

Synthesis of Pyrimidinones with (E/Z)-2-Chlorobutene-2-Enyl Group



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Abstract

Substituted pyrimidines are considered as one of the important building blocks for designing new drugs. The functionalization of the pyrimidine ring with reactive groups creates opportunities for inhibition of intracellular metabolism by ligand-receptor interaction, including the type of irreversible inhibition.

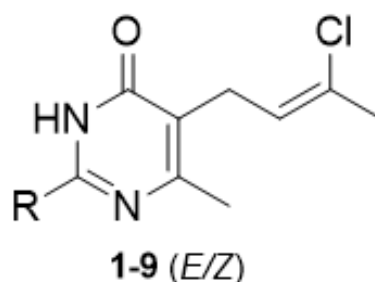
Keywords: Pyrimidines; 5-(2-Chlorobutene-2-enyl) group; Doking; DNA-methylation inhibitors

Introduction

It is known that the affinity of natural pyrimidines for biochemical processes in all living systems creates a rational concept for creating drugs based on molecular target-ligand interactions of substituted pyrimidines. In light of this, it seems important that a reactive chemical group be present in the structure of a biologically active compound, due to which an effective interaction between the receptor and the ligand is possible. In this regard, our attention was drawn to the (E/Z)-2-

chlorobutene-2-enyl group, information on the use of which in works on the synthesis of biologically active compounds is absent.

Obviously, the presence of a reactive 2-chlorobutene-2-enyl group in the pyrimidine ring creates opportunities for the interaction of the ligand molecule with various nucleophilic groups of cellular target macromolecules. In view of the foregoing, in continuation of the research on the search for biologically active pyrimidines [1,2] (Figure 1 & 2).



1-9: R = Me, Ph, SH, OH, NH₂, NPh, SPr, SBn, SCH₂(2-ClC₆H₄).

Figure 1: We synthesized 2-substituted pyrimidin-4(3H)-ones 1-9, functionalized in position 5 of the ring with a residue of reactive (E/Z)-2-chlorobutene-2-enyl group.

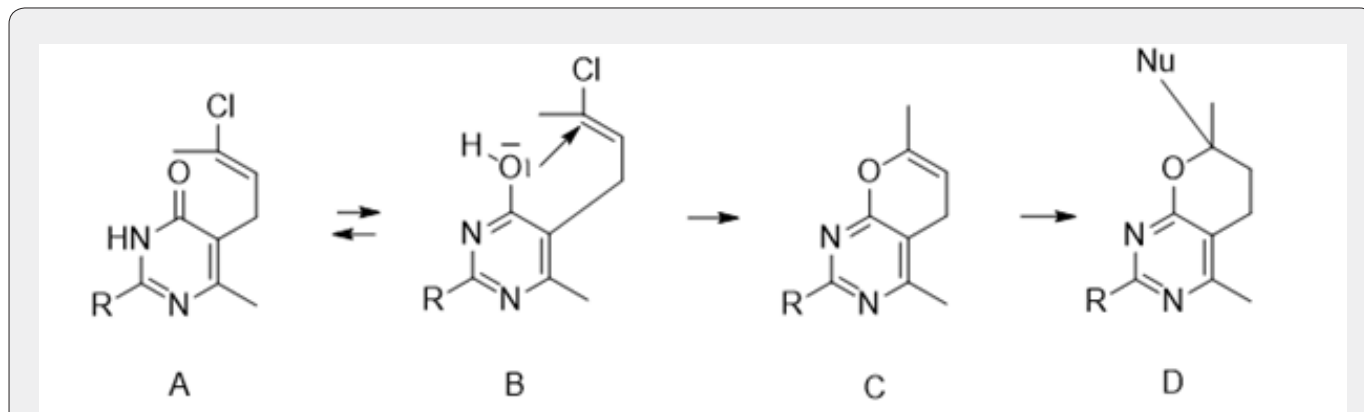


Figure 2: The presence of a 2-chlorobuten-2-enyl group in position 5 of the ring of the pyrimidin-4(3H)-one derivative creates opportunities for the interaction of nucleophilic groups of macromolecules with the pyrimidine ligand according to the proposed mechanism, according to the scheme.

Pyrimidin-4-one A, in the form of pyrimidin-4-ol tautomer B, attacks the C2 atom of the vinyl group to eliminate the chlorine atom and form the 6-methyl-4-dihydro-2H-pyran derivative C. The latter reacts with suitable nucleophilic groups, for example, with hydroxyl groups of macromolecules according to the well-known reaction of protection of hydroxyl groups by interaction with 2,3-dihydropyran, with the formation of compound D. The synthesized compounds were docked and their effect on the level of tumor DNA methylation was studied under in vitro conditions in a 180-mouse sarcoma model.

References

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