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Total Synthesis and Biological Studies of Cryptocin and Derivatives of Equisetin and Fusarisetin A

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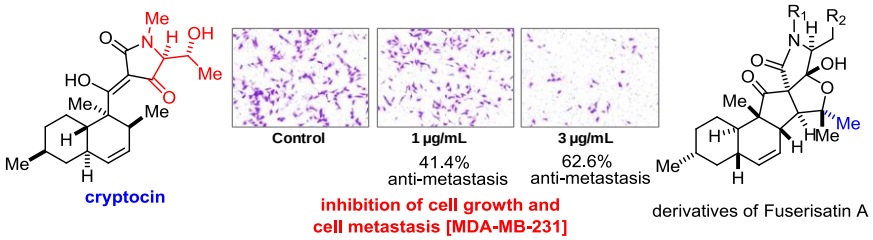
Abstract

Total synthesis of cryptocin, a fungus metabolite, was achieved based the biosynthetic hypothesis. A variety of derivatives of cryptocin, equisetin and fusarisetin A were prepared, wherein the racemization of C-3 and diastereoselectivity of C-5 was investigated. We further examined their inhibitory effects on breast cancer cell survival and metastasis, and summarized the structure-activity relationship.

Keywords

cryptocin • equisetin • fusarisetin A • biomimetic synthesis • cell growth • cell migration

Graphic Abstract:



Introduction:

Tetramic acid type natural products constitute a subgroup which is structurally characterized by the presence of 3-acyl substituted motif.[1] As shown in Figure 1, the basic skeleton of this family typically contains a *trans*-decalin as well as a 3-acyl-tetramic acid. The major differences among these molecules rely on the tetramic acid rings which comprise various amino acids (serine, threonine, tryptophan, etc., shown in red). Most of these molecules belong to fungal metabolites and exhibit diverse biological activities.[1] Considerable interest of the naturally occurring tetramic acids has been attracted from the chemistry community due to their unique structures and potential

biological activities since the 1960s. We are interested in the structure–activity relationship and the target identification of these molecules. As a first step, we aim to develop an efficient and general approach to enable the divergent synthesis of this family of natural products.[2] We proposed that these 3-acyl-tetramic acids should share the same biosynthetic pathway, deriving from a polyenoylamino acid. We previously reported the biomimetic synthesis of two fungal metabolites, equisetin (**1**)[2, 3] and (+)-fusarisetin A (**13**),[2, 4, 5] based on this biosynthetic hypothesis.[2] As a continuance of the chemical and biological studies of 3-acyl-tetramic acids, we report herein the total synthesis cryptocin (**4**)[6] and preparation of derivatives of cryptocin (**4**), equisetin (**1**) and (+)-fusarisetin A (**13**). Based on these advanced natural product-like compounds, we additionally carry out the biological studies using human breast cancer cells to reveal their inhibitory activities of inhibition of cell growth and migration.[4, 7]

