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RESEARCH ARTICLE

Electrophilic Aromatic Synthesis of Radioiodinated Aripiprazole: Experimental and DFT Investigations

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ARTICLE HISTORY

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Abstract: ***Background*:** Aripiprazole is a quinolinone derivative. It shows a high affinity for neurotransmitters dopamine and serotonin receptors, which can overcome the blood-brain barrier (BBB) to reach the central nervous system (CNS) to exert therapeutic effects. Its radioiodination may lead to high radiochemical yield and improved its affinity. Aripiprazole radioiodination is an aromatic electrophilic substitution.

***Objective*:** Herein, we investigate the favorable atom site of the aromatic electrophilic substitution of aripiprazole by calculating the Fukui indices of heavy atoms and ESP charges of the parent molecule.

***Method*:** The calculations have been carried out at the B3LYP/LanL2DZ level of theory. The iodinated aripiprazole structure is confirmed by comparing the experimental and the predicted ^{1}H NMR chemical shifts of the parent molecule and its iodinated forms.

***Result*:** Finally, the electronic properties of aripiprazole and its iodinated form were calculated at the same level of theory. Nucleophilic Fukui indices and ESP charges calculations confirm that C8 is the most favorable site of the electrophilic substitution. The calculated electronic properties (*e.g,* gap energy, electron affinity, and electronegativity) of aripiprazole and its iodinated form reveal the higher reactivity of iodinated aripiprazole compared with aripiprazole.

***Conclusion*:** This may explain the higher affinity of iodinated aripiprazole and the increase of its radiochemical yield.

Keywords: Aripiprazole, oxidative iodination, electrophilic substitution, fukui indices, GIAO, DFT.

1. INTRODUCTION

Radiopharmaceutical compounds that bind to the brain or central nervous system (CNS) receptors *in vivo* are promising for understanding the pathophysiology of a number of psychiatric and neurological disorders, their treatment and diagnosis [1]. A brain-imaging radiopharmaceutical must not only reach its target by passing through the blood-brain barrier, but it should be able to bind with high affinity to the receptor [2]. Single-photon emission computed tomography (SPECT) as compared with positron emission tomography (PET) has the advantage of being easily available globally [3]. Development of Single Photon Emission Computed Tomography (SPECT) radiopharmaceuticals for imaging brain, CNS and their receptors is therefore of great importance [3-4]. SPECT [5-6] and PET radiopharmaceuticals [7] have led the way in the studies of the major brain diseases, and have potentially provided extremely useful information on neurophysiology [8-9] and neuropharmacology [10]. Among the radiopharmaceuticals, aripiprazole is a quinolinone derivative that shows a high affinity for the neurotransmitters dopamine and serotonin receptors, which can overcome the blood-brain barrier (BBB) to reach the CNS to exert therapeutic effects [11]. Electrophilic labeling with radio-iodine *in-situ* requires the presence of the more reactive species with a pronounced I^{+} character or may be carried out using the oxidative activation where the electrophilic I^{+}-type species is generated through oxidation of iodine sources under mild conditions in the presence of chloramine-T as an oxidizing agent, which is a convenient method for radiolabeling aripiprazole in high radiochemical yield (96.1%) [12-13]. The Mechanistic approach *in situ* of oxidative radioiodination of aripiprazole was elucidated leading to the *in situ* generation of the reactive iodonium ion (I^{+}), which seemed to be the most appropriate radiochemical route for the effective, selective radioiodination of aripiprazole *via* direct electrophilic substitution at ambient temperature when an appropriate oxidant such as chloramine-T is present. This kind of radioiodination reaction generally leads to high radiochemical yield [14-17]. The reaction parameters that influenced the radiolabeling yield are concentration, pH and time. *In vitro* studies demonstrated that the radiopharmaceutical was stable for up to 24 h. In general, the reactivity of aripiprazole may be described by calculation global parameters like electronegativity, hardness and softness. However, the favorable atomic site of electrophilic attack might be determined by calculation of the local reactivity parameters such as Fukui function, local softness and charge density at different sites in a molecule.

The electrophilic aromatic iodination of paclitaxel, a natural product that demonstrated anticancer activity with NaI in the presence of peracetic acid, afforded the ^{123}I-labeled paclitaxel [^{123}I], the iodopaclitaxel structure was confirmed by ^{1}H-NMR and HRMS (FAB) analyses [18]. Electrophilic iodination reaction has been used to improve the radiochemical yield of the radioiodinated analog of the adrenergic neurotransmitter, named iodometaiodo-

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benzylguanidine (^{123}I-MIBG) [19]. Tonnesen *et al*., synthesized an iodinated derivative of Tamoxifen, a non-steroidal estrogen analog with an affinity for the estrogen receptor and with anti-estrogenic activity, named l-iodotamoxifen through an electrophilic substitution, and the authors showed that due to steric and metabolic effects the position ortho to the ether side chain of tamoxifen might be the most favorable for radionuclide labeling [20].

In the present study, the main focus is the description of the electrophilic substitution of aripiprazole by iodonium ion (I^+) and the synthesis of ^{nat}I- aripiprazole through the calculation of nucleophilic Fukui indices of heavy atoms of the starting material by using DFT calculations. The favorable nucleophilic site of the electrophilic substitution is confirmed by a comparison of the experimental and predicted chemical shifts of the iodinated aripiprazole. In addition, to emphasize the reactivity and the high affinity of the iodinated aripiprazole, its electronic properties were determined and compared with the parent molecule aripiprazole.

