

Structure analysis of hydroxy/non-hydroxy substituted dihydropyrimidine molecules

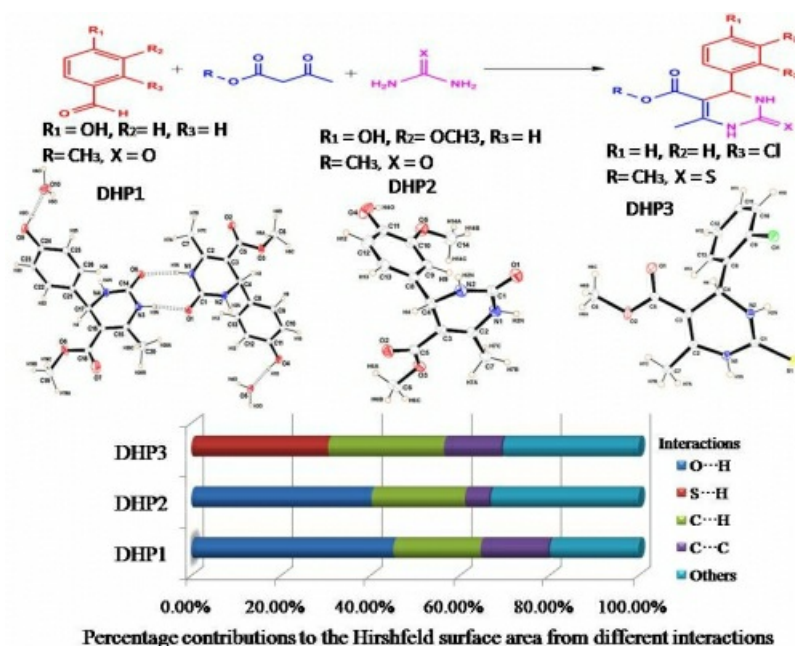
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Dihydropyrimidine (DHP) is the product of one pot condensation reaction between an aldehyde, β -ketoester and urea or thiourea under acid catalysis, which is well known as Biginelli reaction, was first reported by Pietro Biginelli in 1983. This one-pot condensation reaction of DHP products shows interesting pharmacological, calcium channel modulation, antiviral, antibacterial and antimicrobial activities. Considering the view of importance of title compound a different derivative with various hydroxy or non-hydroxy substituent's along with the variant of other functional groups such as methoxy or chloro on aldehyde part of dihydropyrimidine derivatives have been synthesized to evaluate the role of intermolecular interactions in their molecular packing. We analyzed here only the obtained single crystals that were not reported previously, i.e. 4-hydroxy (DHP1), 4-hydroxy-3-methoxy (DHP2), and 2-chloro (DHP3) dihydropyrimidine molecules. The DHP molecules prefer to form dimer either through strong N-H...O or N-H...S hydrogen bonds depending on its constituent which is either urea or thiourea respectively. Hirshfeld Surface analysis shows that DHP molecules prefer H...O interactions in DHP1 and 2, and H...S interactions in DHP3 of 45.2%, 40.3% and 30.6% from their total interactions respectively. DHP1 crystallizes in the monohydrated form whereas DHP2 and DHP3 crystallizes in the anhydrous form, which is reflected in higher percentage of O-H...O interaction in DHP1 due to additional hydrogen bonding with water molecule. Other percentage of interactions including C...H and C...C consolidate the packing for generating a three-dimensional network. Thermal analysis (DSC) revealed that DHP1 is stable below 139 °C and it loses its crystallinity irreversible above 139 °C whereas DHP2 crystal is stable up to 252 °C in comparison to DHP3 which is stable up to 165 °C. To understand the nature of hydrated or non-hydrated form of DHP molecules, the Cambridge Structural Database (CSD, Conquest Version 1.17) has been analyzed, which list sixteen hydroxyphenyl-substituted DHP derivatives including four 2-hydroxyphenyl-substituted DHP molecules, one 3-hydroxy-substituted and eleven 4-hydroxyphenyl-substituted DHP molecules. It is worthy to mention that five of the 4-hydroxyphenyl-substituted DHP molecules prefer to crystallize in a hydrated form. The CSD analysis clearly suggests that 4-hydroxy-substituted DHP molecule are prone to crystallize in their hydrated form compared to 3-hydroxy or 2-hydroxy-substituted DHP molecules; this may be due to the observed O-H...O hydrogen bonding with water molecule acceptors with the hydroxyl group in the preferred 4-position. Further theoretical calculation, biological activity and analysis of single crystal structure of the remaining synthesized molecules of the same series are under progress to rationalize the importance of weak intermolecular interactions in presence of other functional groups to establish structure-property relationship.

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