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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.

Keywords: Melodorinol; Diverted total synthesis; Anticancer; Cytotoxicity

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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.

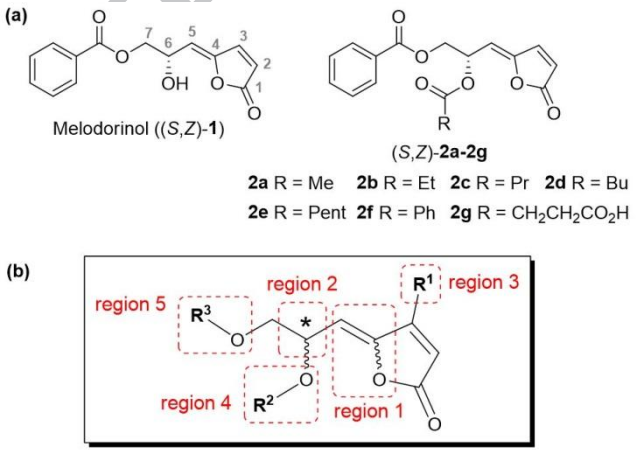
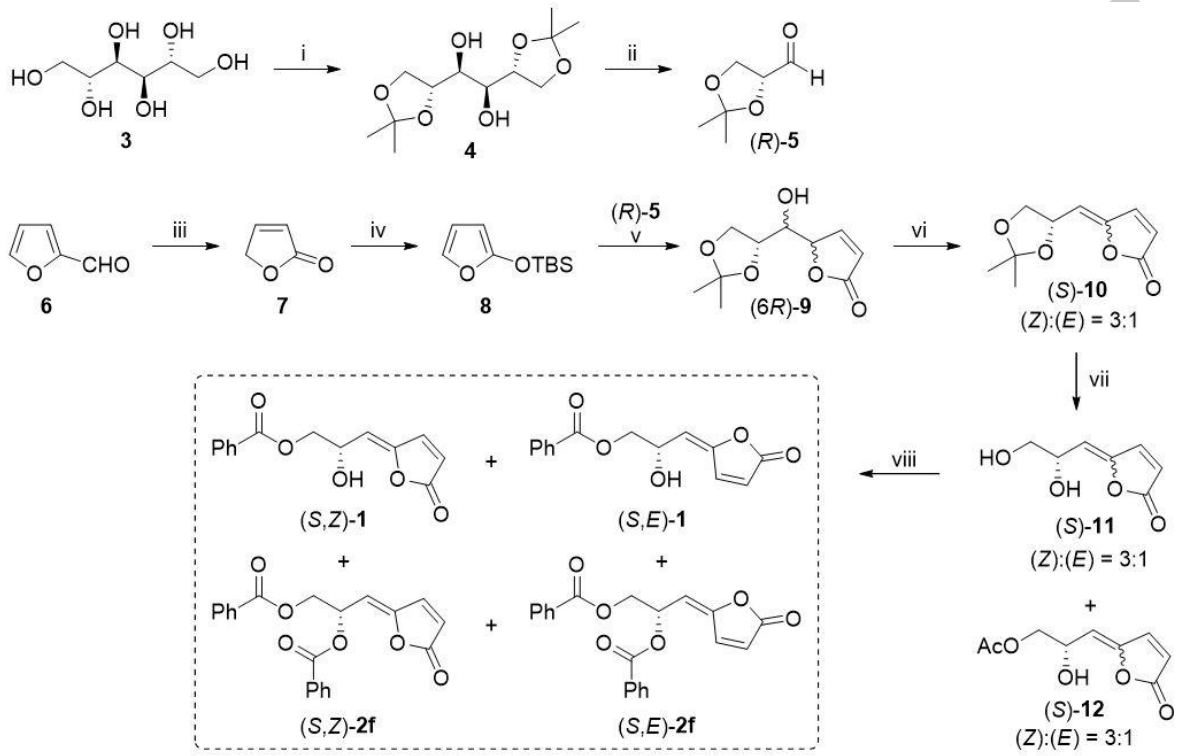


Figure 1. (a) Structures of melodorinol ((*S*,*Z*)-**1a**) and its derivatives ((*S*,*Z*)-**2a-g**); (b) The general structure of the designed melodorinol analogues in this study.

