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RESEARCH ARTICLE

Organic Synthesis of Iodinated Atorvastatin *via* Nucleophilic Substitution Reaction: Experimental and DFT Studies

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Abstract: Atorvastatin is an aromatic compound that acts selectively in the liver as an inhibitor of HMG-CoA reductase and cholesterol synthesis. The iodination of aromatic compounds has been widely applied for the preparation of potential pharmaceuticals and bioactive molecules. Herein, an iodinated atorvastatin was synthesized using chloramine-T (CAT) intermediate *via* an electrophilic substitution reaction. The obtained product was elucidated *via* elemental analysis, mass spectrometry and ^{1}H-NMR techniques. A comparison of experimental ^{1}H-NMR chemical shifts of the iodinated atorvastatin with the corresponding predicted ones obtained with GIAO method at the B3LYP/LanL2DZ confirmed the desired structure. Furthermore, the favourable electrophilic substitution site was confirmed by the Fukui indices calculations of the heavy atoms of the parent atorvastatin at DFT with the same level of theory.

Keywords: Atorvastatin, iodination, electrophilic substitution, Fukui indices, chloramine-T, GIAO, DFT.

1. INTRODUCTION

Atorvastatin is chemically described as (*3R*,*5R*)-7-[2-(4-fluorophenyl)-3-phenyl-4 (phenylcarbamoyl)-5-propan-2-ylpyrrol-1-yl]-3,5-dihydroxyheptanoic acid [1]. It acts selectively in the liver as an inhibitor of HMG-CoA reductase and cholesterol synthesis. Atorvastatin is taken up selectively into the liver (hepatocytes) *via* organic anion transporting polypeptide 1B1 (OATP1B1), excreted into the biliary system and stored by the gallbladder. The lipophilicity/hydrophilicity determined the binding affinity for hepatic transport proteins, the efficiency of their hepatocyte uptake and the excretion rate. Atorvastatin is a lipophilic statin but relatively hydrophilic compared to simvastatin and lovastatin, which makes it more hepatoselective and able to cross cellular membrane either by passive diffusion and/or active carrier-mediated process. The liver-selective uptake and the tissue-specific distribution of atorvastatin *via* organic anion transporters assist them to induce their high pharmacological effect.

The iodination of aromatic compounds has been widely applied for the preparation of potential pharmaceuticals and bioactive molecules. The electrophilic iodination requires the presence of the more reactive species with a pronounced I^+ character. Alternatively, iodination may be carried out using the oxidative activation where the electrophilic I^+-type species is generated through oxidation of iodine sources under mild experimental conditions in the presence of oxidizing agent systems [2, 3]. Ren *et al.*, developed an effective method for the iodination of alkoxy-substituted benzenes and naphthalenes using nitrogen dioxide as the catalyst precursor [4]. Sloan and Sutherland reviewed the recent advances in transition-metal-catalyzed methods over more traditional approaches for efficient and highly regioselective iodination of activated arenes [3]. Recently, Rafiee *et al.*, developed an electrochemical method for selective benzylic iodination of methylarenes using redox mediator N-hydroxyphthalimide (NHPI), which undergoes proton-coupled oxidation at an electrode to afford phthalimido-N-oxyl (PINO), which then mediates HAT for electrochemical oxidation of C−H bonds [5]. In a previous study, we showed that the Chloramine T is a simple and effective oxidizing agent for aripiprazole radioiodination [6].

Synthetic routes for the preparation of radioiodinated compounds are usually more difficult than the other corresponding halogen-containing radiopharmaceuticals because iodine is the largest, the least electronegative, the most polarizable of the halogens and forms the weakest C-X bond. Elemental iodine is slightly reactive, which requiring an activator to be effectively introduced into organic compounds. On the other hand, iodonium ion (I^+), which acts as the electrophile for the radioiodination process can be generated *in situ* in the presence of chloramine-T as a convenient oxidizer, thus enabling the efficient and selective direct iodination of atorvastatin under ambient conditions [7-11]. When No-Carrier-Added (NCA) radioiodide is oxidized *in situ*, it creates an electropositive iodine (I^+), but it is not probable to generate I_2 as it was expected because of extremely low concentrations of radioiodine at the trace level that practically are not feasible for two iodine atoms to combine together [12-14]. Instead, a mixed halogen such as ICl (iodine monochloride) is generated in the existence of an oxidant such as chloramine-T. As a result of the variation in the electronegativity between iodine and chlorine, ICl is extremely polar and

