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ORIGINAL ARTICLE

Effective molecules of some natural product as antidepressant and antihistamine drugs: A NMR study

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Due to increasing rates of depression in recent years, the use of the drug-plants is significantly important. In this work, we have optimized and discussed about several active compounds which are extracted from famous plants such as formononetin (a constituent of Cimicifuga racemosa), Luteolin (fromPerilla frutescens), Myriceti (Clitoria ternatea) and Piper methysticum as antidepressant and antihistamine through NMR study.There are no works in theoretical of a statistical approach in NMR shielding and nucleus independent chemical shifts for study of antidepressant and antihistamine drugs, while the asymmetry(η) and skew(κ) parameters are fluctuated in small distances and are alternative in large distances in the center of heterocyclic rings for Luteolin, Buclizine, Myriceti, formononetin and Cetirizine. By changing asymmetry between $0 \leq \eta \leq +1$ skew will be changed between $-1 \leq \kappa \leq +1$, meanwhile the parameter κ is zero when $\sigma_{22} = \sigma_{iso}$[15].In the case of axially-symmetric tensor, σ_{22} equals either σ_{11} or σ_{33}, skew is $\kappa = \pm 1$. In this work, we have investigated the statistical methods by computing of nucleus-independent chemical shifts-SNICS in point of Bq motions in the center of sphere in shielding and de-shielding spaces of antidepressant and antihistamine drugs.
Keywords: S-NICS; NICS; Luteolin; Buclizine; Myriceti; formononetin; Cetirizine

Introduction

The plant-based remedy has been used by indigenous cultures for thousands of years. Due to increasing rates of depression in recent years, using the drug-plants such as Curcuma longa (RHIZOMA, 2009), Clitoria ternatea (Lijon 2017), Cimicifug racemosa (Thomsen, 2004). Piper methysticum or Kava Kava (LEBO 1991), Morinda officinalis(Dao 2004) and perilla frutescens (Bachheti,2010) are significantly important. Curcuma longa is a rhizomatous herbaceous perennial plant of the ginger families. It is native to the Southeast Asia and Indian subcontinent. Curcuma longa powder has a bitter, warm, pepper-like flavor and mustard-like aroma. Although long used in Ayurvedic medicine, there is some (not more) clinical evidence for use of turmeric or its main constituent, curcumin, as a therapy (Nelson, 2017).

Clitoria ternatea, which is known as a Asian pigeonwings, is a plant species belonging to the Fabaceae families. This plant is native to tropical equatorial Asia countries such as Malaysia, Indonesia and Thailand, but has been introduced to Australia, America and Africa. It is grown as an ornamental plant and as a revegetation species, requiring little care when cultivated. In traditional Ayurvedic medicine, it is ascribed important and various qualities including antistress, memory enhancing, anticonvulsant, anxiolytic, nootropic, antidepressant, tranquilizing, and sedative properties (Mukherjee, 2008). In traditional Chinese medicine, and consistent with the Western concept of the doctrine of signatures, this plant has been ascribed properties affecting female libido due to its similar appearance to the female reproductive organ (Fantz, 1991).

Cimicifuga racemosa is a species of flowering plant of the family Ranunculaceae. It is native to eastern North America from the extreme south of Ontario to central Georgia, and west to Missouri and Arkansas. It grows in a variety of woodland habitats, and is often found in small woodland openings. The roots and rhizomes have long been used medicinally by Native Americans. It contains many organic molecules with biological activities (Nuntanakorn, 2007).

Piper methysticum or Kava-Kava is a crop of the western Pacific. The name is include awa (Hawai), sakau (Balick, 2002). Kava is used in Oceania to make a psychoactive drink that is prepared by grinding the roots of the perennial shrub. Recent work (Lebot and Levesque, 1989) Morinda officinalis is used in traditional Chinese medicine which enhances exercise endurance and possesses protective effects against oxidative or enhance the immune system function (Dao-rong, 2004). Perilla frutescens, is a species of Perilla in the range family of Lamiaceae. It is an annual plant native to Asia and Indian highlands, and grown in

the , India and China (Seo, 2009). This plant was the main parts of folk medicine practiced by the ancient peoples in many parts of the world. Perilla frutescens hasbeen used as an popular traditional herbal medicine to treat several disease including tumor, depression, anxiety, antioxidant, and intoxication. Leaves of the plants are used in traditional Japanese herbal medicine. Perilla is used as one commercial product in other countries like India, Japan, Korea and now, it has also been exported to Europe countries, USA and also Russia as an important seed oil. Antihistamines are drugs which treat allergic rhinitis and other allergies. Anti-histamines can give relief when a person has nasal congestion, sneezing, or hives because of pollen, dust mites, or animal allergy. Typically people take antihistamines as an inexpensive, generic, over-the-counter drug with few side effects. As an alternative to taking an antihistamine, people who suffer from allergies can instead avoid the substance which irritates them (Panula, 2015).Antihistamines are usually for short-term treatment Chronic allergies increase the risk of health problems which antihistamines might not treat including asthma, sinusitis, and lower respiratory tract infection.