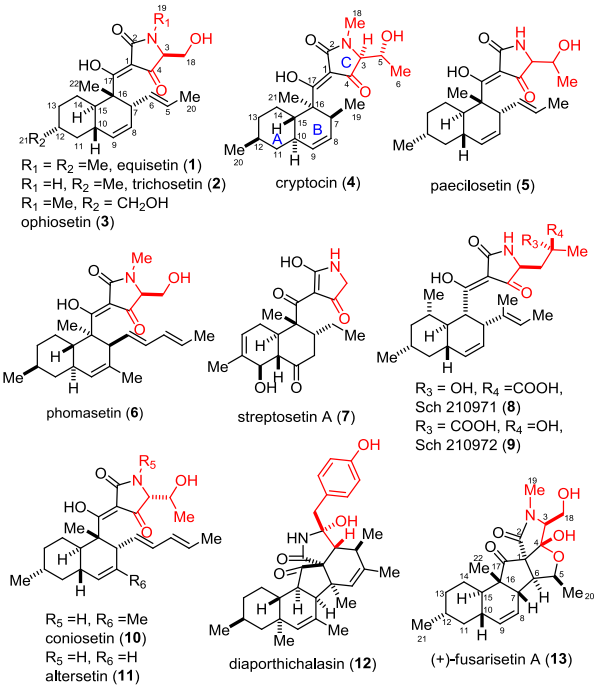


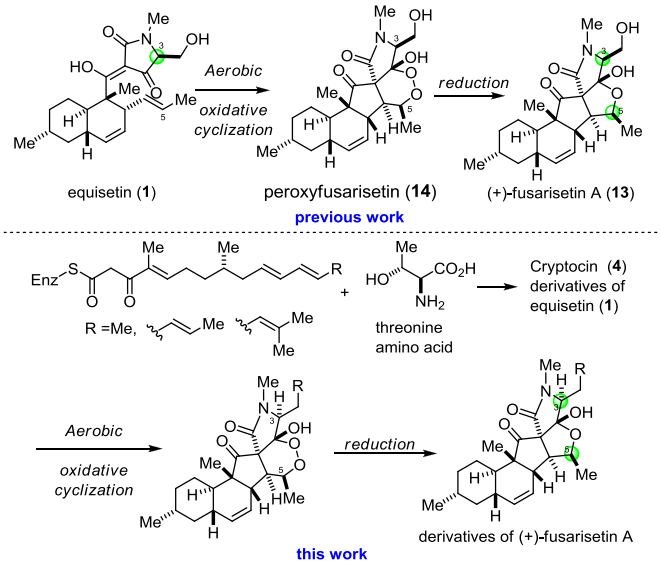
Figure 1. Structures of 3-acyl-tetramic acids.

Results and Discussion

In 2000, Strobel and co-workers reported the isolation of cryptocin (**4**) from the endophytic fungus *Cryptosporiopsis cf. quercina*.[6] **4** exhibits antimycotic activity against *Pyricularia oryzae*, the causal agent of rice blast disease, and it also possesses activity against a wide variety of plant pathogenic fungi.[6] The structure of **4** was determined using X-ray crystallographic analysis, which has the same basic skeleton with equisetin (**1**) and related natural products. The *trans*-decalin skeleton (A-B rings) of **4** contains two relative *cis*-methyl groups at C-7 and C-12. It's different with other structural related tetramic acids which normally have an unsaturated side chain at C-7.[1] It's worthy to note that cryptocin (**4**) comprises *ent*-trans decalin moiety (A-B rings) compared with equisetin (**1**) and (+)-fusarisetin A (**13**) according to the reported structure.[6] The 3-acyl-tetramic acid (C ring) shares the same structural features with paecilosetin (**5**)[8] and

coniosetin (**10**).[9] The structural feature and biological activity of **4** prompted us to initiate a research program to explore its chemical synthesis and biological functions. Furthermore, we wished to optimize the approach to solve the chemo-selectivity and efficiency for preparation derivatives of equisetin (**1**) and fusarisetin A (**13**), which will facilitate related structure-activity studies.

Our research plan is shown in Scheme 1. We previously reported the synthesis of equisetin (**1**) based on the biosynthetic hypothesis from the unsaturated fatty acid and naturally occurring amino acid, however the racemization of C-3 occurred during the Dieckmann cyclization under basic conditions. An aerobic oxidation of equisetin (**1**) mediated by a Mn^{III}/O_2 system or reactive oxygen species (ROS) gave peroxyfusarisetin (**14**) as a mixture of two diastereomers at C-5, which was reduced to (+)-fusarisetin A (**13**) and its C-5 epimer.[2] Using the same strategy, we envisioned that **4** could be prepared from the unsaturated fatty acid and threonine. We wished to address the racemization and diastereoselectivity issues by regulating both the structures of fatty acids and amino acids. In this way, we could prepare the derivatives of equistin and fusarisetin A with a more efficient approach.