2. MATERIALS AND METHODS

2.1. Materials and Equipment

Aripiprazole (M = 448.385 g mol–1) was given as a generous gift from Pharmagene Labs, Egypt. No-carrier-added sodium iodide (Na125I, 3.7 GBq ml–1 in 0.1 N NaOH) for radioiodination was purchased from the Institute of Isotopes, Budapest, Hungary. Chloramine-T, sodium metabisulfite, sodium iodide and methanol were purchased from Sigma-Aldrich. All Chemicals were of analytical or clinical grade and were used directly without further purification. Nuclear Magnetic Resonance (NMR) spectra were performed on Varian XL-500 MHz multinuclear spectrometers; chemical shifts (δ) are expressed in ppm with reference to TMS. Mass spectrum (MS) was performed on Applied Biosystems 3200 Q-TRAP mass spectrometer.

2.2. Synthesis and Characterization Iodinated Aripiprazole

As described in our previous study, the iodinated aripiprazole was synthesized *via* direct electrophilic substitution of aripiprazole with iodine under oxidative conditions and in the presence of chloramine-T (CAT) (Scheme **1**) [17]. The iodinated aripiprazole was characterized by ^{1}H NMR, mass spectrometry and elemental analysis methods [17].

Iodinated aripiprazole: ^{1}H NMR, δ, ppm (DMSO-d6): 2.49 (dd, 2H, J= 13.9, 6.9 Hz), 2.86 (dd, 2H, J= 5.8, 1.6 Hz), 7.15 (d, 1H, J=8.2 Hz), 6.45 (d, 1H, J=8.2 Hz), 4.06 (dd, 2H, J = 10.6, 4.7 Hz), 1.99 (m, 2H), 1.76 (m, 2H), 4.06 (t, 2H, J = 10.6, 4.7 Hz), 4.06 (dd, 2H, J = 11.3, 4.3 Hz), 3.01 (dd, 4H, J=9.6, 3.5 Hz), 3.44 (dd, 4H, J=9.6, 3.5 Hz), 7.36 (d,1H, J=7.9 Hz), 7.30 (dd, 1H, J=7.9, 8.1 Hz), 7.04 (d, 1H, J=8.1 Hz), 10.00 s (1H, NH). Mass spectral analysis showed a molecular ion peak at m/z 573, which confirmed the presence of iodine in the molecule. Elemental analysis, %, calculated for $C_{23}H_{26}Cl_2IN_3O_2$: C 48.10; H 4.56; Cl 12.35; I 22.10; N 7.32; O 5.57; found: C 48.12; H 4.65; Cl 12.37; I 22.11; N 7.40; O 5.65.

2.3. Theoretical Details

Geometry optimization and frequency calculations of neutral and cationic forms of aripiprazole and its iodinated forms have been carried out using Becke Three Parameter Hybrid Functional (B3LYP) hybrid functional combined with the basis set LanL2DZ. This hybrid functional use the non-local correlation provided by the LYP expression and VWN functional III for local correlation [21].

B3LYP is a reliable hybrid functional for the prediction of acceptable experimental results. It contains a fixed 20% HF exchange. DFT calculations have been performed in the presence of a solvent using the implicit polarizable continuum model (PCM) using the integral equation formalism variant (IEFPCM) as implemented in Gaussian 09 [22]. In this model, the solute is placed in a cavity within the solvent reaction field [23]. It is proved that the PCM model correctly major the solvent effects [24]. The standard Gauge-Independent Atomic Orbital (GIAO) approach was used in calculating the magnetic isotropic shielding tensors (σ) of atomic nuclei [25]. The isotropic chemical shifts δ of aripiprazole and its iodinated form were obtained with respect to the reference tetramethylsilane ($Si(CH_3)_4$) through $\delta_{iso}(X) = \sigma_{TMS}(X) - \sigma_{iso}(X)$ formulae, where δ_{iso} is the isotropic chemical shift and σ_{iso} isotropic shielding constant. Their corresponding predicted chemical shifts were obtained using the equation $\delta_{exp}=a\delta_{cal}+b$, where $\delta_{cal}=\delta_{iso}$. The electronic properties of aripiprazole and its iodinated form were calculated at the same level of theory based on the differences between their HOMO and LUMO energies [17]. To determine the favorable nucleophilic atomic site in the parent molecule aripiprazole, Fukui indices of the electrophilic attack were calculated using the following formulae [26]:

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

where $q_k(N)$ and $q_k(N-1)$ are the electronic populations of the atom k in neutral and cationic forms of aripiprazole, respectively. N is the total number of electrons in aripiprazole. The Fukui functions are the key to region selectivity indicators for electron-transfer controlled reactions [26]. DFT calculations were performed using the Gaussian09 package [22].

