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1H and 13C NMR Investigation of Quinoline Pharmaceutical Derivatives: Interpretation of Chemical Shifts and their Comparison with the Experimental Value

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Abstract

In this paper, 1H and 13C chemical shift values have been calculated for the optimized structures of the quinoline pharmaceutical derivatives of compounds by theoretically method and compared to the experimental chemical shift values. Theoretically chemical shifts values were determined at GIAO HF/6-31++G(d,p) level of theory by Gaussian 09 program and are fully interpreted. Highest frequency are observed for the nitrogen, Oxygen and chlorine substitutions occurring in ipso carbons and also on nitrogen heteroatom occur at ortho and para positions in heterocyclic carbons and Hydrogen attached to them. The aliphatic Hydrogen at high frequency for the Hydrogen attached on Carbon adjacent to Oxygen, Nitrogen and carbons include double bond. The correlation analysis of the calculation and experimental data was performed in order to quantify the disagreement.

Keywords: ***NMR; Quinoline; Computational; Comparison; Chemical shift***

Introduction

The use of heterocyclic compounds in our lives is irrefutable. So there is a growing request for heterocyclic compounds, and this has incited research activities in the field of heterocyclic compound chemistry. Amongst the wide diversity of heterocyclic compounds, those containing the nitrogen atom are usual in nature, and their biological usage distinguishes them [1]. Quinoline and its derivatives have evermore engrossed both biological and synthetic chemist due to its various pharmacological and chemical attributes [2]. 1,10-Phenanthroline (**FIG. 1**) has been widely used for decades as a chemically Multipurpose module displaying a good combination of structural and chemical attributes. 1,10-phenanthroline derivatives provided the development of sophisticated synthetic strategies that have yielded fascinating molecular architectures. Remarkable, some of these systems can be designed to work as molecular-level machines. Another capacity of 1,10- phenanthroline is connected to its Flat structure, that prompts intercalation or binding with DNA or RNA [3]. Chloroquine (**FIG. 2**) was introduced in the 1940s and quickly became the mainstay of treatment and

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prevention because it was inexpensive and nontoxic and malaria parasites were generally susceptible to it [4]. Cinchocaine (**FIG. 3**) is a member of a category of drugs known as local anesthetics [5]. Imiquimod (**FIG. 4)** have been shown to have attributes as immune response modifiers in vitro and in vivo, and display antiviral and antitumor activity via endogenous cytokine production [6]. Nitroxoline (**FIG. 5**) is an antibiotic, which does not belong to any known antimicrobial class and is used as a urinary antibacterial agent, active against oversensitive Gram-positive and Gram-negative bacterial strains that generally exist in urinary tracts and cause infections [7]. Primaquine (**FIG. 6**) is the only 8-aminoquinoline which is extensively employed as an antimalarial drug [8]. Proflavine (**FIG. 7**) is the prototype of DNA-intercalating aminoacridines and is a planar polyaromatic chromophore that is mono-protonated in the physiological situation [9]. Quinine and quinidine, two cinchona alkaloids so freely provided by Nature, are not only important pharmacological drugs,' but their contribution to chemistry certainly deserves respect [10]. Quinine (**FIG. 8**) and quinidine (**FIG. 9**) have been used widely in the medical profession as antimalarial and antiarrhythmic drugs, respectively [11]. Tacrine (**FIG. 10**) is the first factor approved by the Food and Drug Administration for the treatment of Alzheimer's disease and has been extensively employed in the infirmary. Tacrine acts as an acetylcholinesterase inhibitor blocking the degradation of acetylcholine in neurons of the cerebral cortex thereby increasing cholinergic transmission [12]. Of the specific importance of NMR studies has been the use of various multidimensional sequences of NMR programs to define the detailed molecular structure. The standard NMR experiences are enough to obtain a perfect assignment of organic compounds, and efficient to obtain molecular structure information [13]. NMR chemical shifts, however, depend on the electronic environment of the nucleus studied. This gives us the unique leisure to quantify the effect of the packing on the chemical shifts in such a complex system [14]. This Presentation is a theoretical study of NMR magnetic shielding spectra of quinoline pharmaceutical derivatives. Presented here is calculated 13C and 1H isotropic NMR chemical shifts for 1,10-Phenanthroline, Chloroquine, cinchocaine, Imiquimod, Nitroxoline, Primaquine, Proflavine, Quinine, quinidine, and Tacrine. The optimized geometrical parameters of quinoline pharmaceutical derivatives which are calculated by HF methods with 6-31++G(d,p) basis sets are consistent with the atom numbering scheme.1H and 13C chemical shift values have been calculated for the optimized structures of the quinoline pharmaceutical derivatives of compounds and compared to the experimental chemical shift values.

Materials and Methods

Ab initio NMR calculations are now attainable and accurate enough to be useful in exploring the relationship between chemical shift and molecular structure. Study on quinoline derivatives the structural formula of the drug. Using the structure molecules were using the software Gauss view drawing. The program Gaussian optimized structures at the beginning of the Gauss view software structure was obtained as a Gaussian input. In general, studies on 10 cases of selected derivatives of quinolines that the computational method ab initio with the level of computational HF calculations with 6-31++G(d,p) basis sets. This basis set was chosen since it had been successfully used in the study of NMR chemical shielding tensors. The term, σ is a second rank tensor called NMR chemical shielding tensor whose elements describe the size of chemical shielding as a function of molecular orientation with respect to the external magnetic field. The isotropic chemical shielding σiso parameters can be related to the principal components by the following equation:

$$\sigma_{iso} = (\sigma 11 + \sigma 22 + \sigma 33)/3$$

and the chemical shift to note is the Isotropic value. To convert the shifts to ppm subtract the isotropic value from the isotropic chemical shift of the protons in TMS:

$$\delta_i\,(ppm) = isotropic(TMS) - isotropic(i)$$

Results and Discussion

In this work, we study magnetic properties of atomic nuclei to determine properties of atoms in the titled compound by NMR spectroscopy. Ab initio calculation of nu0063lear magnetic shielding has become an aid for the analysis of molecular structure. So, NMR is based on the quantum mechanical property of nuclei. Based on NMR study, calculated magnetic shielding tensor (σ, ppm), magnetic shielding anisotropy (σaniso ppm), and chemical shift (δ) were calculated. These results are, listed in **TABLES 1-20**. On the other hand, experimental 13C and 1H NMR data have been extracted from previous research and Along with referrals are presented in **TABLES 1-20** too. Experimental and computational data were compared and full explanations were given on NMR shifts. As can be seen in **FIG. 1**, the molecular structure of the 1, 10-phenanthroline includes tree aromatic ring. It is a heterocyclic compound with five carbon and one nitrogen atoms in the hetero rings. The study of Chloroquine shows 13 different carbon atoms, which is consistent with the structure on the basis of molecular symmetry. It includes two aromatic rings. The molecular structure of the Cinchocaine includes two aromatic ring, the studied molecule shows 20 different carbon atoms, which is consistent with the structure on the basis of molecular symmetry. So the study of Imiquimod shows 14 different carbon atoms, which is consistent with the structure on the basis of molecular symmetry. it includes three aromatic rings. The molecular structure of the Nitroxoline includes two aromatic ring and molecular structure of the Primaquine includes two aromatic ring and the molecular structure of the Proflavine includes tree aromatic ring. it is a heterocyclic compound with 13 carbon, two NH2 and substitutions and one nitrogen atoms in the hetero rings. The molecular structure of the Quinidine includes two aromatic ring and molecular structure of the Quinine includes two aromatic rings. The study of molecule shows 13 different carbon atoms, which is consistent with the structure on the basis of molecular symmetry. The molecular structure of the Tacrine includes two aromatic and one aliphatic rings. Results of all of the compounds show the calculated and experimental values are comparable. There is an excellent agreement between the experimental and theoretical data. We present here the chemical shifts for each compound and we try to present a complete interpretation based on its structure. Let's start with 1, 10-phenanthroline. Chemical shifts of it are given in **TABLE 1 and 2**.

