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Syntheses of Dimeric Tetrahydroxanthones with Varied Linkages: Investigation of “Shapeshifting” Properties

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Abstract

The 2,4'- and 4,4'-linked variants of the cytotoxic agent secalononic acid A and their analogues have been synthesized. Kinetic resolution of an unprotected tetrahydroxanthone scaffold followed by copper-mediated biaryl coupling allowed for efficient access to these compounds. Evaluation of the “shapeshifting” properties of 2,2'-, 2,4'-, and 4,4'-linked variants of the secalononic acids A in a polar solvent in conjunction with assays of the compounds against select cancer cell lines was conducted to study possible correlations between linkage variation and cytotoxicity.

INTRODUCTION

Dimeric tetrahydroxanthone natural products belong to a family of secondary metabolite mycotoxins.¹ Their interesting biological properties and varied structures have attracted significant attention from both the biological and the chemical communities. Among these natural products, the secalononic acids, 2,2'-linked dimeric tetrahydroxanthones,² were found to exhibit interesting bioactivities. For instance, secalononic acid A (**1**)³ has antitumor activity and also reduces colchicine toxicity in rat cortical neurons.⁴ In addition to the 2,2'-linked dimeric natural products, 2,4'- and 4,4'-linked secalononic acids are also found in nature. For

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ASSOCIATED CONTENT

Supporting Information

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Experimental procedures and characterization data for all new compounds, including X-ray structure analysis of compound **34**, and detailed biological methods and results (PDF)

X-ray data for compound **34** (CIF)

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example, the 2,4'-linked isomer penicillixanthone A (**2**)⁵ and the 4,4'-linked secalononic acid E (talaroxanthone, **4**)⁶ have recently been isolated and characterized (Figure 1). In addition to the secalononic acids, biaryl linkage variation has been observed in related natural products. Recently, a related subclass of tetrahydroxanthones, phomoxanthones (**5**), has been isolated and characterized.⁷ The presence of a 4,4' linkage was established by X-ray crystallography. The corresponding 2,2'-linked dimer dicerandrol C (**6**)⁸ and 2,4'-linked dimer phomoxanthone B (**7**) have also been isolated from natural sources.

Because of the presence of varied biaryl linkages, the shape of molecules may change dramatically, which may have a substantial influence on their biological properties. For example, the 4,4'-linked compound phomoxanthone A exhibits a strong cytotoxicity to L5178Y cancer cells ($IC_{50} = 0.3 \mu M$),^{7c} whereas the 2,2'-linked congener dicerandrol C was found to be somewhat less potent ($IC_{50} = 2.8 \mu M$).^{8c} For the secalononic acids, previous studies indicated that the linkage may undergo facile isomerization in polar solvents.⁹ A similar transformation was observed for the monomeric tetrahydroxanthone parnafungins to generate a mixture of isomers A1 (**8**)/A2 (**9**)/B1 (**10**)/B2 (**11**) from each pure isomer at room temperature (Figure 2).¹⁰ The authors propose that *retro-oxa*-Michael reaction of the tetrahydroxanthone to acetophenone intermediates **12/13** was responsible for linkage isomerization. Interestingly, it was determined by affinity-selection/mass spectrometry (AS-MS) that parnafungin A1 (**8**) was the active inhibitor of the fungal enzyme polyadenosine polymerase (PAP).¹¹ The fluxional properties of the tetrahydroxanthone scaffold can be compared to those of other natural products such as coleophomones¹² and the "shapeshifting" bullvallene system reported by Bode and co-workers.¹³

Because of their interesting chemical and biological properties, tetrahydroxanthones have drawn attention from synthetic organic chemists. Recently, our laboratory¹⁴ as well as the laboratories of Bräse,¹⁵ Nicolaou,¹⁶ Tietze,¹⁷ and other groups¹⁸ have accomplished syntheses of monomeric chromone lactones, tetrahydroxanthones, and 2,2'-linked dimeric tetrahydroxanthone natural products. We considered that chemical syntheses of 2,4'-linked and 4,4'-linked secalononic acids would be not only be synthetically challenging but may provide access to dimeric linkage variations to study their "shapeshifting"¹³ properties of this class of compounds. Moreover, along with the previously synthesized 2,2'-linked compounds,¹⁴ these compounds may be used to ultimately construct a tetrahydroxanthone library with potentially interesting biological activities. In this Article, we describe syntheses of 2,4'- and 4,4'-linked variants of the cytotoxic agent secalononic acid A and its analogues. Evaluation of the "shapeshifting" properties of 2,2'-, 2,4'- and 4,4'-linked secalononic acids A in conjunction with assays of the compounds against select cancer cell lines was conducted to study preliminary correlations between linkage variation and cytotoxicity.