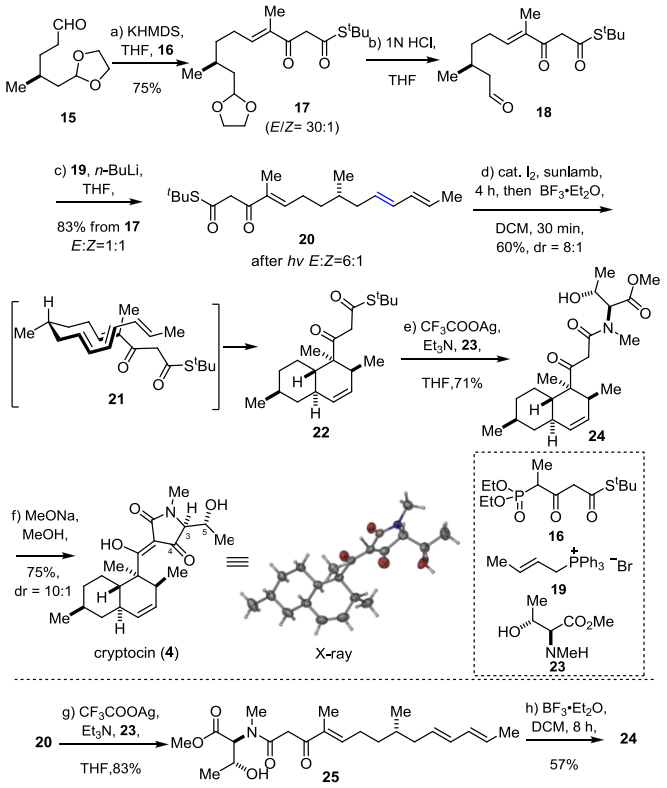


Scheme 1. Research Plan.

Total synthesis of cryptocin

The synthetic approach of cryptocin (**4**) is shown in Scheme 2. The chiral methyl group of **4** was induced from the (-)-citronellal which was converted to aldehyde **15** in a large scale with good yield using a known two step procedure.[10] Utilizing the same strategy we used to synthesize equisetin (**1**), we converted **15** into aldehyde **18** in two steps involving a Horner–Wadsworth–Emmons (HWE) reaction and deprotection.[2] Reaction of **18** with **19**[11] under basic condition smoothly delivered the polyene **20** in 83% yield as a mixture of two isomers (*E*:*Z* = 1:1). The Z isomer could be transformed to *trans*-polyene by a photo-induced isomerization catalyzed with iodine, which was used in the synthesis of fusarisetin A by Theodorakis and co-workers.[5b, c] Then, the intramolecular Diels-Alder (IMDA) reaction promoted by BF_3•OEt_2

effectively converted **20** to *trans*-decalin **22** (dr = 8:1) through the transition state **21** adopting the *endo* approach. Using the aminolysis strategy developed by Dixon, Ley and co-workers,[3d, e] we could couple **22** with the L-threonine derivative **23** to give **24** in 71% yield. We could also introduce the amino acid group and then performed the intramolecular Diels-Alder reaction using polyenoylamino ester **25**. As shown in Scheme 2, direct aminolysis of **20** with **23** promoted by silver trifluoroacetate gave **25**, which was then transformed to **24** in 57% yield. To construct the tetramic acid ring, the NaOMe promoted Dieckmann cyclization of **24** was applied to give cryptocin (**4**) as a major diastereomer (dr = 10:1 at C-3). A single crystal of synthetic **4** suitable for X-ray analysis was obtained, allowing unambiguous determination of its relative configurations, which were fully consistent with crystal structure reported by Strobel and co-workers.[6]

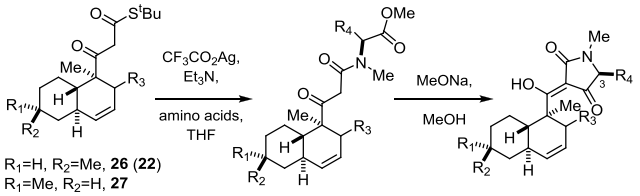


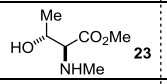
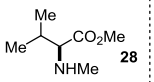
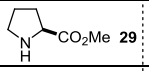
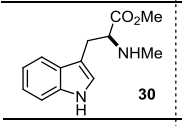
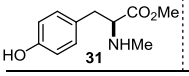
Scheme 2. Total Synthesis of Cryptocin. Reagents and Conditions: a) **16** (1.2 equiv), LHMDS (2.5 equiv), −78 °C→30 °C, THF, 2 h, *E*:*Z* = 30:1, 75% over two steps; b) HCl (1.0 N), 45 °C, 4 h, THF; c) **19** (3.0 equiv), *n*-BuLi (3.3 equiv), −78 °C→0 °C, THF, 40 min, *E*:*Z* = 1:1, 83% over two steps; d) I_2 (5 mmol%), 25 °C, 4 h then BF_3•OEt_2 (2.0 equiv), −78 °C, CH_2Cl_2, 30 min, 0 °C, 5 min, 60%; e) **23** (1.2 equiv), CF_3CO_2Ag (1.5 equiv), Et_3N (4.0 equiv), THF, 0 °C, 15 min, 71% f) NaOMe (3.0 equiv), MeOH, 0 °C, 1.5 h, 75%, dr = 10:1 (at C3) g) **23** (1.2 equiv), CF_3CO_2Ag (1.5 equiv), Et_3N (4.0 equiv), THF, 0 °C, 15 min, 83% h) BF_3•OEt_2 (5.0 equiv), −78 °C, CH_2Cl_2, 8 h, 0 °C, 10 min, 57%.