Buclizine is an antihistamine and anticholinergic of the diphenyl-methyl-piperazine group. It is considered to be an antiemetic, similar to meclizine (Mostafa, 2011).

Active Components

Perilla seed extract is rich in polyphenols such as luteolin, chrysoeriol and apigenin as aglycons. Luteolin and so on are main polyphenols and main active ingredients (Figs 1, 2).

Curcumin which are two form of keto and enol is extracted of Curcuma longa which occur from numerous curcuminoids, such as curcumin, demethoxycurcumin, and bisdemethoxycurcumin (Nelson 2017) - see Figs 1-3.

Gu, 2009 have extracted four antioxidant compounds from fruit of *Perilla* frutescens were isolated. These compounds were identified as rosmarinic acid, luteolin, apigenin, and chrysoeriol through, NMR, and ESI MS. Lee et al(Lee 2013) investigate phenolic compound in the seeds of various perilla cultivars. Phenolic compounds were characterized by nuclear magnetic resonance (NMR) spectroscopy, and ultra-performance liquid chromatography with photodiode array detector and electrospray ionisation/mass (UPLCPDA-ESI/MS) analysis. Nine compounds were elucidated as caffeic acid-3-O-glucoside including, caffeic acid, luteolin-7-O-glucoside, apigenin- 7-O-glucoside, rosmarinic acid-3-O-glucoside, rosmarinic acid, luteolin, apigenin, and chrysoeriol. Indisputably, depression and other common mental disorders are already, and will probably become increasingly, part of an epidemic of comorbidity between physical and mental illhealth, with diet being a crucial common determinant. Loratadine was discovered in 1981 and came to market in 1993. It is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system (Chollet 1993).

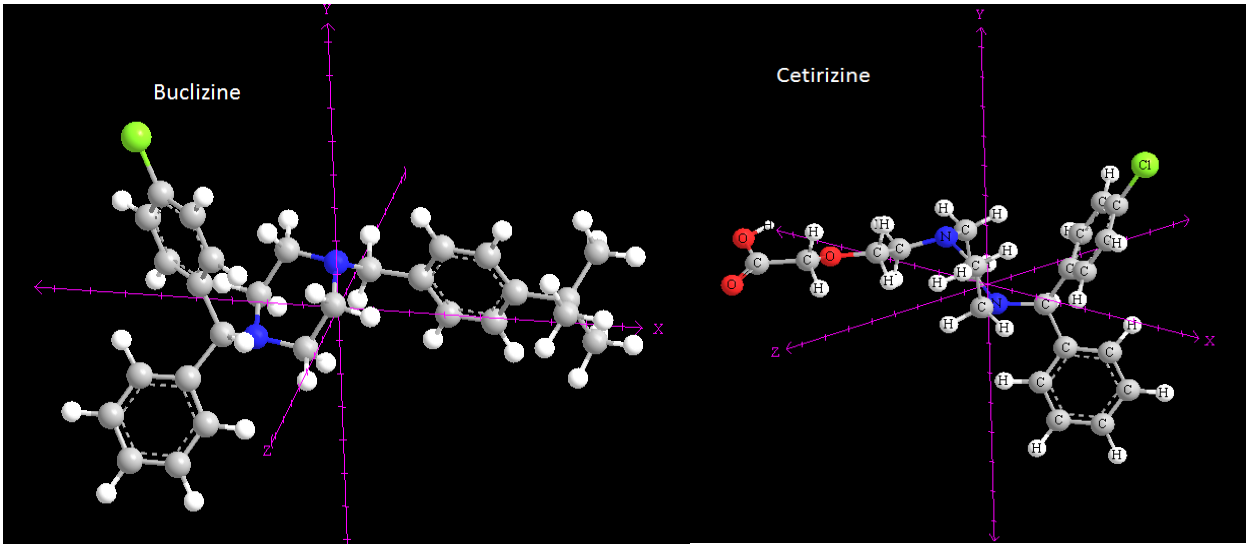
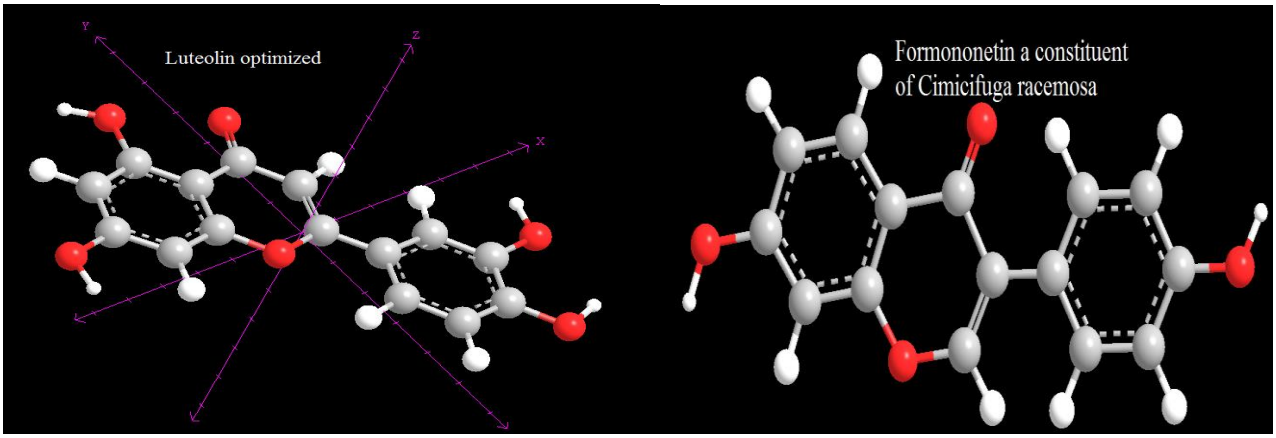


