RESEARCH ARTICLE

# Hydrogen Bond Studies in Interact 6-Mercaptopurine with its Receptor Hypoxanthine-Guanine Phosphoribosyltransferase

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## ABSTRACT

**Objective**: The aim of this study was to study some properties of the pharmaceutical compound (6-mercaptopurine) a number of theoretical methods were carried out to calculate their molecular energy, the length of the bonds and angles, in addition to their chemical forms and the binding sites with the enzyme as important anti-cancer inhibitors.

**Methods:** The intramolecular hydrogen bond, molecular structure, and vibrational frequencies of 6- Mercaptopurine have been investigated by means of density functional (DFT and AM1) methods with 6-311++G basis.

**Results:** The nature of these interactions, known as resonance assisted hydrogen bonds, has been discussed. As a geometrical indicator of a local aromaticity, the geometry-based HOMA index has been applied. Additionally, the linear correlation coefficients between substituent constants and selected parameters in R position have been calculated.

**Conclusion:** The results show that the hydrogen bond strength is mainly governed by the resonance variations inside the chelate ring induced by the substituent groups. The topological properties of the electron density distributions for 6- MP H...N intra molecular bridges have been analyzed .Finally, the natural population analysis methods has been used to evaluate the hydrogen bonding interactions.

**Keywords:** HGPRT, HOMA, 6-Mercaptopurine.

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**Conflict of interest:** None

## INTRODUCTION

Some examples of major purine-based drugs that are currently being used are: anti-cancer agents (6-mercaptopurine).[1,2] Mercaptopurine is one of the antimetabolite antineoplastic agents with immunosuppressant properties. It has been widely used in the treatment of certain types of cancer, human leukemia, and inflammatory bowel disease.[3] The bioavailability of oral mercaptopurine at standard doses is very low, largely as a result of extensive first-pass metabolism by 6-mercaptopurine (purinethol, 6-MP), synthetic analogue of the natural purine bases adenine and hypoxanthine, is a drug used in the maintenance therapy of acute (lymphocytic, lymphoblastic) leukemia. 6-MP has also been used in immunosuppressive therapy and in the treatment of steroid-unresponsive inflammatory bowel disease.[4] 6-MP known chemically as 1,7-dihydro-6H-purine-6-thione. Mercaptopurine is a yellow, odorless or practically odorless, crystalline powder with a molecular formula of $C_5H_4N_4S•H_2O$ and a molecular weight of 170.20 as a monohydrate. The structural formula of 6-mercaptopurine is an analogue of the sulfur-containing purines: 6-mercaptopurine, and azathioprine, have been considered as important and effective drugs used in cancer chemotherapy, for immunosuppression in kidney or heart transplantation and autoimmune diseases.[5-8]

## METHODOLOGY (COMPUTATIONAL METHODS)

Previous theoretical calculations performed on the species studied in this work were performed with the B3LYP and AM1 quantum chemical methods theoretical approach and diffuse basis sets implemented in numerical-based density functional computer software.[9] The present study implements the use of the Gammes suite of codes to carry out a series of calculations.

## DISCUSSION

### Molecular geometry

The 6-MP molecule were fully optimized. GAMESS software using different approximation methods included AM and DFT. DFT, with a hybrid functional B3LYP, is widely used biological and pharmacological system,[10-12] so it will be applied. The measured values in terms of lengths of the bond (BL, degree),

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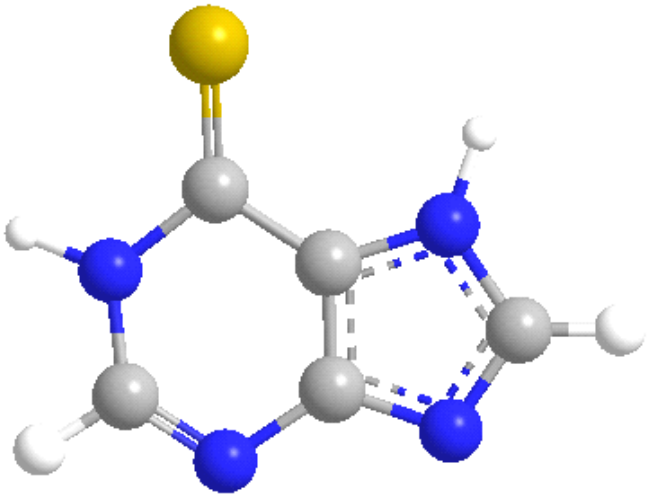