RESULTS AND DISCUSSION

Synthesis of 4,4'-Linked Chromone Lactone Dimers

In addition to the dimeric tetrahydroxanthones, there have been a number of related 4,4'-linked chromone lactone dimers isolated from nature, including gonytolide A¹⁹ and paecilin A.²⁰ On the basis of our strategy for the synthesis of 2,2'-linked chromone lactones,^{14b} we anticipated that the corresponding 4,4'-linked dimers may be accessed using our previously

developed copper-mediated stannane coupling approach if prefunctionalization of the *para*-position of the chromone lactone monomer could be accomplished. However, after investigating various iodination and bromination conditions on monomer **14**, we found that the *para*-halogenated chromone lactone was generally the minor product. For example, treatment of substrate **14** with 1 equiv of NBS led to a mixture of brominated products **15**, **16**, and **17** (Scheme 1). Interestingly, use of $\text{In}(\text{OTf})_3$ as catalyst²¹ for the bromination led to the production of *ortho*-bromide **16** in 62% yield along with *para* isomer **15** (37%). After further evaluation of additives, we found that a catalytic amount of AuCl_3 ²² significantly changed the outcome of the bromination (Scheme 1b). Treatment of **14** with NBS in the presence of 5 mol % of AuCl_3 favored production of the *para*-brominated chromone lactone **15**. This phenomenon was also observed in other related chromone lactone substrates.²³ To understand possible operative mechanisms, chromone lactone **14** was treated with AuCl_3 (72 h) (Scheme 2a) in which case several chlorinated products **19–21** were obtained.²⁴ We considered that the Au(III) catalyst may chelate with the lactone and/or methyl ester moieties of substrate **14** to direct the bromination, potentially via a direct auration process²⁵ to generate the chelated gold(III) aryl intermediate **22** (Scheme 2b). This hypothesis is also supported by the fact that AuCl_3 failed to enhance the yield of the *para* product on tetrahydroxanthone substrates. However, an auration pathway cannot completely explain the unselective chlorination observed using AuCl_3 . As an alternative mechanism, AuCl_3 may also chelate to the phenol²⁶ of substrate **14** to afford a putative aurate complex **23**, which may effectively block the *ortho*-position to bromination with NBS (Scheme 2c). The latter mechanism is also supported by ^1H NMR experiments involving complexation of substrate **14** with AuCl_3 in which case loss of the phenol resonance of **14** was observed.²³ Our current results highlight the importance of the chromone lactone ring system in the gold(III)-catalyzed bromination process.

With the *para*-bromide **15** in hand, it was smoothly converted to the corresponding *para*-stannane **18** in 78% yield (Scheme 1). We next investigated stannane dimerization with different metals (e.g., CuCl) and oxidants (e.g., air, O_2 , CuCl_2).^{14b} Surprisingly, phenolic stannane **18** did not generate the desired 4,4'-linked dimers under these conditions; the main side reaction generally observed was protodestannylation likely due to the low $\text{p}K_a$ of the proximal phenol. Accordingly, we altered our strategy, and compound **14** was *O*-methylated with Me_2SO_4 (Scheme 3). Treatment of **24** with $n\text{Bu}_4\text{NBr}_3$ led to the production of bromide **25** in 93% yield.²⁷ Subsequent stannylation provided compound **26** in 70% yield. When we applied the previously developed CuCl /air-mediated coupling conditions,^{14b} stannane **26** was only converted to dimeric products in trace amounts with a large amount of the starting material remained intact. We thought that use of air as oxidant was difficult to accurately control and that this could lead to the variable conversions observed in the reaction. Fortunately, use of CuCl_2 as oxidant afforded the C_2 and C_s dimers **27** and **28** in reproducible yields (23%).