Fig. 1. Buclizine and Cetirizine Optimized through DFT Calculation as effective molecule for Anti-depressant and antihistamine drugs



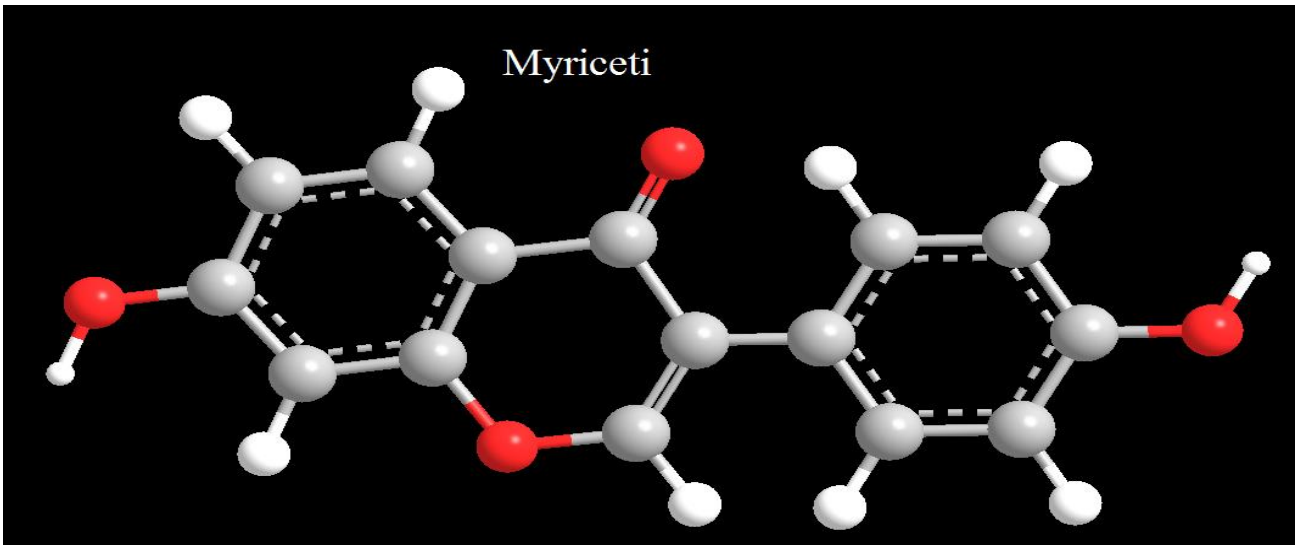


Fig. 2. The optimized of formononetin a constituent of Cimicifuga racemosa, Luteolin from *Perilla frutescens* and Myriceti (*Clitoria ternatea*).