3. RESULTS AND DISCUSSION

3.1. NMR Spectroscopy

The synthesized iodinated aripiprazole is characterized *via* ^{1}H NMR in conjunction with mass spectrometry and elemental analysis methods [17]. The experimental chemical shifts of the aripiprazole and its iodinated form were recorded in deuterated DMSO, where TMS was used as an internal standard (Table **1**). Their corresponding predicted chemical shifts were obtained at the B3LYP/Lan2DZ within the GIAO method in PCM phases (Table **1**, Fig. **1** and Scheme **1**). The predicted chemical shifts of the iodinated aripiprazole were calculated by considering (i) monosubstitution of both aromatic rings (C5, C6, C8, C20, C21, and C22 positions) in aripiprazole; and (ii) disubstitution of the aromatic ring of dihydroquinolin-2(1H)-one in aripiprazole (Table **1**, Fig. **1** and Scheme **1**). The experimental spectra of aripiprazole and its iodinated form displayed similar behavior and almost identical peaks. Relatively, good correlations were obtained between the experimental and predicted chemical shifts for both mono and disubstituted aromatic rings of aripiprazole by iodine with R^2 higher than 99% (Table **1**). Further, the mean average deviation values between the experimental and predicted chemical shifts for both mono and disubstitutions by iodine have slightly differed with variation less than 0.07 ppm (Table **1**). Hence, the correlation coefficients and MAE values may not help in determining the probable aromatic nucleophilic sites for the electrophilic substitution of aripiprazole by the iodine. However, by comparing the effect of the iodination on the proton chemical shifts of both aromatic rings, it appears that the iodination induces a strong upfield of the chemical shifts of protons of dihydroquinolin-2(1H)-one with a maximal deviation of 0.71 ppm, while it slightly affected the proton chemical shifts of the benzene ring with a maximal deviation less than 0.12 ppm. Therefore, the mono-substitution of the benzene ring by the electrophilic substitution maybe not consider further. This result is in accordance with the fact that the electron-donating substituents activate the benzene ring toward electrophilic attack, and electron-withdrawing substituents deactivate the ring (make it less reactive to electrophilic attack)". When the electrophile (I^+) attacks aripiprazole, it could be either directed toward dichlorophenyl or benzene ring fuzed to lactam. In

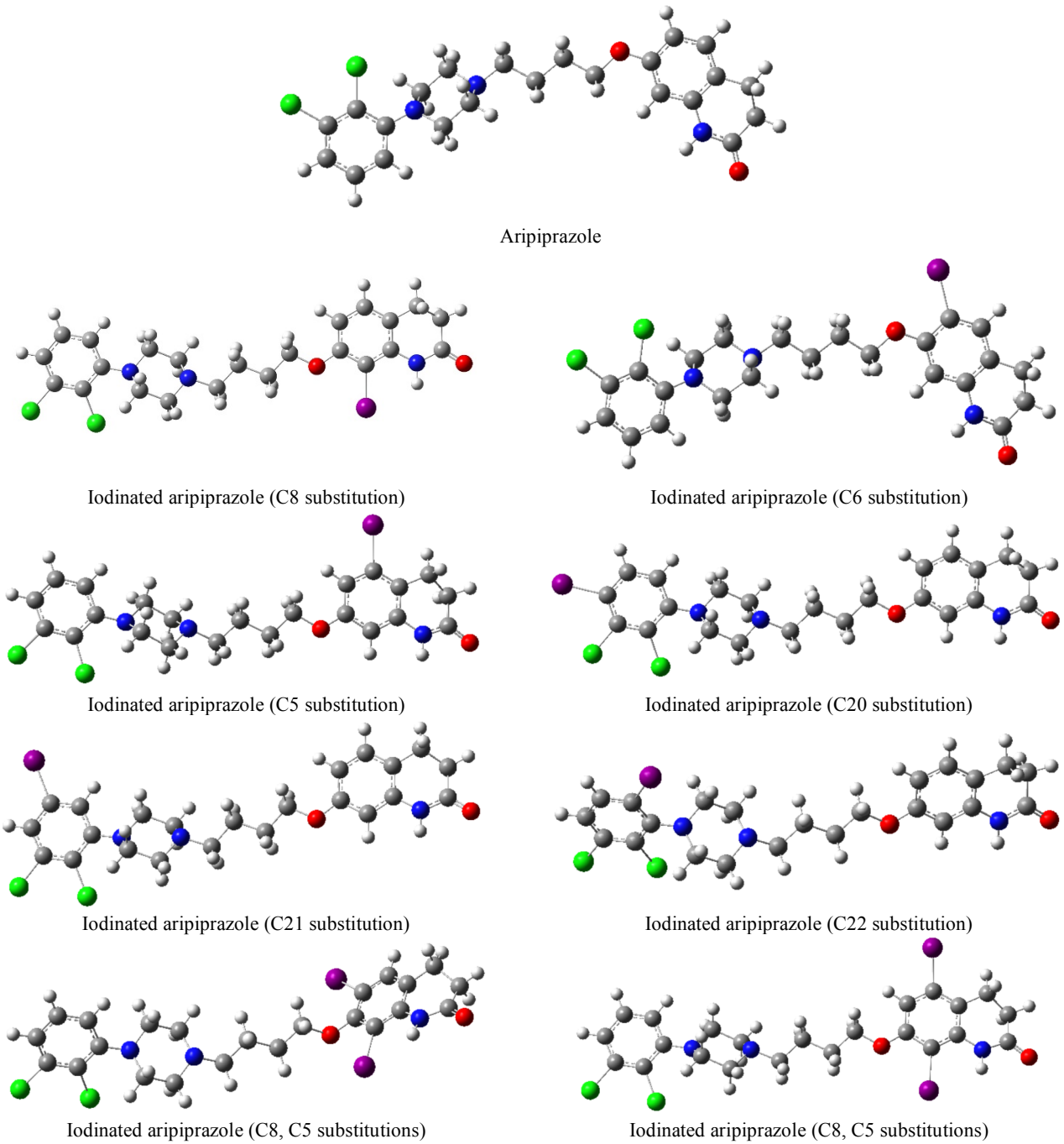


Fig. (1). The optimized structures of (up) and its iodinated form (bottom) obtained at the B3LYP/Lan2DZ level of theory.