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

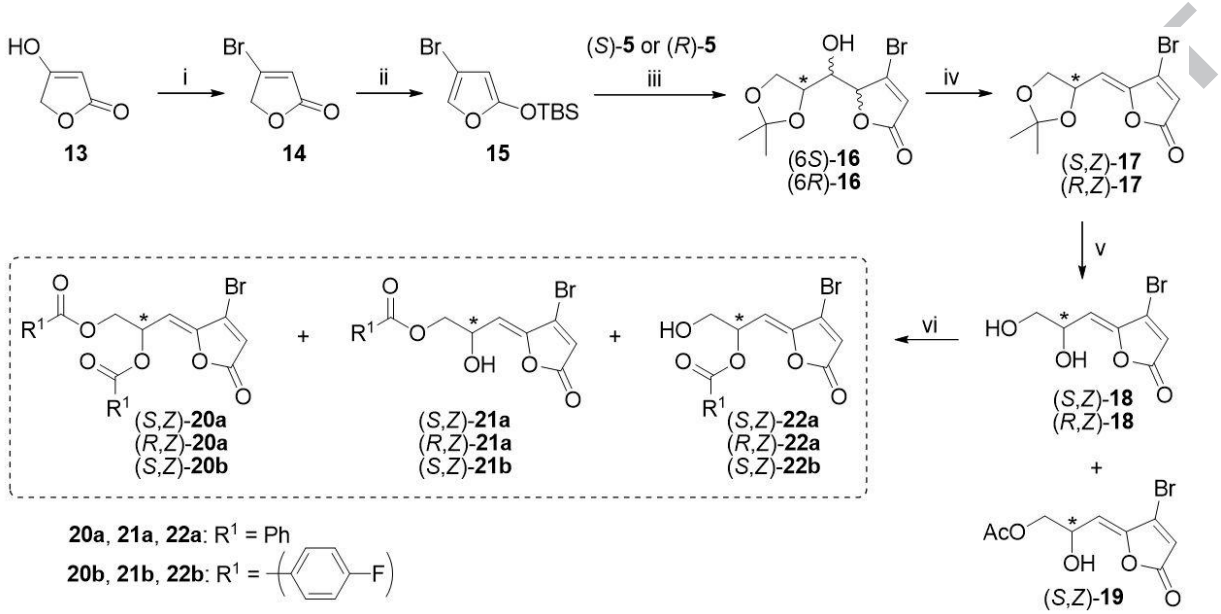
elimination was obtained as a mixture of *E*- and *Z*-isomers.[8] This issue was later addressed by Boukouvalas and co-workers who introduced a bromine atom at the C-3 position as a removable stereocontrolling element.[9] Finally, an alternative route to the heptene core structure was described by Lu and co-workers using palladium-catalyzed enyne coupling as the key step.[10]



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]

According to our proposed structural parameters illustrated in Figure 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 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

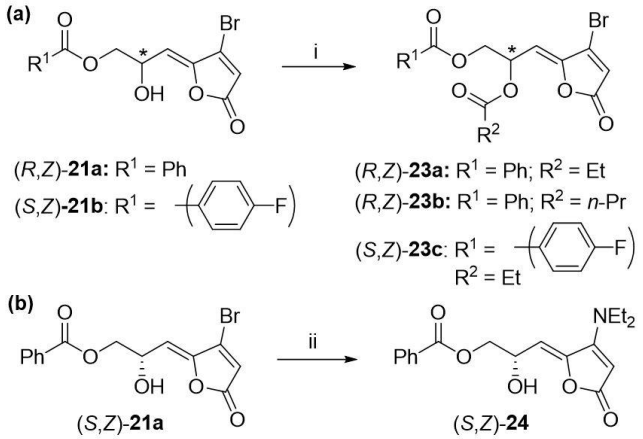
3:1. Finally, acylation of (*S*)-**11** using benzoyl chloride afforded a mixture of mono-substituted, (*S*,*Z*)-**1** (melodorinol) and (*S*,*E*)-**1**, and di-substituted products (*S*,*Z*)-**2f** and (*S*,*E*)-**2f**; the four products can be easily separated by column chromatography.[16]