TABLE 1. **Theoretical and experimental values of chemical shift)^{13}c NMR(and the difference between of 1,10 phenanthroline [15].**

Atom	δtheo	δExp	Δδ
1	129.52	147.42	17.9
3	130.48	151.24	20.76
4	100.45	124.43	23.98
5	117.97	137.24	19.27
6	108.16	130.12	21.96
7	104.88	127.96	23.08
8	104.91	127.96	23.05
9	108.14	130.12	21.98
10	129.63	147.42	17.79

11	117.97	137.24	19.27
12	100.46	124.43	23.97
13	130.35	151.24	20.89

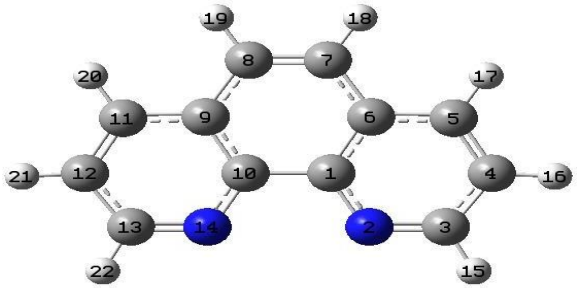

FIG. 1. **The structure of optimized 1,10 Phenanthroline.**

The aromatic carbon in 13C NMR spectra usually locates in the range of 110–135 ppm. As a rule, Ortho-carbon chemical shifts (C1=147.42, C3=151.24, C10=147.42, C13=151.24) oxygen and nitrogen containing rings is further to the left than Meta carbon chemical shifts (C4=124.43, C6=130.12, C9=130.12, C12=124.43) due to Ortho-carbon lower electron density Caused by the high electro-negative of N heteroatom. data for all 12 aromatic carbons for which experimental data are available. It can be seen that the calculated results are comparable. There is excellent agreement with the experimental data. Even though all of the carbons are aromatic, the range of 006Eearly 100 ppm is about half of the total 13C NMR chemical shift range. The prediction of chemical shifts to this accuracy is remarkable, considering that solvent effects were not considered.it can be seen that the aromatic carbons at highest frequency are those in the range of 130-152 ppm for the ortho and para of the N heteroatom (C1, C3, C10, C13, C11 and C5)

Calculated results for all carbons are greater by averages of 20 ppm if polarization functions are included. There are also clear trends in the calculated 13C NMR chemical shifts. All of the 13C NMR chemical shifts in **TABLE 1** for the Theoretical shift are lesser than those experimental data. calculations underestimate the 13C NMR chemical shifts at ortho and para carbons of N heteroatom.

TABLE 2. **Theoretical and experimental values of chemical shift)^{1}H NMR(and the difference between of 1,10 Phenanthroline [15].**

Atom	δ_{theo}	δ_{Exp}	$\Delta\delta$
15,22	9.0762	9.17	0.0938
17,20	8.2974	8.45	0.1526
19,18	7.62435	7.98	0.35565
16,21	7.4327	7.77	0.3373

As in **TABLE 2**, the presence of four peaks in 1H NMR spectra suggests that there are four distinct types of protons in 1, 10-phenanthroline. Normally, the protons on phenyl ring are expected to yield NMR signals in the 1H NMR range of 6–8 ppm. The electronegative property of the N heteroatom causes a decrease in shielding constants around the ortho protons connected to C3 and C13. The calculated chemical shifts of 9.0762 ppm are ascribed to these two hydrogen

atoms. Para protons connected to C5 and C11 behave similarly. The calculated chemical shifts of 8.2974 ppm are ascribed to these two hydrogen atoms. The second drug we are examining is Chloroquine. Chemical shifts of it are given in **TABLE 3 and 4**.

TABLE 3. **Theoretical and experimental values of chemical shift)^{13}C NMR(and the difference between of chloroquine [16].**

Atom	δtheo	δExp	Δδ
8	138.6032	154.8	16.1968
12	134.3873	142	7.6127
3	133.5483	138.9	5.3517
1	121.2667	137.6	16.3333
2	109.704	126.9	17.196
5	107.3318	118.5	11.1682
6	103.6583	123.8	20.1417
4	101.777	114.6	12.823
11	89.2534	98.5	9.2466
19	30.8767	47.1	16.2233
29	30.7723	51.1	20.3277
42	23.2405	49.4	26.1595
35	18.7263	49.4	30.6737
25	13.1495	31.8	18.6505
26	6.3769	20.2	13.8231
20	2.3083	18.6	16.2917
36	-3.8914	8	11.8914
43	-11.5089	8	19.5089

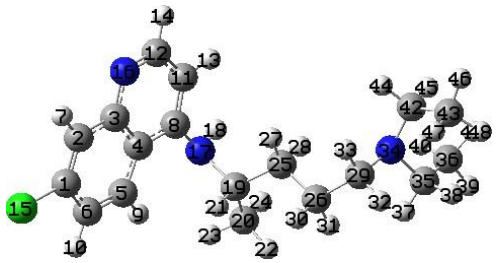

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FIG. 2. **The structure of optimized chloroquine.**

One of Chloroquine`s (**FIG. 2**) rings includes nitrogen atom which shows the electronegative property. On the other side, nitrogen atom substitute shows more electronegative property than chloride atom substitute. Therefore, it can be seen that the aromatic carbons at highest frequency are those in the range of 142-155 ppm for the ipso and meta (C1, C3, C8, and C12) carbons of the NH group. Also, it can be seen that the aliphatic carbons at highest frequency are those in the range of 49-48 ppm for the attached (C19, C29, C35, and C42) carbons of the N atoms. data for all nine aromatic carbons for which experimental data are available. It can be seen that the calculated results are comparable. There is excellent agreement with the experimental data. Even though all of the carbons are aromatic, the range of nearly 100 ppm is about half of the total ^{13}C NMR chemical shift range. The prediction of chemical shifts to this accuracy is remarkable, considering that solvent effects were not considered.it can be seen that the aromatic carbons at highest frequency are those in the range of 130-160 ppm for the ortho and para of the N heteroatom (C3, C8, and C12)

and ipso of Subordinate (C1) carbons. Calculated results for all carbons are greater by averages of 20 ppm if polarization functions are included. There are also clear trends in the calculated ^{13}C NMR chemical shifts. All of the ^{13}C NMR chemical shifts in **TABLE 3** for the Theoretical shift are lesser than those experimental data. calculations underestimate the ^{13}C NMR chemical shifts at ortho and para carbons of N heteroatom and the shifts for ipso carbons.