Theoretical background:

Aaromaticity in terms of nucleus-independent chemical shifts in long distances of NICS, around the ring center, NICS (0), at the center of ring plane and aromatic ring current shielding (ARCS) were compared in several studies. In short range of distances a few works have been done in theoretical and reports the statistical approach in our works (Monajjemi 2010, 2015)

For further discussion of statistical approach in nucleus independent chemical shift calculations, especially in short range of distances, It has been focused in relaxations of CAS, dipole-dipole and contribution . We have shown that the asymmetry(η) and skew(κ) parameters fluctuate in behavior around the center of rings due to minimum isotropy in the center. The most fluctuations are appearing around the minimum or maximum functions mathematically (Monajjemi, 2015). Nuclear spin relaxation studies in the gas phase had started in 1987. Spin-relaxation data in the gas phase provide a stringent test of the anisotropy of an existing intermolecular potential. The basis of this work is on random motions of dummy atom in the shielding and de-shielding spaces of heterocyclic rings for considering maximum abundant of points in due to dipole–dipole, CSA and contribution relaxations . The main purpose of random displacement of various probes inside of shielding and de-shielding spaces are for understanding of mechanism and consequences of anisotropic spin–spin interactions in short ranges .

In this study, the major components Of Herzfeld (Herzfeld, 1980) and Haeberlen (1976) parameters erocyclic rings. The numerous random points around the center of those molecules have been produced by generation of pseudo-random numbers, which are distributed in a Gaussian function in the interval [0, 1). Our result has been compared by the energy decomposition analysis (EDA) method. The total π bonding energy and the "π" conjugation between heteroatoms "π" bonds in heterocyclic rings are significantly accurate. We have optimized the geometries and calculated the carbon NMR for Buclizine, Cetirizine, loratacline, Promethazine molecules for understanding which members of rings are more stable our methods and physical chemistry approach have been done based on our previous works (Monajjemi 2010-2015).

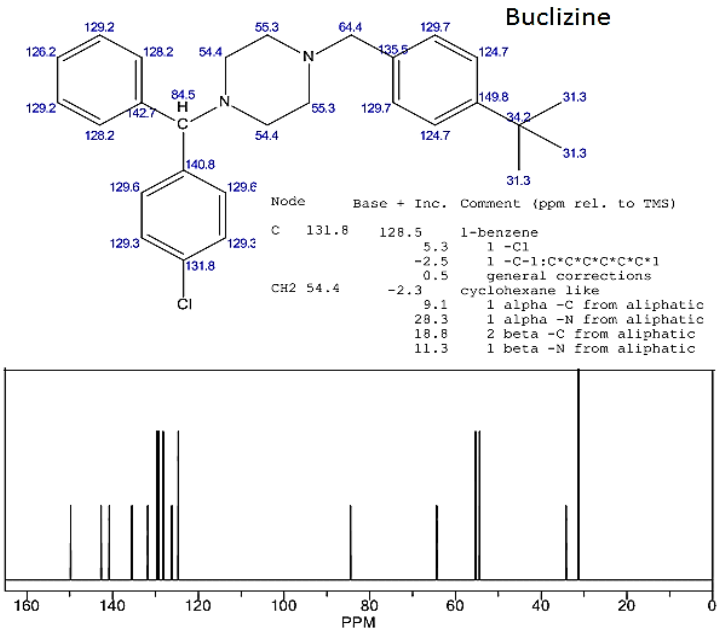


Fig. 3. NMR data of Buclizine.

Computational details

By this work we have optimized the effective molecules of some important natural products through QM/MM calculation using DFT methods. We have investigated density functional theory the exchange-correlation of all molecules. Tight & post-HF ab-initio calculation has applied to model the exchange-correlation energies of the hetero rings of the antidepressant and antihistamine structures. The double ζ-basis set with polarization orbitals (DZP) were used for the aromatic rings.
The charges and electrostatic potential-derived charges of the halogens were also estimated using Merz-Kollman-Singh, chelp, or chelpG. Calculations were performed using packages of Gaussian 09 and GAMESS. In the calculations, we also have mainly focused on getting the optimized results for each item from "advanced DFT" methods including the "m06-L", "m062x", "m06-L", and "m06-HF" which are novel Meta hybrid DFTB. SPSS "Statistical Package" has applied for editing and analyzing all sorts of our S-NICS data of the heterocyclic antibiotics in this work.