Preparation of derivatives of cryptocin and equisetin

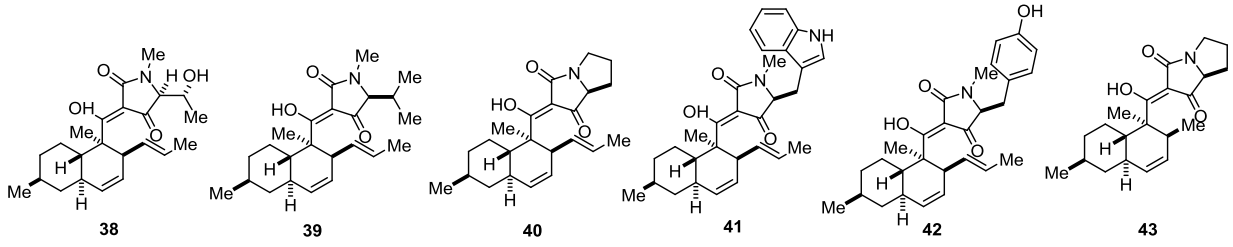
To prepare the derivatives of cryptocin (**4**), equisetin (**1**) and explore the racemization problem during the Dieckmann cyclization, we exepcted to use different amino acid to regulate the

stereochemistry of C-3. Using our reported strategy, we could prepare thioesters **22**, **26** and **27** in large scale with good overall yield (4 steps).[2] Then, the aminolysis of thioesters with different derivatives of naturally occurring amino acids, including threonine, valine, proline, tyrosine and tryptophan, was investigated. As shown in Scheme 3, the aminolysis promoted by silver trifluoroacetate smoothly furnished the corresponding coupling products (**32**-**36, 44**-**48**) in good to excellent yield.[3d, e] We next explored the Dieckmann cyclizaiton under the standard condition (NaOMe, MeOH) to accomplish the ring closure of tetramic acid. Comparison of the substrate to prepare equisetin, we found that the diastereoselectivities were slightly improved (dr > 2:1). We reasoned that activity of the proton on C-3 (**38**-**43** and **49**-**53**) was decreased comparing with the methyl hydroxy group of serine (equisetin (**1**)) and the rate of racemization were inhibited. Eleven derivatives of equisetin (**1**) and cryptocin (**4**) were prepared efficiently (Figure 2).



Amino acids	R_1=H, R_2=Me, **26**				R_1=Me, R_2=H, **27**	
	R_3 Allyl	R_3 Methyl	R_3 1-*E*-propenyl	R_3 Methyl	R_3 =1-*E*-propenyl	
	Aminolysis (yield)		*Dieckmann cyclization* (d.r. at C-3)		*Aminolysis* (yield)	*Dieckmann cyclization* (d.r. at C-3)
 **23**	**32**, 85 %	**24**, 71%	**38**, 69% d.r. = 5:1	**4**, 77% d.r. = 10:1	**44**, 86%	**49**, 74% d.r. = 5:1
 **28**	**33**, 75%	—	**39**, 49% d.r. = 4:1	—	**45**, 50%	**50**, 67% d.r. = 5:2
 **29**	**34**, 90%	**37**, 65%	**40**, 71% d.r. = 4:1	**43**, 90% d.r. > 10:1	**46**, 62%	**51**, 71% d.r. = 2:1
 **30**	**35**, 98%	—	**41**, 82% d.r. = 5:1	—	**47**, 80%	**52**, 78% d.r. =3:1
 **31**	**36**, 77%	—	**42**, 90% d.r. = 3:1	—	**48**, 89%	**53**, 78% d.r. = 3:1

Scheme 3. Preparation of derivatives of equisetin and cryptocin.