Synthesis of 4,4'-Linked Tetrahydroxanthone Dimers

The successful synthesis of 4,4'-linked chromone lactones encouraged us to further investigate syntheses of the corresponding 4,4'-linked dimeric tetrahydroxanthones. We envisioned that an enantiopure, *para*-functionalized tetrahydroxanthone could serve as a key

intermediate. Our initial thought was that a *para*-brominated tetrahydroxanthone could be obtained from a brominated chromone lactone through Dieckmann cyclization (Scheme 4). However, potential linkage isomerization of tetrahydroxanthones could create difficulties in this transformation. Accordingly, we treated the *ortho*-brominated chromone lactone **16** with 10 equiv of NaH in THF for 3 h. In this case, the corresponding tetrahydroxanthone **29** was isolated in 43% yield as a single diastereomer. Surprisingly, when we treated the bromide **15** with 10 equiv of NaH, we obtained three different tetrahydroxanthone products. The desired *para*-brominated tetrahydroxanthone **30** was obtained in only 10% yield. The main byproduct observed was the *ortho*-bromide **31** with an *anti*-configuration between the hydroxyl and ester groups. Even when we shortened the reaction time or lowered the reaction temperature, the undesired tetrahydroxanthones **29/31** were still observed. Thus, we considered that under Dieckmann cyclization conditions, *para*-bromide **15** may generate intermediate **32** in situ. Subsequent *oxa*-Michael reaction could convert **32** to the corresponding tetrahydroxanthone products.

From these results, we hypothesized that production of the desired *para*-bromo-tetrahydroxanthone (cf., **30**) was not favored under Dieckmann cyclization conditions. Therefore, we changed our strategy to prefunctionalize the tetrahydroxanthone moiety. However, when tetrahydroxanthone **33** was treated with chlorinating reagents such as *N*-chlorophthalimide, the chloro-diketone **34** was isolated in near quantitative yield as a single diastereomer (Scheme 5). The *anti*-configuration between the chlorine and the methyl ester moieties was confirmed by X-ray crystal structure analysis (Figure 3).²³ The high diastereoselectivity observed is likely due to steric repulsion between the electrophile and the methyl ester.

As the vinylogous acid should be the most nucleophilic moiety in the tetrahydroxanthone substrate, we thought that use of the enol-protected compound **35** could avoid this problem. After evaluating different iodination and bromination conditions, the *ortho*-halogenated product (cf., **36**) was found to be dominant. We reasoned that the vinylogous acid moiety in the tetrahydroxanthone could be deactivated under acidic conditions. After forming the presumed protonated tetrahydroxanthone **37**, the phenol may become the more nucleophilic site. As an alternative, the added TFA could protonate NIS, which may generate a more active iodination reagent with different selectivity. Indeed, when substrate **33** was treated with NIS in TFA/CH₂Cl₂ (Scheme 5), both *para*-iodo and *ortho*-iodo-tetrahydroxanthones were generated in a 1:1 ratio by crude ¹H NMR analysis. The mixture was further methylated using trimethylsilyldiazomethane to afford *para*-iodide **38** and *ortho*-iodide **36** in 31% and 32% isolated yields, respectively (two steps).

To access chiral, nonracemic 4,4'-linked secalonic acid A, synthesis of an enantiopure, monomeric tetrahydroxanthone was required. Relying on our recently developed kinetic resolution of the tetrahydroxanthone moiety using homobenzotetramisole (HBTM) catalyst **39**,²⁸ we anticipated that an enantiopure *para*-iodide could be obtained in a similar fashion. However, contrary to the excellent kinetic resolution observed for *ortho*-iodide **36**, HBTM catalyst **39** did not successfully catalyze acetylation of *para*-iodide **38** or only yielded moderate levels of enantioselectivity (Scheme 6). This unexpected result indicated that

substitution on the *para*-position of the tetrahydroxanthone jeopardized its reactivity with the HBTM catalyst system.

After the unsuccessful kinetic resolution attempts with the *para*-iodo tetrahydroxanthone, we considered that the kinetic resolution could be performed on unprotected tetrahydroxanthone scaffolds. Indeed, HBTM catalyst **39**^{14b} could convert **33** to the acylated product. However, even with a substoichiometric amount of the base (*N,N*-diisopropylethylamine, DIEA), the tetrahydroxanthone still underwent *syn/anti* and retro-Dieckmann rearrangement (not shown). As tetrahydroxanthone substrates were found to be stable under acidic conditions, we wondered whether base was necessary for acylation. Gratifyingly, without any base, kinetic resolution proceeded smoothly on tetrahydroxanthone **33** to generate (–)-**33** and (+)-**41** in excellent yield and in excellent enantiomeric excess (Scheme 6). The *s* factor for the latter reaction was above 200. For blennolide B (**42**) as substrate, we were concerned that the additional methyl group on the C ring could dramatically decrease the acylation reactivity of the secondary alcohol. For this case, enantioselectivities using propionic anhydride never exceeded 40% conversion after screening various conditions. Fortunately, after switching to the less hindered acylating reagent acetic anhydride, (–)-**42** and the acylated tetrahydroxanthone (+)-**43** were obtained in high yield and ee. Notably, the *s* factor observed for the unprotected blennolide B (*s* = 159) was even higher than that for the enol-protected blennolide B shown previously (*s* = 93).^{14b}

