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The synthesis and biological activity of novel anthracenone-pyranones and anthracenone-furans

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ABSTRACT

An efficient and divergent methodology for the synthesis of new anthracenone-pyranones and anthracenone-furans is described. Key reactions discussed in these syntheses include an aldehyde promoted annulation with a β-keto-sulfoxide, a domino alkyne insertion/carbonylation/Nu-acylation and a DMEDA promoted Castro–Stephens reaction. We also report the in vitro growth inhibition of these compounds in a range of human cancer cells. The natural product BE-26554A displayed good cell growth activity on BE2-C neuroblastoma and SMA glioblastoma cell lines at 0.17 and 0.16 μM (GI_{50}), respectively. Of note, were a CF_3 functionalised anthracenone 4-pyranone (chromone) derivative **22**, and an anthracenone-furan derivative **54** which displayed 0.20 μM and 0.38 μM growth inhibition, respectively, in the BE2-C neuroblastoma cell line.

1. Introduction

The structural class of anthrapyranones have a remarkable range of biological activity mainly as anti-bacterial agents, anti-tumour and anti-fungal compounds. Some examples in this family of compounds include pluramycin A (**1**), kidamycin, altromycin B, hedamycin topopyronone C (**2**), λ-indomycinone[1] and the antibiotic saptomycin E (**3**) (Fig. 1). Generally, the molecular mode of action of this class compounds is thought to go through an intercalation with the major groove of DNA along with covalent bonding with N7 of guanine. The effectiveness of this mode of action, is reliant on substituents at the C5, C8 and C10 positions (mostly carbohydrates) and the C2 epoxide moiety for the guanine alkylation process.[2–4] In one early study an altromycin B-DNA adduct was investigated using two-dimensional ^{1}H–^{15}N HMBC experiments to identify the epoxide alkylation position in DNA. Interestingly, neopluramycin, which differs from pluramycin (**1**) in that it has a single olefin in place of the epoxide, also has anti-tumour activity (leukemia L-1210),[5] however this compound shows little, if any, DNA sequence selectivity compared to pluramycin (**1**).[6]

Simple epoxide-anthrapyranones have also been isolated, for example, in 1994, the Banyu Pharma group isolated the natural product BE-26554A (**4**) from *Streptomyces* A26554 cultures.[7] In this early report and brief study, the natural product epoxide (**4**) was described to have an IC_{50} value of 0.001 μM (or 10 nM) against P338 Leukaemia cells. Unfortunately, any indication of the epoxide stereochemistry was not identified in this isolation study. Aside from the anthrapyranones, the 4-pyranone ring system alone has also been reported to effect murine leukaemia cell (L1210) growth.[8]

Several groups have developed syntheses of anthrapyranones, most commonly through various approaches to the 4-pyranone ring system D ring. These key reactions include; the Baker–Venkataraman rearrangement with cyclisation,[9,10] a 6-*endo-dig* cyclisation of alkyne ketones,[11–15] a Friedel–Crafts acylation[16] and cyclisation of β-diketones[17,18] among others.[19,20] In 2013, we described a racemic synthesis of anthrapyranones through the annulation of a β-keto-sulfoxide and an aldehyde.[21] Interestingly, a recent report on a non-metal mediated synthetic ring forming processes on simple chromones has come to light[22] along with the oxidative alkylation of these ring systems.[23]

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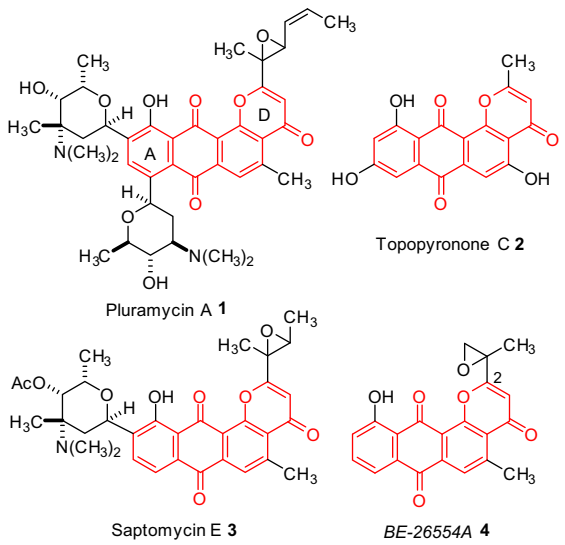


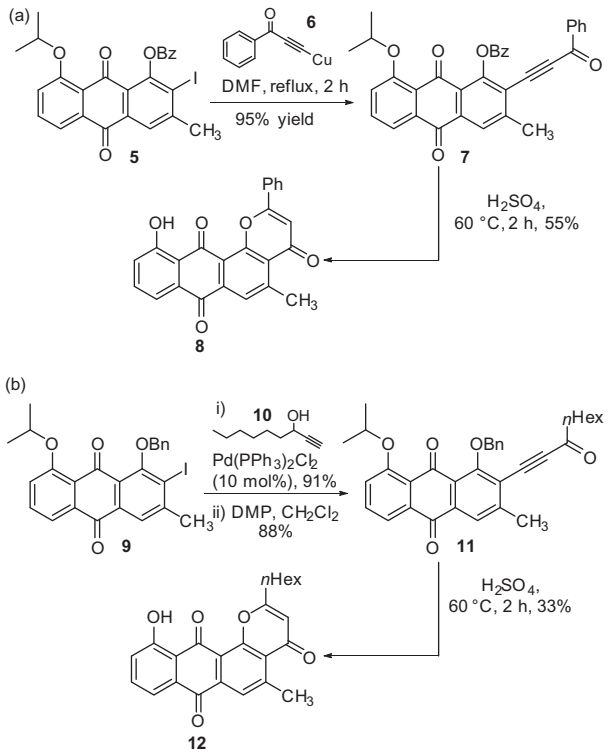
Figure 1. Chemical structures of selected natural product anthrapyranones.

