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Structural basis for molecular recognition, theoretical studies and anti-bacterial properties of three bis-uracil derivatives

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ABSTRACT

Three bis-pyrimidine compounds (**1**, **2** & **3**) have been synthesized by the reaction of 6-[(dimethylamino) methyleneamino]-1,3-dimethyluracil with three different aldehydes viz. *p*-methoxybenzaldehyde, *p*-nitrobenzaldehyde, and 2-thiophenecarboxaldehyde in aqueous media in presence of 'green surfactant' followed by recrystallization in EtOH. The compounds are characterized by elemental analyses, NMR and single crystal X-ray diffraction. N–H···O hydrogen bonds and weak C–H···O interactions are the main non-bonding interactions in the molecular structures of the three compounds. Details of the synthesis, spectroscopic data and structures of the three compounds are presented. Furthermore, we have rationalized some relevant noncovalent interaction involving the aromatic moieties by means of DFT calculations. Finally, we have also analysed the anti-bacterial properties of compounds **1**–**3** and compared to Ofloxacin drug. The anti-bacterial activity has been tested against *Klebsiella pneumoniae*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. All compounds are found to possess from moderate to good anti-bacterial properties (MIC 25–100 μg/ml).

1. Introduction

Beyond traditional boundaries, the field of crystal engineering is being pursued by scientists with varying interests. It is now-a-days treated as a comprehensive subject dealing with modelling, synthesis, evaluation and utilization of crystalline solids having desired functions along with construction of fascinating topological architectures.[1,2] Advances in crystal engineering as a research field has ushered significant interest in the study of intermolecular interactions and their subsequent use in the formation of solid state structures. The arrangement of molecules in the solid state underpins much of modern crystal engineering and thus the subject continues to be driven by the understanding of intermolecular interactions and their use in trying to control solid state structures. Several interactions are very commonly used by chemists to construct supramolecular assemblies, such as hydrogen bonding,[3] π–π stacking,[4] ion–π[5] and C–H···π contacts.[6]

Uracil (U) and its derivatives, constituents of the genetic material, play a pivotal role in basic biological processes. From crystal engineering perspective, uracil based compounds are interesting because of their ability to form hydrogen bonds using the endocyclic nitrogen and exocyclic oxygen centres. Often uracil based supramolecules self-assemble utilizing arrays of multiple hydrogen bonds for holding together the individual building blocks.[7] The bioactivity of 5-substituted uracils induces exceptional interest in their biochemistry and pharmacology, and they are the most interesting and studied uracils. 5-Fluorouracil has been in use as chemotherapy agent the treatment of malignancies including colorectal and breast cancers.[8] Moreover, 5-fluorouracil has been used in crystal engineering since the fluorine substitution modifies the π-binding ability of the ring, favouring the formation of lone pair (lp)–π interactions.[9] Being the most effective inhibitor of 4-aminobutirataminotransferase, 5-ioduracil is an important anti-metabolite. 5-cyanouracil exhibits cellular activity and has been shown to inhibit pyrimidine catabolism in vivo.[10] The biological and physicochemical properties of these compounds depend on the ability of molecules to form hydrogen bonding and also to participate in π-stacking interactions. The synthetic exploitation of nucleophilic double bond of uracil continues to generate interest among researchers in view of great variety of potential products. Though many reports are available in literature for the functionalisation of uracil but most of them suffer from harsh reaction condition or longer synthetic pathway.[11]

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In view of the importance of multitopic uracil linkers as building blocks for supramolecular architectures and considering their bioactivity, design and synthesis functionalized uracil moieties are important. In our earlier paper we reported synthesis and crystal structures of various aryl/alkyl/heteroarylbis-(6-amino-1,3-dimethyluracil-5-yl)methanes in water including those studied herein.[12] In our earlier study, reactions changing the aldehyde moiety were carried out in presence of 'green surfactant' generating different bis-uracil derivatives. Rhamnolipids (mixture of mono- and di-rhamnolipids),[12] a major class of biosurfactant, which is produced by *Pseudomonas aeruginosa* OBPI was used as green surfactant. The X-ray structures of the synthesized uracil derivatives shown in Fig. 1 were obtained exclusively to characterize the compounds; however the solid state structures were not analysed in detail. In this manuscript we report a combined experimental (a new batch of crystals has been synthesized and deposited in the Cambridge Structural Database) and theoretical study (DFT) where the crucial role of lp−π and C−H/π interactions have been analysed. A competition between these two noncovalent forces is useful to explain the disorder of the thiophene ring observed in compound **3**. In addition, we have analysed the antibacterial properties of compounds **1**–**3** and compared them to Ofloxacin drug. The anti-bacterial activity has been tested against *Klebsiella pneumoniae*, *Staphylococcus aureus* and *P. aeruginosa*. All compounds possess from moderate to good anti-bacterial properties.