TABLE 4. **Theoretical and experimental values of chemical shift)^{1}H NMR (and the difference between of chloroquine [16].**

Atom	δtheo	δExp	Δδ
14	8.4867	8.1	-0.3867
7	8.1724	7.4	-0.7724
9	8.0405	7.8	-0.2405
10	7.2674	7.3	0.0326
13	6.4088	6.7	0.2912
21	2.5185	3.9	1.3815
45	2.3429	3	0.6571
18	1.8943	3	1.1057
44,37	1.6919	3	1.3081
38,45	1.6023	3	1.3977
33,23	1.36795	3	1.63205
28	1.0591	1.7	0.6409
22,23,24	0.9238	1.1	0.1762
41,31	0.8503	1.1	0.2497
27	0.7654	1.1	0.3346
48,40	0.62775	1.1	0.47225
24,39	0.5492	1.1	0.5508
47	0.36	1.1	0.74
46,30	-0.01655	1.1	1.11655

The methyl and methylene protons of –NH–CH_2–CH_3 group in Chloroquine showed signals at 3.9 ppm and 1.1 ppm (H21, H22, H23, H32 and H24, Respectively) integrating for three and two protons respectively in its ^{1}H NMR spectra. A broad signal at 3.7273 ppm was observed for the – NH– proton of the amino moiety. Presence of singlets at 3.0 ppm and 1.1 ppm integrating for two protons in ^{1}H NMR of $N(CH_2\text{-}CH_3)_2$ (H37, H38, H44, H45 and H39, H40, H41, H46, H47, H48 respectively). The electronegative property of the N heteroatom causes a decrease in shielding constants around the ortho protons connected to C12. The calculated chemical shifts of 8.4867 ppm are attributed to this hydrogen atom. In this study the third drug is Cinchocaine. Chemical shifts of it are given in **TABLE 5 and 6**.

TABLE 5**. Theoretical and experimental values of chemical shift)^{13}C NMR(and the difference between of cinchocaine [5].**

Atom	δtheo	δExp	Δδ
30	147.3312	167	19.6688
13	140.3558	161.5	21.1442
9	132.7935	147.2	14.4065
3	130.1242	145.1	14.9758
1	112.5122	129.8	17.2878
5	108.9804	125.3	16.3196
2	107.0759	127.5	20.4241
6	101.823	124.5	22.677
4	100.0413	121.5	21.4587
12	89.1233	111.2	22.0767
17	41.7184	65.9	24.1816
35	30.3526	51.2	20.8474
41	26.5909	46.6	20.0091
48	24.5595	46.6	22.0405
34	19.8895	37.4	17.5105
18	11.6443	31	19.3557

21	0.1684	19.3	19.1316
42	-2.484	11.8	14.284
49	-2.5654	11.8	14.3654
24	-3.3412	13.9	17.2412

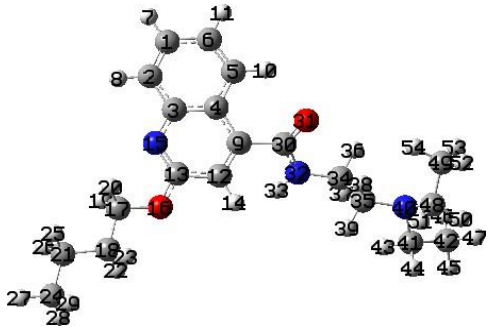

FIG. 3. **The structure of optimized cinchocaine.**

The structure of cinchocaine (**FIG. 3)** shows one of two rings include nitrogen atom which has electronegative property. In **TABLE 5** it can be seen that the signal at 145.1 ppm is assigned to the C3 on account of the strong electronegative property of the N hetero atom. data for all 13 aromatic carbons for which experimental data are available. It can be seen that the calculated results are comparable. There is excellent agreement with the experimental data. Even though all of the carbons are aromatic, the range of nearly 100 ppm is about half of the total ^{13}C NMR chemical shift range. The prediction of chemical shifts to this accuracy is remarkable, considering that solvent effects were not considered. There are also clear trends in the calculated ^{13}C NMR chemical shifts. All of the ^{13}C NMR chemical shifts in **TABLE 5** for the Theoretical shift are lesser than those experimental data. calculations underestimate the ^{13}C NMR chemical shifts at ortho and para carbons of N hetero atom. The carbon of (C=O) group shows the highest chemical shifts, due to carbon lower electron density Caused by the high electro-negative of (=O) and (N-H) attached groups. Also, it can be seen that the aliphatic carbons at high frequency are those in the range of 37- 66 ppm for the attached carbons of the N-H (C34), N(35, 41, 48) and O (C17) atoms.

TABLE 6. **Theoretical and experimental values of chemical shift)^{1}H NMR(and the difference between of Cinchocaine [5].**

Atom	δtheo	δExp	Δδ
10	8.4281	8.1	-0.3281
8	7.9361	7.84	-0.0961
7	7.6519	7.63	-0.0219
11	7.2681	7.39	0.1219
14	6.6085	6.95	0.3415
19, 20	3.6027	4.47	0.8673
36	3.4563	3.55	0.0937
38	2.4875	2.66	0.1725
37	2.082	3.55	1.468
50	1.7692	2.54	0.7708
43, 44	1.61465	2.54	0.92535
51	1.4526	2.54	1.0874
39	1.3442	2.66	1.3158
22, 23	1.3442	1.81	0.4658
54	1.1522	0.99	-0.1622
25,26	0.82554	1.51	0.68446
27	0.82554	0.99	0.16446
47,53	0.82554	0.99	0.16446
46	0.7245	0.99	0.2655
29,28	0.60515	0.99	0.38485
52,45	0.43865	0.99	0.55135

In **TABLE 6** it can be seen that the aliphatic Hydrogen at high frequency for the Hydrogen attached to carbon connected to Oxygen atom (C17) and N atoms (C34 and C35). Normally, the protons on phenyl ring are expected to yield NMR signals in the $\delta_H$range of 6–8 ppm. Unlike the frequency calculations, the basis set effect is rather significant for chemical shifts. The correlation analysis of the calculation and experimental data was performed in order to quantify the disagreement, and the result is listed in **TABLE 5 and 6**. ^{1}H and ^{13}C chemical shift values have been calculated for the optimized structures of the Cinchocaine compound and compared to the experimental chemical shift values. The fourth drug that was studied was Imiquimod. Chemical shifts of it are given in **TABLE 7 and 8.**

TABLE 7. **Theoretical and experimental values of chemical shift)^{13}C NMR(and the difference between of imiquimod [17].**

Atom	δtheo	δExp	Δδ
12	135.2619	148.2	12.9381
4	129.821	137.13	7.309
16	121.3296	145.85	24.5204
9	116.3767	138.74	22.3633
5	109.7951	124.47	14.6749
6	109.0687	130.41	21.3413
13	106.0072	118.89	12.8828
2	102.0309	121.68	19.6491
1	99.7642	136.19	36.4258
3	93.6592	113.34	19.6808
18	30.8647	60.52	29.6553
19	7.4717	30.63	23.1583
22	0.6284	20.07	19.4416
27	-0.3664	20.07	20.4364

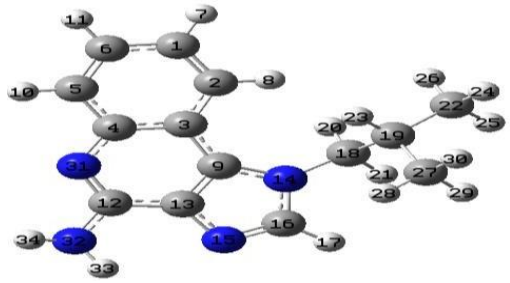

FIG. 4. **The structure of optimized imiquimod**.

