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ARTICLE

Synthesis and biological evaluation of (-)-kunstleramide and its derivatives†

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Stereoselective total synthesis of (-)-kunstleramide, a cytotoxic dienamides from the bark of *Beilschmiedia kunstleri* gamble, has been accomplished by using *Keck's* asymmetric allylation and *Trost* isomerization as a key reactions. Application of the developed strategy for the synthesis of a series of amide analogues (**8**-**22**) were also reported. Furthermore, the synthesized compounds were evaluated their in vitro anti-proliferative activities against human lung carcinoma epithelial (A549), human epithelial cervical cancer (HeLa), human breast adenocarcinoma (MCF7) and human neuroblastoma (IMR32) Cell lines using SRB assay. All the compounds show moderate anti-proliferative activity against all cell lines. Some of the piperazine derivatives (**17**-**22**) strongly inhibit the growth of breast cancer cells with IC_{50} values of 8–20 µM.

Introduction

The unsaturated amide moiety is a wide spread functionality found in numerous naturally occurring plant based alkaloids. These natural products contain a diene moiety as the main carbon backbone, differing from each other by chain-length and/or the number of functional groups.[1] During the last decade several natural products with diene structural motif such as Lobatamides,[2] Salicylihalamides,[3] Apicularen,[4] Saliniketals,[5] Scyphostatin[6] and Crocacins[7] have been isolated and possess significant biological activities.

The Genus Piper is a rich source of dienamides and most of these compounds exhibit a wide range of biological activities, such as immunomodulatory,[8] anticarcinogenic,[9] antiulcer,[10] antideprssant,[11] antifungal,[12] and anticancer activities.[13] The biological importance of unsaturated amides and their pharmacological potential have made them extremely attractive targets for both synthetic and biological researchers to study their synthesis and medicinal properties.[14] As a part of our ongoing research program aimed at developing stereoselective syntheses of biologically interesting molecules[15] originating from natural sources, we developed an enantioselective route to (-)-kunstleramide.

(-)-Kunstleramide, an unsaturated amide was isolated from the bark of *Beilschmiedia kunstleri* Gamble and displayed moderate cytotoxic activity.[16] To the best of our knowledge, only one synthesis has been reported in the literature.[17] With the aim of a developing new synthetic route and structural modifications of (-)-kunstleramide, we would like to report herein an efficient access to the construction of new derivatives **8**-**22** with improved anti-proliferative activity, by employing *Keck's* allylation and *Trost* isomerization as key steps and evaluate their antiproliferative activities against human tumor cell lines such as cervical (HeLa), breast (MCF7), lung (A549) and neuroblastoma (IMR32).

Results and discussion

Retrosynthetic analysis of **1** is outlined in Scheme 1. TPP mediated allene type rearrangement of **5** and amide coupling would provide the target molecule, Whereas, alkyne precursor **5** could be made from **2** by *Keck's* allylation, oxidative cleavage of olefin, followed by alkynylation.

The synthetic route for key intermediate **7** is shown in *Scheme 2*. An improved synthesis of kunstleramide was accomplished in seven steps from commercially available 3,4-dimethoxy phenyl acetaldehyde. The key diene acid fragment **7** was prepared in 3.19 g scale in a five steps with 54% overall yield.

As illustrated in *Scheme 2*, 3,4-dimethoxy phenyl acetaldehyde (**2**), was subjected to *Keck's* asymmetric allylation[18] with (*S*)-Binol, allyl tributyltin and $Ti(^iOPr)_4$ to give allylic alcohol **3** (enantiomeric excess 96%, determined by chiral HPLC). The alcohol **3** was converted into TBDMS ether **4** by silylation with

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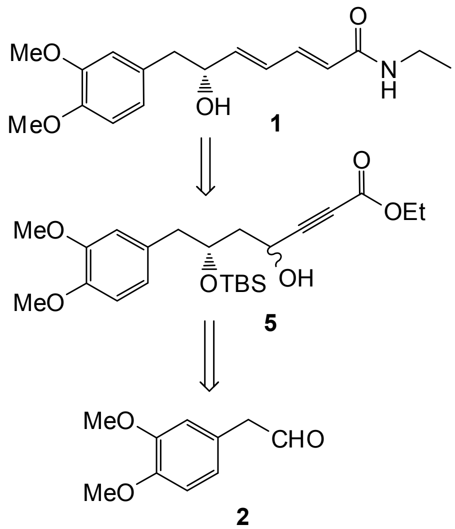
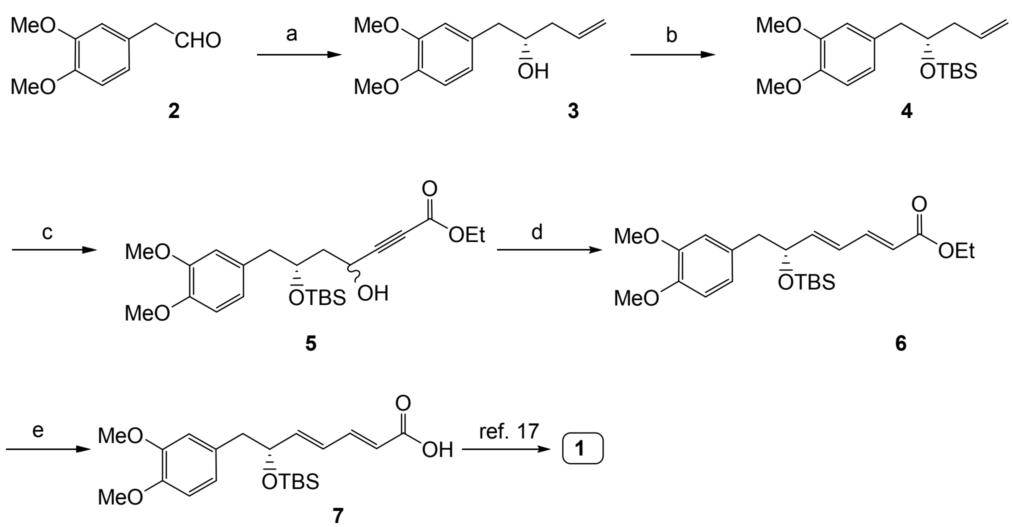
TBDMS-Cl.[19] Then the silyl ether was dihydroxylated with OsO_4, followed by cleavage with $NaIO_4$ to afford the crude aldehyde, which was used for the next step without further purification.[20] The aldehyde was subjected to propargylation using ethyl propiolate and LiHMDS to give **5** as a diastereomeric mixture, treatment of **5** with TPP in benzene at room temperature gave the conjugated diene ester **6**.[21]



Scheme 1. Retrosynthetic analysis of (-)-Kunstleramide (**1**)

Ester **6** was hydrolyzed with $LiOH.H_2O$ to provide the key diene acid fragment **7** on a 3.19 gram scale. Diene acid **7** was converted into amide **1** by using a reported protocol.[17] With the intermediate **7** in hand and a diverse class of acyclic and cyclic amines; we have prepared 15 new analogues of (-)-kunstleramide (**8**-**22**) with the moderate to good yields, *Scheme 3*. All the synthesized compounds were characterized by their ^{1}H, ^{13}C NMR, ESI-MS and HRMS spectral data.

