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Conformational Properties of Novel 1,2,3,4-Tetrahydro-pyrimidinone (thione) Derivatives: A DFT study

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Thirty nine novel 1,2,3,4-tetrahydropyrimidinone (thione)s were subjected to conformational studies. Density functional theory at B3LYP/6-31 G* was performed as the computational method of high accuracy. Important dihedral angles and bond lengths were investigated and the values obtained were explainable. Results of this work confirm a twisted boat tetrahydropyrimidine ring conformation with an axial C4 substituent for most of the compounds. This substituent was oriented toward the C5 atom. The carbonyl group located on the C5 substituent and the C5=C6 bond had both s-*cis* and s-*trans* conformation in the studied molecules.

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Introduction

The importance of the three dimensional (3D) structural properties, i.e., the rigidity or flexibility, of the biologically active molecules was suggested for the first time in the 1950s and early 1960s [1,2]. After investigating the different pharmacological properties of acetyl choline due to different conformational states of the molecule, particular interest has been devoted to the determination of the conformational properties of the biologically active molecules and the receptors for these molecules in the biological system [1-8]. Today the study of accurate conformational features of new compounds is possible using different computational chemistry packages which work based on fundamental physical chemistry equations [9-11].

In the last few decades 1,2,3,4-tetrahydropyrimidine-2-one (thione) moiety which is also called 3,4-dihydropyrimidine-2(1*H*)-one (thione) has attracted considerable attention of medicinal chemists as an interesting scaffold [12]. This chemical entity was introduced to chemistry at the beginning of 1890s by the Italian chemist Pietro Biginelli [13]. A broad range of biological effects, including calcium channel modulation [14], adrenoceptor blocking [15], antitumor [16], antiviral [17], anti-inflammatory [18] and antimicrobial [19] activities have been attributed to this class of heterocyclic compounds. Despite diverse biological properties, conformational studies on this moiety are very limited. Conformational require ements of this type of pyrimidines for the calcium channel blocking ability were more interesting because of the structural similarities between this class of compounds and 1,4-dihydropyridine calcium channel blockers [20-23]. According to these studies, in the receptor-bound conformation, the substituted aryl ring should be positioned axially, perpendicular to, and bisecting the boat-like tetrahydropyrimidine ring. The 4-aryl substituent (X) is prefered to be synperiplanar (*sp*) relative to the C4-H of the tetrapyrimidine ring. A *cis*-carbonyl ester orientation, with respect the tetrahydropyrimidine alkene bond, was also found neccessary for calcium channel modulatory activity (Figure 1) [20].

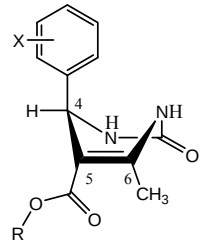


Fig. 1. Conformational features of calcium channel modulating 1,2,3,4 –tetrahydropyrimidinones.

There is also a report on the conformational analysis of monastrol, a tetrahydropyrimidine derivative, which inhibits mitotic kinesin Eg5 as an anti-cancer agent [24]. In this study, semiempirical (AM1) and ab initio (HF/3-21Gp has been carried out for geometry optimi zations of the molecule. For both computational methods the lowest energy conformation was predicted to be the one where the ester group was oriented *cis* and the aryl group had *sp* conformation [24]. In the most recent study on the 3D molecular structure of 1,2,3,4-tetrahydropyrimidine derivatives density functional theory (DFT) has been applied to determine the structural propoerties of some novel compounds regardless of their biological activity. The results of this study show that the six-member ring adopts a boat conformation and the C4-substituent has a pseudoaxial orientation. But, the results account for an s-trans conformation for the carbonyl of the ester group with respect to the adjacent alkene bond of the tetrahydropyrimidine ring [10]. Here, we report the study of conformational properties of novel 1,2,3,4-tetrahydropyrimidinone (thione) derivatives using an accurate quantum mechanics based computational method. Density functional theory at B3LYP/6-31 G* is applied for geometry optimizations of the molecules to reach the lowest energy conformation whose 3D structural featur es were determined. The studied compounds have been recently reported by this research group as antiretroviral agents [17]. Structural features including conformation of the tetrahydropyrimidine ring, orientation of the C4 substituent with respect to this ring, geometrical orientation of the ester (amide) carbonyl group bonded at C-5 of the ring and some bond lengths are investigated in this study.

