DESIGN AND SYNTHESIS OF NOVEL 2-ARYL-QUINAZOLINE-4-ONES AS POTENTIAL TANKYRASE-2 INHIBITORS WITH ANTICANCER ACTIVITY.

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Cancer constitutes a large spectrum of diseases characterized by uncontrolled growth and spread of abnormal cells. Owing to its intricate pathophysiology and the challenge of selectively directing therapeutic interventions towards cancerous cells, the need for drugs that are both non-toxic and efficacious has yet to be met. Tankyrase-2 (TNKS2) is a member of the Poly(ADP-ribose) polymerase (PARP) superfamily, and is considered to be a promising target in anticancer therapy due to its regulatory role in Wnt/β-catenin pathway. Based on the established effectiveness of quinazoline derivatives as PARP inhibitors, we designed and synthesized several potential TNKS2 antagonists, utilizing the quinazoline-4-one scaffold. Interestingly, we report that the relatively large diol substituent at the 8-position, is not only tolerated but also enhances the inhibitory potency of the molecule. The final products were prepared by firstly treating nitro-substituted anthranilic acid with the appropriate chloride. Subsequently, the corresponding amide was formed which was stirred with an excess of base to afford the nitro-quinazoline-4-one nucleus. After hydrogenation, the derived amine was treated with acryloyl chloride, and the resulting derivative reacted with OsO_4 to afford the desired diol. One compound 2,3-dihydroxy-N-(4-oxo-2-phenyl-3,4-dihydroquinazolin-8-yl)propanamide has been pharmacologically evaluated, possessing IC_{50}=180 nM and satisfactory selectivity against other members of the PARP family. The aforementioned ligand has been co-crystallized with the enzyme's active site, revealing its binding motif. The quinazoline-4-one core forms three hydrogen bonds and a pi-stacking interaction, while three additional hydrogen bonds are established with Tyr1050, Tyr1071 and Met1054 through the diol moiety, thereby augmenting the overall binding affinity. Although further evaluation is needed, these compounds could prove to be selective and efficacious TNKS2 inhibitors with anticancer properties.