the benzene ring fuzed to lactam moiety, both oxygen (CH_2O) and nitrogen (NH) groups (activating groups) can donate electron density to the *pi* system, which substantially enhances the stability of the cationic intermediate. In this case, the electrophilic aromatic substitution occurs more readily compared to the dichlorophenyl moiety, causing the incoming electrophile to attach to the benzene ring. Whereas, in the dichlorophenyl moiety, halogen atoms show deactivating characteristics. Due to their high electronegativities, halogen atoms also tend to remove electrons from the benzene ring. These conflicting properties make halogens a weak ortho-para director and also a ring deactivator. Even, the correlation between the experimental chemical shifts of the iodinated aripiprazole and the predicted ones of disubstituted aripiprazole is relatively good with R^2 of 99.5%, the disubstitution is not observed experimentally. Indeed, the mass spectral analysis clearly showed the presence of a molecular ion peak at m/z 573, which confirmed the presence of one iodine group in the iodinated aripiprazole. This result is supported by the HPLC, which reveals the monosubstitution of the aripiprazole (Fig. **2**). Indeed, three peaks appear in HPLC chromatograms that correspond to NaI, aripiprazole, and ^{Nat}I-aripiprazole with retention times of 1.35, 4.4 and 5. 5 min, respectively (Fig. **2**). The CH_2O and nitrogen (NH) groups direct the iodine electrophilic substitution to the ortho and para position. Thus one can easily exclude the meta position of dihydroquinolin-2(1H)-one as a probable nucleophile atomic site. This result is incoherent with the slight upfield of the H5 chemical shift (0.12 ppm) compared with the one of the H6/H8 proton chemical shift (0.71 ppm). As detailed in the DFT section, C8 as a favorable position of the electrophilic attack. For further NMR discussion, we consider that the iodine is substituted at the C8 position (Fig. **1** and

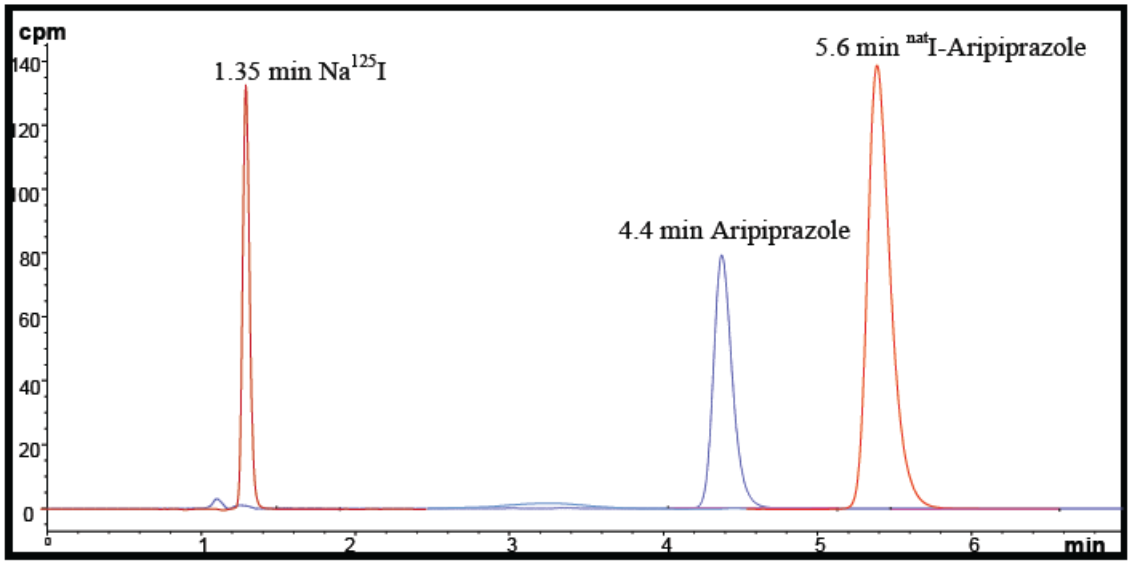


Fig. (2). Chromatogram of aripiprazole and ^{nat}I-aripiprazole. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