The newly synthesized compounds, (-)-Kunstleramide (**1**) and its derivatives (**8-22**) were evaluated to determine their antiproliferative activities against a panel of four different human cancer cells from cervix, breast, lung and neuroblastoma (HeLa, MCF7, A549, IMR32, respectively, which were obtained from American Type culture collection) using the SRB assay. The IC_{50} values (μM) for compounds **1** and **8**-**22** are summarized in Table 1. Most of the synthesized compounds have shown good antiproliferative activities against these cell lines in a concentration-dependent manner. Compounds derived from substituted piperazines (**19**, **20**, **21** and **22**) exhibited potent activity on A549 cell line with IC_{50} values of 8.13, 9.92, 7.58, 10.6 μM respectively. Compounds **9**, **18** and **21** display significant activity on human epithelial cervical cancer cell line (HeLa) with IC_{50} values of 9.45, 9.75 and 8.25 μM, respectively and amides prepared from acyclic amines (**8** and **10**), cyclic amines (**17**, **20** and **22**) showed moderate activity on HeLa cell line. Furthermore, the other kunstleramide analogues **17** and **18** exhibited better anti-proliferative activities on the human breast adenocarcinoma (MCF7) cell line with IC_{50} values 11.51 and 11.97 μM respectively. Similarly, (-)-Kunstleramide **1**, **19** and **21** showed potent activity on a human neuroblastoma (IMR32) cell line with IC_{50} values of 9.43, 9.43 and 8.23 μM, respectively. The IC_{50} values of all these synthesized compounds were comparatively less than that of the standard drug combretastatin (CA4) and exhibited higher activity than piperine.



Scheme 2. *Reagents and Conditions*: (a) (*S*)-BINOL, 4-Å molecular sieves, $Ti(O^iPr)_4$, allyl(tributyl)stannane, anhydrous CH_2Cl_2, -78 °C to -20 °C, 48 h; (b) TBDMS-Cl, imidazole, CH_2Cl_2, 0 °C to rt, 8 h; (c) i) NMO, OsO_4, Acetone-Water (4:1), rt, over night; ii) $NaIO_4$, THF, rt, 1 h; iii) Ethyl propiolate, LiHMDS, THF, -78 °C, 1 h; (d) TPP, Benzene, rt, 6 h; (e) $LiOH.H_2O$, THF: MeOH: H_2O (4:2:1), rt, 6 h.

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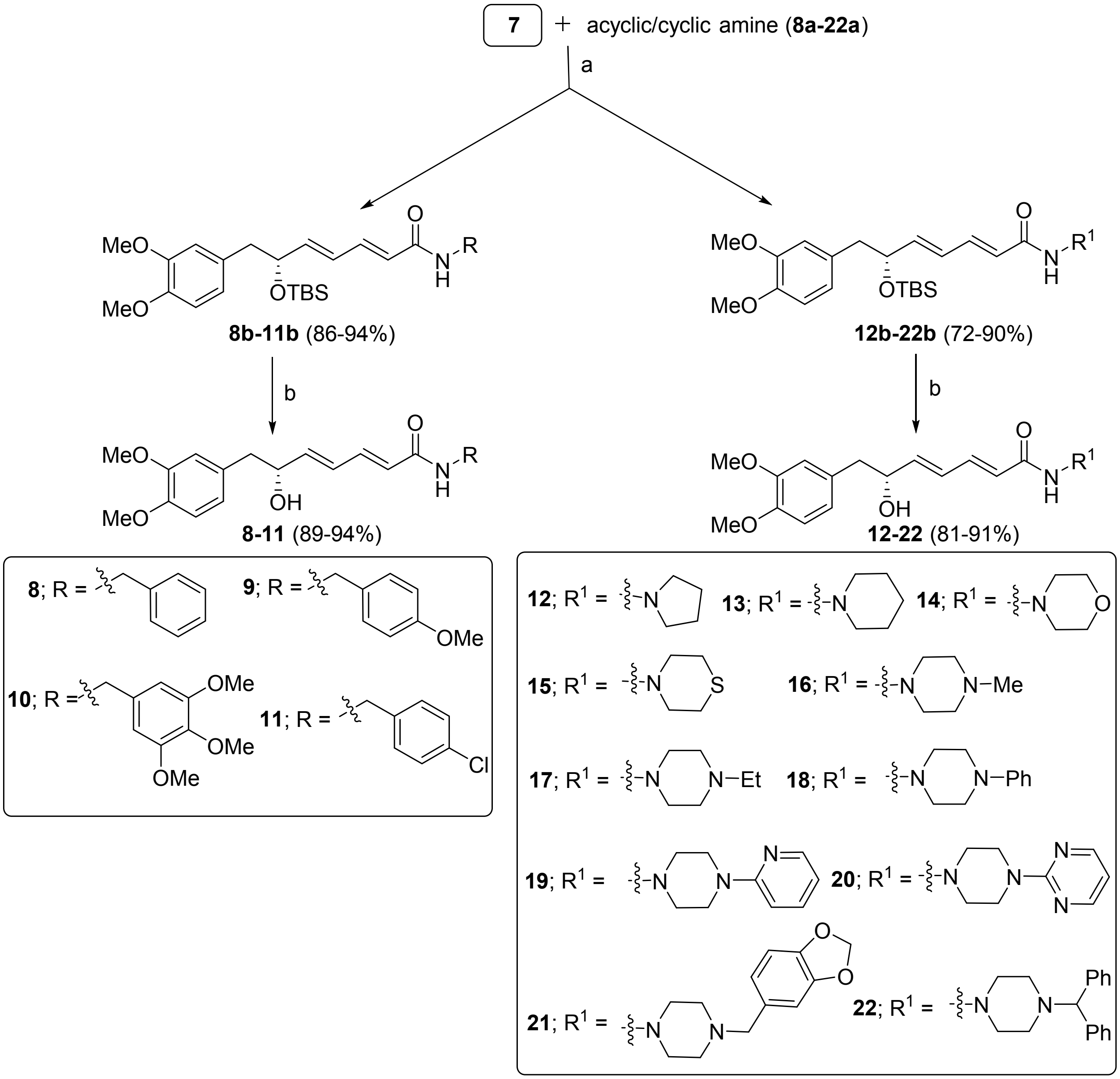

Scheme 3. *Reagents and Conditions*: (a) HATU, DIPEA, acyclic/cyclic amine, anhydrous DMF, 0 ^{o}C to rt, overnight; (b) *P*TSA, MeOH, 0 ^{o}C, 4 h.

