Synthesis, antibacterial and antitubercular evaluation of substituted 2-styryl-4-oxoquinazolin-4(3H)-yl-isonicotinamide derivatives

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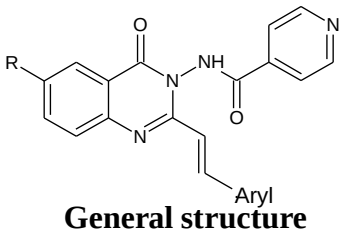
ABSTRACT: Quinazolinone skeleton is found in a number of biologically active molecules. There are various reports regarding molecules with substitution at 2nd and/or 3rd position of quinazolinone skeleton showing a broad range of biological properties. The two heterocyclic moieties quinazolinone and isoniazid, which have been reported to possess potent antimicrobial and antitubercular properties is expected to have a synergistic effect against both Gram-positive, Gram-negative and Mycobacterium. Hence, it is proposed to synthesize isoniazid incorporated-styrylquinazolin-4-one analogs by molecular hybridization approach. Therefore, a new series of isoniazid incorporated-styrylquinazolin-4-one derivatives were prepared by incorporating the hydrazine unit of isoniazid into the 3rd position of quinazolin-4(3H)-one ring. The 2nd position of quinazolinone joined with with various aryl and heteroaryl substituted styryl group. The 6th position of quinazolinone ring is substituted with iodine as shown in **General structure**. All these derivatives are evaluated for their *in vitro* antibacterial (Gram positive and Gram negative) activity and antitubercular activity against *Mycobacterium tuberculosis* (H37Rv, MTB, clinical isolate (MDR-TB)). Among the series, compound **4m** (R = I; Ar = 4-dimethylamino phenyl) showed highest activity against *B. subtilis*, *E. coli* and *P. aeruginosa* with MIC in a range of 4-8µg/ml compared to 2-4µg/ml showed by standard ciprofloxacin and compound **4j** (R = I; Ar = 4-chlorophenyl) also showed equal potency to that of **4m** and standard ciprofloxacin (MIC=2-4µg/ml). The compounds **4c, 4j** and **4m** showed significant potency against Gram+ve and Gram-ve organisms with MIC in the range of 4-16 µg/ml. The compound **4m** (R = I; Ar = 4-dimethylamino phenyl) showed highest antitubercular activity with MIC of 31 µg/ml against *Mycobacterium tuberculosis* H37Rv and MTB strains among the series. However the antitubercular potency was less when compared to the standards employed (INH=<1 µg/ml, Streptomycin= <2µg/ml, Ethambutol=4µg/ml). Compound **4g** (R = I; Ar = 3-pyridyl) exhibited equal potency to that of **4m** against H37Rv. None of the compound in among the series exhibited activity against INH-resistant MDR-TB strain. *In silico* docking studies were carried out on target protein Enoyl-Acyl Carrier Protein Reductase (InhA). The results showed that the ligand **4m** exhibited strong binding affinity with highest docking score of -70.515 and binding energy -52.774 kcal/mole and one H-bond interaction with **Arg-9E** (2.74 Å) and two electrostatic interactions with **Asp-6E** (3.63 Å and 3.92 Å). The biological activity data is in accordance with docking studies.



General structure

Keywords: *Quinazolinone, Isoniazid, Antibacterial activity, Antitubercular activity, Docking*