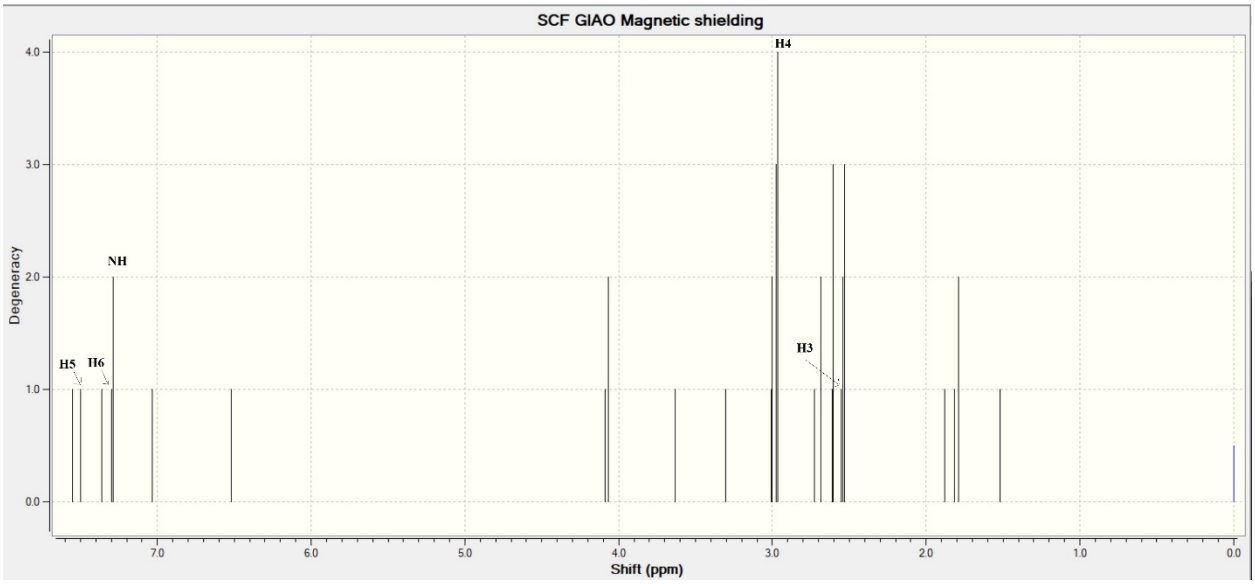


Fig. (3). Calculated ^{1}H NMR spectrum of aripiprazole obtained at the B3LYP/Lan2DZ within the GIAO method in the PCM phase. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

scheme **1**). The calculated ^{1}H NMR spectra of aripiprazole and its iodinated forms obtained at the B3LYP/Lan2DZ within the GIAO method in PCM phase are shown in Figs. (**3**) and (**4**). ^{1}H NMR chemical shifts of H3 and H4 of the aripiprazole were observed at 2.49 and 2.86 ppm, respectively (Table **1**, Fig. **1** and Scheme **1**). These chemical shifts were not influenced by the iodination substitution (Table **1**). Their corresponding predicted ones in the PCM model were well reproduced with variations of 0.04 and 0.08 ppm with respect to the experimental ones, respectively. The influence of the iodination substitution on ^{13}C-NMR chemical shifts of the probable nucleophilic atomic sites in aromatic rings of aripiprazole is investigated by calculating the chemical shifts their corresponding chemical shift before and after iodine substitution (Table **2**). The iodination induces a downfield shift of the chemical shifts of the substituted carbons of both rings of aripiprazole. It is worth to mention that in both mono and disubstituted cases, C8 chemical shift of dihydroquinolin-2(1H)-one of aripiprazole is strongly shifted compared with C5 and C6 ones (Table **2**).

3.2. Electrophilic Substitution of Aripiprazole: DFT Analysis

The iodination of aripiprazole is an electrophilic aromatic substitution. Based on ^{1}H NMR results, the electrophilic substitution was favorable at C8/C6 of the aromatic ring 3,4-dihydroquinoline-2(1H)-one in aripiprazole (Scheme **1**). To determine the favorable nucleophilic site of iodine electrophilic attack, the nucleophilicity of atomic sites of aromatic ring 3,4-dihydroquinoline-2(1H)-one in aripiprazole were calculated (Table **3**). The electrophilic attack is likely favorable in the nucleophilic site with the highest Fukui index value. The higher the value of Fukui function f_k^-, the greater was the probability of electrophilic attack at site k. Langenaeker *et al.,* [9] calculated Fukui functions of a series of *mono*-substituted benzenes and showed that the electrophilic substitution was favorable for the *para* position followed by *meta* and *ortho* positions. Form the nucleophilic indices of atomic sites of the aromatic ring in 3,4-dihydroquinolin-2(1H)-one in aripiprazole calculated based on Mulliken atomic charges, it appears that the C8 is the favorable site of the