These rings include nitrogen atom which shows the electronegative property. On the other side, NH2 substitute shows the more electronegative property. In **FIG. 4** it can be seen that the aromatic carbons at highest frequency are those in the range of 138-149 ppm for the Ipso and Meta (C4, C9, and C12) carbons of the aminopyrimidines and C16 in imidazole ring. Also, it can be seen that the aliphatic carbons at highest frequency are those in the 60.52 ppm for the Attached (C18) carbons to Nitrogen atom. Even though all of the carbons are aromatic, the range of nearly 100 ppm is about half of the total ^{13}C NMR chemical shift range. The prediction of chemical shifts to this accuracy is remarkable, considering that solvent effects were not considered.it can be seen that the aromatic carbons at highest frequency are those in the range of 130-150 ppm for the ortho and para of the N hetero atom (C4, C12, C16 and C9). Calculated results for all carbons are greater by averages of 20 ppm if polarization functions are included. There are also clear trends in the calculated ^{13}C NMR chemical shifts. All of the ^{13}C NMR chemical shifts in TABLE 7 for the Theoretical shift are lesser than those experimental data. calculations underestimate the ^{13}C NMR chemical shifts at ortho and para carbons of N hetero atom.

TABLE 8**. Theoretical and experimental values of chemical shift)^{1}H NMR(and the difference between of imiquimod [17].**

Atom	δ_{theo}	δ_{Exp}	$\Delta\delta$
8.33	8.0206	8.33	0.3094
7.94	7.7768	7.94	0.1632
7.9	7.518	7.9	0.382
9.48	7.3779	9.48	2.1021
7	7.145	8.05	0.905
33	4.8524	5	0.1476
34	4.2008	5	0.7992
20	3.9512	4.8	0.8488
21	3.0832	4.8	1.7168
23	1.7307	2.54	0.8093
24,26	0.8805	1.23	0.3495
25,28,30	0.5252	1.23	0.7048
29	0.2506	1.23	0.9794

The methyl and methylene protons of –N–CH2–CH-CH3 group in Imiquimod showed signals at 4.8 ppm, 2.54 ppm and 1.23 ppm (H20, H21, H23 and H24, H25, H26, H28, H29, H30 Respectively) integrating for two, one and six protons respectively in its ^{1}H NMR spectra. The electronegative property of the N heteroatoms causes a decrease in shielding constants around the protons connected to C12 in the imidazole ring (**FIG. 4**). The fifth drug we are examining is Nitroxoline. Chemical shifts of it are given in **TABLE 9 and 10**.

TABLE 9. **Theoretical and experimental values of chemical shift)^{13}C NMR(and the difference between of Nitroxolin [18].**

Atom	δtheo	δExp	Δδ
6	141.5031	159.9	18.3969
9	129.4509	148.5	19.0491
5	118.6535	136.7	18.0465
7	115.7548	131.7	15.9452
2	114.3525	128.4	14.0475
3	113.2211	122.0	8.7789
4	107.9696	124.4	16.4304
8	104.2444	124.6	20.3556
1	81.4541	109.4	27.9459

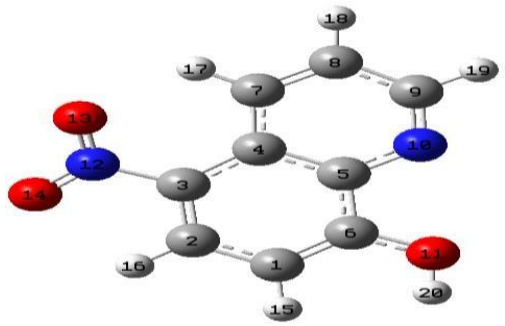

FIG. 5. **The structure of optimized Nitroxoline.**

Nitroxoline: the studied molecule shows nine different carbon atoms (**FIG. 5**), which is consistent with the structure on the basis of molecular symmetry. Due to that fact, nine peaks were observed in ^{13}C NMR spectrum.[19] One of two rings includes nitrogen atom which shows the electronegative property. The aromatic carbon in ^{13}C NMR spectra usually locates in the δ_C range of 110–135 ppm. Due to the conjugation arising from the phenyl ring and the lone-pair electron of an oxygen atom, the signal at 159.9 ppm is assigned to the C6 with high electron density. Equally, the signal at 148.5 and 136.7 ppm is assigned to the C9 and C5 respectively on account of the strong electronegative property of the N hetero atom. Since C1 is located in the meta-position to the NO_2, C4 and C8 are located in the meta-position to the N hetero atom, the induction effect is strong. Thus, the peaks at 109.4 ppm, 124.4 ppm, and 124.6 ppm are assigned to C1, C4, and C8, respectively, due to their lower electron density. The relatively high chemical shifts at 129.9 ppm and 129.4 ppm are ascribed to C3 and C5, respectively. Since C3 is Attachment to the NO_2. Thus, the peaks at 122.0 ppm are assigned to C2, due to their lower electron density. The relatively high chemical shift at 131.7 ppm is ascribed to C7. Data for all nine aromatic carbons for which experimental data are available. Even though all of the carbons are aromatic, the range of nearly 100 ppm is about half of the total ^{13}C NMR chemical shift range. It can be seen that the aromatic carbons at highest frequency are those in the range of 130-160 ppm for the ortho and para of the N hetero atom (C5, C7, and C9) and ipso of OH Subordinate (C6) carbons. Calculated results for all carbons are greater by averages of 20 ppm if polarization functions are included. There are also clear trends in the calculated ^{13}C NMR chemical shifts. All of the ^{13}C NMR chemical shifts in TABLE 9 for the Theoretical shift are lesser than those experimental data. calculations underestimate the ^{13}C NMR chemical shifts at ortho and para carbons of N hetero atom and overestimate the shifts for ipso carbons.