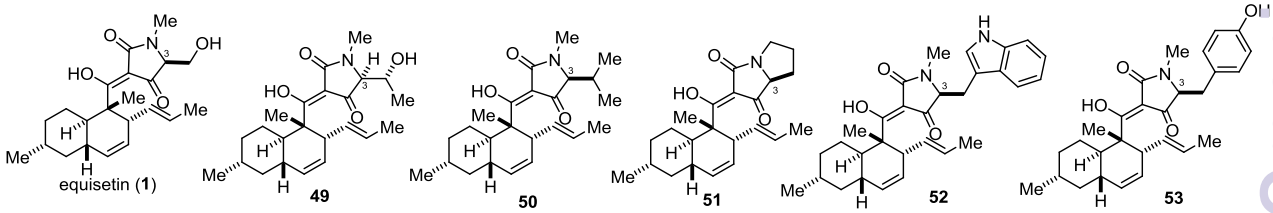
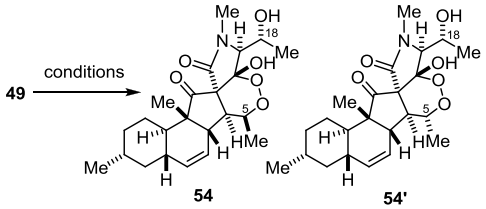


Figure 2. Derivatives of equisetin and cryptocin.

Aerobic oxidation of model substrate 49

With these derivatives of equisetin in hand, we started to prepare the corresponding derivatives of fusarisetin A through the aerobic oxidation. We previously demonstrated that the aerobic oxidation of equisetin (**1**) mediated by a Mn^{III}/O_2 system or reactive oxygen species (ROS) led to the formation of peroxyfusarisetin, which could be reduced to fusarisetin A easily.[2] However, the diastereoselectivity of this oxidation was proven to be challenging, and two diastereomers were obtained as an inseparable mixture in about 1:1 to 3:1 ratio at C-5. Take **49** as a model, which has an extra methyl group at C-18 compare to equisetin (**1**), we wished to find out the influence of tetramic acid rings with different amino acids to the stereochemistry of the aerobic oxidation. As shown in Table 1, we first tested the aerobic radical cascade mediated by a Mn^{III}/O_2 or Ce^{IV}/O_2. We found that the reaction of **49** with catalytic $Mn(OAc)_3$ (10% equiv.) in HOAC under air or O_2 gave corresponding peroxy-products as a mixture of two diastereomers **54** and **54'** at C-5 (d.r.= 1.1:1.0) in 88% combined yield. Oxidation of **37** using CAN as an oxidant under air or O_2, which was developed by Theodorakis group,[5b, c] gave **51** and **54'** in 1.3:1.0 ratio. We also investigated the ROS-mediated oxidation produced by visible-light chemistry. However, the oxidative cascade promoted by superoxide radical anion (dr = 1.5:1) and singlet oxygen (dr = 1:1) didn't give better results.



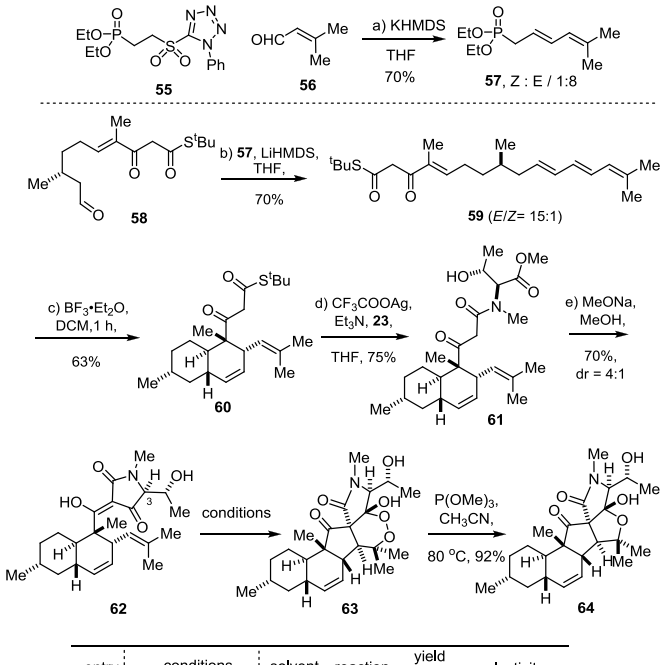
entry	conditions	solvent	reaction	selectivity (**54**: **54'**)	combined yield
1	$Mn(OAc)_3$,air;	HOAc	5 h	1.1 : 1.0	88%
2	CAN, O_2;	HOAc	5 h	1.3 : 1.0	51%
3	$Ru(bpy)_3Cl_2$, Et_3N, air, visible light;	CH_3CN	3.5 h	1.5 : 1.0	47%
4	Methylene blue, air, visible light;	CH_3CN	5 h	1.0 : 1.0	41%

Table 1. Aerobic oxidation of **49**.