Table 1: IC_{50} values for antiproliferative activities of compounds **1** and **8-22** against cancer cell lines [a]

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		IC$_{50}$ (µM)			
S. No	**Compound**	**A-549**	**Hela**	**MCF-7**	**IMR-32**
1	**1**	13.83 ± 0.27	14.58 ± 0.13	12.87 ± 0.71	9.43 ± 0.12
2	**8**	17.12 ± 0.63	12.93 ± 0.94	33.56 ± 0.1	16.59 ± 0.97
3	**9**	16.81 ± 0.74	9.45 ± 0.61	26.61 ± 0.83	17.35 ± 0.26
4	**10**	19.19 ± 0.15	10.72 ± 0.1	15.33 ± 0.91	13.41 ± 0.78
5	**11**	16.46 ± 0.2	13.36 ± 0.1	18.87 ± 0.16	15.66 ± 0.93
6	**12**	24.36 ± 0.92	14.14 ± 0.94	26.23 ± 0.91	12.01 ± 0.58
7	**13**	16.67 ± 0.49	14.09 ± 0.64	39.47 ± 0.83	11.02 ± 0.22
8	**14**	17.9 ± 0.65	16.41 ± 0.73	16.18 ± 0.96	20.36 ± 0.74
9	**15**	18.03 ± 0.49	20.59 ± 0.93	20.15 ± 0.83	16.09 ± 0.24
10	**16**	22.17 ± 0.54	16.49 ± 0.71	17.13 ± 0.96	18.87 ± 0.42
11	**17**	15.68 ± 0.33	11.68 ± 0.48	11.51 ± 0.52	10.79 ± 0.4
12	**18**	14.17 ± 0.67	9.75 ± 0.17	11.97 ± 0.1	9.43 ± 0.29
13	**19**	8.13 ± 0.73	23.57 ± 0.9	23.57 ± 0.9	11.06 ± 0.95
14	**20**	9.92 ± 0.98	12.61 ± 0.42	14.66 ± 0.58	10.79 ± 0.45
15	**21**	7.58 ± 0.11	8.25 ± 0.54	12.3 ± 0.36	8.23 ± 0.34
16	**22**	10.6 ± 0.31	10.48 ± 0.15	12.54 ± 0.23	11.86 ± 0.44
17	**Piperine**[b]	11.89 ± 0.18	19.21 ± 0.73	12.96 ± 0.49	10.19 ± 0.38
18	**Cambretastatin**[c]	6.45 ± 0.41	5.36 ± 0.12	4.63 ± 0.47	5.72 ± 0.4

[a] IC$_{50}$ is defined as the concentration, which results in a 50% decrease in cell number as compared with that of the control cultures in the absence of an inhibitor and were calculated using the respective regression analysis. The values represent the mean ± SE of three individual observations. [b] Piperine and [c] Combretastatin was employed as positive control.

Conclusions

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In conclusion we have achieved the total synthesis of (-)-kunstleramide and its analogues from commercially available starting materials using *Keck's* asymmetric allylation and *Trost* isomerization chemistry as a key maneuvers. The overall yield of target natural product was 46% in a seven steps and the key fragment **7** was synthesized on a 3.19 gram scale. All the compounds were screened for anti-proliferative activity. Most of the synthesized analogues exhibited higher activity than the natural product (-)-Kunstleramide. In particular, compounds with piperazine amide moieties (**18**, **21**, **22**) showed superior activity against all cell lines.

Experimental

Chemistry:

General experimental: ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solvent on Bruker 300 MHz (Avance), Varian Unity 500 MHz (Innova) and 600 MHz spectrometers at ambient temperature. Chemical shifts are reported in ppm relative to TMS as internal standard. FTIR spectra were recorded on a Perkin-Elmer 683 infrared spectrophotometer, neat or as thin films in KBr. Optical rotations were measured on an Anton Paar MLP 200 modular circular digital polarimeter by using a 2-mL cell with a path length of 1 dm. Low-resolution MS were recorded on an Agilent Technologies LC-MSD trap SL spectrometer. All the reagents and solvents were of reagent grade and used without further purification unless otherwise stated. Technical-grade EtOAc, hexanes, CH_2Cl_2 and EtOAc used for column chromatography were distilled before use. THF, when used as solvent for the reactions, was freshly distilled from sodium benzophenone ketyl. Column chromatography was carried on silica gel (60–120 mesh) packed in glass columns. All the reactions were performed under N_2 in flame- or oven dried glassware with magnetic stirring.

(*S*)-1-(3,4-dimethoxyphenyl)pent-4-en-2-ol (3): A mixture of (*S*)-BINOL (3.8 g, 13.32 mmol, 0.4 equiv.), Ti(O-*i*-Pr)$_4$ (6.66 mL, 6.66 mmol, 1M in CH_2Cl_2, 0.2 equiv.), CF_3CO_2H (333 μL, 0.333 mmol, 0.1M in CH_2Cl_2, 0.01 equiv.), and oven-dried 4Å molecular sieves (10 g) in 150 mL of CH_2Cl_2 was heated to reflux for 1 h. The resulting red-brown mixture was cooled to rt and 2-(3,4-dimethoxyphenyl)acetaldehyde **2** (6 g, 33.3 mmol, 1 equiv.) was added. This mixture was stirred at rt for 15 min before it was cooled to –78 ^{o}C and allyltributylstannane (22.05 g, 20.65 mL, 66.6 mmol, 2 equiv.) was then added. The reaction flask was placed in a –20 ^{o}C freezer for 48 h without stirring. The resulting mixture was quenched by the addition of 150 mL of saturated $NaHCO_3$ solution and stirred for 10 min at rt, then filtered through a plug of Celite. The filtrate was diluted with 150 mL of CH_2Cl_2 and washed with 100 mL of water. The organic layer was dried over anhydrous Na_2SO_4 and then concentrated. The residue was purified by flash chromatography on a silica gel column, eluting with EtOAc / hexanes (1:10) to give 6.95 g (94%) of the product **3** as a colorless oil. $[\alpha]_D^{25}$: +79.8 (*c* 0.02, $CHCl_3$); IR (KBr): 3451, 2920, 2851, 1633, 1514, 1461, 1264, 1140, 1024, 770; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.95-6.85 (m, H), 6.83-6.79 (m, 1H), 6.66-6.58 (m, 1H), 5.85-5.74 (m, 1H), 5.14-4.95 (m, 2H), 3.90 (s, 3H), 3.90-3.85 (m, 1H), 3.87 (s, 3H), 2.81-2.70 (m, 1H), 2.65-2.62 (m, 1H), 1.84-1.79 (m, 2H), 1.58 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.3, 147.5, 130.2, 121.5, 115.3, 113.2, 111.0, 71.4, 55.9, 55.8, 43.5, 42.1; ESIMS: 245 $[M + Na]^+$; HRMS (ESI) (*m/z*): calcd. for $C_{13}H_{18}O_3Na$ $[M+Na]^+$ 245.1148; found 245.1152. The enantiomeric purity was determined by chiral HPLC (CHIRALCEL-OJ-H column, 250 × 4.6 mm, 5 mm); mobile phase, 15% IPA in hexane; flow rate, 1 mL/min; detection, 210 nm; *t*R 13.196 min) 96% ee.