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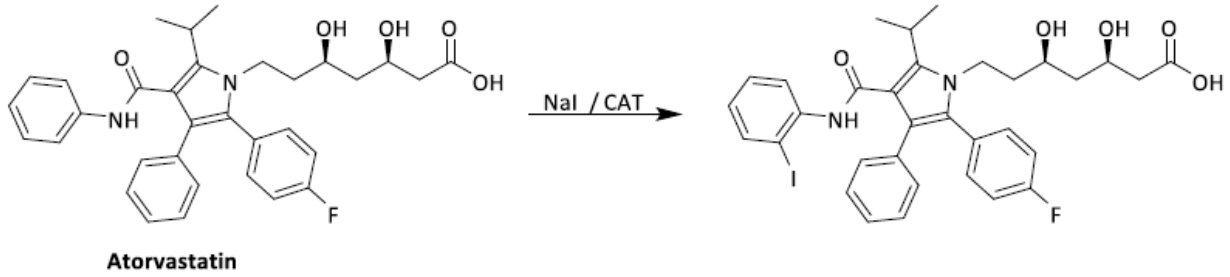

Scheme 1. Synthesis of ^{nat}I-atorvastatin.

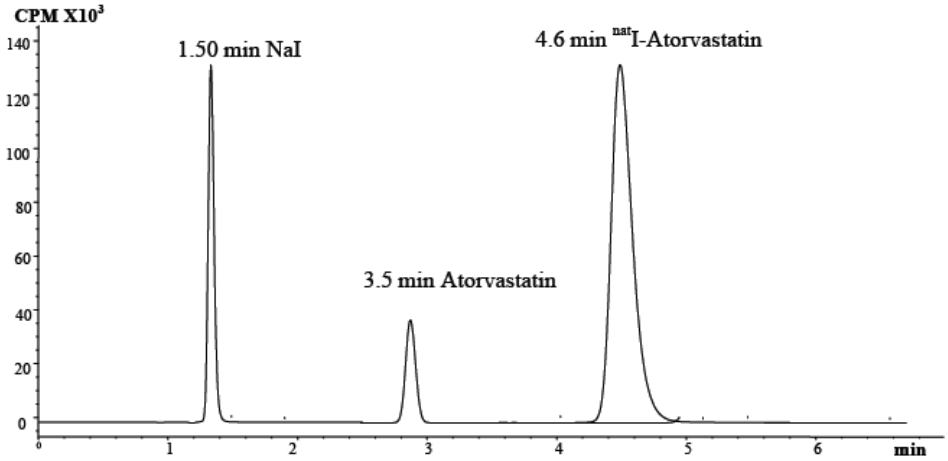

Fig. (1). Chromatogram of NaI, atorvastatin and ^{nat}I-atorvastatin.

acts as a source of iodonium ion (I^+). Consequently, aromatic electrophilic labeling with electropositive radioiodide usually proceeds in high radiochemical yield compared to 50% yield if the molecular iodine is used because ICl is a stronger iodinating agent than I_2 [12-16].

The present study aims to describe the electrophilic substitution of atorvastatin by iodonium ion (I^+) and the synthesis of ^{nat}I-atorvastatin by calculating Fukui indices of heavy atoms. The final product elucidated structure is confirmed by DFT calculation using the hybrid functional B3LYP combined with LanL2DZ basis set in gas and in a polarisable continuum model (PCM), for which IEF-PCM formalisms is considered.

2. RESULTS AND DISCUSSION

2.1. The Formation of ^{nat}I-atorvastatin

Synthesis of iodinated atorvastatin was performed by direct electrophilic substitution with iodine under oxidative conditions and in the presence of chloramine-T (CAT) (Scheme **1**).

Iodination of atorvastatin generally follows the same chemistry used for radioiodination at the microscopic scale. Thin-layer chromatography (TLC) results showed that iodide remained near the origin (R_f = 0–0.1), while the iodide compound shifted with the solvent front (R_f = 0.8–1). The chemical yield was 94.3 ± 1.41 % (n = 3). High performance liquid chromatography(HPLC) was further used to confirm the yield and the formation of the iodide compound, where the retention times of free iodide and ^{nat}I-atorvastatin were 1.5 and 4.6 min, respectively (Fig. **1**).