Materials and Methods

Computational Methods

Thirty nine 1,2,3,4-tetrahydropyrimidinone (thione) derivatives were subjected to this study. Preparation of all has been reported previously [19,25-31]. General structure and structural details of the studied compounds are provided in Table 1. The two-dimensional structures of molecules were drawn in HyperChem software [32]. All structures were minimized with molecular mechanics/MM+ calculations and the obtained geometries were used as starting structures in semi-empirical PM3 optimizations in Hyperchem software. The molecular structures were optimized using the Polak-Ribiere algorithm until the root mean square gradient was 0.1 kcal mol^{-1}. The PM3-optimized structures were used as initial guess geometries for the *ab initio* calculations. All geometries were optimized using the density functional theory (DFT) B3LYP method with 6-31 G* basis set.

The conformational features considered in this study were: (i) C2-N3-C5-C6 impropoer dihedral angle (α_1) as a measure of the amount of tetrahydropyrimidine ring twisting. (ii) C5=C6 bond length indicative of the amount of resonance betrween the ring and C7=O8 bond. (iii) Geometrical orientation of the ester (amide) carbonyl group bonded at C-5 reflected by C6-C5-C7-O8 dihedral angle (α_2). (iv) C7=O8 bond length whose changes should be parallel with changes in C5=C6 bond length. (v) Relative position of the C-4 substituent with respect to the tetrahydropyrimidine ring measured by the summation of Z11-C10-C4-C5 and Z11-C10-C4-N3 dihedral angles (α_3) and (α_4). (vi) C2=X9 bond length and finally (vii) C4-H, N1-H and N3-H bond lengths.

Results and Discussion

The numerical results for the conformational features considered in this study are provided in Table 2. Deviation of the 1,2,3,4-tetrahydropyrimidinone (thione) ring from planarity is measured by the amount of C2-N3-C5-C6 impropoer dihedral angle (α_1). In fact, this is an indicative of tetrahydropyrimidine ring twisting. Rings with α_1 values between 1º and -1º are flattened and with values greater than 1º or smaller than -1º are twisted boats. When this dihedral angle is greater than 0º, N3 and C6 atoms approach to the above of the C2/N3/C5/C6 plane and when it is smaller than this value, C2 and C5 atoms are above the indicated plane. The results provided in Table 2 show different amounts of ring twisting in the studied compounds, from almost flattened boats, compounds **36**, **38** and **39**, to the most twisted ones (compounds **2**,**3** and **4**). In all flattened rings the N3 and C6 atoms are above the C2/N3/C5/C6 plane. In all twisted ones twisting is in a way that C2 and C5 atoms approach to the above of this plane. No special relationship was observed between the C-4 substituent and and the amount of ring twisting. The C5=C6 bond length in all the studied compounds was more than the expected value for alkenes, 1.33 Å. This can be easily explained considering the resonance between N1 lone pair, C5=C6 and C7=O8 which gives some single bond character to C5=C6 bond. The ease of resonance in this system determines the difference between the lengths of this bond in different studied compounds, which will be discussed more in the following.

Structural features for the B3LYP/6-31G* optimized geometries are analyzed as followes. All computations were carried out using the Gaussian 98 package [33]. GaussView 5.0.8 software was used for measurming bond lengths and dihedral angles [34]. Numbering of the ring system and substituents of the compounds used in the conformational studies are shown in Figure 2.