(*S*)-*tert*-butyl((1-(3,4-dimethoxyphenyl)pent-4-en-2-yl)oxy)dimethylsilane (4): To a stirred solution of alcohol **3** (5 g, 22.49 mmol, 1 equiv.) in dry DMF (60 mL) was added imidazole (2.29 g, 33.7 mmol, 1.5 equiv.), DMAP (cat.), followed by *tert*-butyldimethylsilyl chloride (4.07 g, 27.0 mmol, 1.2 equiv.) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 8 h. The reaction mixture was then diluted by the addition of ice cold water (80 mL) and the aqueous phase was extracted with diethyl ether (2 x 70 mL). The combined organic layer was washed with cold water (100 mL), brine (100 mL), dried over Na_2SO_4 and evaporated the organic solvent under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, hexanes: EtOAc = 95:05) to give **4** (7.19 g, 95%) as a colorless oil. $[\alpha]_D^{25}$: +3.09 (*c* 0.13, $CHCl_3$); IR (KBr): 3401, 2925, 2854, 1712, 1513, 1461, 1262, 1139, 1025, 984, 763; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.74-6.71 (m, 1H), 6.68-6.65 (m, 2H), 5.74-5.72 (m, 1H), 5.10-4.98 (m, 2H), 3.85 (s, 3H), 3.90-3.85 (m, 1H), 3.82 (s, 3H), 2.79-2.76 (m, 1H), 2.59-2.55 (m, 1H), 1.82-1.79 (m, 2H), 0.86 (s, 9H), -0.07 (s, 3H), -0.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.8, 147.4, 131.2, 121.6, 115.4, 113.5, 111.1, 72.9, 56.1, 56.0, 43.7, 42.2, 25.6, 18.1, -4.8, -5.2; ESIMS: 359 $[M + Na]^+$; HRMS (ESI) (*m/z*): calcd. for $C_{19}H_{32}O_3NaSi$ $[M+Na]^+$ 359.2013; found 359.2017.

(6*R*)-ethyl 6-((*tert*-butyldimethylsilyl)oxy)-7-(3,4-dimethoxyphenyl)-4-hydroxyhept-2-ynoate (5): To a stirred solution of silyl ether **4** (5 g, 14.86 mmol) and NMO (2.09 g, 17.83 mmol, 1.2 equiv.) in H_2O (20 mL) and acetone (100 mL) was slowly added a solution of OsO_4 (4% in H_2O, 944 μL, 0.149 mmol, 0.01 equiv.), and the mixture was stirred at rt overnight. The reaction was quenched with an aqueous solution of $Na_2S_2O_3$ (100 mL), and EtOAc (100 mL) was added. The phases were separated, and the aqueous layer was extracted with EtOAc (2 × 80 mL). The organic layers were combined, dried over Na_2SO_4, and filtered, and the solvents were removed under reduced pressure to give a brown residue (5.3 g), which was used for next step without further purification.

To a stirred solution of crude diol compound in THF/H_2O (1:1, 100 mL) was added $NaIO_4$ (12.71 g, 59.4 mmol, 4 equiv.). The mixture was stirred at rt for 30 min. before adding EtOAc (80 mL) and H_2O (80 mL). The phases were separated, and the aqueous layer was extracted with EtOAc (2 × 60 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and the solvents were

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removed under reduced pressure to give a yellow oil. The crude aldehyde was used for next step without further purification.

To a solution of ethylpropiolate (1.47 g, 1.51 mL, 14.95 mmol, 1.1 equiv) in dry THF (80 mL) at -78 ^{o}C was added LiHMDS (15.85 mL, 19.02 mmol, 1.2 M solution in THF, 1.4 equiv), and the mixture was stirred at -78 ^{o}C for 1.5 h. crude aldehyde (4.5 g, 13.59 mmol) in THF (20 mL) was added at -78 ^{o}C and stirring was continued for 1 h. The reaction mixture was quenched with a saturated aqueous NH_4Cl solution and warmed to room temperature. It was diluted with water and extracted with EtOAc (3 x 60 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography (hexanes: EtOAc = 80:20) to give **5** (4.7 g, 72% overall three steps) as a colorless oil. $[\alpha]_D^{25}$: +13.08 (*c* 0.01, $CHCl_3$); IR (KBr): 3488, 2931, 2856, 2235, 1713, 1514, 1465, 1256, 1078, 1028, 834, 775; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.81-6.66 (m, 3H), 4.47-4.62 (m, 1H), 4.28- 4.18 (m, 2H), 4.16-4.09(m, 1H), 3.87 (d, *J* = 3.0 6H), 2.91- 2.82 (m, 1H), 2.77- 2.66 (m, 1H), 1.95- 1.76 (m, 2H), 1.30 (t, *J* = 7.1, 3H), 0.90 (d, *J* = 3.0, 9H), 0.1- 0.02 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.2, 148.5, 147.4, 130.4, 130.2, 121.5, 121.4, 112.7, 111.2, 111.1, 87.5, 71.4, 70.8, 61.8, 60.3, 60.1, 58.9, 55.6, 43.5, 43.2, 42.7, 41.7, 29.5, 25.6, 17.8, 13.8, -4.6, -4.66, -5.0; ESIMS: 459 [M + Na]$^+$; HRMS (ESI) (*m/z*): calcd. for $C_{23}H_{36}O_6NaSi$ [M+Na]$^+$ 459.2173; found 459.2180.

(*R*,2*E*,4*E*)-ethyl 6-((*tert*-butyldimethylsilyl)oxy)-7-(3,4-dimethoxyphenyl)hepta-2,4-dienoate (6): To a solution of **5** (4.5 g, 10.31 mmol, 1 equiv.) in benzene (80 mL) was added PPh_3 (3.24 g, 12.37 mmol, 1.2 equiv) at room temperature and the resulting mixture was stirred for 6 h. It was then diluted with hexanes/EtOAc (95:5, 80 mL) and filtered through a pad of silica gel. The filtrate was concentrated and the residue purified by silica gel column chromatography (hexanes: EtOAc = 95:05) to give **6** (3.86 g, 89%) as a colorless oil. $[\alpha]_D^{25}$: –6.8 (*c* 0.7, $CHCl_3$); IR (KBr): 2954, 2932, 2856, 1715, 1644, 1515, 1465, 1263, 1237, 1139, 1031, 835, 776; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (dd, *J* = 15.3, 10.9 Hz, 1H), 6.81-6.64 (m, 3H), 6.29 (dd, *J* = 15.3, 10.9 Hz, 1H), 6.11 (dd, *J* = 15.3, 5.4 Hz, 1H), 5.84 (d, *J* = 15.3 Hz, 1H), 4.41-4.31 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.85 (s, 6H), 2.77-2.67 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.85 (s, 9H), -0.09 (s, 3H), -0.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.0, 148.4, 147.5, 145.2, 143.9, 130.4, 126.8, 121.7, 121.0, 113.1, 110.9, 73.9, 60.2, 55.8, 55.7, 44.3, 25.7, 18.1, 14.2, -4.9, -5.2; ESIMS: 443 [M + Na]$^+$; HRMS (ESI) (m/z): calcd. for $C_{23}H_{36}O_5NaSi$ [M+Na]+ 443.2224; found 443.2228.