The HPLC system allowed the separation of the cold-iodinated atorvastatin from the free iodide and the unlabeled atorvastatin as well as the purification and quality control assessment of the formed compound. Iodonium ion (I^+), which acts as the electrophile for the radioiodination process can be generated *in situ* in the presence of chloramine-T as a convenient oxidizer, thus enabling the efficient and selective direct iodination of atorvastatin under ambient conditions. Synthetic routes for the preparation of iodinated compounds are usually more difficult than other corresponding halogen-containing radiopharmaceuticals because iodine is the largest, the least electronegative, the most polarizable of the halogens and forms the weakest C-X bond. Elemental iodine is slightly reactive, requiring an activator to be effectively introduced into organic compounds. The rate of electrophilic substitution in atorvastatin compounds depends on the basicity of the aromatic ring. The presence of activating substituents such as NHR makes the aromatic ring more basic than the unsubstituted benzene by inductive effect and resonance. Introduction of an iodo group into atorvastatin through direct aromatic electrophilic iodination *ortho* to the amino group increased the logP value to 5.4. The lipophilicity of the iodinated atorvastatin enhanced its binding affinity for hepatic transport proteins, which determines the hepatobiliary properties of this therapeutic agent such as the efficiency of the hepatocyte uptake and the excretion rate. The retention time of atorvastatin was detected before iodinated atorvastatin on reversed phase HPLC chromatogram due to the attachment of iodine to atorvastatin structure.

2.2. Characterization of ^{nat}I-atorvastatin

The formation of cold-iodinated atrovastatin was characterized and confirmed by ^{1}H-NMR, mass spectroscopy and elemental analysis. ^{1}H-NMR: δ ppm (DMSO-d_6) showed peaks at 1.28 (d, 6H, CH_3 of methyl); 1.92 (q, 2H, CH_2 of methylene); 1.59 (t, 2H, CH_2 of methylene); 2.00 (s, 2H, OH of alcohol); 2.38 (d, 2H, CH_2 of methylene); 3.12 (m, 1H, CH of methine); 3.85 (t, 2H, CH_2 of

Table 1. Experimental and predicted ^{1}H chemical shifts (ppm) for atorvastatin and its iodinated form in gas and PCM solvent phases obtained at the B3LYP/Lan2DZ of theory.

	Atrovastatin			Iodinated atrovastatin		
	Gas	**PCM**	**Exp**	**Gas**	**PCM**	**Exp**
H7/H11	7.96	7.87	6.96-7.27	8.52	8.42	6.96-7.27
H8/H10	7.77	7.86		7.94	8.12	
H9	7.66	7.82		7.60	7.85	
H13/H17	7.20	7.35		7.19	7.40	
H14/H16	7.20	7.44		7.14	7.38	
H19 /H20	1.67	1.38	1.28	1.57	1.44	1.28
H32/H34	2.96	3.18	3.37	2.85	3.01	3.37
H35	2.28	2.45	2.38	2.28	2.38	2.38
H30	3.22	3.47	3.12	3.08	3.28	3.12
H31	1.78	1.78	1.92	1.88	1.81	1.92
H33	1.56	1.58	1.59	1.69	1.62	1.59
H25	5.92	6.40	6.96-7.27	7.25	7.56	6.77-7.62
H26	7.34	7.67		7.46	7.82	
H27	7.42	7.70		7.54	7.90	
H28	7.75	7.96		8.01	8.18	
H29	9.75	9.41		-	-	-

methylene); 3.21-3.54 (s, 2H, CH of methine); 6.77-7.62 (d, 8H, CH of ArH); 7.22-7.48 (m, 5H, CH of ArH); 8.00 (s, 1H, NH); 11.00 (s, 1H, OH of carboxylic acid). Mass spectral analysis showed a molecular ion peak at *m/z* 684.15, which confirmed the presence of iodide in the molecule. Elemental analysis calculated for $C_{33}H_{34}FIN_2O_5$: %C, 57.90; %H, 5.01; %F, 2.78; %I, 18.54; %N, 4.09; %O, 11.69; found: %C, 57.85; %H, 4.97; %F, 2.77; %I, 18.55; %N, 4.09; %O, 11.68.