TABLE 10. **Theoretical and experimental values of chemical shift)^{1}H NMR(and the difference between of Nitroxolin [18].**

Atom	δtheo	δExp	Δδ
17	9.7063	9.14	-0.5663
16	8.9323	8.53	-0.4023
19	8.8514	9.025	0.1736
18	7.596	7.87	0.274
15	6.3845	7.2	0.8155
20	4.5302	4.93	0.4

As in **TABLE 10**, the presence of other six peaks in 1H NMR spectra suggests that there are six distinct types of protons in Nitroxoline. Normally, the protons on phenyl ring are expected to yield NMR signals in the δHrange of 6–8 ppm. The substitution of the proton for NO_2 and nitrogen atom in ring changes the chemical environment of the remaining aryl protons. The strong electronegative property of the N heteroatom and More than that NO_2 substitution causes a decrease in shielding constants around the meta-protons connected to C8 and C1 (**FIG. 5**). The calculated chemical shifts of 7.596 ppm and 6.3845 ppm are attributed to this two hydrogen atom. Unlike the frequency calculations, the basis set effect is rather significant for chemical shifts. The correlation analysis of the calculation and experimental data was performed in order to quantify the disagreement, and the result is listed in TABLE 9 and 10. 1H and 13C chemical shift values have been calculated for the optimized structures of the Nitroxoline compound and compared to the experimental chemical shift values. In this study the sixth drug is Primaquine. Chemical shifts of it are given in **TABLE 11 and 12**.

TABLE 11. **Theoretical and experimental values of chemical shift)1c NMR(and the difference between of Primaquine [8].**

Atom	δtheo	δExp	Δδ
13	137.0734	159.6	22.5266
10	132.1573	145.2	13.0427
5	126.219	144.3	18.081
4	121.1624	135.5	14.3376
2	118.2818	134.8	16.5182
3	112.4115	130	17.5885
1	100.4469	121.8	21.3531
12	91.5396	98.9	7.3604
9	87.3098	91.9	4.5902
19	37.8414	55.2	17.3586
23	27.2771	48.1	20.8229
33	21.541	41.7	20.159
29	13.9052	34.1	20.1948
30	10.5073	29.3	18.7927
25	2.0535	20.5	18.4465

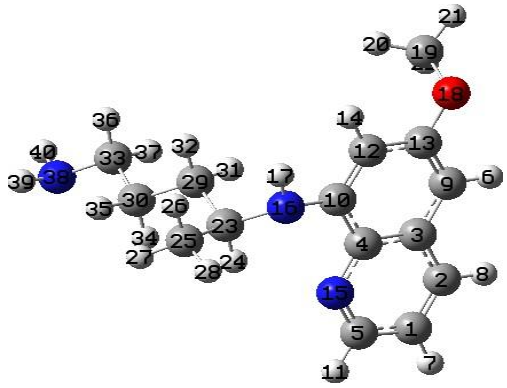

FIG. 6. **The structure of optimized Primaquine.**

As in **TABLE 11**, the studied molecule (**FIG. 6**) shows 15 different carbon atoms, which is consistent with the structure on the basis of molecular symmetry. Due to that fact, nine peaks are observed in ^{13}C NMR spectrum. One of two rings includes nitrogen atom which shows the electronegative property. On the other side, NH substitute shows the more electronegative property. The aromatic carbon in ^{13}C NMR spectra usually locates in the δ_C range of 110–135 ppm. Due to the conjugation arising from the phenyl ring and the lone-pair electron of an oxygen atom, the signal at 159.9 ppm is assigned to the C13 with high electron density. also In TABLE 1 it can be seen that the aromatic carbons at high frequency are those in the range of 130-146 ppm for the ipso (C10=145.2)and meta (C3= 130) carbons of the NH2 groups and the signal at 135.5 and 144.8 ppm is assigned to the C4 (135.5) and C5 (144.3) respectively on account of the strong electronegative property of the N heteroatom. data for all 13 aromatic carbons for which experimental data are available. It can be seen that the calculated results are comparable. There is excellent agreement with the experimental data. Even though all of the carbons are aromatic, the range of nearly 100 ppm is about half of the total ^{13}C NMR chemical shift range. The prediction of chemical shifts to this accuracy is remarkable, considering that solvent effects were not considered. There are also clear trends in the calculated ^{13}C NMR chemical shifts. All of the ^{13}C NMR chemical shifts in TABLE 11 for the Theoretical shift are lesser than those experimental data. calculations underestimate the ^{13}C NMR chemical shifts at ortho and para carbons of N hetero atom and oVerestimate the shifts for ipso carbons. Also, it can be seen that the aliphatic carbons at highest frequency are those in the range of 40-49 ppm for the attached (C23 and C33) carbons of the N atoms.

TABLE 12. **Theoretical and experimental values of chemical shift)^{1}H NMR(and the difference between of Primaquine [8].**

Atom	δ_{theo}	δ_{Exp}	Δδ
11	8.6757	8.45	-0.2257
8	8.0959	7.8	-0.2959
7	7.2151	7.15	-0.0651
6	6.8982	6.25	-0.6482
14	6.5108	6.25	-0.2608
24	4.2927	3.5	-0.7927
21	3.5456	3.75	0.2044
20	3.1717	3.75	0.5783
22	2.9055	3.75	0.8445
17	1.8816	6	4.1184
36	1.8816	2.55	0.6684
37	1.5463	2.55	1.0037
28	1.4396	1.2	-0.2396
27	0.9474	1.2	0.2526
31	0.76985	1.6	0.83015
34	0.76985	1.5	0.73015
35	0.6117	1.5	0.8883
26	0.2443	1.2	0.9557
32	0.2443	1.6	1.3557
40	-0.0197	1.8	1.8197
39	-0.4114	1.8	2.2114

The methyl and methylene protons of –NH–CH_2(CH_3)–CH_2-CH_2-CH_2-NH_2 group in Primaquine showed signals in the δ_H range of 1.2-3.5 ppm. In **TABLE 12** it can be seen that the aliphatic Hydrogen at high frequency for the Hydrogen attached on carbons connected to the NH and NH_2 groups on account of the strong electronegative property of the N atom. A broad signal at 6 and 1.8 ppm was observed for the –NH– and –NH_2- protons respectively. Normally, the protons on phenyl ring are expected to yield NMR signals in the δ_H range of 6–8 ppm. The electronegative property of the N heteroatom causes a decrease in shielding constants around the ortho protons connected to C5 (**FIG. 6**). The calculated chemical shifts of 8.6757 ppm are attributed to this hydrogen atom. Unlike the frequency calculations, the basis set effect is rather significant for chemical shifts. The Seventh drug that was studied was Proflavine (**FIG. 7**). Chemical shifts of it are given in **TABLE 13 and 14**.

