Synthesis, Electronic Structure and Anti-Cancer Activity of the Phenyl Substituted Pyrazolo[1,5-a][1,3,5]triazines

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Source: Current Organic Chemistry, Volume 25, Number 12, 2021, pp. 1441-1454(14)
Publisher: Bentham Science Publishers
DOI: https://doi.org/10.2174/1385272825666210607004536

Background: Synthesis of a series of 2-(dichloromethyl)pyrazolo[1,5- a][1,3,5]triazines was carried out and evaluated in vitro for their anticancer activity against a panel of 60 cell lines derived from nine cancer types.

Methods: The joint quantum-chemical and experimental study of the influence of the extended πconjugated phenyl substituents on the electron structure of the pyrazolo[1,5- a][1,3,5]triazines as Pharmacophores were performed. It is shown that the decrease in the barriers to the rotation of phenyl substituents in compounds 1-7 possibly leads to an increase in the anti-cancer activity, which is in agreement with the change in the parameter biological affinity Φ_0. Analysis of the $S_0 \rightarrow S_1$ electronic transitions ($\pi \rightarrow \pi^*$) of the pyrazolo[1,5- a][1,3,5]triazines shows that an increase in their intensity correlates with anti-cancer activity.

Results: Thus, the introduction of phenyl substituents increases the likelihood of investigated pyrazolo[1,5-a][1,3,5]triazines interacting with protein molecules (Biomolecule) by the π-stacking mechanism. In both methyl and phenyl derivatives of pyrazolo[1,5-a][1,3,5]triazines, the second electronic transition includes the n- MO (the level of the lone electron pair in two-coordinated nitrogen atoms). The highest intensity of the $\eta \rightarrow \pi^*$ electronic transition is observed in pyrazolo[1,5-a][1,3,5]triazine with pyridine residue, which does not exhibit anticancer activity, but exhibits antiviral activity [13].

Conclusion: It can be assumed that the possibility of the formation of [Pharmacophore-Biomolecule] complex by hydrogen bonding ([H-B]) mechanism with protein molecules increases.

Keywords: 3; 5-a][1; 5]triazines; Pyrazolo[1; anti-cancer activity; barriers of rotation; parameter Φ_0; quantum-chemical; spectral methods