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Synthesis and *in vitro* cytotoxic activity of novel pyrazolo [1,5-a]pyrimidines towards breast adenocarcinoma MCF-7 cell line, cell cycle analysis and QSAR studies

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The cyclin-dependent kinases (CDKsa) are a family of serine/threonine protein kinases that play essential roles in the regulation of cell division. Individual CDKs phosphorylate distinct substrates in different phases of the cell cycle. Motivated by the widely reported anticancer activity of 4 arylazo-3,5-diamino-1H-pyrazoles as a novel cytotoxic agents against CDK2-cyclin E, new series of 3,5-diamino-4-arylazopyrazoles (3,4), were synthesized by cycloaddition of N2H4 on aryl(diazenyl) malononitrile 1 in 1:1 or 1:2 molar ratios. In addition, 5,7-diarylpyrazolo[1,5-a] pyrimidines possessing CDK2 inhibitory activity have been reported. Herein, we described the synthesis of 2-amino-3-arylazopyrazolo[1,5-a]pyrimidine derivatives (5-18) by reflux of 3,4 with ethoxymalononitrile, chalcones or arylidinemalononitriles in EtOH/Pip. 16 compounds were evaluated for the in vitro cytotoxic activityagainst human breast adenocarcinoma MCF-7cell line using MTT technique. Some of the tested compounds exploited moderate growth inhibitory activity (IC50's = 15.32-40.70 μM); in particular compound 7 exhibited superior potency (IC50 = 3.25 μM). Its effect was furtherstudied on cell cycle progression. A significantincrease in the percentage of cells at S-phase by 1.4 folds compared to control which indicates that the mechanism of action is related to S cell cycle arrest. Molecular docking simulation was also carried out for CDK2 enzyme to investigate their binding affinity. A 2D QSAR model was builtto explore the structural requirements controlling the observed cytotoxic properties.

Breast centers: Inspiring quality in breast care

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Breast Centers are considered the optimal expression of breast care. The concept of Breast Centers reflects the culmination and the results of the changes that occurred in the treatment of Breast Cancer. The direction of breast carcinoma care has moved towards specialization and towards an evidence-based multifaceted approach with the involvement of a spectrum of disciplines, in both diagnostic and therapeutic areas. The European Parliament called on the Member States to ensure nationwide provision of interdisciplinary breast centers by 2016, since treatment in an interdisciplinary breast center has proven to raise chances of survival and to improve the quality of life. The International School of Senology of the SIS studied and analyzed the main accreditation programs from the USA and from Europe and elaborated its International Accreditation Program for Breast Centers/Units for its worldwide affiliated societies. In February 2012, at the 2nd International Congress of Breast Disease Centers in Paris, we proposed the following Declaration, inspired by the "Florence Statement: "All women across the world should have access to fully equipped, quality assured, dedicated breast centers/units that provide competent and comprehensive care". The Paris Statement was approved by the Chairmen of the main Accreditation Programs for Breast Centers: the SIS/ISS, the NAPBC and EUSOMA and was endorsed by the Chairman of the UICC as well. This was the first step of a Project aimed to elaborate a Common Global Platform for Breast Centers/Units Accreditation. We are confident that, by joining efforts and sharing experiences, a significant improvement in worldwide Breast Care can certainly be achieved.