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DYNAMIC FATIGUE DISPERSION CHARACTERIZATION OF AQUEOUS CLAY SUSPENSIONS BY METHOD

A series of thiazoline and thiazolidinone-based 4-hydroxycoumarin derivatives were synthesized using both conventional synthesis procedures and microwave-assisted techniques. The new compounds were evaluated for their cytotoxic effect against three human cancer cell lines; MCF-7, HCT-116 and HepG2 and one normal human cell line (BJ-1). The promising anti-proliferative compounds 2a, 2b, 6a and 6b were assessed for inhibiting EGFR and PI3K/mTOR. Compound 6a showed the highest inhibition activity towards the signaling pathway. The apoptotic effect and cell cycle arrest potential of derivative 6a were examined. Moreover, the molecular docking, physicochemical properties and pharmacokinetic parameters of the promising compound were investigated, as well.

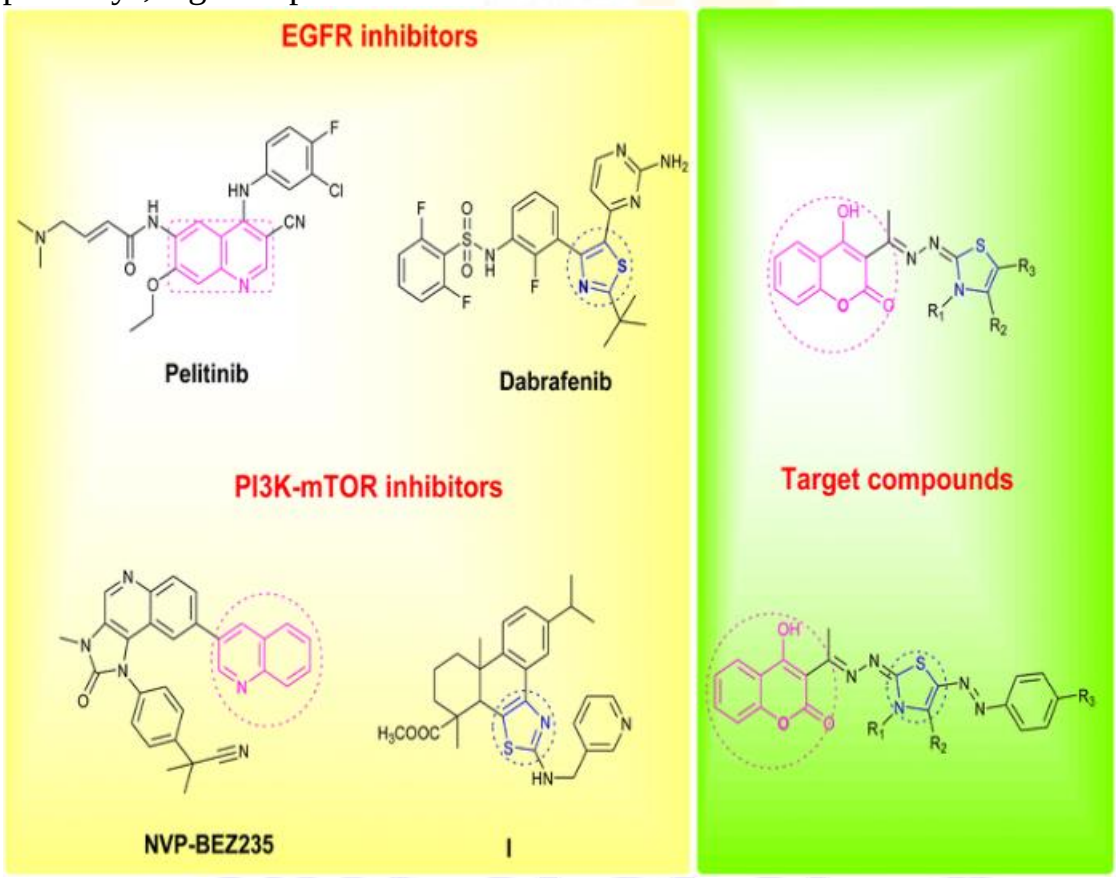
Cancer is a disease of a multifactorial nature that ranks as the second leading cause of death worldwide, resulting in about 10 million deaths in 2020.It has been noted that a number of signaling pathways when dysregulated are subsequently involved in cancer pathogenesis. The PI3K/AKT/mTOR pathway is an intracellular signaling pathway related to a number of biological processes such as apoptosis, cell proliferation and angiogenesis. Dysregulation of this pathway is associated with a vast disturbance in cell growth, survival and metastasis which results in cancer development. Somatic mutations or gaining and losing of key genes are among the factors affecting this pathway in a number of different tumors such as breast, colon and liver cancers.

