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Diverted total synthesis of melodorinol analogues and evaluation of their cytotoxicity

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ABSTRACT

A series of melodorinol analogues were synthesized *via* a diverted total synthesis approach, leading to structural modifications on several regions of the molecule. Their cytotoxicity was evaluated against five human cancer cell lines (KB, HeLa-S3, MCF-7, HT-29 and A549). Structure-activity relationship studies revealed key parameters that affect the cytotoxicity. In particular, the novel 4-bromo-furanone analogues exhibited greater cytotoxicity compared to the corresponding non-brominated analogues. The stereochemistry at C-6 and the nature of acyl substituents on the C-6 and C-7 hydroxyl groups also play an important role. The most potent analogues exhibit approximately 15-fold higher cytotoxicity towards KB and HeLa-S3 than melodorinol and also show exceptionally high potency against MCF-7, HT-29 and A549 cell lines.

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Melodorinol ((*S*,*Z*)-**1**) (Fig. 1a) is a bioactive heptene isolated from various plants such as *Melodorum fruticosum* Lour.,[1] *Artabotrys madagascariensis*,[2] *Xylopia pierrei*,[3] and *Cleistochlamys kirkii*.[4] This compound, along with its natural derivatives such as acetylmelodorinol ((*S*,*Z*)-**2a**) (Fig. 1a), has been reported to exhibit significant cytotoxic activities against several human tumour cell lines[1–4] as well as antimalarial properties;[4,5] however, the molecular target of these compounds has not yet been identified. Recently, a range of semi-synthetic melodorinol derivatives ((*S*,*Z*)-**2b-g**) (Fig. 1a) were prepared from naturally occurring melodorinol by acylation of the hydroxyl group at the C-6 position.[1d] The *in vitro* cytotoxicity studies of these derivatives revealed that short alkyl and phenyl side-chains significantly enhanced the antiproliferative activity; however, the compound became inactive when a carboxyl side-chain was introduced. The synthesis of achiral 6-deoxy-melodorinol analogues was also reported;[6] however, the biological activity of these derivatives were not studied. The dramatic impact of C-6 modification towards cytotoxicity encouraged us to further investigate the structure-activity relationships at the other positions of the molecule (Fig. 1b). This includes the effect of the geometry of the double bond across C-4 and C-5 (region 1), the stereochemistry at C-6 (region 2), and the substituents at C-3 on the furanone ring (region 3) as well as the hydroxyl groups at the C-6 and C-7 positions (regions 4 and 5, respectively). Due to the limitation of the semi-synthetic approach to modify the core structure of the molecule, we instead employed a diverted total synthesis approach in order to achieve such modifications.

The first total synthesis of melodorinol was reported by Shen and co-workers utilizing the reaction between (*R*)-2,3-isopropylidene glyceraldehyde and 5-lithio-2-alkoxyfuran as a key step to construct the seven-carbon skeleton.[7] Pohmakotr and co-workers also utilized a similar approach starting from lithiated butenolide; however, the alkene which resulted from the subsequent elimination was obtained as a mixture of *E*- and *Z*-isomers.[8] This issue was later addressed by Boukouvalas and co-workers who introduced a bromine atom at the C-3 position as a removable stereocontrolling element.[9] Finally, an alternative route to the heptene core structure was described by Lu and co-workers using palladium-catalyzed enyne coupling as the key step.[10]

According to our proposed structural parameters illustrated in Fig. 1b, variations of the double bond geometry (region 1) can be readily achieved by the synthetic route modified from that previously reported by Boukouvalas and co-workers (Scheme 1).[9] First, (*R*)-2,3-isopropylidene glyceraldehyde ((*R*)-**5**) was prepared by