2.3. ^{1}H NMR Spectroscopy

The molecular structure of iodinated atorvastatin is elucidated *via* ^{1}H-NMR spectrum. The observed spectra of the atorvastatin and its iodinated derivative were recorded in deuterated DMSO solvent where TMS is used as an internal standard. The corresponding calculated ^{1}H chemical shifts of atorvastatin and it's iodinated were calculated at the B3LYP/Lan2DZ within GIAO method in the gas phase and PCM model (Table **1** and Fig. **2**). The solvent effects on ^{1}H chemical shift values weretaken into consideration using IEF-PCM formalism, where DMSO is used as a selected solvent. Both experimental spectra of atorvastatin and its iodinated form showed similar behavior and almost identical peaks. ^{1}H NMR chemical shifts of methyl groups at C19 and C20 were observed at 1.28 ppm. The corresponding predicted chemical shifts appeared in PCM at 1.38 and 1.44 ppm for atorvastatin and its iodinated form, respectively. The experimental ^{1}H NMR chemical shift of the single proton H18 was observed at 3.85 ppm, and the corresponding calculated ones in PCM were 3.68 and 3.97 ppm for atorvastatin and its iodinated form, respectively. It is worth mentioning that the solvent improved the results compared to the gas phase. For instance, the ^{1}H NMR chemical shift of H18 was obtained at 4.16 and 3.97 ppm in gas and PCM solvent with a variation of 0.12 and 0.31 ppm, respectively. The strongest effect of the electrophilic substitution on ^{1}H NMR chemical shifts of the starting material atorvastatin is the downfield shifts of chemical protons of the benzene ring (C24-C29, Fig. **2**), mainly the proton (H25) at *ortho* position in the benzene ring. The comparison between experimental chemical shifts of atorvastatin and its ^{nat}I-atorvastatin showed that the iodine electrophilic substitution had a negligible effect on the chemical shifts of aromatic rings (C6-C11 and C12-C17, Fig. **2**), isopropyl and long-chain (C30-C36, Fig. **2**). These effects are more obvious when considering the predicted ^{1}H chemical shifts of atorvastatin and its iodinated form. Indeed, in PCM, the variations between the predicted chemical shifts of aromatic rings (C6-C11 and C12-C17), isopropyl and long-chain (C30-C36) for both atorvastatin and ^{nat}I-atorvastatin were observed to be less than 0.55, 0.06, 0.19 ppm in PCM, respectively. A strong variation was observed in ^{1}H chemical shifts of the substituted aromatic ring (C24-C26) of 1.33 and 1.16 ppm in gas and PCM, respectively. This confirmed the electrophilic substation of iodine at C29.

Relatively a good correlation was obtained between the predicted and experimental ^{1}H and chemical shifts for both atorvastatin and its iodinated form. For instance, in the gas phase, correlation coefficient of 93.08 and 91.77% were calculatedbetween the predicted and experimental ^{1}H NMR chemical shifts for atorvastatin and its iodinated form, respectively. Furthermore, the correlations were significantly improved when the solvent effects were considered with correlation coefficients of 96.02 and 96.38% for atorvastatin and its iodinated form, respectively (Fig. **3**).