Using the enantioenriched tetrahydroxanthones, the *para*-iodo tetrahydroxanthones were prepared in a similar manner. With compound (–)-**38** in hand (Scheme 7), we followed our previous sequence to protect the free phenol. However, in this case, MOM protection was found to be low yielding and irreproducible. Fortunately, stannylation could be cleanly performed on the unprotected substrate (–)-**38**. Remarkably, the *para*-iodide (–)-**38** was not transformed to a dimeric product under our previous one-pot Suzuki dimerization conditions^{14c} (Pd-SPhos-II, BPin₂, K₃PO₄).

As there are no literature reports of stannane dimerizations with substrates containing a free phenol, we were concerned that a free phenol could jeopardize the dimerization step. Nevertheless, the resulting stannane (–)-**44** was subjected to dimerization conditions. Applying our previously developed CuCl/air conditions to stannane (–)-**44** cleanly produced a protodestannylated product. After further evaluation of oxidants (e.g., Cu(ethylhexanoate)₂, Cu(OAc)₂, FeCl₃, Mn(acac)₃), we found that CuCl₂ and ferrocenium tetrafluoroborate could provide the corresponding 4,4'-linked dimer (–)-**45** in 40–50% conversion (Scheme 7). However, the yield/conversion remained inconsistent over several experimental trials. After further screening of additives (e.g., Na₂SO₄, CaCO₃, NaHCO₃), we found that trace amounts of water decreased the yield dramatically. Use of freshly dried stannane (–)-**44** afforded the corresponding C₂ symmetric dimer (–)-**45** in 39% yield. Treatment of (–)-**45** with 3 M HCl led to the formation of the deprotected 4,4'-linked tetrahydroxanthone dimer (+)-**46** in 91% yield.

After successfully establishing access to a model 4,4'-linked dimeric tetrahydroxanthone, we considered that 4,4'-secalonic acid A could be synthesized in a similar manner (Scheme 8). Blennolide B (–)-**42** was iodinated with NIS in TFA/CH₂Cl₂. The resulting *para*- and *ortho*-

iodides were *O*-methylated to afford (–)-**47** and (–)-**48** (32% yield for both compounds). Stannylation proceeded smoothly following the previously described protocol to generate (–)-**49**. The C₂ dimer (–)-**50** was successfully synthesized by treating freshly dried stannane (–)-**49** with CuCl/CuCl₂. The presence of a 4,4'-linkage was further verified through a key HMBC correlation between C-2 and 1-OH.²³ Finally, 4,4'-linked secalononic acid A (+)-**51** was obtained after acidic deprotection. In a similar manner, the C_s symmetric tetrahydroxanthone dimer **53** was synthesized from dimer **52**, the latter obtained from the chiral, racemic monomer **42**.²³

Synthesis of 2,4'-Linked Tetrahydroxanthone Dimers

With our success in synthesizing 2,2'- and 4,4'-secalononic acids, we anticipated that we could also obtain the 2,4'-linked tetrahydroxanthones from heterodimerization of 2- and 4-stannyl tetrahydroxanthone monomers. Equimolar amounts of (–)-**54** and (–)-**44** were treated with CuCl/CuCl₂ in DMA. The desired 2,4'-linked dimer (–)-**56** was obtained in 32% yield (Scheme 9), along with 15% of the 2,2' dimer (–)-**55** and less than 5% of the 4,4' dimer (–)-**45**. After acidic deprotection, the 2,4'-linked model tetrahydroxanthone dimer (–)-**57** was obtained in 85% yield. In a similar manner, protected 2,4'-linked secalononic acid A (–)-**59** was constructed from (–)-**58** and (–)-**49** (Scheme 10). The corresponding 2,2'-linked dimer (–)-**62** and 4,4'-linked dimer (–)-**50** (not shown) were also produced in this reaction in around 20% and <5% yields, respectively. The 2,4'-linked dimer secalononic acid A (penicillixanthone A) (–)-**2** was obtained smoothly after deprotection with 3 M HCl. NMR spectra and α_D values for (–)-**2** were found to be identical to those reported for the natural sample.^{5a,d}