**Figure 1:** Optimized structure of 6-Mercaptopurine

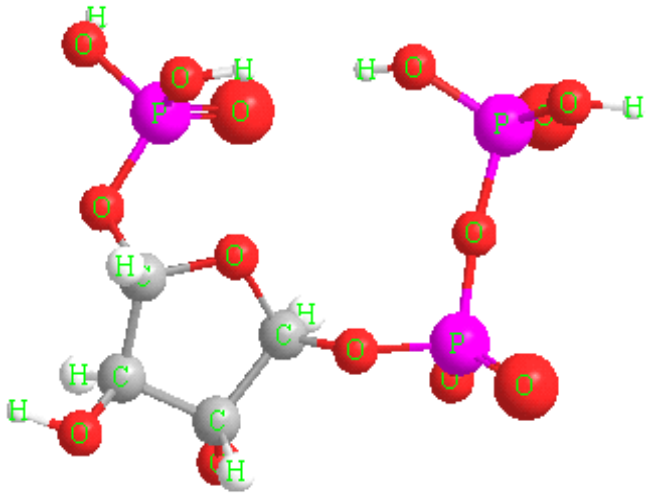

**Figure 2:** Optimized structure of receptor Hypoxanthine-guanine

**Table 1:** 6 Mercaptopurine bond lengths and bond angles calculated by different methods

| *Property* | *Actual AM1 optimal* | | *Actual DFT optimal* | |
|---|---|---|---|---|
| C(2)-H(11) | 1.1 | 1.1 | 1.076 | 1.100 |
| N(3)-H(12) | 1.05 | 1.05 | 1.013 | 1.050 |
| C(2)-N(3) | 1.404 | 1.364 | 1.399 | 1.364 |
| C(4)-N(3) | 1.392 | 1.364 | 1.384 | 1. 364 |
| C(9 )-C(4) | 1.419 | 1.42 | 1.415 | 1.420 |
| C(9)-N(1) | 1.412 | 1.358 | 1.396 | 1.358 |
| N(1)-C(2) | 1.348 | 1.358 | 1.325 | 1.358 |
| C(4)-C(9)-N(1) | 111.011 | 120 | 110.781 | 120 |
| N(3)-C(4)-C(9) | 105.44 | 120 | 104.982 | 120 |
| H(12)-N(3)-C(4) | 125.601 | 118 | 125.728 | 118 |
| H(12)-N(3)-C(2) | 127.737 | 118 | 127.491 | 118 |
| C(4)-N(3)-C(2) | 106.657 | 124 | 106.780 | 124 |
| N(3)-C(2)-N(1) | 113.078 | 126 | 112.791 | 126 |
| H(11)-C(2)-N(3) | 122.036 | 113.5 | 121.987 | 113.5 |
| H(11)-C(2)-N(1) | 124.886 | 116.5 | 125.220 | 116.5 |
| C(2)-N(1)-C(9) | 103.814 | 115 | 104.666 | 115 |

the distance between the atoms, and the angle (BA degree) of continuity. The results are set in a Table 1 for 6-MP and its structure in Figure 1.

Theoretical studies and the calculation values of the bond lengths and bonds angles of importance, which are taken into consideration for many researchers in the field of pharmaceutical manufacturing to compare the pharmacological compounds with the synthesis of the nitrogen bases of the DNA stand.[13]

## Drug-Receptor Interaction

Computational modeling has become a powerful tool in understanding detailed protein-ligand interactions at the molecular level and in rational drug design. To study the binding of a protein with multiple molecular species of a ligand, one must accurately determine both the relative free energies of all of the molecular species in solution and the corresponding microscopic binding free energies for all of the molecular species bindings with the protein.[14] Many computational approaches, at different levels of complexity, have been developed and applied to different ligand-target systems.[15] They essentially differ in the accuracy and resolution level of structural description and in the derived descriptors of ligand-target interactions.[16,17] 6-MP molecule was fully optimized at the B3LYP shown in Table 1. The structure of 6-MP and receptor showed in Figures 1 and 2.

## Phosphoribosyl Ransferees (HGPRTs)

It is well known that the geometrical parameters of the drugs reflect the strength of the bond. Usually, the shorter the N...H distance, the stronger is the hydrogen bonding (HB). In the case of H...N bond, this is accompanied by the lengthening of [6-MP...Receptor] bond and shortening of N...O distance. Comparing of geometrical parameters of 6-MP molecule gives a clear understanding of substitution effects on the structure and hydrogen bond strength of these systems.