Scheme 2. Reagents and conditions: (i) oxalyl bromide, DMF, CH_2Cl_2, 0 °C to rt, 4 h, 84%;[17] (ii) TBSOTf, NEt_3, CH_2Cl_2, 0 °C, 2 h, 47%;[14] (iii) $BF_3{\cdot}OEt_2$, CH_2Cl_2, -78 °C, 4 h, (6*S*)-**16** 27%, (6*R*)-**16** 35%;[9] (iv) MsCl, pyridine, 0 °C to rt, 2 h, (*S*,*Z*)-**17** 90%, (*R*,*Z*)-**17** 68%;[8] (v) AcOH/H_2O (1:1), rt, 48 h, (*S*,*Z*)-**18** 74%, (*R*,*Z*)-**18** 91%, (*S*,*Z*)-**19** 4%;[9] (vi) R^1COCl, NEt_3, CH_2Cl_2, 0 °C to rt, 12 h, (*S*,*Z*)-**20a** 18%, (*S*,*Z*)-**21a** 44%, (*S*,*Z*)-**22a** 8%, (*R*,*Z*)-**20a** 17%, (*R*,*Z*)-**21a** 46%, (*R*,*Z*)-**22a** 9%, (*S*,*Z*)-**20b** 12%, (*S*,*Z*)-**21b** 27%, (*S*,*Z*)-**22b** 5%.[9]

In order to investigate the effect of the substituent at C-3 (region 3), we also synthesized analogues which contain a bromine atom at the *β*-position of the furanone ring following the synthetic route outlined in Scheme 2. First, tetronic acid **13** was treated with oxalyl bromide to provide 4-bromofuran-2(5*H*)-one **14**,[17] which was then converted to the corresponding silyloxyfuran **15** using the same protocol as described in Scheme 1. The Mukaiyama aldol reaction of compound **15** with (*R*)-**5**, followed by dehydration yielded the corresponding bromine-substituted heptene (*S*,*Z*)-**17** as a single diastereomer. Deprotection with AcOH/H_2O provided diol (*S*,*Z*)-**18** together with a small amount of the acetylated by-product (*S*,*Z*)-**19**. Benzoylation of (*S*,*Z*)-**18** afforded novel brominated melodorinol analogues including dibenzoylated product (*S*,*Z*)-**20a** as well as two monobenzoylated products (*S*,*Z*)-**21a** and (*S*,*Z*)-**22a**. To observe the effect of the substituent on the aromatic ring(s), (*S*,*Z*)-**18** was treated 4-fluorobenzoyl chloride to provide three novel fluorinated analogues (*S*,*Z*)-**20b**, (*S*,*Z*)-**21b** and (*S*,*Z*)-**22b**. To examine the effect of the stereochemistry at C-6 (region 2), the synthesis described in Scheme 2 was repeated using (*S*)-**5** instead of (*R*)-**5** in the Mukaiyama aldol reaction. The corresponding novel enantiomers (*R*,*Z*)-**20a**, (*R*,*Z*)-**21a** and (*R*,*Z*)-**22a**

were obtained in good yields. The previous study revealed that melodorinol analogues containing short alkyl side-chains at the C-6 position showed greater cytotoxicities.[1d] In this context, C-6 acylation of (*R*,*Z*)-**21a** and of (*S*,*Z*)-**21b** with propionic anhydride or butyric anhydride was conducted, leading to three novel melodorinol analogues (*R*,*Z*)-**23a**, (*R*,*Z*)-**23b** and (*S*,*Z*)-**23c** (Scheme 3a). Finally, the bromine atom at the C-3 position was replaced by substitution with $HNEt_2$ at room temperature.[18] Under these mild reaction conditions, (*S*,*Z*)-**21a** was smoothly converted into the novel analogue (*S*,*Z*)-**24** containing a diethylamino group at the C-3 position (Scheme 3b). To the best of our knowledge, the formation of *N*-dialkyl tetronamides from 5-alkylidne-4-bromofuranones is unprecedented; the installation of amino groups *via* aza-Michael addition/elimination reactions of 5-alkylidne-4-bromofuranones is extremely rare,[18b] and the reaction of such compounds with primary amines typically leads to the formation of hydroxylactams instead of tetronamides.[18c]



