyde (217 mg, 1.75 mmol) were added. The mixture was agitated, then heated with shaking at a bath temp of 67 °C for 1.5 h to give a clear viscous liquid, and then at 60 °C for 12 h. To the resulting mass of solid was added 3.7 mL of isopropyl alcohol, and the mixture was heated at 70 °C for 5 min under argon. After cooling, the mixture was filtered and washed with cold isopropyl alcohol and dried in vacuo to give 428 mg (59% yield) of **10** as essentially white crystals. HPLC [water:acetonitrile:THF:MeOH/5.564:3:2:1.8] showed radiochemical purity of 98.5%. The yield and purity in various runs were variable, with an average yield of 43% and the best yield of 62%, and the major contaminants being the desfluoro analog (**10b**) and the difluoro analog (**10c**). A representative retention time profile (in min) is 14.6–15.6 (**10b**), 17.7–21.3 (**10**), and 21.3–23.3 (**10c**). Impure preparations could be purified by crystallization achieved by addition of isopropyl alcohol to a concentrated solution of the crude product in THF, using a weight ratio of alcohol:THF:product of approximately 5:2:1.

[4R-cis]-1,1-Dimethylethyl-6-[2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-[3- ^{14}C]pyrrol-1-yl]ethyl]-2,2-dimethyl-1,3-dioxane-4-acetate (12). A 15-mL 2-neck conical flask containing 327 mg (0.78 mmol, 28.4 mCi) of **10** and 314 mg (0.835 mmol) of the pivalate salt of [4R-cis]-1,1-dimethylethyl-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate (**11**) was subjected to high vacuum for 1.5 h and then filled with argon. A 4.65-mL solution consisting of *n*-heptane:toluene:THF/4:1:1.1, all dried, containing 0.17% of 2,6-di-*tert*-butyl-hydroxytoluene, was added, and the reaction mixture was heated with stirring at a bath temperature of 88.5–90.5 °C for 20 h. TLC showed the presence of product **12** (system 1, 4% ethyl acetate in dichloromethane, *R_f* 0.4, 77% by radioactivity; system 2, ether:hexane/1:2, 0.25, 71%) and starting material **10** (system 1, 0.57, 10%; system 2, 0.10, 9%). The reaction was repeated using 743 mg (63.7 mCi) of **10**, 703 mg of **11**, and 10.6 mL of the solvent mixture in a 25-mL flask. The two reaction mixtures, together with 11 mL of *tert*-butyl methyl ether, were combined and extracted, in sequence, with 3.4 mL of 1 N aqueous sodium hydroxide, 2.1 mL of 0.45 M citric acid, 2.3 mL of saturated sodium bicarbonate, and 3.5 mL of saturated sodium chloride. Each of the aqueous phases was extracted sequentially with 2.5 mL of *tert*-butyl methyl ketone, and the combined organic phases were evaporated to give crude **12** (1.78 g, 89 mCi) as a solid foam. The crude product was extracted with ether:hexane/1:5 in portions and added to a column of 28 g of silica gel packed in hexane. The column was eluted with 66 mL of ether:hexane/1:4.5, followed by 300 mL each of ether:hexane/1:4 and ether:hexane/1:3. Fractions containing pure **12** (radiochemical purity >99%, largest single impurity <0.5%), mostly obtained during the second half of the ether:hexane/1:4 elution, were combined (43 mCi, 47% yield) and evaporated to 746 mg of solid residue (approx. 1.14 mmol), which had a strong tendency to form airborne particles during high vacuum drying.