(*R*,2*E*,4*E*)-6-((*tert*-butyldimethylsilyl)oxy)-7-(3,4-dimethoxyphenyl)hepta-2,4-dienoic acid (7): To a stirred solution of ester **6** (3.6 g, 8.56 mmol, 1 equiv.) in a 4:2:1 mixture of THF: MeOH: H_2O (35 mL) was added LiOH.H_2O (1.08 g, 25.7 mmol, 2 equiv.), and stirred for 6 h at room temperature. The reaction mixture was quenched with saturated aqueous $KHSO_4$ (50 mL), and extracted with EtOAc (2 x 80 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated and the residue purified by silica gel column chromatography (silica gel, hexanes: EtOAc = 70:30) to give **7** (3.19 g, 95%) as a colorless oil. $[\alpha]_D^{25}$: –50 (*c* 0.4, $CHCl_3$); IR (KBr): 3447, 2930, 2855, 1685, 1640, 1613, 1512, 1463, 1416, 1257, 1139, 1105, 1001, 831, 771; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (dd, *J* = 15.1, 10.5 Hz, 1H), 6.79 (d, *J* = 8.1 Hz, 1H), 6.73-6.67 (m, 2H), 6.34 (dd, *J* = 15.1, 10.5 Hz, 1H), 6.17 (dd, *J* = 15.8, 4.5 Hz, 1H), 5.85 (d, *J* = 15.1 Hz, 1H), 4.43-4.34 (m, 1H), 3.86 (s, 6H), 2.77-2.70 (m, 2H), 0.86 (s, 9H), -0.08 (s, 3H), -0.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.1, 148.6, 147.6, 146.5, 146.1, 130.3, 126.6, 121.8, 120.1, 113.3, 111.2, 73.8, 55.8, 55.7, 44.2, 25.7, 18.0, -4.9, -5.1; ESIMS: 415 [M+ Na]$^+$; HRMS (ESI) (m/z): calcd. for $C_{21}H_{32}O_5NaSi$ [M+Na]+ 415.1911; found 415.1914.

(*R*,2*E*,4*E*)-6-((*tert*-butyldimethylsilyl)oxy)-7-(3,4-dimethoxyphenyl)-*N*-ethylhepta-2,4-dienamide (1a): To a solution of **7** (200 mg, 0.508 mmol) in dry DMF (20 mL) was added HATU (196 mg, 1.02 mmol) and DIPEA (0.220 mL, 1.27 mmol) at 0 ^{o}C, stirred at same temperature for 5 min. Then raise temperature to rt, added ethylamine (1M in THF, 0.104 mL, 1.02 mmol). The mixture was stirred at rt overnight. After completion of reaction, the reaction was diluted with EtOAc (20 mL) and washed with water (2 x 30 mL). The organic layer was dried and concentrated and the residue was purified by column chromatography over silica gel using hexanes/EtOAc (80:20) to afford **1a** (196 mg, 93%) as light yellow liquid. $[\alpha]_D^{25}$: –18 (*c* 1, $CHCl_3$); IR (KBr): 3288, 2930, 2856, 1661, 1616, 1515, 1462, 1260, 1150, 834, 773; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19 (dd, *J* = 15.1, 11.3 Hz, 1H), 6.79 (d, *J* = 8.3Hz, 1 H), 6.70 (s, 2H), 6.23 (dd, *J* = 15.1, 11.3 Hz, 1H), 6.06 (dd, *J* = 15.1, 5.2 Hz, 1H), 5.79 (d, *J* = 15.8 Hz, 1H), 5.59 (br s, 1H), 4.35 (m, 1H), 3.86 (s, 6H), 3.37 (q, *J* = 7.5 Hz, 2H), 2.72 (m, 2H), 1.17 (t, *J* = 7.5 Hz, 3H), 0.85 (s, 9H), -0.09 (s, 3H), -0.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.9, 148.4, 147.5, 143.7, 140.1, 130.6, 126.9, 123.5, 121.8, 113.2, 111.0, 74.0, 55.8, 55.7, 44.3, 34.4, 25.7, 18.1, 14.8, -4.8, -5.1; ESIMS: 442 [M + Na]$^+$; ESIMS: 415 [M+ Na]$^+$; HRMS (ESI) (m/z): calcd. for $C_{23}H_{37}NO_4NaSi$ [M+Na]+ 442.2384; found 442.2390.

(*R*,2*E*,4*E*)-7-(3,4-dimethoxyphenyl)-*N*-ethyl-6-hydroxyhepta-2,4-dienamide (1): A solution of **1a** (145 mg, 0.253 mmol) in THF (5 mL) was cooled to 0 °C and TBAF (0.38 mL, 0.38 mmol, 1.0 M solution in THF) was added dropwise. The resulting brown solution was stirred at room temperature for 2 h. The reaction was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexanes: EtOAc = 90: 10) to give **1** (105 mg, 91%) as a white solid. $[\alpha]_D^{25}$: –54.2 (*c* 0.042, MeOH); IR (KBr): 3432, 3310, 2922, 1649, 1593, 1536, 1258, 1148, 1027, 991, 805; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.13 (dd, *J* = 14.3, 9.0 Hz, 1H), 6.74 (d, *J* = 8.3 Hz, 1H), 6.67 (d, *J* = 9.0 Hz, 2H), 6.25 (dd, *J* = 14.3, 11.3 Hz, 1H), 6.04 (dd, *J* = 14.3, 5.2 Hz, 1H), 5.75 (d, *J* = 14.3 Hz, 1H), 5.61 (br s, 1H), 4.36 (m, 1H), 3.79 (s, 6H), 3.30 (q, *J* = 7.5 Hz, 2H), 2.79 (dd, *J* = 13.5, 4.5 Hz, 1H), 2.66 (dd, *J* = 13.5, 4.5 Hz, 1H), 2.03 (br s, 1H), 1.10 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.9, 148.9, 147.8, 142.3, 139.9, 129.6, 127.6, 124.1, 121.5, 112.7, 111.3, 72.5, 55.8, 43.3, 34.5, 14.8; HRMS (ESI) (*m/z*): calcd. for $C_{17}H_{23}NO_4Na$ [M + Na]$^+$ 328.1519; found 328.1525.