The varying biological activity of the pluramycin class of compounds, with different substitution at C2, reflects the importance of this region of the molecule. As part of furthering our investigations into this class of compounds we were interested in developing efficient syntheses of the anthracenone ring system with varying D-rings, as well as investigating the role which this ring system plays in the biological activity. In our synthetic studies several approaches to the 4-pyranone core of the anthrapyranones were developed. Initially, an approach using an acid induced ring closure of anthraquinone-yne-ones was conceived (Scheme 1a). This tactic has been pursued by several groups including that of Shvartsberg.[24,25] The anthraquinone-yne-one could be prepared either using a Castro–Stevens reaction or the related Sonogashira palladium catalysed process. Thus treatment of benzoyl protected phenol **5** with phenyl copper acetylene **6** provided the yne-one **7** in excellent yield (95%).[24] Subjection of compound **7** to sulphuric acid provided the phenyl 4-pyranone **8** in 55% yield through hydration of the alkyne and cyclisation through a phenoxide. Alternatively, hydration using *p*-TsOH provided a crude mixture of the isopropyl-ether 4-pyranone and phenol-4-pyranone **8** (1:3.7 by NMR analysis of the crude product).[26]

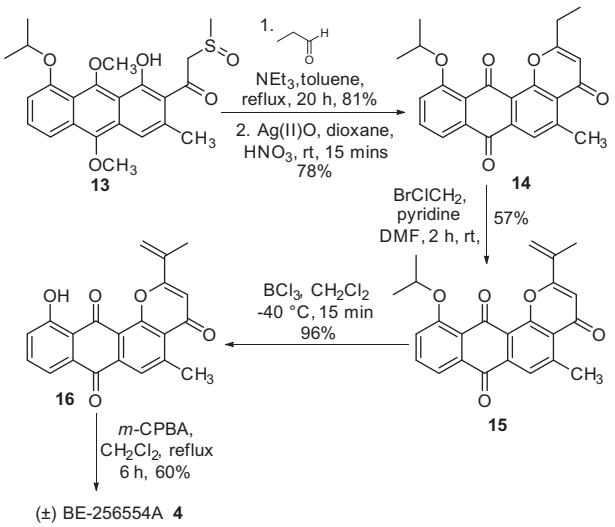
As we required an alkyl, or alkenyl, substituent at the C2 position to begin SAR studies, an alkyl substituted alkyne was incorporated into the initial C–C bond forming process. Following several unsuccessful reaction trails with the benzoyl protected derivative **5** the corresponding benzyl protected phenol **9** was used (Scheme 1b). Treating compound **9** with the alkyne alcohol **10** gave the desired alkyne in excellent yield (91%). Oxidation of this product with Dess–Martin periodinane furnished yne-one **11**, in 88% yield. Unfortunately, treatment with *p*-TsOH did not provide any pyranone compound **26**, however revisiting the previously used sulfuric acid conditions only resulted in 33% of the desired alkyl anthrapyranone **12**. As this annulation process was low yielding we decided to pursue a more efficient synthetic route. Unfortunately, following the piperidine and aminovinyl ketone method devised by the Shvartsberg group,[24] only afforded a complex mixture of products.

A synthetic route through key β-keto sulfoxide **13** was ultimately successful in the efficient preparation of the 4-pyranone ring system bearing an alkyl side chain.[21,27–29] Eventually this intermediate **13** was also used *en route* to the natural product (±)-BE-26554A (**4**) (Scheme 2).[21] The β-keto-sulfoxide-annulation procedure with propionaldehyde was especially high yielding (81%) which provided the impetus to expand this reaction to other aldehydes. Coupled with the Augustine olefination procedure by Krohn et al., this sequence could provide a range of substituted 4-pyranone derivatives.[10,30]

We next examined this first group of compounds (**4**, **8** and **12**, **14** and **16**) for in vitro cell growth inhibition against a panel of nine human cancer cell lines including: HT29 (colorectal carcinoma); MCF-7 (breast adenocarcinoma); A2780 (ovarian carcinoma); H460 (lung carcinoma); A431 (epidermoid carcinoma); DU145 (prostate carcinoma); BE2-C (neuroblastoma); SJG2 (glioblastoma); MIA (pancreatic carcinoma) and SMA (glioblastoma). As in previous investigations,[31–33] an initial screen was carried out



Scheme 1. Synthesis of (a) phenyl and (b) alkyl anthrapyranones.



Scheme 2. Summary of the final stages of the synthesis of (±)-BE-26554A (4).[21]