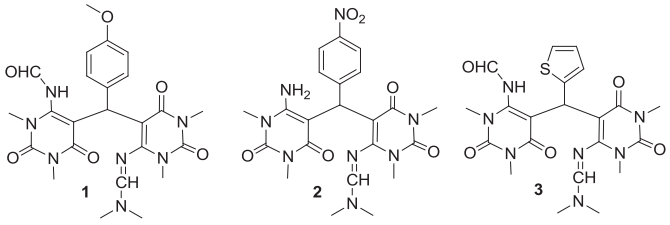


Fig. 1. Structure of compounds **1**–**3**.

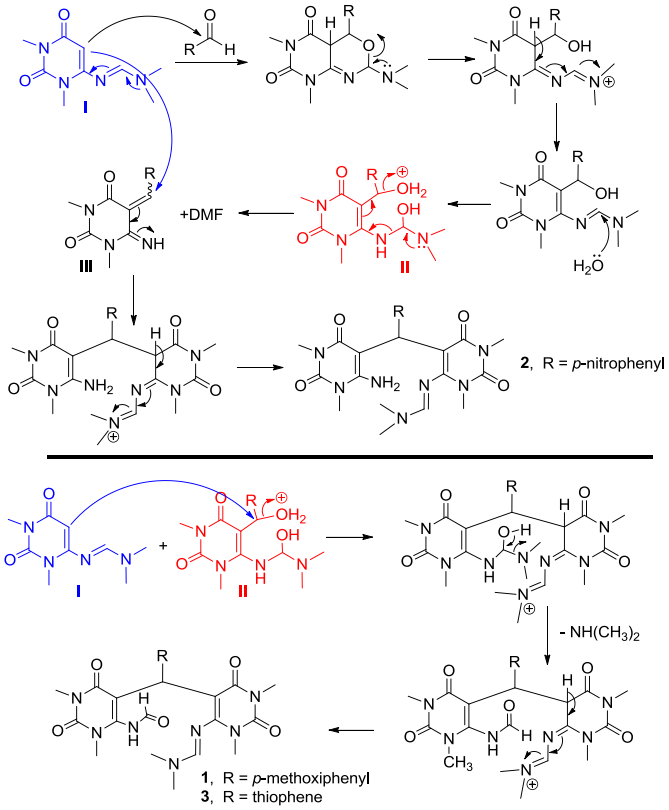
2. Results and discussion

2.1. Synthesis

As we have previously demonstrated, the reaction of 6-[(dimethylamino)methyleneamino]-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione with aldehydes in the absence of biosurfactant in water progressed over a long time interval.[12] Interestingly, when the reaction was carried out using biosurfactant produced by *P. aeruginosa* OBPI in water with *p*-toluene sulfonic acid(*p*-TSA, 15 mol %) as catalyst, the duration of the reaction was shortened remarkably. A plausible mechanism is proposed to account for the formation of the products in Scheme 1. It involves an initial nucleophilic attack at the 5-position of 6-[(dimethylamino)methyleneamino]-1,3-dimethyluracil (**I**) to the carbon centre of the aldehyde, which is followed by some hydrogen transfer reactions to finish with an addition-elimination of a water molecule (intermediates **II** and **III**). A second molecule of I then reacts at the nucleophilic 5-position with intermediate **III** to afford the product **2**. Compounds **1** and **3** are produced via a nucleophilic attack of compound **I** to intermediate **II**, followed by the elimination of dimethylamine (see Scheme 1, bottom). Because aldehydes are more reactive than ketones toward nucleophilic attack, the reaction occurs with aldehydes only.

2.2. Structural description of (1)

The molecular structure of the compound with the atom numbering scheme is shown in Fig. 2. The packing diagram is shown in



Scheme 1. A plausible mechanism for the formation of products **1**–**3**.

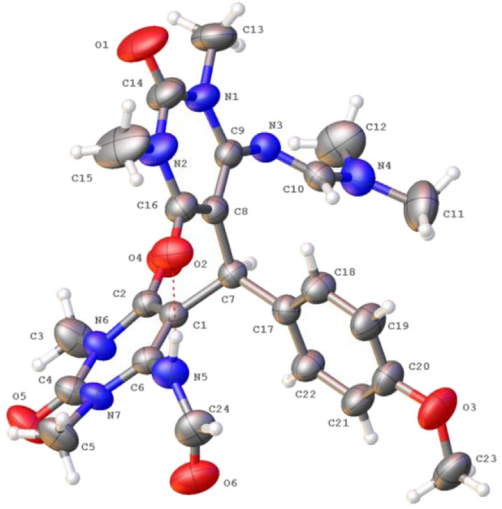


Fig. 2. View of the molecule with displacement ellipsoids drawn at 50% probability level.

Fig. S1 and bond distances and bond angles are shown in Tables S1 and S2 (see Supplementary data). In the compound, the dihedral angle between the two uracil rings A (N6/N7/C1/C2/C4/C6) and B (N1/N2/C8/C9/C14/C16) is 105.23(7)° with centroid-centroid separation of 4.8423(12) Å. The phenyl group makes a dihedral angle of 72.68(6)° with ring A with centroid−centroid separation of 4.9382(13) Å and dihedral angle of 108.36(7)° with ring B with centroid−centroid separation of 5.0814(11) Å. Intramolecular N−H···O hydrogen bonds and weak C−H···O interactions lend stability to the structure.