General experimental procedure for amide formation (8b-22b): To a solution of acid **7** (1 mmol) in dry DMF (5 mL) was

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added HATU (1 mmol) and DIPEA (1.5 mmol) at 0 ^oC, stirred at same temperature for 5 min. Then temperature raised to rt, and added amine (**8a**-**22a**) (1 mmol). The mixture was stirred at rt. for overnight. After completion of reaction, the mixture was diluted with EtOAc and washed with water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude residue, which was purified on silica gel column chromatography using hexanes/EtOAc as the eluent to give the product (**8b**-**22b**).

General experimental procedure for kunstleramide analogues (8-22): To a cooled (0 ^oC) solution of TBS ether compound (**8b**-**22b**) (1 mmol) in MeOH (5 mL) was added catalytic amount of *P*TSA (0.1 mmol) and stirred at same temperature for 0.5 h. After completion of the reaction, the mixture was quenched with solid sodium bicarbonate and filtered and MeOH was evaporated under reduced pressure to afford a crude product, which was purified on silica gel column chromatography using hexanes/EtOAc as the eluent to give the corresponding amide product (**8-22**).

The spectral (IR, ^1H and ^{13}C NMR and HRMS) data of TBS protected amide intermediates (**8b**-**22b**) and kunstleramide analogues (**8**-**22**) are given below.

(*R*,2*E*,4*E*)-*N*-benzyl-6-((*tert*-butyldimethylsilyl)oxy)-7-(3,4-dimethoxyphenyl)hepta-2,4-dienamide (8a): Pale yellow oil, 94% yield; $[\alpha]_D^{25}$: –12.9 (*c* 0.2, $CHCl_3$); IR (KBr): 2929, 2855, 1661, 1613, 1515, 1461, 1260, 1150, 1029, 833, 773; ^1H NMR (600 MHz, $CDCl_3$): δ 7.36-7.27 (m, 5H), 7.24 (dd, *J* = 15.0, 11.2 Hz, 1H), 6.78 (d, *J* = 8.6 Hz, 1H), 6.70 (d, *J* = 6.4 Hz, 1H), 6.69 (s, 1H), 6.24 (dd, *J* = 15.0, 11.2 Hz, 1H), 6.08 (dd, *J* = 15.0, 5.2 Hz, 1H), 5.81 (d, *J* = 15.0 Hz, 1H), 5.78-5.73 (m, 1H, NH), 4.52 (d, *J* = 5.6 Hz, 2H), 4.37-4.32 (m, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 2.76-2.67 (m, 2H), 0.84 (s, 9H), -0.10 (s, 3H), -0.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.9, 148.4, 147.4, 143.9, 140.4, 138.1, 130.5, 128.5, 127.6, 127.2, 126.8, 123.2, 121.7, 113.2, 111.0, 73.9, 55.7, 55.6, 44.3, 43.5, 25.7, 18.0, -4.8, -5.2; ESIMS: 504 $[M+Na]^+$.

(*R*,2*E*,4*E*)-*N*-benzyl-7-(3,4-dimethoxyphenyl)-6-hydroxyhepta-2,4-dienamide (8): Pale yellow solid, 92% yield; $[\alpha]_D^{25}$: –17.3 (*c* 0.3, $CHCl_3$); IR (KBr): 3426, 3303, 2922, 2853, 1649, 1594, 1540, 1516, 1259, 1235, 1141, 1025, 747, 699; ^1H NMR (300 MHz, $CDCl_3$): δ 7.36-7.23 (m, 6H), 6.82 (d, *J* = 7.9 Hz, 1H), 6.75 (d, *J* = 8.3 Hz, 1H), 6.73 (s, 1H), 6.34 (dd, *J* = 15.1, 11.2 Hz, 1H), 6.13 (dd, *J* = 15.1, 5.1 Hz, 1H), 5.85 (d, *J* = 15.1 Hz, 1H), 5.83 (br s, 1H), 4.52 (d, *J* = 4.8 Hz, 2H), 4.47-4.41 (m, 1H), 3.86 (s, 6H), 2.86 (dd, *J* = 13.5, 5.0 Hz, 1H), 2.74 (dd, *J* = 13.5, 7.9 Hz, 1H), 1.82 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.9, 148.8, 147.7, 142.7, 140.4, 138.0, 129.6, 128.6, 127.7, 127.5, 127.4, 123.7, 121.6, 112.6, 111.2, 72.4, 55.8, 43.6, 43.2; HRMS (ESI) (*m/z*): calcd. for $C_{22}H_{26}O_4N$ $[M+H]^+$ 368.1856; found 368.1858.

(*R*,2*E*,4*E*)-6-((*tert*-butyldimethylsilyl)oxy)-7-(3,4-dimethoxyphenyl)-*N*-(4-methoxybenzyl)hepta-2,4-dienamide (9a): Pale yellow oil, 86% yield; $[\alpha]_D^{25}$: –19.3 (*c* 0.4, $CHCl_3$); IR (KBr): 2930, 2855, 1661, 1612, 1513, 1252, 1031, 833, 775; ^1H NMR (300 MHz, $CDCl_3$): δ 7.24 (dd, *J* = 14.9, 10.7 Hz, 1H), 7.22 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.78 (d, *J* = 8.6 Hz, 2H), 6.72 (m, 2H), 6.24 (dd, *J* = 15.2, 11.1 Hz, 1H), 6.07 (dd, *J* = 15.2, 5.2 Hz, 1H), 5.79 (d, *J* = 14.9 Hz, 1H), 5.70-5.61 (m, 1H), 4.46 (d, *J* = 5.6 Hz, 2H), 4.39-4.30 (m, 1H), 3.86 (s, 6H), 3.80 (s, 3H), 2.75-2.70 (m, 2H), 0.84 (s, 9H), -0.09 (s, 3H), -0.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.8, 158.8, 148.3, 147.3, 143.9, 140.4, 130.5, 130.2, 129.0, 126.8, 123.2, 121.7, 113.8, 113.0, 110.9, 73.9, 55.6, 55.1, 44.2, 43.0, 25.6, 18.0, -4.9, -5.2; ESIMS: 534 $[M+Na]^+$.

(*R*,2*E*,4*E*)-7-(3,4-dimethoxyphenyl)-6-hydroxy-N-(4-methoxybenzyl)hepta-2,4-dienamide (9): White solid, 89% yield; $[\alpha]_D^{25}$: –30.0 (*c* 0.1, $CHCl_3$); IR (KBr): 3311, 2932, 2837, 1650, 1618, 1590, 1516, 1253, 1156, 1026, 991, 805; ^1H NMR (300 MHz, $CDCl_3$): δ 7.22 (dd, *J* = 14.8, 11.1 Hz, 1H), 7.19 (d, *J* = 8.3 Hz, 2H), 6.83 (d, *J* = 8.3 Hz, 2H), 6.79 (d, *J* = 7.9 Hz, 1H), 6.72 (m, 2H), 6.28 (dd, *J* = 14.9, 11.1 Hz, 1H), 6.09 (dd, *J* = 14.9, 5.3 Hz, 1H), 6.09-6.05 (m, 1H, NH), 5.82 (d, *J* = 14.9 Hz, 1H), 4.43-4.37 (m, 1H), 4.40 (d, *J* = 5.1 Hz, 2H), 3.84 (s, 6H), 3.77 (s, 3H), 2.82 (dd, *J* = 13.5, 5.0 Hz, 1H), (dd, *J* = 13.5, 7.7 Hz, 1H), 2.23 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.8, 158.8, 148.6, 147.6, 142.7, 140.2, 130.1, 129.6, 129.1, 127.4, 123.8, 121.4, 113.9, 112.5, 111.1, 72.4, 55.7, 55.1, 43.1, 43.0; HRMS (ESI) (*m/z*): calcd. for $C_{23}H_{28}O_5N$ $[M+H]^+$ 398.1962; found 398.1963.