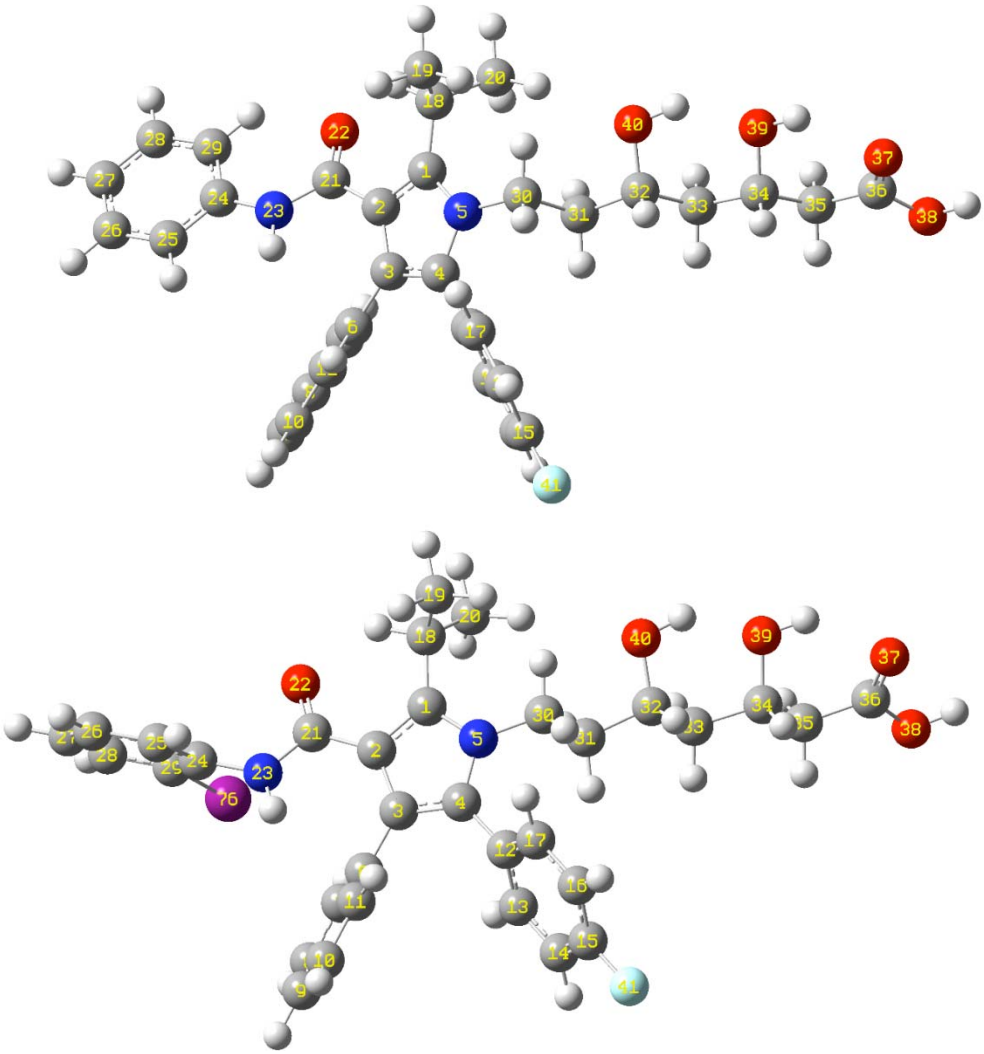

Fig. (2). Optimized structures of atorvastatin (up) and its iodinated form (bottom) obtained at the B3LYP/Lan2DZ level of theory.

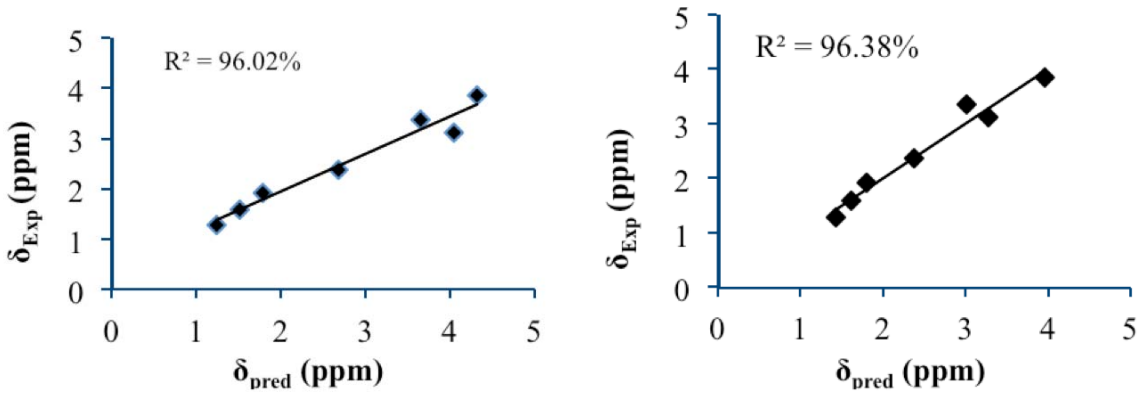

Fig. (3). Correlation curves between predicted and experimental ^{1}H NMR chemical shifts of the atorvastatin (left) and its iodinated form (right).