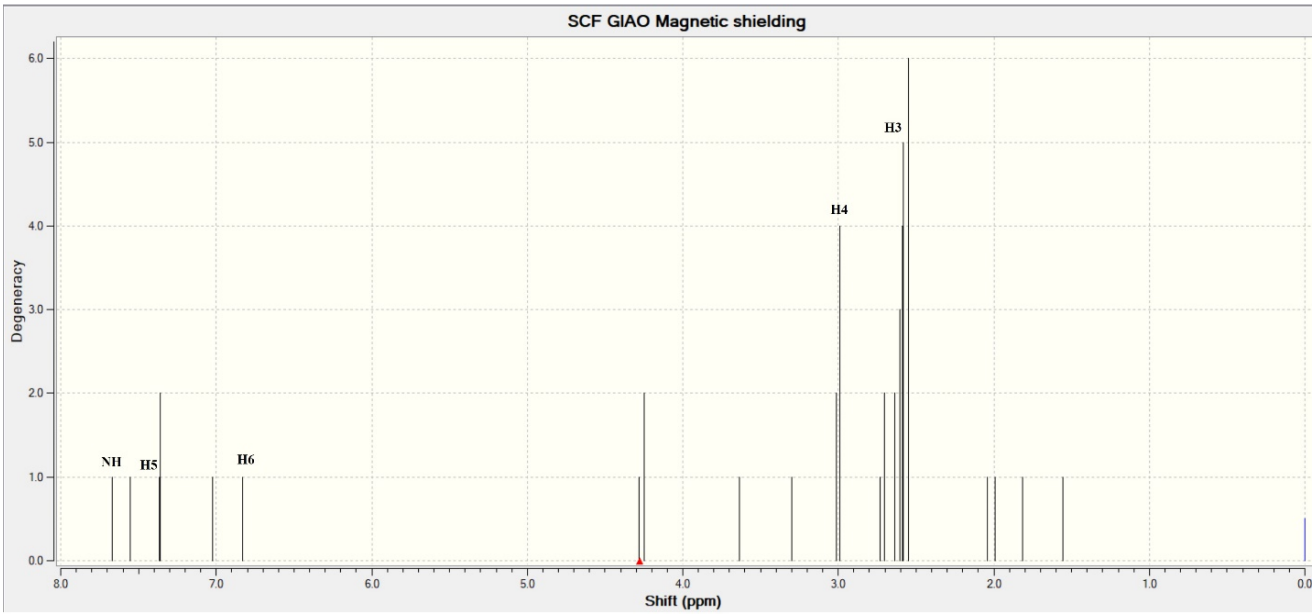


Fig. (4). Calculated ^{1}H NMR spectrum of the iodinated aripiprazole obtained at the B3LYP/Lan2DZ within the GIAO method in the PCM phase.

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

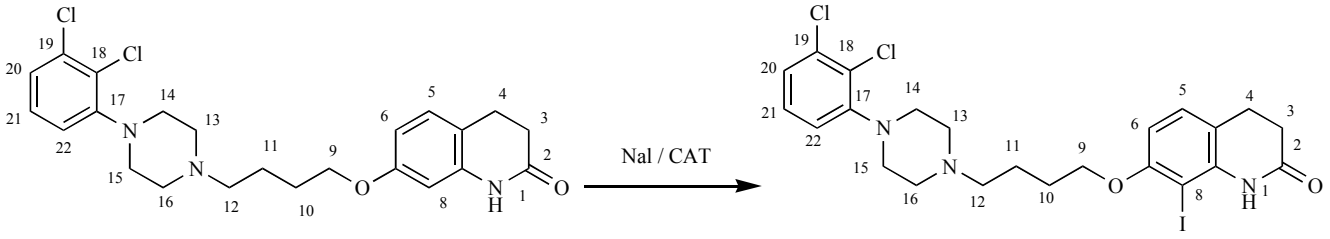
Aripiprazole			Iodinated Aripiprazole								
			Predicted								Exp
	Pred	Exp	C5	C6	C8	C20	C21	C22	C8C6	C8C5	
H3	2.53	2.49	2.60	2.58	2.62	2.49	2.65	2.49	2.55	2.49	2.49
H4	2.94	2.86	2.87	2.69	3.01	2.86	2.74	2.86	2.70	2.86	2.86
H5	7.45	7.30	-	7.60	7.19	7.15	7.42	7.15	7.40	-	7.15
H6	7.25	7.16	6.79	-	6.68	6.45	6.75	6.45	-	6.45	6.45
H8	6.48	6.88	6.82	6.48	-	7.31	6.90	7.31	-	-	-
H9	4.06	4.06	4.06	4.23	4.21	4.06	4.10	4.06	4.22	4.06	4.06
H10	1.86	1.76	1.89	2.03	2.10	1.99	1.92	1.99	2.03	1.99	1.99
H11	1.77	1.76	1.79	1.83	1.88	1.76	1.83	1.76	1.78	1.76	1.76
H12	2.58	2.76	2.60	2.64	2.67	2.76	2.63	2.76	2.62	2.76	2.76
H13	2.98	3.01	3.00	3.01	2.59	3.01	2.97	3.01	3.00	3.01	3.01
H14	3.60	3.44	3.63	3.62	3.30	3.44	3.57	3.44	3.58	3.44	3.44
H20	7.31	7.3	7.31	7.32	7.19	-	7.31	7.36	7.16	7.36	7.36
H21	7.51	7.42	7.49	7.51	7.37	7.3	-	7.3	7.35	7.3	7.30
H22	6.99	7.1	6.98	6.99	6.87	7.04	6.88	2.49	6.84	7.04	7.04
MAE	0.10	-	0.13	0.19	0.15	0.16	0.15	0.19	0.12	0.10	-
Max. Dev	0.40	-	0.49	0.83	0.42	0.46	0.41	0.48	0.25	0.24	-
Min. Dev	0.00	-	0.00	0.00	0.04	0.01	0.04	0.01	0.01	0.01	-
R^2 (%)	99.6	-	99.4	99.6	99.2	99.1	99.3	98.8	99.6	99.6	-

Ci = Substitution of iodine position in aripiprazole; CiCj = disubstitution of iodine positions in aripiprazole.

electrophilic attack with a f_K^- of -0.52. However, by considering the natural atomic charge in calculating Fukui indices, it appears that C6 was the favorable atomic site of an electrophilic attack with a Fukui index of -0.04.