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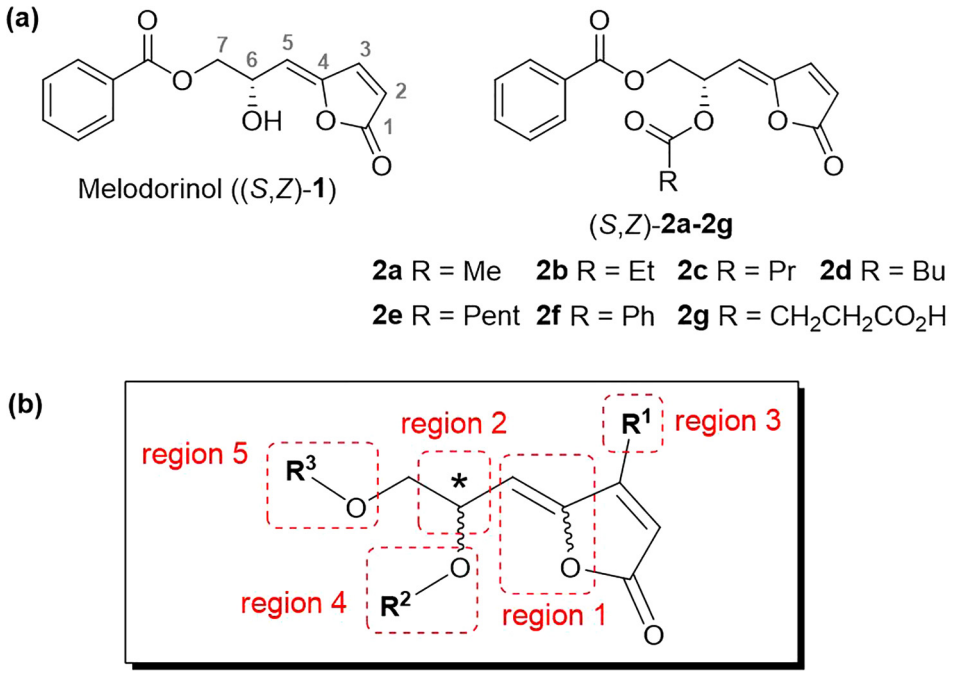
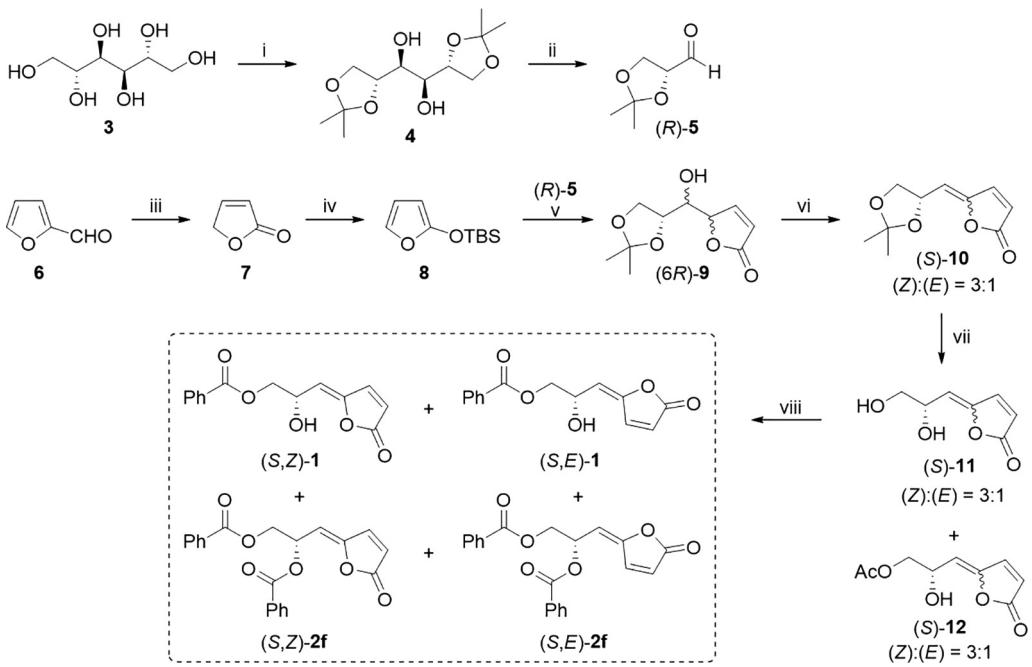


Fig. 1. (a) Structures of melodorinol ((*S*,*Z*)-**1a**) and its derivatives ((*S*,*Z*)-**2a-g**); (b) The general structure of the designed melodorinol analogues in this study.



Scheme 1. Reagents and conditions: (i) $ZnCl_2$, acetone, rt, 12 h, 35%;[11] (ii) $NaIO_4$, sat. $NaHCO_3$ (aq.), CH_2Cl_2, rt, 1 h, 99%;[12] (iii) HCOOH, H_2O_2, Na_2SO_4, K_2CO_3, CH_2Cl_2, reflux, 12 h, 35%;[13] (iv) TBSOTf, NEt_3, CH_2Cl_2, 0 °C, 12 h, 65%;[14] (v) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 78 °C, 4 h, 30%;[9] (vi) MsCl, pyridine, 0 °C to rt, 2 h, 100%;[8] (vii) AcOH/H_2O (1:1), rt, 48 h, (*S*)-**11** 58%, (*S*)-**12** 7%;[9] (viii) PhCOCl, NEt_3, CH_2Cl_2, 0 °C to rt, 12 h, (*S*,*Z*)-**1** 31%, (*S*,*E*)-**1** 32%, (*S*,*Z*)-**2f** 19%, (*S*,*E*)-**2f** 24%.[9]

selective acetonation of D-mannitol (**3**) using $ZnCl_2$,[11] followed by oxidative cleavage with $NaIO_4$.[12] Next, silyloxyfuran **8** was prepared by Baeyer-Villiger oxidation of furfural to obtain 2(5*H*)-furanone **7**,[13] which was then treated with TBSOTf and NEt_3 to give **8**.[14] The two components, **8** and (*R*)-**5**, were combined *via* Mukaiyama aldol reaction at −78 °C using $BF_3{\cdot}Et_2O$ as a Lewis acid,[9] followed by dehydration with mesyl chloride in pyridine to give (*S*)-**10** as an inseparable mixture of (*Z*)- and (*E*)-isomers in the ratio of 3:1.[15] The hydrolysis of (*S*)-**10** afforded (*S*)-**11** in good yield, along with a by-product (*S*)-**12** obtained *via* acetylation by acetic acid. Both (*S*)-**11** and (*S*)-**12** were also obtained as mixtures of (*Z*)- and (*E*)-isomers in the ratio of 3:1. Finally, acylation of (*S*)-**11** using benzoyl chloride afforded a mixture of mono-substituted, (*S*,*Z*)-**1** (melodorinol) and (*S*,*E*)-**1**, and di-substituted products (*S*,*Z*)-**2f** and (*S*,*E*)-**2f**; the four products can be easily separated by column chromatography.[16]

In order to investigate the effect of the substituent at C-3 (region 3), we also synthesized analogues which contain a bromine

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