Scheme 3. Reagents and conditions: (i) $(R^2CO)_2O$, NEt_3, cat. DMAP, CH_2Cl_2, rt, 2 h, ((*R*,*Z*)-**23a**) 68%, ((*R*,*Z*)-**23b**) 96%, ((*S*,*Z*)-**23c**) 48%;[1d] (ii) $HNEt_2$, THF, rt, 12 h, 78%.[18a]

The *in vitro* cytotoxicity of the synthesized compounds which contain the seven-carbon skeleton (**1**, **2**, **9**-**12** and **16**-**24**) was evaluated by the MTT assay method[19] using five human tumour cell lines including KB, HeLa-S3, MCF-7, HT-29 and A549 (Table 1).[20] The synthesized melodorinol (*S*,*Z*)-**1** exhibited similar cytotoxicity compared to the naturally isolated compound (see ESI Section 4 for the comparison). The geometry of the double bond across C-4 and C-5 has little to no impact on the inhibition activity, as observed by comparing the cytotoxicity between (*S*,*Z*)-**1** and (*S*,*E*)-**1**, and between (*S*,*Z*)-**2f** and (*S*,*E*)-**2f**. The higher activity of the dibenzoylated products **2f** is in agreement with the previous report.[1d] However, no inhibition was observed for the derivatives which do not contain the benzoyl group ((6*R*)-**9**, (*S*)-**10**, (*S*)-**11** and (*S*)-**12**). This indicates that hydrophobicity of the side-chains is crucial for good activity, although other types of interaction such as pi-stacking or charge-transfer interactions cannot be excluded. Strikingly, the corresponding

analogues with a bromine substituent at C-3 showed much higher activity, clearly demonstrated by comparing (*S*)-**10**/(*S*,*Z*)-**17**, (*S*)-**11**/(*S*,*Z*)-**18**, (*S*)-**12**/(*S*,*Z*)-**19**, and (*S*,*Z*)-**1**/(*S*,*Z*)-**21a**. Many studies have demonstrated that the *α*,*β*-unsaturated lactone scaffold, as a Michael acceptor, is a crucial moiety to induce cytotoxicity through various mechanisms,[21] and has been found in various drug candidates.[22] In this context, the introduction of a bromine atom as a good leaving group at the *β*-position on the furanone ring could enhance the Michael acceptor ability through an efficient addition-elimination mechanism, hence leading to greater cytotoxicity.[23] This assumption was supported as replacement of the bromine atom by the diethylamino group in (*S*,*Z*)-**24** led to complete loss of cytotoxic activity; the enamionate compound is expected to be less reactive towards both addition and addition-elimination reactions due to delocalization of the nitrogen lone pair. The activity was further improved by the introduction of a fluorine atom at the *para*-position on the benzoyl group(s); for example, the IC_{50} against KB was improved from 4.73 μM for (*S*,*Z*)-**21a** to 1.43 μM for (*S*,*Z*)-**21b**. This result reveals an opportunity to further optimize the potency of melodorinol analogues by varying the substituents on the benzoyl moiety to achieve optimal lipophilicity and/or steric/electronic parameters. The stereochemistry at C-6 also has a slight impact on the cytotoxicity. In all cases, the (*R*)-analogues ((*R*,*Z*)-**17**-**19** and (*R*,*Z*)-**20a**-**22a**) exhibit higher activity compared to the corresponding (*S*)-analogues. The introduction of acyl substituents at the C-6 hydroxyl groups, including propionyl ((*R*,*Z*)-**23a** and (*S*,*Z*)-**23c**), butyryl ((*R*,*Z*)-**23b**) and benzoyl ((*S*,*Z*)-**20a-b** and (*R*,*Z*)-**20a**) side-chains, led to slight decrease in activity for the series of brominated furanone analogues. This is in contrast with the trend observed for non-brominated furanone analogues ((*S*,*Z*)-**2f** and (*S*,*E*)-**2f**) where the introduction of a benzoyl group led to an improvement in the cytotoxicity. Notably, brominated analogues such as (*R*,*Z*)-**21a** and (*S*,*Z*)-**21b** exhibit exceptionally high cytotoxicity against MCF-7, HT-29 and A549 cell lines compared to the non-brominated analogues.

