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Study on Synthesis and Activity of Thiouracil as Antibacterial Lead Compounds

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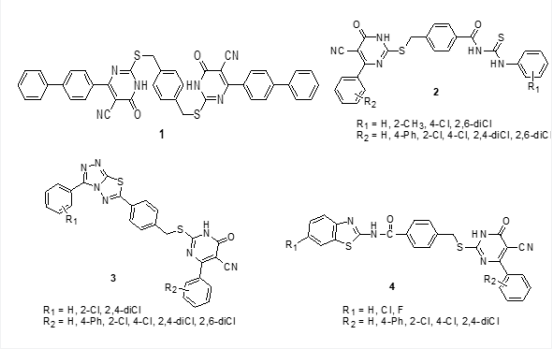

Derivatives: Synthesis of thiouracil derivatives of compounds 1, 2, 3 and 4.

At present, bacterial resistance has become one of the great potential threats to human life and health, which has attracted great attention all over the world [1,2]. SecA is a key protein in the secretion pathway of bacteria, which has ATPase activity. It is found that SecA can inhibit the secretion of toxic proteins in bacteria, which is expected to overcome the "efflux pump" effect of multidrug resistance. SecA, as the target of new antibacterial drug design, is likely to find the next generation of antibacterial drugs [3-6]. Recently, we chose SecA as the target site, the ATP binding site in SecA and the active structural region of IRA2 and NBD close to the ATP region as the target binding sites of the designed compounds, and the more active SecA inhibitor 1 [7] of thiouracil as the leading structure, using the active substructure splicing, skeleton transition, bioelectronics and other strategies in drug design, a series of new compounds containing thiouracil were designed and synthesized by introducing chain acyl thiourea, benzothiazole and triazolothiadiazole which have antibacterial activity and have strong interaction with protein (such as hydrogen bond and hydrophobic force). Some compounds with high antibacterial activity and SecA inhibitory activity were found, and the structure-activity of the compounds was preliminarily discussed relationship (Derivatives).

Synthesis of Thiouracil Derivatives 2 [8], 3 [9], 4 [10]

The aromatic amine on reaction with acyl isothiocyanate generated acyl thiourea and further reacted with thiouracil intermediates to yield the 24 compounds 2; With aromatic acid as raw material, through multi-step reactions (esterification, hydrazine reaction, etc.) to get the triazolo-thiadiazoles deritives, further on reaction with thiouracil intermediates gave 12 compounds 3. 2-aminobenzothiazole derivatives reacted with the 4-(chloromethyl) benzoyl chloride, further on reaction with thiouracil intermediates gave 15 compounds 4.

The evaluation of the antibacterial activity of compounds 2, 3, 4 and the SecA inhibitory activity of some representative com pounds: The inhibitory activity of the compounds 2, 3, 4 against Bacillus amyloliquefaciens, Staphylococcus aureus and Bacillus subtilis were tested by plate colony counting method, with the norfloxacin and lead compound 1 as control. some compounds had very strong inhibitory effects against the tested strains. The inhibition rate against the three tested bacteria of some compounds even reached 100% in the 24-hour inhibition test (25 μg/mL). The inhibitory activity against the SecA showed that compounds 3d (R1=H, R2=2,4-diCl) had the higher activity. The IC50 (50% inhibitory concentrations) value of compound 3d was 9.7 μg/mL, which was significantly lower than that of compound 1 (20.8 μg/mL).

In order to investigate the bonding mode between the newly compounds with the SecA, the compounds 3d were docked into the SecA crystal structure (Figure 1). Two possible binding pockets were selected: the ATPase ATP-binding site and the pocket between IRA2 and NBD domain that is close to the ATP domain. The result showed that the new inhibitors binded at a similar position as the lead structure 1. In addition to forming hydrogen bonds with ARG566, GLN570 and ARG642 and forming hydrophobic interaction with VAL131 and ILE216 in the crystal structure of SecA, the compound 3d can also form cation-π interaction with ARG642

which effectively enhances the bond strength between the compounds and enzymes and this has great theoretical significance to optimize the structure design of the compounds and find the highly active precursor compounds.

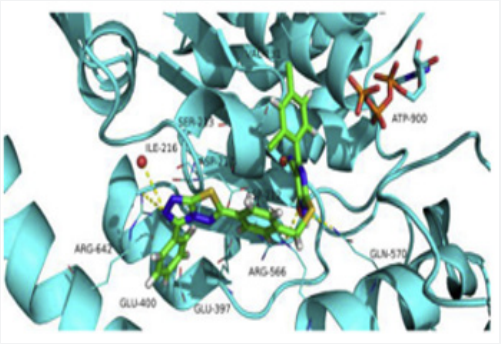

Figure 1: The proposed docking conformation of the compound 3d with SecA.

Acknowledgement

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