TABLE 13. **Theoretical and experimental values of chemical shift)^{13}c NMR(and the difference between of proflavine [19].**

Atom	δtheo	δExp	Δδ
5,9	136.7097	149.66	12.9503
14,1	131.5815	140.85	9.2685
7	121.625	134.87	13.245
12	113.5437	128.59	15.0463
3	113.4859	128.59	15.1041
8,4	96.93065	122.47	25.53935
2,13	94.6209	121.00	26.3791
15	84.3246	115.13	30.8054
6	84.1013	115.13	31.0287

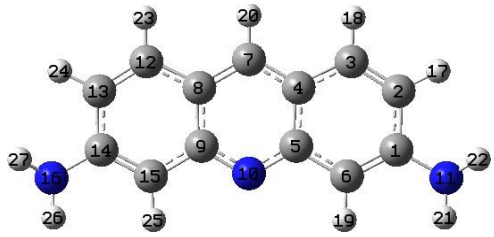

FIG. 7. **The structure of optimized Proflavine.**

As a rule, Ortho (C9 and C5 =149.66) and para (C7= 134.87) carbon chemical shifts oxygen and nitrogen-containing rings are further to the left than Meta carbon chemical shifts (C4 and C8=122.47) due to Ortho-carbon lower electron density Caused by the high electro-negative of N hetero atom also in **TABLE 13** it can be seen that the aromatic carbons at high frequency are those in the range of 128-141 ppm for the ipso (C1 and C14=140.85) and meta (C12 and C3= 128.59) carbons of the NH2 groups. data for all nine aromatic carbons for which experimental data are available. It can be seen that the calculated results are comparable. There is excellent agreement with the experimental data. Even though all of the carbons are aromatic, the range of nearly 100 ppm is about half of the total ^{13}C NMR chemical shift range Calculated results for all carbons are greater by averages of 20 ppm, if polarization functions are included. There are also clear trends in the calculated ^{13}C NMR chemical shifts. All of the ^{13}C NMR chemical shifts in **TABLE 13** for the Theoretical shift are lesser than those experimental data. calculations underestimate the ^{13}C NMR chemical shifts at ortho and para carbons of N hetero atom and the shifts for ipso carbons.

TABLE 14. **Theoretical and experimental values of chemical shift)^{1}H NMR(and the difference between of Proflavine[19].**

Atom	δ_{theo}	δ_{Exp}	$\Delta\delta$
20	8.5304	8.731	0.2006
18,23	7.7528	7.811	0.0582
19,25	7.1074	6.78	-0.3274
17,24	6.63095	7.019	0.38805
21,26	3.1124	7.2	4.0876
22,27	2.7359	7.2	4.4641

Regularly, the protons on the aromatic ring are expected to yield NMR signals in the $\delta_H$range of 6–8 ppm. The substitution of the proton for NH_2 and the presence of nitrogen hetero atom in the ring changes the chemical environment of the remaining aryl protons and consequently protons chemical shift (**TABLE 14)**. The presence of other six peaks in 1H NMR spectra suggests that there are six distinct types of protons in Proflavine. The Eighth drug we are examining is Quinidine. Chemical shifts of it are given in **TABLE 15 and 16**.

TABLE 15. **Theoretical and experimental values of chemical shift)13C NMR(and the difference between of Quinidine [20].**

Atom	δtheo	δExp	Δδ
33	8.5971	8.474	-0.1231
29	8.4089	7.864	-0.5449
34	7.5363	7.495	-0.0413
27	7.3471	7.113	-0.2341
28	7.1686	7.213	0.0444
42	6.4429	6.065	-0.3779
35	4.9705	5.593	0.6225
44	4.8888	5.45	0.5612
43	4.7923	5.04	0.2477
31	3.6708	3.788	0.1172
30,32	3.24495	3.788	0.54305
41	2.9419	3.404	0.4621
48	2.2943	2.969	0.6747
40	2.2229	2.87	0.6471
47	2.0596	2.84	0.7804
24	1.982	2.711	0.729
37	1.7031	2.206	0.5029
39	1.3917	2.07	0.6783
23,45	0.8213	1.73	0.9087
46	152.889	1.039	-151.85

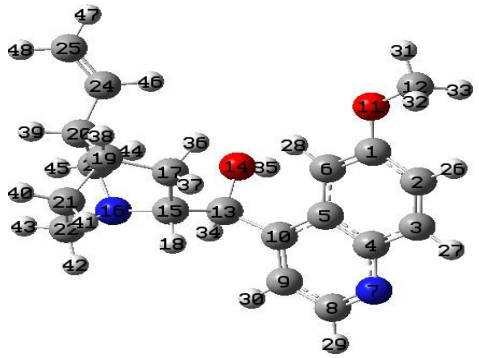

FIG. 8. **The structure of optimized Quinidine.**

As in **TABLE 15**, the studied molecule (**FIG. 8**) shows 19 different carbon atoms, which is consistent with the structure on the basis of molecular symmetry. Due to that fact, 19 peaks are observed in ^{13}C NMR spectrum. One of two rings includes nitrogen atom which shows the electronegative property. The aromatic carbon in ^{13}C NMR spectra usually locates in the δC range of 110–135 ppm. Due to the conjugation arising from the phenyl ring and the lone-pair electron of an oxygen atom, the signal at 157.55 and 147.11 ppm is assigned to the C1 and C10 respectively with high electron density. Also in **TABLE 15**, it can be seen that the signal at 148.69 and 143.66 ppm is assigned to the C10 and C1 respectively on account of the strong electronegative property of the N hetero atom. data for all 13 aromatic carbons for which experimental data are available. It can be seen that the calculated results are comparable. There is excellent agreement with the experimental data. Even though all of the carbons are aromatic, the range of nearly 100 ppm is about half of the total ^{13}C NMR chemical shift range. The prediction of chemical shifts to this accuracy is remarkable, considering that solvent effects were not considered. There are also clear trends in the calculated ^{13}C

NMR chemical shifts. All of the ^{13}C NMR chemical shifts in **TABLE 15** for the Theoretical shift are lesser than those experimental data. calculations underestimate the ^{13}C NMR chemical shifts at ortho and para carbons of N hetero atom. In general, the terminal =CH2 group absorbs (C22=114.44) to the right relative to an internal =CH- group (C21=140.78), Also it can be seen that the aliphatic carbons at highest frequency are those in the range of 43-72 ppm for the attached carbons of the N(C14, C20, and C26) and O (C8 and C13) atoms.

TABLE 16. **Theoretical and experimental values of chemical shift)^{1}H NMR(and the difference between of Quinidine[20].**

Atom	δ_{theo}	δ_{Exp}	Δδ
33	8.5971	8.474	-0.1231
29	8.4089	7.864	-0.5449
34	7.5363	7.495	-0.0413
27	7.3471	7.113	-0.2341
28	7.1686	7.213	0.0444
42	6.4429	6.065	-0.3779
35	4.9705	5.593	0.6225
44	4.8888	5.45	0.5612
43	4.7923	5.04	0.2477
31	3.6708	3.788	0.1172
30,32	3.24495	3.788	0.54305
41	2.9419	3.404	0.4621
48	2.2943	2.969	0.6747
40	2.2229	2.87	0.6471
47	2.0596	2.84	0.7804
24	1.982	2.711	0.729
37	1.7031	2.206	0.5029
39	1.3917	2.07	0.6783
23,45	0.8213	1.73	0.9087
46	152.889	1.039	-151.85