The geometrical parameters showed that the O...N and N...H and S...H distances in a chelated ring of 6-MP. Here we would like to address the situations concerning [6-MP], H...N intermolecular H-bond, such as, the estimation of its strength, an p-electron delocalization on the substituent that effects the strength and geometry of intermolecular H-bonded system utilizing DFT and AM1 calculations and in optimized of 6-MP with its receptor (R) (Figure. 3). Hydrogen bonds are denoted by dashed lines. The interaction energies ΔEn for the formation complex of 6-MP...R was defined as the difference between the electronic energy of the complexes, En and energy of an appropriate number of interactions, nE(6-MP), where E(6-MP), and the receptor is the energy of the complex and n is the drugs molecule present in the complexes. Where, R: HGPRT.

**Table 2:** Total AM1 energies En and ΔE

| *Interaction* | | | *WITH (D R)* | | *Bond (kcal./Mole)* | |
|---|---|---|---|---|---|---|
| Without (D, R) molecule | One H bond 2 complexes | Two H bond 3 complexes | Three H bond 3 complexes | Four H bond 3 complexes | Five H bond 2 complexes | Six H bond 1 complex |
| 818.4705 | 0.7254<br>1.2595 | 0.3395<br>0.7988<br>1.0438<br>4.6971 | 1.4959<br>1.5368<br>1.5920 | 1.6477<br>1.7155<br>2.6120 | 1.6904<br>2.1104 | 1.6865 |
| | | | *Location* | | | |
| | | | N7H14...O29 | H12...O21 | N5...H41 | S10...C32H43 |
| | | N1H11...O19 | N1H...O19 | N7...C15H46 | C6H13...O20 | N7H14...O31 |
| | | C15H3...N3 | N5...H41 | N1H11...O19 | N1H11...O19 | N3...C34H45 |
| | | | | N5...H41 | H12...O28 | C2H12...O28 |
| | N3...C5H36 | | | | N7...H36 | N5...H44 |
| | | N1...C16H37 | | | | N7...H46 |
| | | C15H3...N3 | N7...C15H46 | C2H12...O28 | | |
| | | | N1H11...O19 | N5... H36 | | |
| | | | N5...H41 | H11...O19 | | |
| | | | | N7...H41 | | |
| | | N7H14...O26 | | | | |
| | | N1H...O19 | | | S10...C32H43 | |
| | | | | S10...C32H43 | N7H14...O31 | |
| | S10..C32H43 | | S10...C32H43 | N7H14...O31 | N3...C34H45 | |
| | | | N7H14...O31 | N3...C34H45 | C2H12...O28 | |
| | | S10...C32H43 | N3...C34H45 | C2H12...O28 | N5...H44 | |
| | | N7H14...O31 | | | | |

$$\Delta En = ER + E\ (6\text{-}MP) \quad (1)$$

Stabilization energies for the molecule, $\Delta E_{tot}$, are defined as the difference between the energy of a molecule in the complex, 6-MP...R, and the energy of the drug molecule with R and E(6-MP, R)

$$\Delta E_{tot.} = E(6\text{-}MP...R) - \Delta En \quad (2)$$

The total energies and interactions energies are reported in Table 2, showed molecular energies and stabilization energies for (6-MP...R). Negative and positive changes indicate stabilized and destabilized molecular.

There is strong evidence for the presence of charge transfer in the formation of hydrogen bonds.[18,19] in the charge transfer description, the long pair on the accepting oxygen interacts with an empty hydride anti-bond of the donating O–H or F–H, N–H atoms

$$no \rightarrow {}^{*}\sigma\ OH$$

Occupancy of the antibonding orbital raises the energy of the O–H species while stabilizing the oxygen. The stabilization increases with a number of hydrogen bond increases.

This can be described through changing complexes geometry, decreasing intermolecular distances for both drug and receptor coupled with increasing O–H covalent bond length of receptor, indicate a weakening of the covalent OH bond and strengthening of the(O...H) hydrogen bond interaction.

Furthermore, there is increasingly linear O-H...O, C8-N2 energies changes observed here. The destabilization of the bridging hydrogen increases from 0.7254 kcal./mole for single H bond as indicate to 4.6971 kcal./mole for dabbles H bond too related to complexes of 6-MP...R.