2.4. Electrophilic Substitution of Atorvastatin: DFT Highlights

The iodination of atorvastatin is an electrophilic aromatic substitution. Based on our previous studies, the electrophilic substitution will be favorable in C29 of the aromatic ring in atorvastatin (Fig. **1**). In order to confirm this result, the nucleophilicity of atomic sites of aromatic rings in atorvastatin was calculated (Table **2**) *i.e*, the electrophilic attack is favorable in nucleophilic site with the highest Fukui index value. The higher the value of Fukui function f_k^-, the greater is the probability of electrophilic attack at site k. Langenaeker *et al*., calculated Fukui functions of a series of *mono*-substituted benzenes, and showed that the electrophilic substitution is favorable for the *para* position followed by *meta* and *ortho* positions [17]. By comparing the nucleophicity of atomic sites of the three aromatic rings in atorvastatin, it appears that the

Table 2. Nucleophilic Fukui indices of heavy atoms of atorvastatin calculated at B3LYP level of theory.

	$q_k(N)$	$q_k(N-1)$	f_k^-
6 C	-0.050	-0.034	-0.016
7 C	-0.322	0.016	-0.339
8 C	-0.143	-0.014	-0.129
9 C	-0.175	0.059	-0.233
10 C	-0.262	-0.022	-0.240
11 C	-0.156	-0.088	-0.068
12 C	-0.644	0.106	-0.750
13 C	-0.112	-0.034	-0.077
14 C	0.202	0.095	0.106
15 C	-0.029	-0.026	-0.003
16 C	0.127	0.082	0.045
17 C	-0.156	-0.088	-0.068
25 C	-0.322	0.003	-0.324
26 C	-0.525	0.000	-0.525
27 C	-0.095	0.002	-0.096
28 C	-0.590	0.000	-0.590
29 C	0.730	0.001	0.729

ortho position C29 is the best favorable site of electrophilic attack with an f_k^- of 0.729. According to f_k^-, it is very unlikely for an electrophilic attack to occur at the *para* position (C27) due to the negative values in this position.

3. MATERIALS AND METHODS

3.1. Chemicals and Reagents

Atorvastatin ($C_{33}H_{35}FN_2O_5$; M.wt. = 558.64 g/mol) was a generous gift from EIPICO, Egypt. All reagents and solvents used were of analytical reagent grade and used without further purification. Deionized water was used in all experiments. Sodium iodide (NaI) for iodination, chloramine-T, sodium metabisulfite, sodium iodide phosphate buffered saline (PBS) and acetonitrile were purchased from Sigma-Aldrich. Mass spectrum (MS) was carried out on an Applied Biosystems 3200 Q-TRAP mass spectrometer. Chemical shifts (δ) are expressed in ppm with reference to TMS using Varian Nuclear Magnetic Resonance XL-500 MHz.

3.2. Synthesis of Iodinated Atorvastatin

An aliquot of 400 µL solution containing 13 mM CAT in methanol was transferred to a reaction vial. Then a portion of 75 µL KI solution consisting of 2.1 mM was added. Furthermore, a freshly prepared solution of 100 µL containing 0.9 mM atorvastatin in acetonitrile was added to the reaction vial. Thereafter, the reaction mixture was adjusted to pH 5 using phosphate buffer. The iodination reaction was allowed to carry on for 15 min and stopped by adding 10 % saturated $Na_2S_2O_5$ solution in H_2O (400 mg/mL).