Results and discussion

The results have been listed in three tables and figured in five curves. The isotropy in all NMR calculations are positive which indicates negative values for aromaticity, but the slopes are decreased from the replacing from 0.1 to center . It is obvious that the difference between isotropies for NICS data can explain the quality of the aromaticity for a natural product molecules. In the S-NICS method through the statistical calculations, the best point of the shielding space around the center of symmetric or non-symmetric the aromatic molecules in our can evaluated as an aromaticity criterion and in this method the expectation of the (η*)and (*κ**) (monajjemi 2010-2015) have been estimated as the Gaussian curve functions versus one , two or three dimensional distances around the center of the aromatic rings. The isotropy (σ_{iso}^{*}) which is related to all of (η*),(κ *),(Ω*) and (*ζ**) is the best criterion for various aromatic molecules by the S-NICS method, which can express both qualitative and quantitative magnitudes for symmetric or non-symmetric aromatic molecules .

Table 1. S-Nics Value for some atoms of Buclizine and Cetirizine

			Myriceti							Cetirizine			
atom	**charge**	**σiso**	**S-NICS**	**η**	**Δδ**	**Ω**	**atom**	**charge**	**σiso**	**S-NICS**	**η**	**Δδ**	**Ω**
1 C	-0.144	60.136	62.73	0.9667	114.6	-76.41	**8 O**	-0.355	159.279	158.25	0.42814	-10.89	10.1699
2 C	0.193	47.631	46.57	0.8814	140.8	-93.91	**9 N**	0.177	29.0585	30.74	0.65815	-11.39	9.1619
3 C	-0.351	159.2	158.18	0.601	-12.1	10.112	**3 C**	-0.0825	149.74	149.3	0.3712	-26.14	-17.43
4 O	-0.357	158.67	149.16	0.641	9.998	8.1202	**4 C**	-0.2144	148.93	146.5	0.2412	-23.71	15.809
10 O	-0.135	63.73	60.94	0.358	21.01	20.623	**5 C**	0.1569	46.89	47.5	0.7240	-142.0	109.82
6 N	-0.102	127.67	124.79	0.4661	-18.1	16.47	**10 O**	-0.2185	148.70	145.59	0.265	-24.64	-16.4
7 C	-0.055	50.54	51.76	0.295	-6.32	6.5076	**11 N**	0.1750	29.3883	28.487	0.7976	-9.442	-6.2952

Optimization and NMR shielding constants including orientations of the principal data such as standard components, Haeberlen-Mehring (Mehring 1978) and Herzfeld-Berger(Herzfeld 1980 parameters for Buclizine, Cetirizine, loratacline, Promethazine compounds in various statistical situations have been calculated through DFT methods and the data are listed in tables1,2.
Similar to the NICS method, in S-NICS, negative nucleus-independent-chemical-shifts denote aromaticity. Therefor positive values denote anti-aromaticity. In S-NICS methods, the shielding and de-shielding spaces are significant to discuss the mechanism of the aromatic molecules in point of ring currents, which are the circulating π electrons in an aromatic molecule produce opposite to the applied magnetic field.
The stability of the isotropy criterion is highly affected on the best places in the shielding area spaces and it is dependent on the structures of the aromatic rings. So by using this method, a suitable and stable magnitude of isotropy can calculated as an aromaticity criterion.
It is obvious that structural factors cause changes in the magnetic field experienced by the nuclei and change the resonant frequency. Therefore the chemical shielding and many other factors such as electronegativity, hydrogen bonding, and magnetic anisotropy of π-systems will be changed because of the electrons around the proton which produce a magnetic field, countering the applied field. This reduces the field experienced at the nucleus. The electrons are said to shield the proton, an effect that is exactly dependent on the distance of the center.
In addition, S-NICS can find the most accurate places for effective points for calculation of isotropy as an aromaticity criterion. The chemical shielding is a vector orientation function for all of the shielding parameters that can change in various places inside the shielding area of the rings for aromatic compounds.