Shapeshifting Properties of 2,2'-, 2,4'-, and 4,4'-Secalononic Acids A

Burobane and co-workers⁹ reported that 2,2'-secalononic acids could isomerize to the corresponding 2,4'- and 4,4'-linked congeners in polar solvents (e.g., pyridine and CH₃CN). Intrigued by this phenomenon, and with the synthetic 2,2'-, 2,4'-, and 4,4'-linked secalononic acids A in hand, we were interested to monitor this process using UPLC analysis to determine the ratio of products obtained on the basis of thermodynamic equilibration. We first considered use of DMSO as solvent for our isomerization study based on use of this solvent in biological assays.²⁹ We first prepared a solution of the 4,4'-linked secalononic acid (+)-**51** in DMSO (0.5 mg/mL) at room temperature, and the solution was monitored by UPLC analysis. As shown in Figure 4, we observed that the 4,4'-linked secalononic acid (+)-**51** was converted to 2,2'- (–)-**1** and 2,4'-linked secalononic acids (–)-**2** slowly at room temperature. After 13 h, the secalononic acids reached thermodynamic equilibrium. A similar equilibrium process was observed starting with the pure 2,2'- or 2,4'-linked secalononic acids A.²³ The thermodynamic ratio of 2,2'-, 2,4'-, and 4,4'-secalononic acids was determined to be 3.2:2:1 as determined by crude ¹H NMR analysis.²³ The isomerization process was also found to be faster in 10% pyridine/DMSO,²³ which indicates that base can promote isomerization (cf., Figure 2). Forming the less sterically hindered biaryl bond may be a driving force for this equilibrium and the basis for favoring the 2,2'-linkage isomer in the equilibration process.

Biological Studies

We explored the biological activity of the synthetic xanthenes using a 48 h cancer cell growth inhibition assay with two renal cancer cell lines (A498, UO-31) and two colon cancer cell lines (Colo205 and KM12). The results are tabulated in Table 1, and dose response curves are provided in the Supporting Information.²³ The known compounds secalononic acids A (–)-**1**, D (+)-**1**, and penicillixanthone (–)-**2** all showed potent activity similar to that reported previously in L1210 leukemia cells³⁰ and MDA-MB-435 melanoma and SW-620 colon cancer cells.^{5d} The response for (+)-**1** was also similar in comparison to the NCI 60 screen, wherein GI₅₀ values of 550, 150, 66, and 55 nM were recorded for the above-mentioned cell lines.³⁰ A major difference between the present biological assay and the NCI 60 screen is the use of a formazan XTT end point in contrast to the protein stain SRB in the NCI 60, as well as the use of higher cell densities and a 384 well format in the present assays. It is interesting to observe that both (–)-**1** and (+)-**1** have similar activities, which was also reported for both enantiomers of the anticancer agent simaomicin α.³¹

Chromone lactones **27** and **28** had no activity against any of the four cell lines at 40 μM, showing that the tetrahydroxanthone skeleton is necessary for cell growth inhibition. Comparable patterns of cell growth inhibition were seen for all three dimer linkage types, for example, (–)-**1**, (–)-**2**, and (+)-**51**, via likely interconversion and equilibration of linkage isomers to a mixture of 2,2′-, 2,4′-, and 4,4′-linked compounds as shown in Figure 4. While no specific attempt was made to control this process during bioassays, dry compounds were dissolved in DMSO and immediately frozen at –20 °C and then thawed the day of assay. While we are not able to judge the extent of equilibration that has occurred during the 48 h cell growth assays, the similar patterns observed for the three compounds support interconversion of the secalononic acid A linkage isomers in the assay. Interestingly, in our studies, we found that the *O*-methyl enol ether appears to prevent dynamic (shapeshifting) behavior. However, methyl enol ethers such as (–)-**56** (2,4′-linked) and (–)-**50** (4,4′-linked) were found to have reduced biological activities, while the protected compounds (–)-**62** and (+)-**63** (2,2′-linked) maintained modest bioactivities. Nevertheless, all methyl-protected substrates have reduced bioactivities in comparison to the unprotected dimeric tetrahydroxanthenes, which leads us to believe that the tetrahydroxanthone moiety is crucial for their cytotoxicity. It is also noteworthy that compounds such as (–)-**61** and (–)-**62** (Figure 5) appear to have different patterns of cell growth inhibition from the others, perhaps indicating a different mode of action. Of the tetrahydroxanthenes, only the rugulotrocin derivative (–)-**60**^{14c} was found to be inactive against all cell lines tested. Moreover, compound (+)-**46** has reduced cytotoxicity in comparison to (+)-**51**, which contains an additional methyl group on the tetrahydroxanthone C ring. A similar pattern also was observed for compounds (–)-**57** and (–)-**2**. These results indicate that the methyl group on the C ring may provide a hydrophobic site, which is crucial for cytotoxicity. These conclusions about selectivity and potency are preliminary, and a more meaningful analysis will require testing in the full NCI 60 screen.