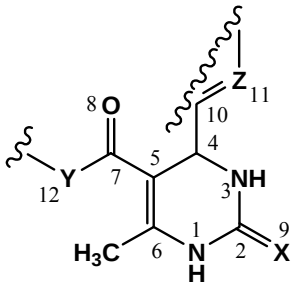
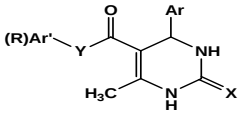


Fig. 2. Numbering of the ring system and substituents of the compounds studied.

Table 1. General structure and structural details of the studied compounds



Compnd.	Ar	Ar'(R)	X	Y
1	N_1-Phenylamino-2-mercaptomethyl-5-imidazolyl	2-Chlorophenyl	O	NH
2	N_1-Phenylamino-2-mercaptomethyl-5-imidazolyl	3-Chlorophenyl	O	NH
3	N_1-Phenylamino-2-mercaptomethyl-5-imidazolyl	4-Chlorophenyl	O	NH
4	N_1-Phenylamino-2-mercaptomethyl-5-imidazolyl	2-Pyridyl	O	NH
5	N_1-Phenylamino-2-mercaptomethyl-5-imidazolyl	3-Pyridyl	O	NH
6	N_1-Phenylamino-2-mercaptomethyl-5-imidazolyl	Methyl	O	O
7	N_1-Phenylamino-2-mercaptomethyl-5-imidazolyl	Ethyl	O	O
8	N_1-Benzyl-2-mercaptomethyl-5-imidazolyl	2-Chlorophenyl	O	NH
9	N_1-Benzyl-2-mercaptomethyl-5-imidazolyl	3-Chlorophenyl	O	NH
10	N_1-Benzyl-2-mercaptomethyl-5-imidazolyl	4-Chlorophenyl	O	NH
11	N_1-Benzyl-2-mercaptomethyl-5-imidazolyl	2-Pyridyl	O	NH
12	N_1-Benzyl-2-mercaptomethyl-5-imidazolyl	3-Pyridyl	O	NH
13	N_1-Benzyl-2-mercaptomethyl-5-imidazolyl	Methyl	O	O
14	N_1-Benzyl-2-mercaptomethyl-5-imidazolyl	Ethyl	O	O
15	2-Thienyl	*iso*-Propyl	O	O
16	2-Thienyl	*tert*-Butyl	O	O
17	2-Imidazolyl	*tert*-Butyl	O	O
18	2-Furyl	*tert*-Butyl	O	O
19	2-Thienyl	2-Chlorophenyl	O	NH
20	2-Thienyl	3-Chlorophenyl	O	NH
21	2-Thienyl	4-Chlorophenyl	O	NH
22	2-Thienyl	2-Pyridyl	O	NH
23	2-Thienyl	3-Pyridyl	O	NH
24	2-Thienyl	Methyl	S	O
25	2-Thienyl	Ethyl	S	O
26	2-Thienyl	*iso*-Propyl	S	O
27	2-Thienyl	*tert*-Butyl	S	O
28	2-Hydroxyphenyl	2-Chlorophenyl	O	NH
29	2-Hydroxyphenyl	3-Chlorophenyl	O	NH
30	2-Hydroxyphenyl	4-Chlorophenyl	O	NH
31	2-Hydroxyphenyl	Methyl	O	O
32	2-Hydroxyphenyl	Ethyl	O	O
33	Phenethyl	Mthyl	O	O
34	Phenethyl	Ethyl	O	O
35	Phenethyl	*iso*-Propyl	O	O
36	Phenethyl	*tert*-Butyl	O	O
37	Phenethyl	Benzyl	O	O
38	Phenethyl	Methyl	S	O
39	Phenethyl	Ethyl	S	O