Preparation of derivatives of fusarisetin A

Based on these results, we preliminary concluded that the diastereoselectivity of this aerobic oxidation could not be improved by changing the tetramic acid rings. In order to efficiently prepare derivatives of fusarisetin A, we envisioned to keep all the functional groups of **13** and expediently introduce a methyl group on C-5. This rational design should not only make the diastereoselectivity of C-5 vanish but also simplify the chemical process. Based on this synthetic analysis, we prepared the phosphonate **57** according to a known Julia coupling with sulfate **55** and aldehyde **56**.[12] Coupling of aldehyde **58** with **57** through the HWE reaction gave polyene **59** in 70% yield (E:Z = 15:1). Using the same strategy (Scheme 4), we could efficiently transform **59** into **62**, derivative of equisetin (**1**), by a three-step sequence involving the Diels-Alder reaction,

aminolysis and Dieckmann cyclization.[2] In turn, the aerobic oxidation of **62** was explored and the representative results were summarized in the Scheme 4. We were pleased to find that the aerobic oxidation of **62** using oxidant/O_2 or ROS-mediated conditions gave the desired peroxy-product **63** as a single diastereomer in medium to excellent yield. Reduction of **63** using $P(OMe)_3$ and furnished the derivative of fusarisetin A in 92% yield.



entry	conditions	solvent	reaction	yield (brsm)	selectivity
1	$Mn(OAc)_3$, air;	HOAc	50 min	93%	—
2	CAN, O_2;	HOAc	2 h	80%	—
3	$Ru(bpy)_3Cl_2$, Et_3N, air, visible light;	CH_3CN	8 h	34%	—

Scheme 4. Preparation of derivatives of fusarisetin A. Reagents and Conditions: a) **56** (1.5 equiv), KHMDS (1.2 equiv), −78 °C→0 °C, THF, 1 h, *E*:*Z* = 8:1, 70%; b) **57** (3.0 equiv), LHMDS (3.3 equiv), −78 °C→30 °C, THF, 16 h, *E*:*Z* = 15:1, 70% over two steps; c) BF_3•OEt_2 (2.0 equiv), −82 °C, CH_2Cl_2, 1 h, 0 °C, 2 min, 63%; d) **23** (1.2 equiv), CF_3CO_2Ag (1.5 equiv), Et_3N (4.0 equiv), THF, 0 °C, 15 min, 75% e) NaOMe (3.0 equiv), MeOH, 0 °C, 3 h, 74%, dr = 4:1 (at C3).

Based on this modified strategy, we could prepare additional derivatives of equisetin and fusarisetin A in a more efficient approach. As shown in Scheme 5, started from thioester **60**, a four-step sequence including aminolysis, Dieckmann cyclization, aerobic oxidation and reduction efficiently transformed **60** into derivatives of equisetin and fusarisetin A. Notably, we obtained single crystals of **69** and **70** suitable for X-ray analysis, which allowed unambiguous determination of responding relative configurations.

60 —(*Aminolysis*; *Dieckmann cyclization*)→ **derivatives of equisetin** —(*aerobic oxidation*; *reduction*)→ **derivatives of fuserisatin A**

Amino acids	*Aminolysis* (yield)	*Dieckmann cyclization* (yield) (d.r. at C-3)	*aerobic oxidation (yield)*	*reduction (yield)*
HO, CO_2Me, NHMe	82 %	**65**, 100% d.r. = 1.4:1	**66**, 54%	**67**, 55%
28	76 %	**68**, 84% d.r. = 3:1	**69**, 94%	**70**, 76%
29	80 %	**71**, 68% d.r. = 1.3:1	**72**, 99%	**73**, 82%

Scheme 5. Preparation of derivatives of equisetin and fusarisetin A.