CONCLUSION

We have developed a copper-mediated aryl stannane coupling protocol to access chromone lactone dimers as well as 4,4'- and 2,4'-linked dimeric tetrahydroxanthones. A highly selective kinetic resolution was performed on an unprotected tetrahydroxanthone scaffold to enable access to chiral, nonracemic monomers. Asymmetric syntheses of 2,4'-linked (penicillixanthone A) and 4,4'-linked secalonic acids A and their analogues have been achieved. Our investigation also led to the discovery of a gold(III)-catalyzed *para*-bromination of a chromone lactone substrate. With a varied linkage series of secalonic acids A, the “shapeshifting” properties were evaluated and monitored by UPLC analysis. Initial biological studies of secalonic acid A analogues revealed that the dimeric tetrahydroxanthone moiety was crucial for cytotoxicity against select cancer cells and that isomerization of the biaryl linkage likely occurs during the cell-based assays. Further biological studies of secalonic acid derivatives, as well as the chemistry of the secalonic acid core structure, are ongoing and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 2.
Shapeshifting, dynamic equilibration of the parnafungins.

Figure 3.
X-ray crystal structure of chlorinated tetrahydroxanthone **34**.

Figure 4.
Equilibration of 4,4'-linked secalonic acid A in DMSO.

Figure 5.
Structure of additional dimeric tetrahydroxanthones investigated.

Scheme 1.
Bromination of a Chromone Lactone Substrate

Scheme 2.
Possible Mechanisms for *para*-Bromination

Scheme 3.
Synthesis of a Chiral, Racemic 4,4'-Linked Chromone Lactone

Scheme 4.
Dieckmann Cyclization of Brominated Tetrahydroxanones

Scheme 5.
Synthesis of a *para*-Iodo Tetrahydroxanthone

Scheme 7.

Asymmetric Synthesis of a Model 4,4'-Linked Tetrahydroxanthone Dimer

Scheme 8.

Asymmetric Synthesis of a 4,4'-Linked Secalonic Acid A

Scheme 9.

Asymmetric Synthesis of Model 2,4'-Linked Tetrahydroxanthone Dimer

Scheme 10.

Asymmetric Synthesis of a 2,4'-Linked Secalonic Acid A (Penicillixanthone A)

Cytotoxicities of Secalonic Acids and Related Compounds with Varied Linkages against Four Human Tumor Cell Lines^a

Table 1

compound	A498	UO31	Colo205	KM12	linkage
(-)- 1	6.0	0.12	0.044	0.072	2,2
(-)- 60 ^{14c}	>40	>40	>40	>40	2,2
(-)- 61 ^{14b}	5.5	4.9	2.8	2.8	2,2
(-)- 62 ^{14b}	3.9	3.6	2.9	n.d. ^b	2,2
(+)- 1	3.9	0.40	0.052	0.19	2,2
(+)- 63 ^{14b}	4.8	6.8	4.0	n.d. ^b	2,2
(-)- 56	6.3	9.9	8.6	8.2	2,4
(-)- 57	14	35	>40	31	2,4
(-)- 2	n.d. ^b	0.10	0.067	0.099	2,4
(+)- 46	11	33	>40	>40	4,4
(+)- 51	1.1	0.060	0.010	0.012	4,4
(-)- 50	>40	18	>40	39	4,4
53	33	6.3	>40	27	4,4
(-)- 45	28	30	22	16	4,4
27	>40	>40	>40	>40	4,4
28	>40	>40	>40	>40	4,4

^aIC₅₀ values in μ M.

^bConflicting values observed in two experiments.