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

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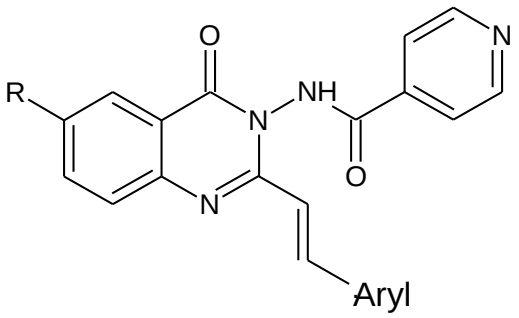
ABSTRACT:

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. In synthetic medicinal chemistry, hybridization is one of the techniques to design new drugs with improved biological activity with respect to the corresponding lead compounds. 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