In conclusion, we have conducted the structure-activity relationship of melodorinol, which can be summarized as follows: (1) The geometry of the double bond across C-4 and C-5 of the heptene core structure has little to no effect on the cytotoxicity. (2) The substituent on the C-3 position can lead to a dramatic impact on the cytotoxicity; introduction of a good leaving group such as bromine raised the activity significantly. On the other hand, blocking this position with a diethylamino group completely inhibits the activity. (3) The (*R*)-enantiomers, which are less commonly found in Nature, exhibit higher activity compared to the corresponding (*S*)-enantiomers. (4) The acyl substituents on both hydroxyl groups at C-6 and C-7 also greatly affect the cytotoxicity. Among all of the synthesized melodorinol analogues, the most potent compounds were the

brominated analogues (*R*,*Z*)-**21a** and (*S*,*Z*)-**21b** with approximately 15-fold higher activity against human tumour cell lines compared to the parent melodorinol. The knowledge obtained in this SAR study could provide valuable information for the development of new naturally-derived anticancer compounds.

Table 1. *In vitro* cytotoxicity of melodorinol analogues.

Compound	IC_{50} (μM)[a]				
	KB	HeLa-S3	MCF-7	HT-29	A549
(*S*,*Z*)-**1**	21.47 ± 0.35	20.44 ± 0.55	-[b]	-[b]	-[b]
(*S*,*E*)-**1**	21.65 ± 0.28	21.26 ± 0.12	-[b]	-[b]	-[b]
(*S*,*Z*)-**2f**	5.43 ± 0.03	5.12 ± 0.26	16.19 ± 0.28	7.21 ± 0.57	53.02 ± 1.02
(*S*,*E*)-**2f**	6.86 ± 1.15	5.93 ± 0.18	18.74 ± 0.95	9.84 ± 0.83	-[b]
(6*R*)-**9**	>100	>100	-[b]	-[b]	-[b]
(*S*)-**10**[c]	>100	>100	-[b]	-[b]	-[b]
(*S*)-**11**[c]	>100	>100	-[b]	-[b]	-[b]
(*S*)-**12**[c]	>100	>100	-[b]	-[b]	-[b]
(6*S*)-**16**	>100	>100	-[b]	-[b]	-[b]
(6*R*)-**16**	> 100	> 100	-[b]	-[b]	-[b]
(*S*,*Z*)-**17**	7.79 ± 0.35	6.64 ± 0.09	7.79 ± 0.59	6.41 ± 0.37	-[b]
(*R*,*Z*)-**17**	3.38 ± 0.07	2.49 ± 0.10	3.27 ± 0.31	2.44 ± 0.09	-[b]
(*S*,*Z*)-**18**	8.63 ± 0.32	6.10 ± 0.38	10.35 ± 0.17	7.72 ± 0.63	-[b]
(*R*,*Z*)-**18**	6.54 ± 0.80	6.47 ± 0.30	7.35 ± 0.43	5.93 ± 0.29	-[b]
(*S*,*Z*)-**19**	5.75 ± 0.44	4.38 ± 0.22	9.38 ± 0.67	6.38 ± 0.17	-[b]
(*S*,*Z*)-**20a**	17.66 ± 0.93	11.16 ± 1.34	-[b]	-[b]	-[b]
(*R*,*Z*)-**20a**	4.79 ± 1.82	5.99 ± 0.19	10.55 ± 0.22	9.37 ± 0.59	-[b]
(*S*,*Z*)-**20b**	13.06 ± 0.88	16.35 ± 0.43	-[b]	-[b]	-[b]
(*S*,*Z*)-**21a**	4.73 ± 0.07	2.26 ± 0.07	4.93 ± 0.40	4.44 ± 0.23	-[b]
(*R*,*Z*)-**21a**	1.40 ± 0.03	1.75 ± 0.03	1.65 ± 0.09	1.86 ± 0.10	3.94 ± 0.15
(*S*,*Z*)-**21b**	1.43 ± 0.04	1.69 ± 0.03	1.69 ± 0.14	2.37 ± 0.24	3.46 ± 0.33
(*S*,*Z*)-**22a**	6.53 ± 1.03	4.97 ± 0.08	12.81 ± 0.47	8.50 ± 0.29	-[b]
(*R*,*Z*)-**22a**	4.65 ± 0.10	6.10 ± 0.63	5.49 ± 0.10	6.53 ± 0.08	-[b]
(*S*,*Z*)-**22b**	1.69 ± 0.08	2.26 ± 0.19	2.49 ± 0.14	3.75 ± 0.23	-[b]
(*R*,*Z*)-**23a**	2.03 ± 0.26	4.43 ± 0.79	2.83 ± 0.19	3.71 ± 0.23	-[b]
(*R*,*Z*)-**23b**	6.37 ± 0.17	6.72 ± 0.59	5.81 ± 0.15	6.70 ± 0.22	-[b]
(*S*,*Z*)-**23c**	2.06 ± 0.05	2.53 ± 0.32	3.08 ± 0.42	3.32 ± 0.18	-[b]
(*S*,*Z*)-**24**	>100	>100	-[b]	-[b]	-[b]
Doxorubicin	0.21 ± 0.07	0.07 ± 0.02	0.79 ± 0.04	0.33 ± 0.06	0.29 ± 0.02