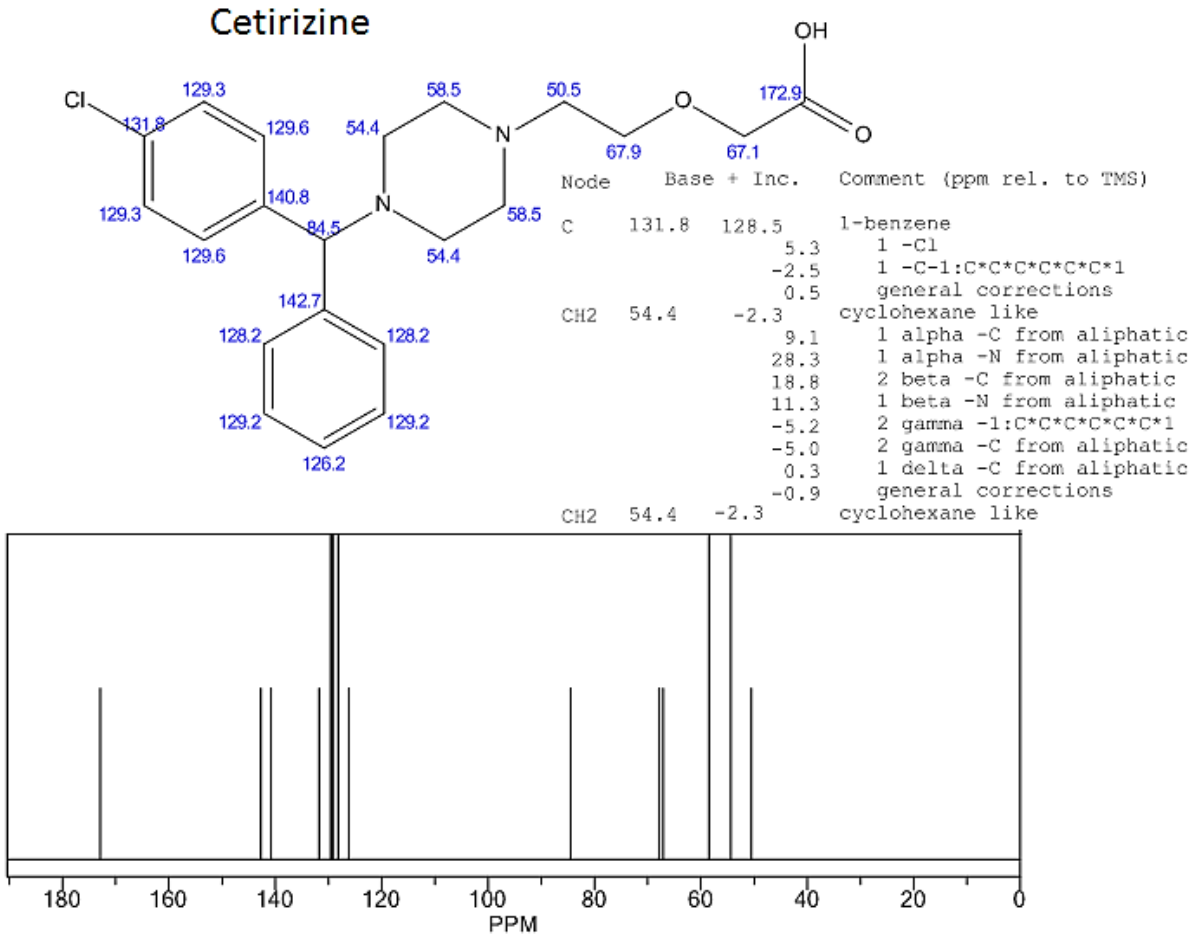


Fig. 4. Carbon NMR of cetirizine

Table 2. S-NICS Value for some atoms of loratacline, Promethazine

Luteolin							Formononetin						
atom	**charge**	**σiso**	**S-NICS**	**η**	**Δδ**	**Ω**	**atom**	**charge**	**σiso**	**S-NICS**	**η**	**Δδ**	**Ω**
4 C	-0.3399	160.293	19.011	0.91141	-18.16	12.67	**3 C**	-0.3306	160.85	14.22	0.5809	-11.2	9.4806
6 C	-0.2909	155.86	26.4304	0.40322	37.670	-25.11	**7 C**	-0.2954	157.821	14.266	0.607	-17.75	-11.83
4 O	-0.1059	145.36	26.4726	0.97410	26.819	-17.87	**6 C**	-0.1374	142.53	25.751	0.7379	-22.37	17.16
8 O	-0.2084	148.53	12.7529	0.09509	23.291	-15.52	**10 C**	-0.200	149.09	11.618	0.8986	-12.23	-8.158
6 N	0.1545	46.580	166.345	0.70001	141.39	110.86	**3 N**	0.1706	47.019	156.92	0.7332	-135.9	104.6
7 C	0.1119	51.883	112.723	0.80410	-124.9	-83.30	**4 O**	0.1171	56.977	112.4	0.9435	-115.6	-77.12