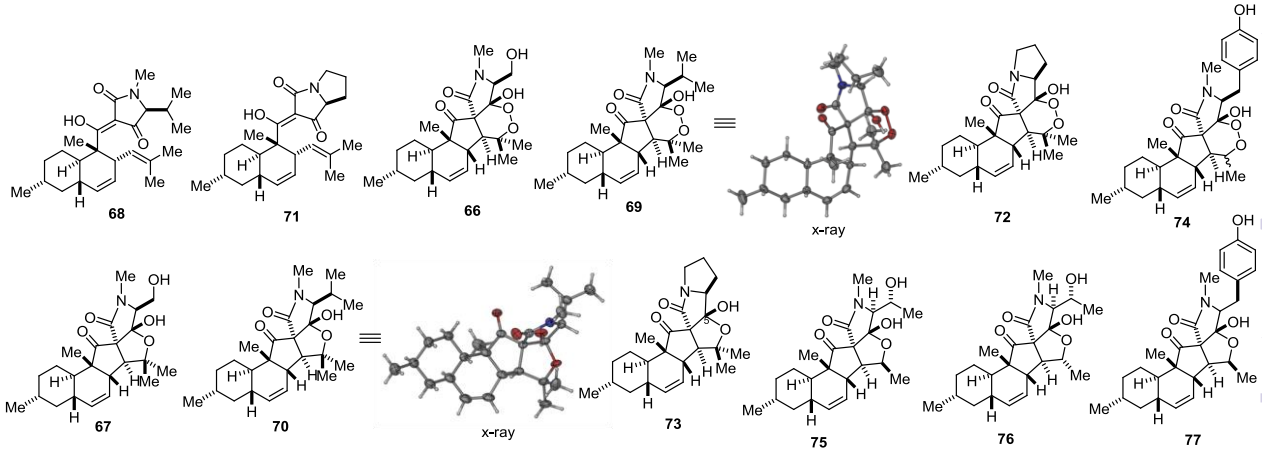


Figure 3. Derivatives of equisetin and fusarisetin A.

Biological studies of derivatives of cryptocin, equisetin and fusarisetin A

Kim, Osada, Ahn and colleagues initially reported that fusarisetin A (**13**) potently inhibited acinar morphogenesis, cell migration and invasion of the MDA-MB-231 breast cancer cells. Interestingly, tests of cancer cell viability using the same cell line show that **13** does not exhibit significant cytotoxicity at a concentration of 30 μg/mL.[4, 7] Cryptocin (**4**) and equisetin (**1**) have similar structural features and biosynthetic pathway with fusarisetin A (**13**). It's reasonable to assume that both **1** and **4** should have related biological activities with **13**. Having resolved the supply issue through biomimetic synthesis, we are now pursuing further biological studies focused on the functions of prepared derivatives of cryptocin (**4**), equisetin (**1**) and fusarisetin A (**13**) on the growth and migration properties of MDA-MB-231 cells. We hope to find out the structure-activity relationships.

Using the high metastatic MDA-MB-231 breast cancer cells, we first tested the inhibitory activity of those derivatives on cell viability. For these cell-based assays, MDA-MB-231 cells were purchased from American Type Culture Collection (Manassas, VA) and cultured in L-15 medium (GIBCO, Grand Island, NY) supplemented with 10% fetal bovine serum (FBS; GIBCO). Treatment of MDA-MB-231 cells with prepared analogues for 48 h, half-inhibitory concentration (IC_{50}) values were calculated by Origin software. As shown in table 2, we found that cryptocin (**4**, IC_{50} = 27.0 μg/mL) and equisetin (**1**, IC_{50} = 45.0 μg/mL) exhibited weak cytotoxicity in

MDA-MB-231 cells. Similar results were observed for the most members of analogues of **4** and **1**, which demonstrated IC_{50} values ranging from 23.5 μg/mL to 46 μg/mL, except compound **39** which showed relative strong cytotoxicity (IC_{50} = 3.0 μg/mL). As a comparison, the most complex derivatives of fusarisetin A (**13**), including analogues of peroxyfusarisetin, showed no cytotoxicity with > 100 μg/mL IC_{50} values in MDA-MB-231 cells, which is consistent to the results reported by Kim, Osada, Ahn and colleague. [4]

derivatives of **1** and **4**	IC_{50} [a] (μg/mL)	derivatives of **13**	IC_{50} [a] (μg/mL)
4	27.0	**14**	100
39	3.0	**54**	>100
40	24.8	**63**	>100
41	30.0	**66**	>100
42	41.3	**69**	>100
43	28.5	**72**	>100
1	45.0	**74**	52.4
49	30.0	**64**	>100
50	46.5	**67**	>100
51	40.0	**70**	>100
52	41.5	**73**	>100
53	31.0	**75**	94.3
62	36.9	**76**	100
68	23.5	**77**	36.9