Depending on equations of 4.1, 4.2 hydrogen bonding energy values, which be calculated by AM1 method, fixed in Table 4, that we found different and variable value to drug-receptor interactions of 6-MP...R. The calculation obtains three stable configurations (A6, A11, and A13), and their interaction energies range from 2 kcal./mole to extremely strong 4.6971 kcal./mole. Typical to standard measured value of hydrogen bond.[20,21] Appears with dabbling hydrogen bond of 6-MP–HGPRT, which observed importance and active role among the binding of guanine (G) and cytosine (C)[22] that Selective hydrogen bonds formed between complementary nucleic acid bases have two important biological roles. First, selective hydrogen bonding determines the fidelity of replication and transcription processes, and second, hydrogen bonds contribute to the stabilization of the nucleic acid secondary and tertiary structure.

Beyond hydrogen bonding, other interactions are important for the drug-receptor complex formation was appeared, which are described in Table 3. The number of van der Waals interactions is expressed in less value record.[21] and they are calculated according to the atomic distances, angles, and the van der Waals radii.[23,24] It is well established and accepted that the number of van der Waals contacts is determinant for the stability of any protein-ligand complex. As binding of doxorubicin with DNA,[25] indicates that more than one type

**Table 3:** Hydrogen bond energy values, with figures to drug

| *H-bond and or other interaction (kcal/Mole)* | | *Figure* | *Notes* |
|---|---|---|---|
| 1H-bond | 0.7254 | A1 | van der Waals bond |
| 1H-bond | 1.2595 | A2 | Hydrogen bond |
| 2H-bond | 0.3395 | A3 | London force |
| 2H-bond | 0.7988 | A4 | van der Waals bond |
| 2H-bond | 1.0438 | A5 | Hydrogen bond |
| 2H-bond | 4.6971 | A6 | Hydrogen bond |
| 3H-bond | 1.4959 | A7 | Hydrogen bond |
| 3H-bond | 1.5368 | A8 | Hydrogen bond |
| 4H-bond | 1.6477 | A9 | Hydrogen bond |
| 4H-bond | 1.7155 | A10 | Hydrogen bond |
| 4H-bond | 2.612 | A11 | Hydrogen bond |
| H-bond | 1.6904 | A12 | Hydrogen bond |
| 5H-bond | 2.1104 | A13 | Hydrogen bond |
| 6H-bond | 1.6865 | A14 | Hydrogen bond |

of binding may be present. The exact mode of interaction cannot be established merely by this technique. Hence further experiments were required to explore the binding mode.

Energy values of all hydrogen bonds, number of bonds, and the distance between each pair of atoms. According to the donor-acceptor, mean distance can be classified as very strong. (1.2–1.5 Å), strong (1.5–2.2 Å), moderate (2.2–3.2 Å), and weak (3.2–4.0 Å).[23,24]

The observed binding location of those complexes S10…H48, O33…H14, H13…O29 and N7…H41 with distance values of 11.761, 10.427, 9.186 and 11.164 (Å). As fixed in Tables 3 and 4 indicates to a weak van der Waal and other interactions, like Coulomb interaction energy, is a reward for favorable hydrophobic interactions.[28] That was reviled in another theoretical studies.[29] The intermolecular interactions depended on physiological pH of 7.4, as well as, bond angle depends on the nature of the hydrogen bond donor. The length of hydrogen bonds depends on bond strength, temperature, and pressure. The bond strength itself is dependent on temperature, pressure, bond angle, and environment (usually characterized by local dielectric constant). Water is 197 pm. The ideal bond angle depends on the nature of the hydrogen bond donor.

## CONCLUSION

Although much progress has been made recently in theories, algorithms, and computer capacity, the quest for larger and more realistic models remains a challenge for quantum chemistry. Even though the study of small models at a very high level of calculation can now be carried out, this is not the case for most chemical or biological systems, which must be studied faster, and thus, less accurate methods. In this work, small 6-MP H–active site models, including O- and N–donor ligands, have been studied at low to very high levels of calculation to evaluate the level of accuracy of the former methods. Furthermore, some of these methods have been applied to larger zinc-active site models. Optimization of geometry with the AM1 or the hybrid DFT functional B3LYP and mPW1PW91 methods with basis sets, to study large compounds of several numbers of atoms.

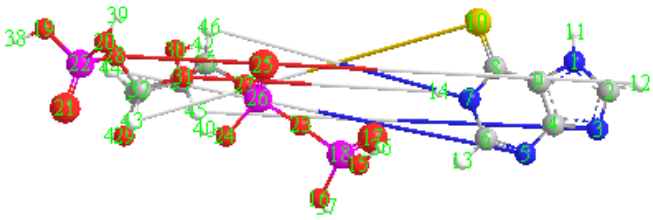

**Figure 3:** Three-dimensional structure of 6-MP with ligand-binding represented by 6 H bond energy 1.6865 kcal/mole

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