PI3K/AKT/mTOR pathway is initially activated by the binding of extracellular growth factors to epidermal growth factor receptor (EGFR), then phosphatidylinositol 3-kinase (PI3K) is activated which consequently activates the serine/threonine protein kinase B (PKB/AKT). This leads to some downstream effects as the activation of mechanistic target of rapamycin (mTOR). Agents that target the regulators in this pathway are either single PI3K, AKT or mTOR inhibitors or dual inhibitors of PI3K and mTOR. In theory, inhibiting EGFR and PI3K/mTOR would probably lead to the strongest inhibition of the whole PI3K/Akt/mTOR pathway.5,6

Coumarin as a privileged heterocyclic ring that displays multifarious biological activities has been utilized to design useful antitumor compounds.7–12 A closer look at the coumarin chemical structure and physicochemical properties reveals that the 2H-chromen-2-one ring is planar and lipophilic, which grants the scaffold the ability to interact with a variety of biological counterparts, whereas,

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the lactone group of the coumarin enable the molecule to form strong polar bonds and to acylate different protein targets.13 On the other hand, the thiazole ring is a versatile moiety that demonstrated many desirable biological activities, dabrafenib is an example of a thiazole drug that underwent clinical trials for its selectivity towards tyrosine kinase inhibition.14,15 Moreover, thiazoles are reported as potent anticancer agents that are capable of targeting certain kinase pathways, e.g. compound.

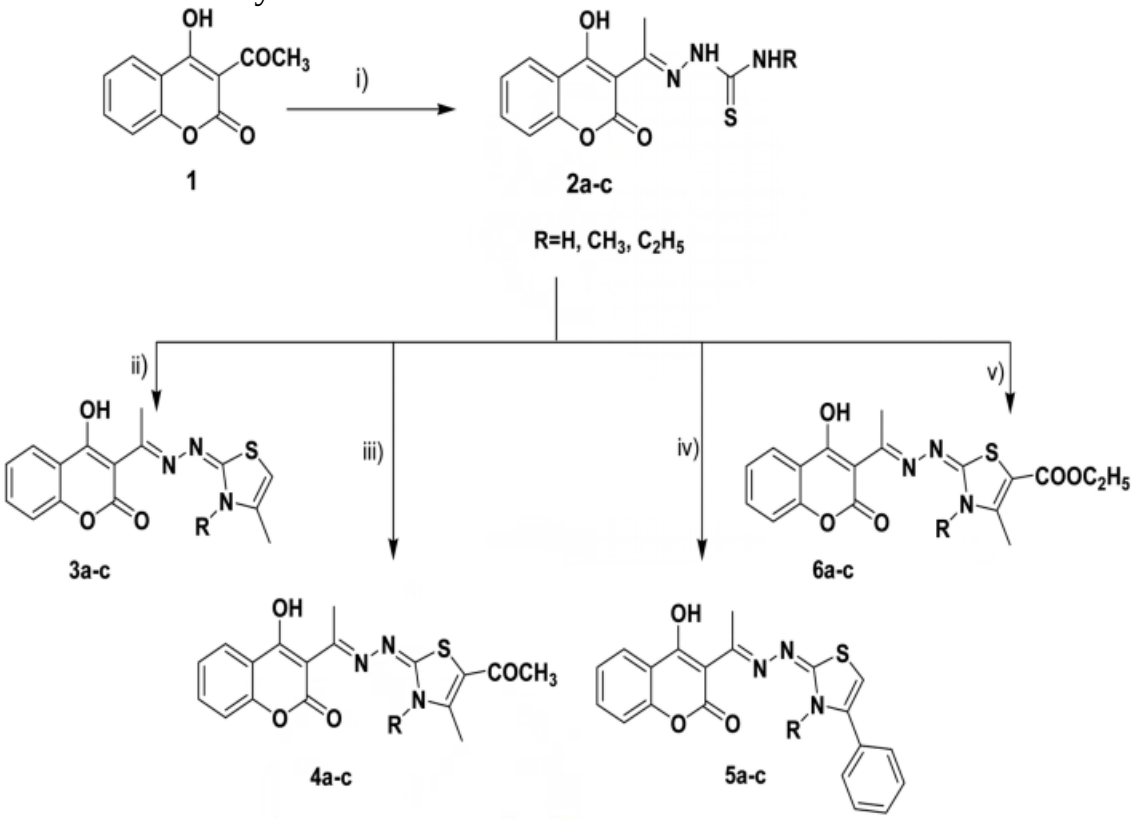


In an attempt to pursue new antitumor agents, considering the aforementioned information, and as a continuation to our research work in cancer field,17–26 the target compounds were rationally developed by using one of the FDA approved drugs that inhibits EGFR (pelitinib) and another that is developed by Novartis and involved in PI3K/AKT/mTOR signaling pathway (NVP-BEZ235) as models, replacing their biologically active quinoline ring with its bioisostere coumarin scaffold, and hybridizing the scaffold with the bioactive thiazole moiety.

The target thiazolines and thiazolidinones were prepared from the intermediate thiosemicarbazones 2a–c through the reaction with different α-haloketones as outlined in Scheme 1. Thus, cyclocondensation of thiosemicarbazones 2a–c with chloroacetone and/or 3-chloroacetylacetone in ethanol using a catalytic amount of anhydrous sodium acetate yielded the corresponding 4-methylthiazolines 3a–c and/or 5-acetyl-4-methylthiazolines 4a–c, respectively. While the reaction of 2a–c with phenacyl bromide afforded the 4-phenylthiazoline congeners 5a–c.

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Similarly, the 4-methylthiazole-5-carboxylates 6a–c were obtained via the reaction with ethyl-2-chloroacetoacetate.



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