3.3. Molecular Electrostatic Potential

In addition to Fukui indices, the electrostatic potential (ESP) may help in determining electrophilic and nucleophilic attack sites [27-28]. To predict the reactive nucleophilic sites for the



Aripiprazole **Iodinated Aripiprazole**

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

Table 2. Calculated 13C-NMR chemical shifts (ppm) for aripiprazole carbons before and after iodination substitution in PCM solvent obtained at the B3LYP/Lan2DZ of theory.

	Chemical shift, δ (ppm)		Δδ (ppm)
	Before substitution	After Substitution	
Monosubstitution			
C5	135.19	149.67	14.48
C6	116.42	126.93	10.50
C8	105.01	122.73	17.72
C20	126.50	136.98	10.47
C21	133.95	145.81	11.86
C22	126.48	151.77	25.29
Disubstitution			
C8 and C5			
C5	135.19	150.01	14.82
C6	116.42	120.63	4.21
C8	105.01	124.41	19.40
C8 and C6			
C5	135.19	142.64	7.45
C6	116.42	137.15	20.72
C8	105.01	133.92	28.91
MAE	-	-	15.49
Max. Dev	-	-	28.91
Min. Dev	-	-	4.21

Ci = Substitution of iodine position in aripiprazole; CiCj = disubstitution of iodine positions in aripiprazole.

electrophilic attack in aripiprazole, the ESP surface was obtained at the B3LYP/ LanL2DZ level of theory from the starting optimized geometry of aripiprazole (Fig. **5**). Generally, the negative (red to yellow) regions in ESP were related to the electrophilic attack, while the positive (blue) ones correspond to the nucleophilic attack. As can be seen from the ESP plot (Fig. **5**), the density region around C8 was approached to the yellow color, while for C5 and C6 atoms its approach to the blue color. That means that the position C8 was more favorable for an electrophilic attack. In order to make it more obvious, the ESP charges of corresponding atoms of dihydroquinoline-2(1H)-one were calculated (Fig. **5**). The atomic site C8 has the highest negative ESP charge of -0.58 in 3,4-dihydroquinoline-2(1H)-one compared with C6 of -0.27. This confirmed that the C8 is the most probable site of an electrophilic attack and hence the formation of the substituted iodinated aripiprazole.

3.4. Electronic Properties of Aripiprazole and its Iodinated Form

The calculated electronic properties of aripiprazole and its iodinated form were displayed in Table **4**. The calculated solvation energy of aripiprazole and its iodinated form in DMSO were -14.80 and -14.28 kcal/mol. These values indicated that these dissolution of aripiprazole and its iodinated form were favorable processes in DMSO. The calculated permanent dipole moment (μ) of aripiprazole and its iodinated from in DMSO were 1.29 and 9.68 Debye, respectively. These values demonstrated that both systems were polar and the polarity increased in iodinated form due to the presence of iodine. The high value of the dipole moment of iodinated aripiprazole indicated its relative capacity to polarize vicinity systems. The calculated gap energies of aripiprazole and its iodinated form in the PCM phase were 4.82 and 4.60 eV,

Table 3. Nucleophilic Fukui indices of main heavy atoms of aripiprazole calculated at the B3LYP/LanL2DZ level of theory by considering Mulliken and Natural atomic charges.

	Mulliken Atomic Charges			Natural Atomic Charges		
	$q_k(N)$	$q_k(N-1)$	f_K^-	$q_k(N)$	$q_k(N-1)$	f_K^-
C3	-0.435	0.003	-0.44	-0.497	-0.500	0.003
C4	-0.502	-0.007	-0.49	-0.429	-0.436	0.007
C5	-0.382	-0.042	-0.34	-0.189	-0.188	0.000
C6	-0.395	0.093	-0.49	-0.256	-0.218	-0.039
C8	-0.534	-0.009	-0.52	-0.330	-0.332	0.003