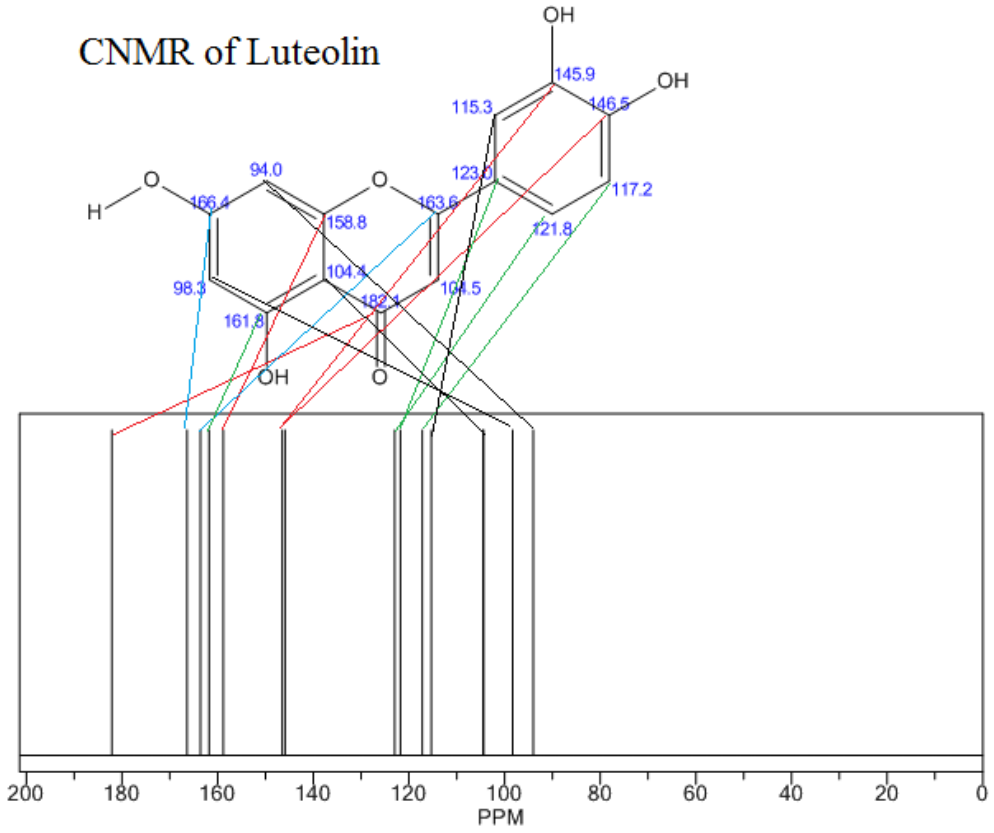


Fig. 5. Carbon NMR of Luteolin

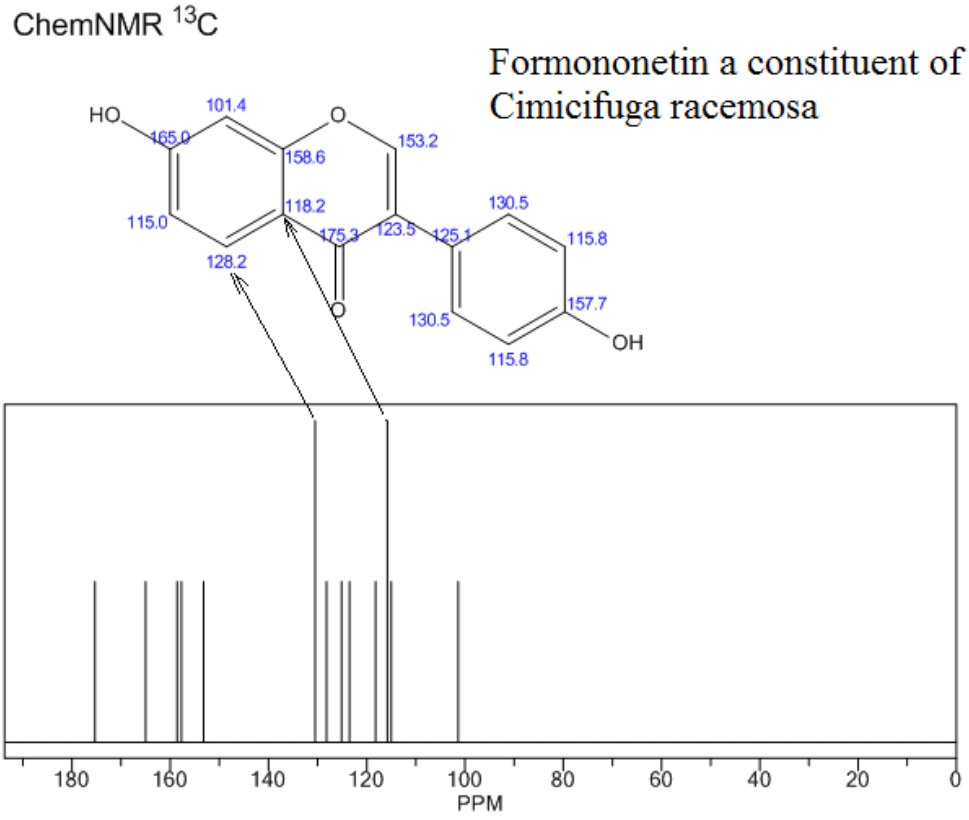


Fig. 6. Carbon NMR of " Formononetin " a constituent of Cimicifuga racemosa