In **TABLE 16** it can be seen that the aliphatic Hydrogen at high frequency for the Hydrogen attached on carbons include double bond (C21 and C22). Also, Hydrogen attached to carbon connected to Oxygen atom (C8) showed a chemical shift at 3.778. Normally, the protons on phenyl ring are expected to yield NMR signals in the $\delta_H$range of 6–8 ppm. The electronegative property of the N heteroatom causes a decrease in shielding constants around the ortho protons connected to C10 (**FIG. 8**). The calculated chemical shifts of 8.474 ppm are attributed to this hydrogen atom. Unlike the frequency calculations, the basis set effect is rather significant for chemical shifts. In this study the ninth drug is Quinine. Chemical shifts of it are given in **TABLE 17 and 18.**

TABLE 17. **Theoretical and experimental values of chemical shift)^{13}C NMR(and the difference between of Quinine [21].**

Atom	δ_{theo}	δ_{Exp}	Δδ
1,10	133.3377	157.7	24.36235
8	128.0208	147.3	19.2792
4	125.4435	143.8	18.3565
24	123.3287	141.7	18.3713
3	114.7397	131.2	16.4603
5	108.7657	126.2	17.4343
9	99.8936	118.5	18.6064
2	93.9553	121.4	27.4447
25	92.4771	114.4	21.9229
6	90.4357	101.3	10.8643
13	57.0937	71.52	14.4263
15	37.9491	59.94	21.9909
12	29.7441	56.6	26.8559
23	26.0446	56.9	30.8554
22	25.9823	43.24	17.2577
20	20.4145	39.85	19.4355
19	8.724	27.83	19.106
21	6.8739	27.49	20.6161
17	1.2289	21.48	20.2511

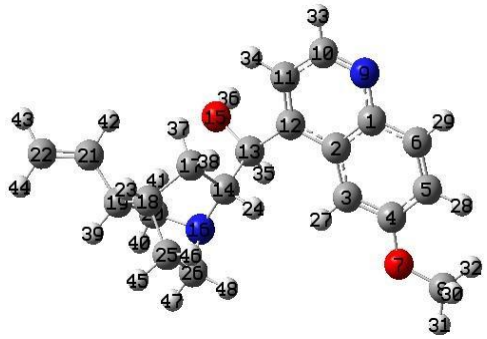

FIG. 9. **The structure of optimizedQuinine.**

As in **TABLE 17,** the studied molecule (**FIG. 9**) shows 19 different carbon atoms, which is consistent with the structure on the basis of molecular symmetry. Due to that fact, 19 peaks are observed in 13C NMR spectrum. One of two rings includes nitrogen atom which shows the electronegative property. The aromatic carbon in 13C NMR spectra usually locates in the δC range of 110–135ppm. Due to the conjugation arising from the phenyl ring and the lone-pair electron of an oxygen atom, the signal at 157.7 ppm is assigned to the C1 and C10 with high electron density. Also in **TABLE 17**, it can be seen that the signal at 143.8 and 147.3 ppm is assigned to the C4 and C8 respectively on account of the strong electronegative property of the N hetero atom. data for all 13 aromatic carbons for which experimental data are available. It can be seen that the calculated results are comparable. There is excellent agreement with the experimental data. Even though all of the carbons are aromatic, the range of nearly 100 ppm is about half of the total 13C NMR chemical shift range. The prediction of chemical shifts to this accuracy is remarkable, considering that solvent effects were not considered. There are also clear trends in the calculated 13C NMR chemical shifts. All of the 13C NMR chemical shifts in **TABLE 1** for Theoretical shift are lesser than those experimental data. calculations underestimate the 13C NMR chemical shifts at ortho and para carbons of N hetero atom. In general, the terminal =CH2 group absorbs (C25=114.4) to the right relative to an internal =CH- group (C24=141.7), Also it can be seen that the aliphatic carbons at highest frequency are those in the range of 43-72 ppm for the attached carbons of the N(C21, C22, and C23) and O (C12) atoms.

TABLE 18. **Theoretical and experimental values of chemical shift)^{1}H NMR(and the difference between of Quinine [21].**

Atom	δ_{theo}	δ_{Exp}	Δδ
29	8.5036	8.67	0.1664
27,28	8.39215	7.82	-0.57215
26	7.2142	7.38	0.1658
30	7.0167	7.5	0.4833
46	6.4852	5.86	-0.6252
48	4.9213	5	0.0787
47	4.8505	5	0.1495
34	4.7449	5.24	0.4951
31	3.6896	3.89	0.2004

32,33	3.2389	3.89	0.6511
44	2.8285	2.85	0.0215
42,45	2.19835	3.19	0.99165
36	2.0644	1.64	-0.4244
43	2.0093	2.43	0.4207
18	1.7185	3.05	1.3315
39	1.3932	2.19	0.7968
38	0.8956	1.72	0.8244
40	0.7941	1.72	0.9259
35,41	0.71795	1.72	1.00205
37	152.7406	1.64	-151.101

In **TABLE 18** it can be seen that the aliphatic Hydrogen at high frequency for the Hydrogen attached on carbons include double bond (C24 and C25). Also, Hydrogen attached to carbon connected to Oxygen atom (C12) showed a chemical shift at 3.89. Normally, the protons on phenyl ring are expected to yield NMR signals in the $\delta_H$range of 6–8 ppm. The electronegative property of the N heteroatom causes a decrease in shielding constants around the ortho protons connected to C8 (**FIG. 9**). The calculated chemical shifts of 8.5036 ppm are attributed to this hydrogen atom. Unlike the frequency calculations, the basis set effect is rather significant for chemical shifts. The correlation analysis of the calculation and experimental data was performed in order to quantify the disagreement, and the result is listed in **TABLE 17 and 18**. ^{1}H and ^{13}C chemical shift values have been calculated for the optimized structures of the Quinine compound and compared to the experimental chemical shift values. The last drug we studied is Tacrine. Chemical shifts of it are given in **TABLE 19 and 20**.

TABLE 19. **Theoretical and experimental values of chemical shift)^{13}C NMR(and the difference between of Tacrine [22].**

Atom	δ_{theo}	δ_{Exp}	$\Delta\delta$
4	145.7461	157	11.2539
8	131.007	152	20.993
7	128.8446	138	9.1554
14	111.1168	136	24.8832
13	109.4853	129	19.5147
10	102.0501	124	21.94995
12	102.0501	116	13.94995
9	97.7301	120	22.2699
3	87.8941	115	27.1059
5	11.7331	32	20.2669
2	1.1847	26	24.8153
1	0.9807	24	23.0193
6	-0.6916	23	23.6916