The C6-C5-C7-O8 dihedral angle (α_2) determines the geometrical orientation of C5=C6 and C7=O8 to each other. If α_2 dihedral angle is between -90º and +90º, the orientation of the carbonyl group is considered *cis*. If this dihedral angle is between (+90º)-(+180º) or (-90º)-(-180º), the orientation is *trans*. C6-C5-C7-O8 dihedral angle also implies the extent of coplannirity of C5=C6 and C7=O8 bonds. When this angle is close to 0º or 180º, the two double bonds are located in the same plane. For values greater than 0º, C7=O8 will orient to the above and for values smaller than 0º this bond will orient to the below of the plane. In compounds **1**, **7**, **16**, **22**, **26-36**, **38** and **39** the geometrical orientation of C5=C6 and C7=O8 to each other is s-*cis* and in the rest of the compounds this orientation is s-*trans*. Compounds **6**, **7**, **15-18**, **24-27** and **31-35** show the coplannarity of these two double bonds. It is easier for π electrons to delocalise and participate in resonance in plannar systems. As a result of resonance, double bonds will adopt some single bond characteristics. Thus, it is expected that C5=C6 and C7=O8 bonds have greater lengths in some compounds. In the molecules with the highest coplannarity, the C5=C6 bond length is remarkably longer compared with other compounds. For example, compounds **15**, **16** and **17** with the highest amount of coplannrity have the highest values for the C5=C6 bond length, 1.363, 1.365 and 1.372 Å, respectively. For the compounds **1**, **8** and **11** with the lowest degree of coplannarity this bond length is closer to the double bond length: 1.355, 1.354 and 1.356 Å.

The carbonyl bond length is usually about 1.220 Å in carboxamides and 1.207 Å in carboxylate esters [35]. The C7=O8 bond length in the studied compounds is higher than these values. In fact, this bond length is influenced by two different resonances. One is the resonance between this bond and nitrogen (amide derivatives) or oxygen (ester derivatives). The C7=O8 bond in compounds **1-4**, **8-12**, **19-23** and **28-30** which are all amide derivatives at C-5 position of the 1,2,3,4-tetrahydropyrimidine ring is remarkably longer (1.227-1.231 Å) compared with ester derivatives (1.219-1.224 Å). The nature of the heteroatom attached to this carbonyl bond has an important impact on its length. In amide derivatives this atom is nitrogen whose lone pair delocalises easier than oxygen lone pairs in ester derivatives. This explains the longer bond length measured in amide compounds. The other resonance which occurs between N1 lone pair, C5=C6 and C7=O8 is the reason for the increased C=O bond lengths in both amide and ester compounds. This resonance is prominent in the compounds with a high degree of coplannarity of C5=C6 and C7=O8 bonds. Compounds **6**, **7**, **15-18**, **24-27** and **31-35** which possess this coplannarity, are all ester derivatives so can be compared with other ester containing compounds in terms of C7=O8 bond length. This comparison reveales a little greater bond length as a result of higher coplannarity and easier resonance in the N1 lone pair, C5=C6 and C7=O8 system. For example in **27** this length is 1.223 Å and in **39** with a lower coplannarity is 1.221 Å.