[a] The results are expressed as IC_{50} values (the concentration of compound that inhibit 50% of the cell multiplication after 48 h of treatment) taken as a mean from three experiments in μM ± standard deviation; Doxorubicin was used as a positive control; Cell lines used are KB (human epidermoid carcinoma), HeLa-S3 (human cervix adenocarcinoma), MCF-7 (human breast adenocarcinoma), HT-29 (human colon adenocarcinoma) and A549 (human lung carcinoma); [b] Not tested; [c] Mixture of (*Z*):(*E*) = 3:1.

Acknowledgments

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Conflicts of interest

We declare that we have no conflict of interest.

Supplementary Material

Supplementary data associated with this article can be found, in the online version, at …

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20. All substrates were tested against KB and HeLa-S3. 17 substrates with IC_{50} values lower than 10 μM against KB were selected to investigate their cytotoxicity against MCF-7 and HT-29. The most potent analogues, (*S*,*Z*)-**2f**, (*R*,*Z*)-**21a** and (*S*,*Z*)-**21b**, were selected to further investigate their cytotoxicity against A549.
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Graphical Abstract

Diverted total synthesis of melodorinol analogues and evaluation of their cytotoxicity

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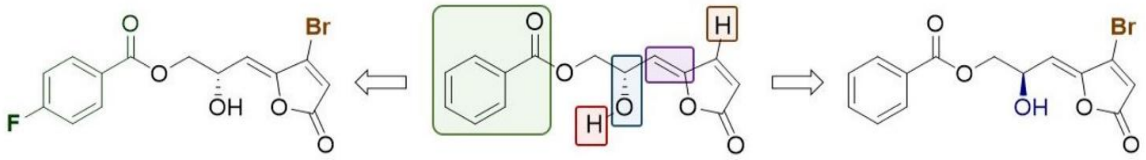
Tanatorn Khotavivattana, Thitiphong Khamkhenshorngphanuch, Kitiya Rassamee, Pongpun Siripong and Tirayut Vilaivan



- Structural modification of melodorinol was achieved by diverted total synthesis.
- 28 derivatives were subjected to antitumor activity test.
- SAR studies revealed key parameters that affect the cytotoxicity.