3.3. Analysis of ^{nat}I-atorvastatin

The chemical purity of ^{nat}I-atorvastatin complex was assessed by silica-gel thin layer chromatography (SG-TLC). Samples were spotted 2 cm above the lower edge of the strip (1 cm width, 13 cm length). The TLCs were developed in a mixture of benzene: ethyl acetate (7:3 v/v) and allowed to evaporate spontaneously. The chemical purity was expressed as the retention factor (R_f), which is defined as the ratio of the distance migrated by ^{nat}I-atorvastatin divided to the distance migrated by the solvent front. The reported R_f value represented the mean value of three experiments. Chromatographic analysis and purification of the iodinated compound were performed on Agilent HPLC system. An aliquot of 10 µL was withdrawn, purified and injected into an HPLC column under the following conditions: a reversed phase Waters C18 column (150 × 4.6 mm; 5 µm) kept at 25ºC with a mobile phase consisting of 0.05 M sodium acetate buffer and acetonitrile (40:60, v/v) adjusted to pH 4.0. Atorvastatin was detected by ultraviolet absorbance at 246 nm. The mobile phase was filtered and degassed before use, then pumped at a flow rate of 1.00 mL/min. All the collected fractions from HPLC were evaporated to dryness at 40°C under vacuum and re-dissolved in DMSO-d_6 to perform ^{1}H-NMR or 80 % ACN to carry out MS/MS.

3.4. Lipophilicity (Partition Coefficient logP)

The partition coefficient (logP) is the ratio of the concentration of the iodinated compound in the organic phase (octanol) and the aqueous phase (PBS) at equilibrium. The lipophilicity of ^{nat}I-atorvastatin was measured experimentally by adding 5 mL of *n*-octanol and PBS (50:50) to a centrifuge tube containing a 1 mL aliquot of the iodinated compound. The tube was shaken for 10 min at room temperature and centrifuged at 4500 rpm for 15 min. Each phase was separated, transferred to new glass tubes and evaporated to dryness with N_2 at 40ºC. The residue was reconstituted in 250 µl of mobile phase (50% 0.05M sodium acetate buffer:50% acetonitrile). A portion of 5µl was injected into the HPLC. In order to estimate the lipophilicity, the logarithm of the partition coefficient (log P) is commonly used. The partition coefficient (logP) is the

ratio of the concentration of the iodinated compound in the organic phase (octanol) and the aqueous phase (PBS) at equilibrium. Extractions were performed in triplicate and the reported logP value represented the average of three determinations.

3.5. Theoretical Details

Quantum chemical calculations have been carried out at the DFT level of theory. Geometry optimization of neutral and cationic forms of atorvastatin, and iodinated atorvastatin ground-states were carried out using the hybrid functional B3LYP combined with the basis set LanL2DZ. The minima of optimized ground-state structures were confirmed by the absence of imaginary frequencies. The predicted ^{1}H magnetic isotropic shielding tensors (σ) were calculated using the standard Gauge-Independent Atomic Orbital (GIAO) approach at the same level of theory [18]. The isotropic shielding values were used to calculate the isotropic chemical shifts δ with respect to tetramethylsilane ($Si(CH_3)_4$). $\delta_{iso}(X) = \sigma_{TMS}(X) - \sigma_{iso}(X)$, where δ_{iso} is the isotropic chemical shift and σ_{iso} is the isotropic shielding constant. The predicted chemical shifts were obtained using the equation $\delta_{exp}=a\delta_{cal}+b$, where $\delta_{cal}=\delta_{iso}$. The solvent effects were taken into account implicitly by using polarisable continuum model (PCM) [19]. In PCM model, the solute is embedded into a shape-adapted cavity surrounded by a dielectric continuum solvent, described by its dielectric constant (*e.g.*, ε_{dmso} = 46.826). The PCM has been reported to correctly model major solvent effects such as electrostatic effects of the medium providing no specific solute-solvent interactions such as hydrogen bond interactions, dipole-dipole interactions, or induced dipole-dipole interactions [20]. In DFT, the Fukui functions are the key of region selectivity indicators for electron-transfer controlled reactions. The condensed Fukui functions were computed using Mulliken population analysis method [21].The nucleophilicity of atomic sites in atorvastatin was obtained using the following formula (Fukui index of electrophilic attack).

$$F_k^- = q_k(N) - q_k(N-1)$$

where N is the total number of electrons in atorvastatin. All quantum chemical calculations were performed using Gaussian09 package [22].

CONCLUSION

Radioiodination *via* direct electrophilic substitution is an applicable radiochemical route for labeling atorvastatin at an ambient temperature in the presence of an *in situ* oxidant such as chloramine-T in high radiochemical yield (94.3%). This study is a combination of experimental and quantum chemical calculation of the characterization of radioiodinated atorvastatin, crucial for designing a potentially convenient radiopharmaceutical for targeting hepatobiliary tumors.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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