(*R*,2*E*,4*E*)-6-((*tert*-butyldimethylsilyl)oxy)-7-(3,4-dimethoxyphenyl)-N-(3,4,5-trimethoxybenzyl)hepta-2,4-dienamide (10a): Pale yellow oil, 91% yield; $[\alpha]_D^{25}$: –29.1 (*c* 0.2, $CHCl_3$); IR (KBr): 2931, 2854, 1661, 1593, 1512, 1462, 1260, 1236, 1128, 1003, 833, 774; ^1H NMR (500 MHz, $CDCl_3$): δ 7.25 (dd, *J* = 14.9, 11.2 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 1H), 6.71-6.67 (m, 2H), 6.50 (s, 2H), 6.25 (dd, *J* = 14.9, 11.2 Hz, 1H), 6.09 (dd, *J* = 14.9, 5.1 Hz, 1H), 5.83 (d, *J* = 14.9 Hz, 1H), 5.83-5.79 (m, 1H, NH), 4.44 (d, *J* = 5.1 Hz, 2H), 4.38-4.33 (m, 1H), 3.85 (s, 6H), 3.84 (s, 6H), 3.82 (s, 3H), 2.77-2.69 (m, 2H), 0.84 (s, 9H), -0.10 (s, 3H), -0.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.8, 152.9, 148.2, 147.2, 143.9, 140.3, 136.6, 133.9, 130.4, 126.7, 123.2, 121.6, 112.9, 110.8, 104.5, 73.7, 60.5, 55.7, 55.6, 55.5, 44.1, 43.7, 25.5, 17.9, -5.0, -5.3.
EIMS: 594 $[M+Na]^+$.

(*R*,2*E*,4*E*)-7-(3,4-dimethoxyphenyl)-6-hydroxy-*N*-(3,4,5-trimethoxybenzyl)hepta-2,4-dienamide (10): White solid, 92% yield; $[\alpha]_D^{25}$: –32.6 (*c* 0.15, $CHCl_3$); IR (KBr): 3442, 2925, 2853, 1597, 1511, 1454, 1236, 1122, 1023; ^1H NMR (300 MHz, $CDCl_3$): δ 7.24 (dd, *J* = 14.9, 10.9 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.74-6.70 (m, 2H), 6.48 (s, 2H), 6.30 (dd, *J* = 15.1, 11.1 Hz, 1H), 6.16-6.12 (m, 1H, NH), 6.10 (dd, *J* = 15.1, 5.3 Hz, 1H), 5.85 (d, *J* = 15.1 Hz, 1H), 4.43-4.38 (m, 1H), 4.41 (d, *J* = 5.3 Hz, 2H), 3.84 (s, 6H), 3.81 (s, 6H), 3.79 (s, 3H), 2.84 (dd, *J* = 13.7, 5.0 Hz, 1H), 2.72 (dd, *J* = 13.7, 7.7 Hz, 1H), 2.10 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.7, 153.3, 148.8, 147.8, 142.7, 140.5, 133.8, 129.5, 127.5, 123.6, 121.4, 112.5, 111.2, 104.8, 72.4, 60.7, 56.0, 55.8, 44.0, 43.2; HRMS (ESI) (*m/z*): calcd. for $C_{25}H_{32}O_7N$ $[M+H]^+$ 458.2173; found 458.2175.

(*R*,2*E*,4*E*)-6-((*tert*-butyldimethylsilyl)oxy)-*N*-(4-chlorobenzyl)-7-(3,4-dimethoxyphenyl)hepta-2,4-dienamide (11a): Viscous liquid, 93% yield; $[\alpha]_D^{25}$: –13.4 (*c* 0.2, $CHCl_3$); IR (KBr): 2928, 2855, 1661, 1613, 1514, 1463, 1259, 1149, 1029, 834, 772; ^1H NMR (300 MHz, $CDCl_3$): δ 7.38-7.18 (m, 5H), 6.82-6.65 (m, 3H), 6.24 (dd, *J* = 14.9, 11.3 Hz, 1H), 6.09 (dd, *J* = 14.9, 4.1 Hz, 1H), 5.82 (d, *J* = 14.3 Hz, 1H), 5.79 (br s, 1H), 4.49 (s, 2H), 4.40-4.31 (m, 1H), 3.85 (s, 6H), 2.73 (d, *J* = 4.3 Hz, 2H), 0.85 (s, 9H), -0.09

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(s, 3H), -0.16 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 166.0, 148.3, 147.4, 144.2, 140.7, 136.8, 133.0, 130.5, 128.9, 128.5, 126.7, 122.9, 121.7, 113.1, 110.9, 73.8, 55.7, 55.6, 44.2, 42.7, 25.7, 18.0, -4.8, -5.2; EIMS: 538 [M+Na]$^+$.

(*R*,2*E*,4*E*)-*N*-(4-chlorobenzyl)-7-(3,4-dimethoxyphenyl)-6-hydroxyhepta-2,4-dienamide (11): Pale yellow solid, 94% yield; $[\alpha]_D^{25}$: –15.7 (*c* 0.35, CHCl$_3$); IR (KBr): 3286, 2925, 1659, 1609, 1555, 1513, 1265, 1233, 1138, 1035, 800, 743; ^{1}H NMR (600 MHz, CDCl$_3$): δ 7.29 (d, *J* = 8.2 Hz, 2H), 7.24 (dd, *J* = 15.0, 4.1 Hz, 1H), 7.22 (d, *J* = 8.2 Hz, 2H), 6.81 (d, *J* = 8.2 Hz, 1H), 6.74 (d, *J* = 8.2 Hz, 1H), 6.72 (s, 1H), 6.33 (dd, *J* = 15.0, 11.2 Hz, 1H), 6.13 (dd, *J* = 15.0, 5.2 Hz, 1H), 5.98-5.94 (m, 1H), 5.84 (d, *J* = 15.0 Hz, 1H), 4.47 (d, *J* = 6.0 Hz, 2H), 4.45-4.41 (m, 1H), 3.86 (s, 6H), 2.86 (dd, *J* = 13.5, 4.8 Hz, 1H), 2.73 (dd, *J* = 13.5, 7.9 Hz, 1H), 1.79 (br s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 166.0, 148.7, 147.6, 143.0, 140.6, 136.6, 133.0, 129.5, 129.0, 128.6, 127.3, 123.4, 121.4, 112.5, 111.1, 72.4, 55.7, 43.1, 42.7; HRMS (ESI) (*m/z*): calcd. for $C_{22}H_{25}O_4NCl$ [M+H]$^+$ 402.1466; found 402.1466.