[R-(R*,R*)]-2-(4-Fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-[phenyl-4-[(phenylamino)carbonyl]-1H-[3- ^{14}C]pyrrole-1-heptanoic acid calcium salt (2:1) (15) (Atorvastatin). The purified **12** was dissolved in 7.7 mL of methanol, and 0.89 mL of 1 N HCl was added with swirling. The lump which formed was brought into solution by sonication at 29 °C, and the reaction mixture was allowed to stand at room temperature in the dark overnight. A small amount of solid formed upon standing and could not be solubilized by addition of 1.3 mL of methanol. TLC (5% methanol in chloroform) showed main components at *R_f* 0.54 (88%, probably *tert*-butyl ester, and 0.37, 6.4%, probably methyl ester). After another day at room temperature, the reaction mixture completely solidified.

The solidified reaction mixture containing the esters derived from **12** was treated with 610 mg of 4 N sodium hydroxide, 0.17 mL of water, and 1.17 mL of methanol, followed by sonication, to give an essentially clear solution. The solution was reduced to 7.45 g by evaporation and then diluted with 14 mL of water and 1 mL of methanol. The solution was washed with one 6.75-mL and then two 6-mL portions of *tert*-butyl methyl ether. The three organic washes were sequentially washed with one mL of water. The combined aqueous phase (21.9 g) contained 43 mCi of essentially pure CI-981 in the sodium salt form (**13**).

To 5.48 g (10.76 mCi) of the solution containing **13** was added THF (6 mL), followed by an aqueous solution of calcium acetate hemihydrate (40.2 mg in 0.5 mL of water) added dropwise with swirling. The solution was evaporated to a solid residue (225 mg), which was then partitioned between 1.2 mL of water and 6 mL of ethyl acetate. The aqueous phase was further extracted with two 3-mL portions of ethyl acetate. The ethyl acetate extracts were sequentially washed with 0.8 mL of 1% aqueous calcium acetate hemihydrate. The three organic extracts were combined and evaporated to an amorphous solid residue (175 mg). Upon stirring in the dark with 1.2 mL of water under argon for ten or more hours, the residue was gradually transformed into a white thick slurry of flocculent solid, which was filtered, pressed, and washed with a small amount of water. The solid was dried at 0.1 mm Hg for 40 h to give 155 mg (9.96 mCi) of the calcium salt of [^{14}C]CI-981 (**15**); specific activity, 64.3 $\mu\text{Ci}/\text{mg}$; radiochemical composition by HPLC, system (A) : CI-981, 97.46% , largest impurity 1.43% (desfluoro analog of **15**, derived from **10b**); chemical composition at 254 nm, 98.05%, 0.79%.

Preparative HPLC purification of [^{14}C]atorvastatin. In a typical purification, 107 mg (0.19 mmol) of the CI-981 calcium salt (**15**) was partitioned between 0.7 mL of 1 N HCl and 3.5 mL of *tert*-butyl methyl ether. (Mixtures of **15** and its corresponding lactone **16** were also similarly purified). The organic phase was further washed sequentially with 0.5 mL of 1 N HCl, 1-mL and 0.5-mL portions of water. The aqueous phases were sequentially washed with 2 mL of *tert*-butyl methyl ether. Evaporation of the organic phases gave a residue consisting of a mixture of the free acid (**14** i.e., **13** Na = H) and lactone of CI-981 (**16**). The residue was dissolved in a little methanol and immediately treated with 0.2 mmol of sodium hydroxide in about 475 mg of water. More methanol was added so that the total methanol content was about 1.2 g. After 2 to 3 h, HPLC showed the absence of lactone or esters, and the solution was filtered through a Gelman 0.45 μm filter and the filter was washed with 0.65 g of methanol to give 2.42 g of combined filtrate and washing. This was used as a stock solution for HPLC purification.