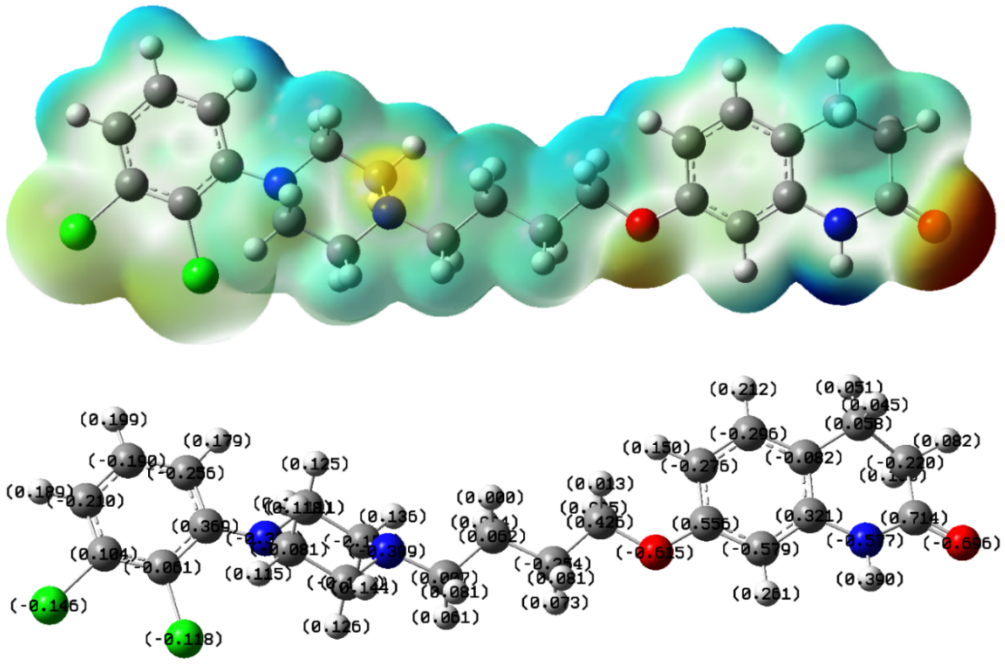


Fig. (5). Electrostatic potential (up) and ESP charges (bottom) of aripiprazole obtained at the B3LYP/LanL2DZ level of theory. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

respectively. These values indicated that aripiprazole was less reactive than its iodinated form. The gap energy was found to be directly proportional to the stability and inversely proportional to the reactivity of the system. Aripiprazole and its iodinated form have similar IP values with a difference of 0.01 eV. However, the EA of iodinated aripiprazole is higher than that of aripiprazole, which indicated the higher tendency of the former to accept electron than the latter. The lower is the ionization potential, the easier the molecular system loses electrons, while the greater is the electronic affinity, the easier the tendency of a molecular system to take electrons. The values of hardness and electronegative of aripiprazole and its iodinated form indicated the higher ability of the latter to attract electron and to resist to charge transference than the former [29].

3.5. Reactivity of Aripiprazole with Iodine and Bromine Electrophiles

Table **5** displayed the calculated free Gibbs energies reactions (ΔG) of the reactivity of aripiprazole from one side, and the iodine and bromine electrophiles from another side. The iodo/bromo electrophilic aromatic substitution of the starting material aripiprazole may lead to the formation of mono or disubstituted aripiprazole derivatives. The calculated ΔG may be used as a sign spot in determining the most probable possibilities, *i.e.*, mono or disubstitution of the starting material as well as the most favorable aromatic substitution sites. According to ΔG values in Table **5**, it appears that the formation of disubstituted iodine requires more energy than the formation of monosubstitution aripiprazole. For instance, diiodine substitution at C5 and C8 atoms require an energy of 314 Kcal/mol, while monusubstitution of C5 and C8 requires an energy of 155.12 and 156.40 Kcal/mol, respectively. Indeed, the probability of aripiprazole monosubstitution is in accordance with mass spectral analysis, elemental analysis and ^{1}H-NMR of the iodinated aripiprazole. ΔG values of the electrophilic bromine substitution confirm that the aromatic monosubstitution of aripiprazole is more favorable than the electrophilic disubstitution (Table **5**). Similarly, ΔG values may be used in determining the favorable monosusbtition site. For both iodo and bromo substitution, it appears that C5, C6 and C6 are the most probable sites for electrophilic monosubstitution (Table **5**).

CONCLUSION

The aromatic electrophilic iodination of aripiprazole was investigated by means of DFT calculations at the B3LYP/LanL2DZ level of theory in the polarizable continuum model (PCM). Iodinated structure was confirmed by comparing the predicted and experimental ^{1}H NMR chemical shifts, which showed a correlation coefficient higher than 99%. Furthermore, the most favorable

Table 4. Electronic properties of aripiprazole obtained at the B3LYP/LanL2DZ level of theory.

Properties	Aripiprazole	Iodinate aripiprazole
Ionization potential (eV)	5.76	5.77
Electron affinity (eV)	0.94	1.17
Electronegativity	3.35	3.47
Hardness	4.82	4.60
Softness	0.10	0.11
Electrophilicity	1.16	1.31
Gap energy (eV)	4.82	4.60
Isotropic polarizability ($Bohr^3$)	372.07	402.6

Table 5. Free Gibbs energies (Kcal/mol) of the reactivity of aripiprazole with iodine and bromine electrophiles and considering the formation of mono and disubstituted aripiprazole derivatives.

	Monosubstitution					
	C5	**C6**	**C8**	**C20**	**C21**	**C22**
Mono-Iodoaripiprazole	155.12	154.73	156.40	157.77	154.33	160.99
Mono-Bromaripiprazole	116.94	118.44	119.78	121.15	117.98	123.63
	Di-substitution					
	C5C8	C8C8				
Mono-Iodoaripiprazole	312.04	314.52	-	-	-	-
Mono-Bromaripiprazole	238.98	241.53	-	-	-	-

nucleophilic site for an electrophilic attack was explored by calculating the nucleophilic indices of heavy atoms and electrostatic potential (ESP) of aripiprazole. Finally, the electronic properties of iodinated aripiprazole were calculated and compared with aripiprazole. The results showed the higher reactivity of iodinated aripiprazole compared with aripiprazole. Free Gibbs energies of the reactivity of aripiprazole with iodine and bromine reveal that the electrophilic is monosubstitution rather than disubstitution in good agreement with the experimental mass spectrum analysis, elemental analysis and ^{1}H-NMR of the iodinated aripiprazole.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The data supporting the findings of the article is presented in the materials and methods section.

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CONFLICT OF INTEREST

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

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