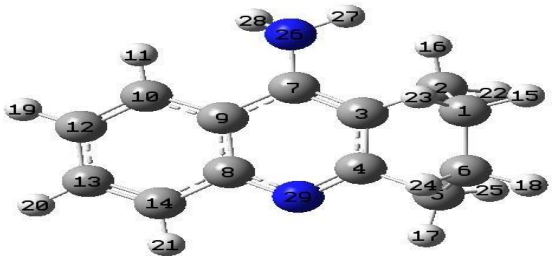

FIG. 10. **The structure of optimizedTacrine.**

These rings include nitrogen atom which shows the electronegative property. On the other side, NH2 substitute shows the more electronegative property. In **TABLE 19** it can be seen that the aromatic carbons at highest frequency are those in the range of 138-157 ppm for the Ipso and Meta (C4, C9, and C12) carbons of the aminopyrimidines and C16 in imidazole ring. Also, it can be seen that the aliphatic carbons at highest frequency are those in the 60.52 ppm for the Attached (C18) carbons to Nitrogen atom. data for all 13 aromatic carbons for which experimental data are available. It can be seen that the calculated results are comparable [23]. There is excellent agreement with the experimental data. Even though all of the carbons are aromatic, the range of nearly 100 ppm is about half of the total ^{13}C NMR chemical shift range. The prediction of chemical shifts to this accuracy is remarkable, considering that solvent effects were not considered. It can be seen that the aromatic carbons at highest frequency are those in the range of 130-150 ppm for the ortho and para of the N hetero atom (C4, C7, and C8). Calculated results for all carbons are greater by averages of 20 ppm if polarization functions are included. There are also clear trends in the calculated ^{13}C NMR chemical shifts. All of the ^{13}C NMR chemical shifts in **TABLE 19** for the Theoretical shift are lesser than those experimental data. calculations underestimate the ^{13}C NMR chemical shifts at ortho and para carbons of N hetero atom.

TABLE 20. **Theoretical and experimental values of chemical shift)^{1}H NMR(and the difference between of Tacrine[22].**

Atom	δtheo	δExp	Δδ
21	8.0924	7.5	-0.5924
11	7.6334	7.2	-0.4334
20	7.5626	7.2	-0.3626
19	7.2678	6.75	-0.5178
28	3.3913	4.9	1.5087
27	3.1576	4.9	1.7424
17	2.5144	2.3	-0.2144
25	2.1965	2.3	0.1035
16	2.0933	1.9	-0.1933
22	1.9699	1.9	-0.0699
15,18	1.4176	1.7	0.2824
24	1.1499	1.7	0.5501
23	1.0093	1.7	0.6907

The methylene protons of Ar–(CH2)4-Ar group in Tacrine showed at 2.3 ppm, 1.9 ppm and 1.7 ppm (H17, H25, H16, H22 and H15, H18, H23, H24 Respectively) integrating for two, two and three protons respectively in its 1H NMR spectra. The electronegative property of the N heteroatoms causes a decrease in shielding constants around the protons connected to C2 in the aliphatic ring (**FIG. 10**).

REFERENCES

1. Kiasat AR, Noorizadeh S, Ghahremani M, et al. Experimental and theoretical study on one-pot, three component route to 2H-indazolo[2,1-b]phthalazine- triones catalyzed by nano-alumina sulfuric acid. J Mol Struct. 2013;1036:216-25.
2. Kumar S, Bawa S, Gupta H. Biological Activities of Quinoline Derivatives: Mini- Reviews in Medicinal Chemistry. 2009;9(14):1648-54.
3. Gale P. 2009 Themed issue dedicated to Professor Jean-Pierre Sauvage materials and metal complexes w. 2009;6.
4. F R. C. P. DAVID C. WARHURST, D.SC.A MOLECULAR MARKER FOR CHLOROQUINE -RESISTANT FALCIPARUM MALARIA M. N Engl J Med. 2001;344(4):299-302.
5. LaPlanche LA. 13 C NMR Chemical Shift Assignments in Dibucaine and Dibucaine Hydrochloride Determined by Two-Dimensional NMR Spectroscopy. Spectroscopy Letters. 1991;24(2):209-28.
6. Dockrell DH, Bighorn GR. Imiquimod and resiquimod as novel immunomodulators. J Antimicrob Chemother. 2001;48(6)751-55.
7. Wakil El N, Ghamry El H. Nitroxoline. Azo Dye Complexes as Effective Heterogeneous Catalysts for Color Removal and Degradation of Some Organic Textile Dyes. Int J Chem Kinet. 2017;7:464-76.
8. Kristensen S, Grislingaas AL, Greenhill JV, et al. Photochemical stability of biologically active compounds: V. Photochemical degradation of primaquine in an aqueous medium. Int J Pharm. 1993;100(1-3):15-23.
9. Ruiz R, García B, Ruisi G, et al. Computational study of the interaction of proflavine with d(ATATATATAT)2 and d(GCGCGCGCGC)2. J Mol Struct. 2009;915(1-3):86-92.
10. Dijkstra G D H, Kellogg RM, Wynberg H, et al. Conformational study of cinchona alkaloids. A combined NMR, molecular mechanics, and x-ray approach. J Am Chem Soc.1989;111(21):8069-76.
11. Díaz-Araúzo H, Cook JM, Christie DJ. Synthesis of 10, 11- Dihydroxydihydroquinidine N-oxide, a New Metabolite of Quinidine. Preparation and 1 H-NMR Spectroscopy of the Metabolites of Quinine and Quinidine and Conformational Analysis via 2D COSY NMR Spectroscopy. J Nat Prod.1990;53(1):112-24.
12. Lou Y. The acute hepatotoxicity of tacrine explained by 1 H NMR based metabolomic profiling. Toxicol Res. 2015;4(6):1465-78.
13. Alver Ö, Parlak C, Şenyel M. FT-IR and NMR investigation of 1- phenylpiperazine: A combined experimental and theoretical study. Spectrochimica Acta - Part A: Molecular and Biomolecular Spectroscopy. 2007;67(3-4):793-801.
14. F. A. A. Paz, Dudenko D, Spiess HW. Packing Interactions in Hydrated and Anhydrous Forms of the Antibiotic Ciprofloxacin: a Solid-State NMR, X-ray Diffraction, and Computer Simulation Study.2012;71-74.
15. Frechette M, Ian R, Hynes R, et al. Structures in Solution and in the Solid State of the Complexes of Lanthanum (II1) with Solution NMR Studies.1992;1650-56.
16. Dongre VG, Ghugare PD, Karmuse PD et al. Identification and characterization of process related impurities in chloroquine and hydroxychloroquine by LC / IT / MS, LC / TOF / MS and NMR. J Pharm Biomed Anal.2009;49:873-79.

17. Xia SJ, Guangxin, Zhang Rongxia, et al. Spectral data analysis and identification of imiquimod. Fresenius J Anal Chem.2003;31(10):1183-86.
18. Kidrič J, Hadži D, Kocjan D, et al. 1H and13C NMR study of 8- hydroxyquinoline and some of its 5-substituted analogs.
19. Benchabane Y, Boyer G, Faure R. 1Hand 13C NMR signal assignments of some new N, N???-diacyl proflavine derivatives. Magn Reson Chem.2009;47(8);706-10.
20. "Quinidine." [Online]. Available: http://www.hanhonggroup.com/nmr/nmr_en/6064.html.
21. "QUININE." [Online]. Available: http://www.allfordrugs.com/2014/11/28/quinine/.
22. "QUININE." [Online]. Available: http://www.allfordrugs.com/2014/11/28/quinine/
23. Chapman OL. Spectrometric Identification of Organic Compounds. J Am Chem Soc.1963;85(20):3316-16.