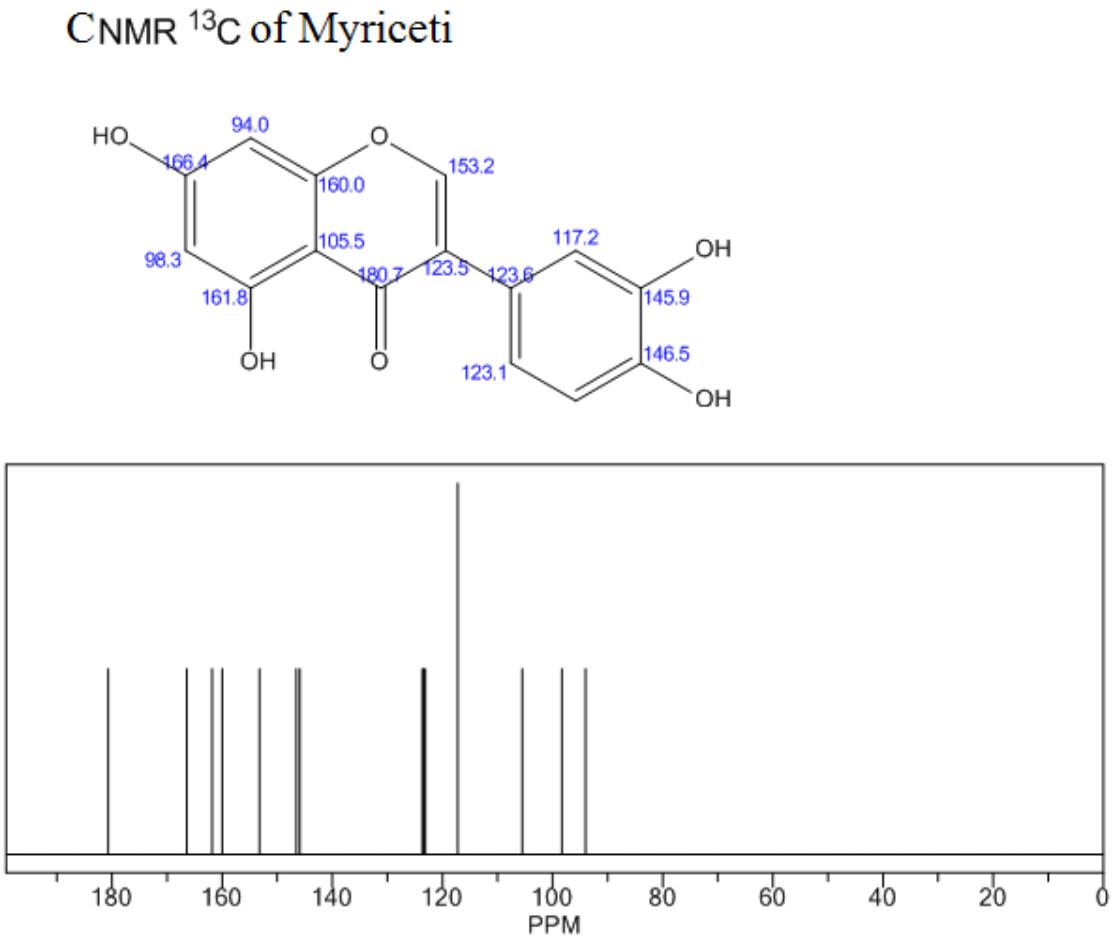


Fig. 7. Carbon NMR of Myriceti from Clitoria ternatea

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