Table 2. Evaluation of inhibiton of cell growth with derivatives of **1**, **4** and **13** in MDA-MB-231 breast cancer cells. a. variation < ±5%

We then investigated the inhibition of cell migration applied by Boyden chamber migration assay.[13] Based on the inhibitory activity of derivatives of **1**, **4** and **13**, we planned to evaluate the anti-migration with MDA-MB-231 cells in the concentration of 3 μg/mL of synthesized derivatives. We assumed that inhibition of cell migration should not be affected by the cytotoxicity of these compounds since most of them exhibited weak cytotoxicity (IC_{50} > 25μg/mL). Using DMSO as control, the MDA-MB-231 cells were starved and pre-incubated with synthesized derivatives of cryptocin (**4**), equisetin (**1**) and fusarisetin A (**13**) in the concentration of 3 μg/mL at 37 ℃ for 1 h. A total of 5×10^4 cells in 100 μL starvation medium were seeded on the upper chamber and 500 μL of medium supplemented with FBS was added in the lower chamber as a chemo-attractant. Cells were then incubated for additional 18-20 h. Non-migrated cells were removed with a cotton swab. Those migrated cells on the lower surface of the membrane were fixed in 4% paraformaldehyde, stained with 0.5% crystal and counted under an inverted microscope (Olympus, Center Valley, PA; magnification, ×100).[14] The suppressive effects of prepared derivatives on cell motility were summarized in table 3. The bioactivity data indicated that most derivatives of **13** exhibited moderate antimetastatic activity at the concentration of 3 μg/mL. As shown in table 3, equisetin (**1**), cryptocin (**4**) and most derivatives of them showed more potent antimetastasis activity than analogues of **13**. Equisetin (**1**) inhibited 84.6% cell metastasis at the concentration of 3 μg/mL, cryptocin (**4**) and **40** prevented 62.6% and 66.3% cell migration under the same concentration respectively. In conclusion, these synthetic derivatives

might be used as promising leads for the development of a new class of antimetastatic agents.

derivatives of **1** and **4** [a]	anti-migration (%) [b]	derivatives of **13** [a]	anti-migration (%) [b]
4	62.6	**14**	20.8
39 [c]	48.8	**54**	38.5
40	66.3	**66**	13.8
41	41.7	**69**	27.7
42	34.2	**72**	29.7
43	30.5	**74**	23.4
1	84.6	**64**	41.7
49	55.5	**67**	8.9
50	35.8	**70**	26.6
51	14.8	**73**	43.3
52	25.6	**75**	8.8
53	15.5	**76**	9.0
68 [c]	16.8	**77**	36.5

Table 3. Evaluation of inhibition of cell migration with derivatives of **1**, **4** and **13** in MDA-MB-231 breast cancer cells. a. concentration of derivatives was 3 μg/mL; b. variation < ±5%, c. concentration of derivatives was 1 μg/mL.

Based on these results, we concluded that the biological activities of these tested substrates mainly related to the structural features of both *trans*-decalin and 3-acyl-tetramic acid motif, regarding to the inhibition of cell growth and cell migration in MDA-MB-231 breast cancer cells. Changing the configuration of *trans*-decalin didn't affect the activity (**4**, **39**-**43**). Substrates bearing different tetramic acid rings, which contain distinct amino acids, show consistent inhibition of cell growth and migration properties in MDA-MB-231 cells (Table 2). Strikingly, substrates with higher oxidation state, containing C and D rings (**67**, **70**, **73**, **75**-**77**) or peroxy-bridge (**66**, **69**, **72**, **74**), proved detrimental to the inhibition of cell growth. However, these non-cytotoxicity substrates still have the properties to inhibit the cell migration.

Conclusion

In summary, we have accomplished the total synthesis of cryptocin, a fungus metabolite, using a biomimetic approach. A variety of derivatives of cryptocin, equisetin and fusarisetin A were prepared, wherein the racemization of C-3 and diastereoselectivity of C-5 were investigated. We found that the racemization of C-3 could be slightly improved when the activity of the proton on C-3 was decreased using different amino acids. The distereoselectivity of C-5 was expediently solved through introduction of an extra methyl group on C-5. Further biological studies were investigated using the high metastatic MDA-MB-231 breast cancer cells. We found that derivatives fusarisetin A and its analogues inhibited cell migration at the similar level of equisetin and cryptocin without measurable cytotoxicity. These finding laid a foundation for the mechanism studies and target identification of these molecules.

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