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Nature-inspired design of tetraindoles: Optimization of the core structure and evaluation of structure–activity relationship

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ABSTRACT

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 IC_{50} 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.

Indole-3-carbinol (I3C), a naturally occurring phytochemical found in cruciferous vegetables, has received much attention due to its translational potential in cancer prevention and therapy.[1–4] Under acidic conditions in vitro, and following ingestion, I3C readily selfcondenses to form a mixture of oligomeric products including cyclic tetraindole (CTet).[5,6] I3C and its oligomeric products are under study as cytostatic and tumor-suppressive agents, in particular, CTet.[4] Development of CTet as a drug faces some problems; poor solubility, its synthetic procedures are low-yielding that requires HPLC purification of product from the complex acid reaction mixture of I3C. Inspired by CTet structure and activity, we discovered novel tetraindoles as anticancers. In particular compound SK228 (Fig. 1) showed promising activity against breast adenocarcinoma, various human lung and esophageal cancer cell lines.[7] In that study, we have investigated the structural features of tetraindoles.[7–10] Several indole derivatives were synthesized and tested.[7,10] 5-Hydroxyindole moiety showed the highest activity. The core structure was also found to affect the activity (phenyl showed much better activity than 2-thienyl).[7] In continue of our

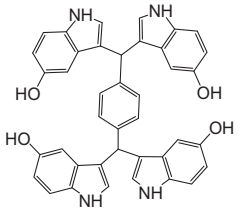

Figure 1. The structure of SK228.[7]

Abbreviations: CCR2, CC chemokine receptor 2; CCL2, CC chemokine ligand 2; CCR5, CC chemokine receptor 5; TLC, thin layer chromatography.

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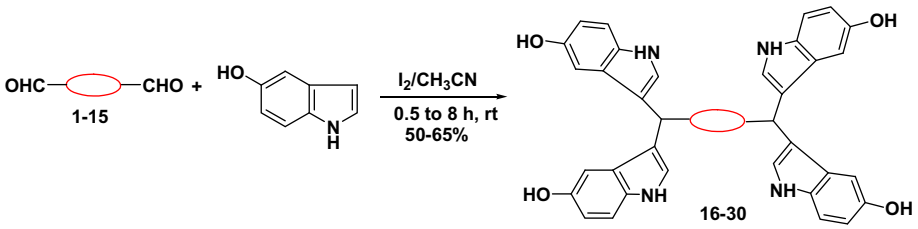


Scheme 1. Synthesis of the target compounds **16**–**30**.

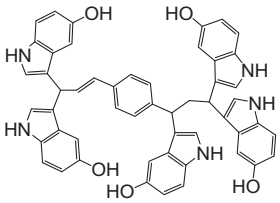
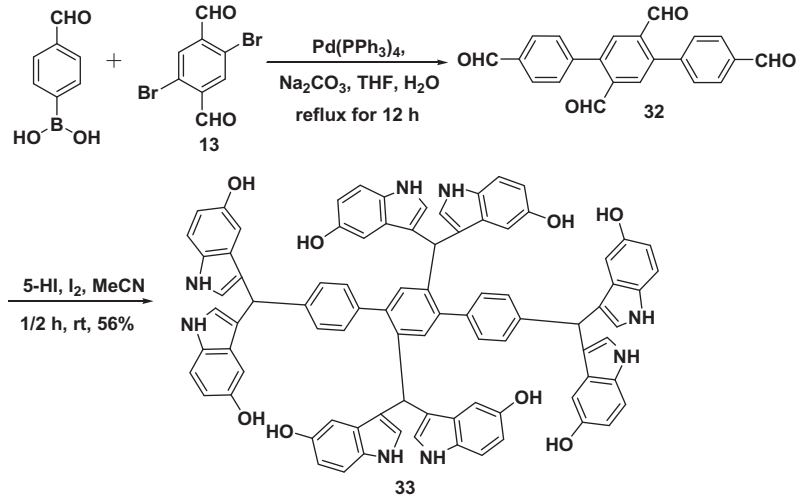


Figure 2. Structure of pentaindole **31**.

interest in tetraindoles; this study aims to explore-in more detail – the structural features of the core structure. Thereby development of tetraindoles which are expected to act by I3C-like mechanisms against several cancers and to offer substantially improved potency and activity that would make them applicable to cancer therapy.

We speculated that the rigidity and conjugation of the core structure of tetraindoles might play important roles in their anticancer effects. Moreover, core structures containing napthalene, anthracene and phenanthroline may act as DNA intercalating-crosslinkers. In order to identify the key structural features of phenylenebis(methylene)-linked tetraindoles, a series of compounds were prepared in which the core structure was systematically varied. Accordingly, tetraindoles **16**–**30** were generated by the reaction of 5-hydroxyindole with various dialdehydes **1**–**15** in acetonitrile and presence of catalytic amounts of molecular iodine at room temperature (Scheme 1).[11,12] The crude products were subsequently purified by column then recrystallization to give the pure compounds in yields ranging from moderate to very good yield. Dialdehydes were synthesized by standard methods.[13–21] Pentaindole **31** (Fig. 2) was obtained as a side product during synthesis of tetraindole **18**, due to Micheal addition of indole to α,β-unsaturated aldehyde.[22] While octaindole **33** was obtained from the tetraaldehyde **32** (Scheme 2). Aromatic dicarboxaldehydes were generally synthesized either by double oxidation of benzylic alcohols, double reduction of dinitriles or directed dilithiation strategies followed by electrophilic quenching with DMF. Accordingly, 1,4-benzene-diacetaldehyde **2** was synthesized from the commercially available 1,4-benzenediacetic acid by esterification, reduction to the corresponding alcohol then selective oxidation.[13] In analogy, 2,7-naphthalenedicarbox-aldehyde **4** and 2,6-naphthalenedi-carboxaldehyde **5** were obtained from their corresponding dimethyl esters.[14] 1,4-Benzenediacryaldehyde **3** was prepared by an aldol condensation between terephthalaldehyde and acetaldehyde.[15] 1,5-naphthalene-dicarboxaldehyde **6** obtained from 1,5-diaminona-phthalene by Sandmyer reaction to get diiodo which is converted into dicyano that reduced with DIBAL-H.[16] Similarly, dialdehydes **7**, **8** and **10** were generated by reduction of the corresponding dicyano derivative.[17] 1,10-Phenanthroline-2,9-dicarboxaldehde **9** was prepared by oxidation of the commercially available neocuproine by selenium dioxide in 4% water in dioxane.[18] 2,5-Dimethylbenzene-1,4-dicarboxaldehyde **11** was obtained from 1,4-dibromo-*p*-xylene by reacting with *n*-BuLi and DMF.[19] The same starting material was used for the synthesis of 2,5-dibromobenzene-1,4-dicarboxaldehyde **13** by controlled oxidation via chromium trioxide in presence of acetic anhydride, acetic acid and sulfuric acid.[20] Compound **13** was used for the synthesis of *p*-terephenyl-4,3′,6′,4″-tetracarb-aldehyde **32** via the Suzuki coupling reaction with 4-formylphenylboronic acid (Scheme 2). On the other hand, 2,3,5,6-tetramethylterephthalaldehyde **12** was synthesized from 1,2,3,5-tetramethylbenzene as repoted.[21] Finally, tetrachloroterephthalaldehyde **14** and tetrafluoroterephthalalde-hyde **15** were prepared from commercially available 2,3,5,6-tetrachloro-1,4-dicyanobenzene as reported.[23]



Scheme 2. Synthesis of octaindole **33**.