Table 2. Results for the measured dihedral angles and bond lenghts

Compnd.	α_1	C5=C6	α_2	C7=O8	$\alpha_3+\alpha_4$	C2=X9	C4-H	N1-H	N3-H
1	-1.6	1.355	53.7	1.229	-46.5	1.223	1.095	1.010	1.012
2	-14.2	1.359	-139.1	1.231	34.0	1.224	1.093	1.010	1.012
3	-9.7	1.355	-135.5	1.228	1.1	1.223	1.096	1.010	1.012
4	-9.3	1.355	-137.8	1.229	2.0	1.223	1.095	1.010	1.012
5	-7.9	1.357	135.6	1.229	-8.6	1.222	1.097	1.010	1.013
6	-8.8	1.364	-171.5	1.221	8.4	1.223	1.094	1.010	1.012
7	-11.0	1.363	8.5	1.221	22.1	1.226	1.093	1.010	1.013
8	-2.2	1.354	-130.1	1.227	22.7	1.222	1.096	1.011	1.011
9	-2.5	1.354	-130.9	1.228	20.1	1.221	1.096	1.011	1.011
10	-2.4	1.354	-130.5	1.228	23.5	1.222	1.096	1.011	1.011
11	-1.2	1.356	46.1	1.230	-1.0	1.222	1.096	1.011	1.012
12	-3.0	1.355	-130.4	1.227	19.3	1.221	1.097	1.011	1.011
13	-1.9	1.362	-163.2	1.219	7.6	1.220	1.096	1.011	1.011
14	-1.6	1.362	-162.1	1.220	8.1	1.221	1.096	1.010	1.011
15	-4.8	1.363	-175.0	1.223	39.5	1.221	1.094	1.010	1.012
16	-6.5	1.365	1.6	1.223	-32.0	1.221	1.094	1.010	1.012
17	-4.4	1.372	170.7	1.260	107.4	1.246	1.097	1.009	1.010
18	-7.2	1.363	-178.3	1.224	13.5	1.221	1.093	1.010	1.012
19	-3.3	1.361	157.0	1.231	70.6	1.220	1.093	1.011	1.012
20	-5.4	1.356	-136.1	1.230	50.6	1.221	1.096	1.011	1.011
21	-5.3	1.356	-135.5	1.230	47.6	1.221	1.096	1.010	1.011
22	-5.3	1.356	38.2	1.230	-11.1	1.221	1.096	1.010	1.011
23	-5.8	1.356	-136.5	1.230	47.6	1.221	1.096	1.010	1.011
24	-3.5	1.362	-175.1	1.221	32.6	1.674	1.094	1.011	1.012
25	-3.5	1.361	-174.2	1.222	30.1	1.674	1.094	1.011	1.012
26	-4.8	1.362	5.7	1.221	-28.8	1.674	1.093	1.011	1.012
27	-4.7	1.363	3.0	1.223	-32.0	1.674	1.094	1.011	1.012
28	-5.2	1.361	36.7	1.228	5.4	1.222	1.095	1.010	1.012
29	-5.2	1.362	34.8	1.229	4.3	1.222	1.095	1.010	1.012
30	-5.4	1.361	35.9	1.229	5.4	1.222	1.095	1.010	1.012
31	-6.8	1.365	5.9	1.222	3.6	1.222	1.095	1.010	1.012
32	-6.8	1.365	6.2	1.223	2.4	1.222	1.095	1.010	1.012
33	-5.1	1.364	5.0	1.221	-10.7	1.223	1.095	1.010	1.011
34	-5.2	1.364	5.5	1.222	-6.9	1.223	1.095	1.010	1.011
35	-5.4	1.364	8.6	1.223	-18.8	1.224	1.095	1.010	1.011
36	0.1	1.371	10.5	1.250	60.7	1.248	1.100	1.009	1.009
37	-1.2	1.365	-166.7	1.224	70.5	1.221	1.100	1.010	1.011
38	1.0	1.363	12.5	1.221	54.3	1.675	1.101	1.010	1.011
39	0.8	1.363	12.7	1.221	54.9	1.675	1.100	1.010	1.011

The summation of Z11-C10-C4-C5 and Z11-C10-C4-N3 dihedral angles (α_3) and (α_4) is a measure of the relative position of the C-4 substituent with respect to the tetrahydropyrimidine ring. The C4-C10 bond is perpendicular to the tetrahydropyrimidine plane as can be seen in Figure 3.

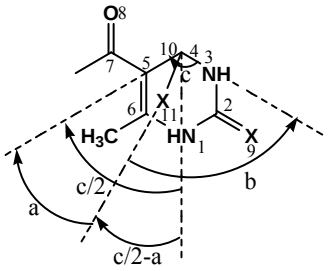


Fig. 3. The relationship between the Z11-C10-C4-C5 and Z11-C10-C4-N3 dihedral angles (α_3 and α_4) and the bisector of the C5-C4-N3 angle (α_5).

