DESIGN AND SYNTHESIS OF NOVEL DIAZAQUINAZOLINE UREA SUBSTITUTED ANALOGUES AS POTENT ANTICANCER AGENTS

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Over the past few decades, cancer has been one of the leading causes of death in developed countries worldwide. Although many efforts have been taken to design potent anticancer agents, most of the efficient cytotoxic procedures that have been developed, lead to compounds with no selectivity. Quinazoline is a heterocyclic scaffold that belongs to the family of benzodiazines, and is one of the most common cores in medicinal chemistry due to its broad spectrum of pharmacological activities. Synthesized quinazoline derivatives possess antiviral, anticancer, antimicrobial, antifungal, anti-inflammatory, antihypertensive, anti-malarial and anticonvulsant activities. Based on this, we present here the design and synthesis of diazaquinazoline derivatives substituted on C 4 and C 7. Commercially available drugs, such a sorafenib and erlotinib were used as leading compounds. The desired analogues were afforded in good yields, applying a seven step procedure, starting from thiourea and 2-chloro-4-nitroaniline.

The synthesized compounds were evaluated for their anticancer activity against cancer cell lines and a panel of 110 proteins (106 kinase and 4 bromodomains). Most of them are active against all the tested cell lines, while three of them proved to be very potent. According to the thermal shift assay four of the new inhibitors displayed very interesting results for the BRAF kinase (Tm = 10.0, 12.0, 12.5 and 22.0 °C). Interestingly the results for the most cytotoxic derivatives imply the existence of another target. Thus a new approach based on proteomic analysis is under procedure for discovering the new target.