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Investigation of intramolecular hydrogen bond in anthra [2,3-b]thiophene-5,10-dione derivatives

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Abstract

Anthracene 9, 10-diones such as ametantrone and mitoxantrone are among the antitumor drugs. Synthesized derivatives of anthra [2, 3-b] thiophene -5,10-dione, demonstrated high therapeutic and antitumor potency. The aim of this research is investigating the geometry and intramolecular hydrogen bond of anthra [2,3-b] thiophene -5,10-dione derivatives. We also considered a derivative of 4, 11-diamino naphtho [2, 3-f] indole -5, 10- diones.

*Theoretical calculations of these compounds have been analyzed by means of DFT calculations at B3LYP level by using 6-311++ G** basis set. All of these calculations were carried out with Gaussian 09 software program. Our results revealed that the structure of distal amino groups and the kind of heteroatom in the structure of these compounds have wide effects on the intramolecular hydrogen bonds that have been analyzed by natural bond orbital (NBO) analysis. By NBO method, the effect of substitution on hydrogen bond strength, steric effects and energies of interactions in the studied compounds were considered. ^{1}H NMR for studied compounds have been calculated at the B3LYP/6-311++G** theoretical level. The calculated chemical shifts of the chelated proton for all molecules, using GIAO method, are well correlate with the calculated geometrical parameters results.*

Keywords: anthra [2,3-b] thiophene -5,10- dione, 4,11-diamino naphtho [2,3-f] indole -5,10- dione, Intramolecular hydrogen bond, NBO, DFT

1. INTRODUCTION

The anthracycline antibiotics have the widest range of utility among anticancer drugs [1], however the efficiency of treatment is limited by organ toxicity [mostly blood, bone marrow and heart] and by emergence of multidrug resistance (MDR) in tumor cells. In an effort to make more antitumor agents with lower organ toxicity, new generations of synthetic analogues of anthracyclines have been designed. the derivatives of anthracene-9,10-dione such as (mitoxantrone and ametantrone) [2] (Fig.1), nevertheless, MDR cells are often resistant to the majority of these agents, which is a serious reason for limiting their therapeutic potency [3], so this problem remain a serious reason for therapeutic failures [4]. Ametantrone does not generate superoxide product but instead of that shows an antioxidant activity [5]. The function of anthracycline antibiotics is multimodal. The anthraquinone moiety of these antibiotics and their analogues, determines the potency of these compounds intercalate in to DNA, so they can interfere with the replication and transcription. There is unbelievable effort in to develop new agents that maintain the core anthracene-9,10-dione moiety and exhibit different spectra of potency , with reduced toxicity [6,7]. We report here the studies of a derivative of naphtho[2,3-f]indole-5,10-dione with improved activity against (MDR) cells. One can suggest that the adjustment of an additional pyrole ring in the ametantrone moiety would lead to redistribution of charges in the chromophore, which influence drug-DNA interactions, on the other hand there is evidence for the importance of amino group for milder side effects [8]. These compounds demonstrated significant cytotoxicity against human cancer cell lines and higher potency than mitoxantrone for drug resistance. Moreover, an additional heterocyclic moiety can increase the binding of ametantrone analogues to their intracellular targets. Krapcho and his coworkers [9] have shown high potency of thio analogues of ametantrone against leukemia cells. In further work for potential chemotherapeutic compounds, for evaluating the role of heteroatom cyclic moiety in cytotoxicity, series of thiophene-fused tetracyclic analogues of ametantrone, the derivatives of anthra[2,3-