In this figure, the C10 is overlaping the the C4 atom. If the sum of α_3 and α_4 dihedral angles is considered as Δ and C5-C4-N3 is named as α_5, the following relationship between these angles will be true:

$\alpha_4 = \alpha_3 - \alpha_5$

$\Delta = \alpha_3 + \alpha_4 = \alpha_3 + \alpha_3 - \alpha 5$ (1)

$\Delta = -2\ (\alpha_5/2 - \alpha_3)$

Thus, the sum of Z11-C10-C4-C5 and Z11-C10-C4-N3 dihedral angles will be equal to the twice of the angle of deviation of Z11 atom from the bisector of C5-C4-N3 angle. Values smaller than 0º account for the deviation of the substituent at C-4 position of the tetrahydropyrimidine ring from 90º (the bisector of C5-C4-N3 angle) towards the C5 atom. Values greater than 0º imply that the substituent at C-4 position is orienting to the N3 atom.

$\alpha_3 + \alpha_4$ values in compounds **1**, **5**, **11**, **16**, **22**, **26** and **33-35** show that Z11 atom is approaching to the C5 atom. In all other compounds this atom is approaching to N3.

The C2=X9 bond length does not vary meaningfully among the studied compounds. It means that neither of the substituents at the C-4 or C-5 positions and ring twisting have an impact on this bond. As it is obvious, C2=S9 bond is longer than C2=O9.

The C4-H, N1-H and N3-H bond lengths are almost the same in all the studied compounds. N1-H is a little shorter than N3-H in all molecules. As a reason for this observation, the possibility of N1-H to participate in two different resonances compared with N3-H which contributes in only one resonance can be provided. These resonances are depicted in Figure 4.

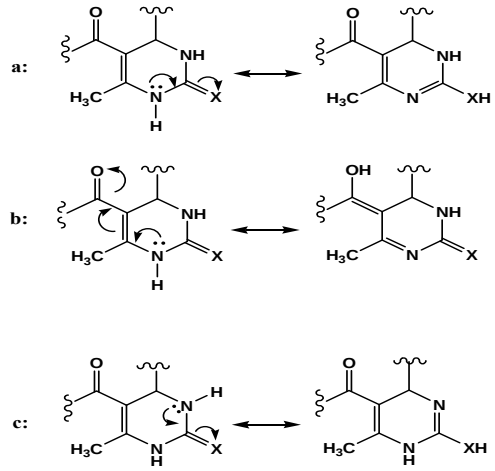


Fig. 4. Diferrent resonances possible for N1-H (a,b) and N3-H (c) bonds.

N-H bond will become shorter in resonance; this can be explained by considering the transition state in the N-H resonance in Figure 5.

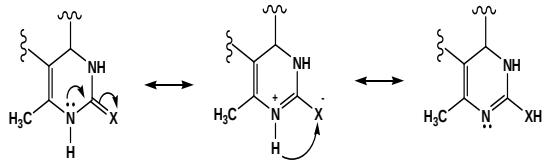


Fig. 5. The transition state in the N-H resonance

In the transition state, the nitrogen hybridization is sp^2 with a higher s character compared with its hybridization before resonance which is sp^3. s orbitals are shorter than p ones so they are closer to the nuclei and atoms with hybridized orbitals having higher s orbital proportion attach through shorter bonds to other atoms.

Conclusion

1,2,3,4-Tetrahydropyrimidinone (thione) compounds are known to be conformationally flexible molecules in which the C-4 aryl ring and the ester (amide) groups can rotate and the conformation of the tetrahydropyrimidine ring can change. In this study thirty nine novel 1,2,3,4-tetrahydropyrimidinone (thione)s were subjected to conformational studies. DFT quantum chemical calculations were performed as the computational method of high accuracy. Important dihedral angles and bond lengths were

investigated and the values obtained were explainable. Results of this work confirm a twisted boat tetrahydropyrimidine ring conformation with an axial C4 substituent for most of the compounds. This substituent was oriented toward the C5 atom. The carbonyl group located on the C5 substituent and the C5=C6 bond had both s-*cis* and s-*trans* conformation in the studied molecules.

Conflict of interest

Authors certify that no actual or potential conflict of interest in relation to this article exists.

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