Title: Nature-Inspired Design of Tetraindoles: Optimization of the Core Structure and Evaluation of Structure–Activity Relationship

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Building on the initial successful optimization of a novel series of tetraindoles, a second generation of the compounds with changes in the core phenyl ring was synthesized to improve anticancer properties. 17 new compounds with different rigidity, planarity, symmetry and degree of conjugation of their core structures to 5-hydroxyindole units were synthesized. All the compounds were fully characterized and tested against breast cancer cell line (MDA-MB-231). The results revealed that the core structure is required for activity and it should be aromatic, rigid, planar, symmetrical and conjugated for optimal
activity. Compound 29, which has strong anticancer activity against various tumor-derived cell lines, including Mahlavu (hepatocellular), SK-HEP-1 (hepatic), HCT116 (colon), MIA PaCa-2 (pancreatic), H441 (lung papillary), A549 (lung), H460 (non-small cell lung) and CL1-5 (lung carcinoma) with IC₅₀ values ranging from 0.19 to 3.50 µM, was generated after series of successive optimizations. It was found to induce cell cycle arrest and apoptosis in vitro and inhibit tumor growth in the non-obese diabetic-severe combined immunodeficiency (NOD/SCID) mice bearing xenografted MIA PaCa-2 human pancreatic cancer.