The prep HPLC was achieved with an Alltech Econosil C18-10 μ column, 22.5 mm x 250 mm; mobile phase, 0.05 M citric acid pH 4:MeCN:THF:MeOH/6.8:3:2:1.8, 8 mL/min; UV monitor at 280 nm (off the absorption maximum of atorvastatin). A stock solution containing 0.0336 mmol (19.5 mg) to 0.0462 mmol (26.8 mg) of the sodium salt, depending on the purity, may be used per run. The desfluoro impurity (analog of **13**, cf. **10b**), was collected at 55 - 65 min, then 6 to 8 fractions, 15 sec. each, were collected, followed by larger fractions with high absorbance ($A > 2.0$ to $A = 1.2$, 58 - 65 min), which contained pure **13**. More dilute fractions ($A < 0.9$) were discarded. The composition of the solvent was changed to 7:3 at 75 - 109 min, and 1:1 for an additional 20 min to elute impurities. All operations were carried out so that solutions were protected from light and air as much as possible.¹⁰

The pure fractions collected from eight runs were combined and evaporated in vacuo at a bath temperature of less than 27 °C. An aspirator was used first then followed by a vacuum pump while the distillate was condensed with a Dry Ice trap. The eluates were thus evaporated to give 18.8 g of a concentrate, which was then extracted with 30-mL and 14-mL portions of *tert*-butyl methyl ether. The organic phases were sequentially washed with 9 mL of water. The combined organic phases, containing 9.4 mCi of activity, were evaporated to 209 mg of a residue. The residue was treated with a solution consisting of 146 mg of 2 N sodium hydroxide and 2 mL of methanol containing 6.4% of water. Any residue at the side of the flask was rinsed down with 4.6 mL of methanol. The solution was allowed to stand 1 h at room temp and then at 0 °C overnight. HPLC showed the absence of any ester or lactone. Under an argon atmosphere, a solution of 36.5 mg (0.218 mmol) of calcium acetate hemihydrate in 825 mg of water was added. After 1 h at 0 °C, the solution was evaporated to 627 mg of residue with an aspirator, and partitioned between 6 mL of water and 12 mL of ethyl acetate. The aqueous phase was further extracted with two 5.75 mL portions of ethyl acetate, and the three organic phases were sequentially washed with 2 mL of an aqueous solution containing 12.5 mg of calcium acetate hemihydrate, then filtered to remove any insoluble material. The filtrate was evaporated in vacuo to 189 mg of a residue, which was stirred with 2 mL of water overnight. The flocculent solid was filtered and washed with a little water as above and dried in vacuo at <0.005 mm Hg for 68 h to give 139 mg of **15** (CI-981 calcium salt, 63.3 $\mu\text{Ci}/\text{mg}$, 8.757 mCi total). HPLC analysis showed a radiochemical purity of >99%, chemical purity >99%.

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7. In cold runs, the *E*- and *Z*- components were separated by silica gel column chromatography (elution with hexane:dichloromethane:EtOAc/9:1:1). TLC (silica gel, pentane:ether/2:1): *E*-isomer, Rf 0.52; *Z*- isomer, Rf 0.31. The configuration of the *Z*-isomer, crystals from ethyl acetate-cyclohexane, was established by single crystal X-ray crystallography. The *Z*-isomer is favored thermodynamically and the *E*-isomer is favored kinetically during synthesis.
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9. Besides HPLC, the labeled compound 15 was characterized by ^1H and ^{13}C NMR and IR against an authentic reference standard. The assay by UV absorbance per unit weight vs. a reference standard sample isolated from non-hydroxylic solvents was generally 98 to 99%. The λ_{max} of reference standard is 240 nm (pH 7), $36.8 \text{ mL}\cdot(\text{mg}\cdot\text{cm})^{-1}$, $\log \epsilon = 4.33$, and is 247 nm in the mobile phase under HPLC conditions. Chemical purity by HPLC is defined as purity by area normalization at a chosen wavelength (e.g., 254 nm for 15, as specified for purity determination of the drug), generally near the absorption maximum with consideration being given to the the absorption characteristics of the impurities. During melting point determination (glass capillary, oil bath), atorvastatin, being a calcium salt, decomposed (shrinking, then expanding, and finally melting) over a wide temperature range of approximately -160 to 240 °C.
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