(*R*,2*E*,4*E*)-6-((*tert*-butyldimethylsilyl)oxy)-7-(3,4-dimethoxyphenyl)-1-(pyrrolidin-1-yl)hepta-2,4-dien-1-one (12a): Pale yellow oil, 85% yield; $[\alpha]_D^{25}$: –4.2 (*c* 0.22, CHCl$_3$); IR (KBr): 2953, 2856, 1625, 1514, 1445, 1261, 1152, 1029, 834, 769; ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.27 (dd, *J* = 15.2, 11.7 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 1H), 6.72-6.67 (m, 2H), 6.26 (dd, *J* = 15.2, 11.7 Hz, 1H), 6.12 (d, *J* = 14.8 Hz, 1H), 6.07 (dd, *J* = 15.2, 5.4 Hz, 1H), 4.38-4.31 (m, 1H), 3.85 (s, 6H), 3.58-3.48 (m, 4H), 2.77-2.67 (m, 2H), 2.00-1.92 (m, 2H), 1.90-1.82 (m, 2H), 0.84 (s, 9H), -0.09 (s, 3H), -0.16 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 164.8, 148.3, 147.3, 143.8, 141.1, 130.5, 127.2, 121.7, 121.4, 113.0, 110.8, 74.0, 55.7, 55.6, 46.4, 45.8, 44.3, 25.9, 25.7, 24.1, 18.0, -4.8, -5.2; EIMS: 468 [M+Na]$^+$.

(*R*,2*E*,4*E*)-7-(3,4-dimethoxyphenyl)-6-hydroxy-1-(pyrrolidin-1-yl)hepta-2,4-dien-1-one (12): Pale yellow oil, 88% yield; $[\alpha]_D^{25}$: –12.6 (*c* 0.3, CHCl$_3$); IR (KBr): 3402, 2924, 1720, 1623, 1591, 1514, 1445, 1623, 1234, 1025, 808, 72; ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.29 (dd, *J* = 14.9, 11.1 Hz, 1H), 6.81 (d, *J* = 7.9 Hz, 1H), 6.77-6.69 (m, 2H), 6.37 (dd, *J* = 15.1, 11.1 Hz, 1H), 6.16 (d, *J* = 15.1 Hz, 1H), 6.13 (dd, *J* = 15.1, 5.4 Hz, 1H), 4.48-4.38 (m, 1H), 3.86 (s, 6H), 3.52 (br s, 4H), 2.86 (dd, *J* = 13.5, 5.2 Hz, 1H), 2.74 (dd, *J* = 13.5, 7.7 Hz, 1H), 2.04 (br s, 2H), 1.91 (br s, 2H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 164.8, 148.7, 147.6, 142.5, 140.9, 129.7, 127.9, 122.0, 121.4, 112.5, 111.1, 72.5, 55.8, 55.7, 46.4, 45.9, 43.2, 25.9, 24.2; EIMS: 454 [M+Na]$^+$.

(*R*,2*E*,4*E*)-6-((*tert*-butyldimethylsilyl)oxy)-7-(3,4-dimethoxyphenyl)-1-(piperidin-1-yl)hepta-2,4-dien-1-one (13a): Pale yellow oil, 81% yield; $[\alpha]_D^{25}$: –8.7 (*c* 0.3, CHCl$_3$); IR (KBr): 2932, 2855, 1649, 1623, 1514, 1442, 1259, 1137, 1026, 834, 774; ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.19 (dd, *J* = 14.8, 11.1 Hz, 1H), 6.76-6.71 (m, 1H), 6.68-6.63 (m, 2H), 6.30-6.18 (m, 2H), 6.01 (dd, *J* = 15.1, 5.3 Hz, 1H), 4.34-4.27 (m, 1H), 3.81 (s, 6H), 3.57 (br s, 2H), 3.44 (br s, 2H), 2.73-2.63 (m, 2H), 1.64-1.47 (m, 6H), 0.81 (s, 9H), -0.13 (s, 3H), -0.21 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 165.1, 148.2, 147.2, 143.1, 141.6, 130.4, 127.2, 121.6, 120.0, 112.9, 110.7, 73.8, 55.6, 55.5, 46.6, 44.2, 42.9, 26.4, 25.5, 25.3, 24.3, 17.9, -4.9, -5.3; EIMS: 482 [M+Na]$^+$.

(*R*,2*E*,4*E*)-7-(3,4-dimethoxyphenyl)-6-hydroxy-1-(piperidin-1-yl)hepta-2,4-dien-1-one (13): Pale yellow oil, 92% yield; $[\alpha]_D^{25}$: –14.3 (*c* 0.28, CHCl$_3$); IR (KBr): 3334, 2931, 2849, 1644, 1614, 1568, 1514, 1464, 1258, 1232, 1138, 1002, 803, 763; ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.24 (dd, *J* = 14.3, 11.3 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 6.75 (d, *J* = 8.3 Hz, 1H), 6.74 (s, 1H), 6.43-6.30 (m, 2H), 6.10 (dd, *J* = 15.1, 5.2 Hz, 1H), 4.47-4.38 (m, 1H), 3.87 (s, 6H), 3.54 (br s, 4H), 2.86 (dd, *J* = 13.5, 5.2 Hz, 1H), 2.75 (dd, *J* = 13.5, 8.3 Hz, 1H), 1.71-1.51 (m, 6H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 165.2, 148.5, 147.4, 142.1, 141.5, 129.7, 127.9, 121.3, 120.5, 112.4, 111.0, 72.4, 55.7, 55.6, 46.7, 43.2, 43.0, 26.4, 25.4, 24.3; EIMS: 368 [M+NH$_4$]$^+$.

(*R*,2*E*,4*E*)-6-((*tert*-butyldimethylsilyl)oxy)-7-(3,4-dimethoxyphenyl)-1-morpholinohepta-2,4-dien-1-one (14a): Pale yellow oil, 80% yield; $[\alpha]_D^{25}$: –9.3 (*c* 0.3, CHCl$_3$); IR (KBr): 2928, 2855, 1649, 1621, 1594, 1514, 1460, 1263, 1238, 1114, 1032, 837, 770; ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.28 (dd, *J* = 15.1, 11.3 Hz, 1H), 6.77 (d, *J* = 9.0 Hz, 1H), 6.71-6.65 (m, 2H), 6.27 (dd, *J* = 15.1, 11.3 Hz, 1H), 6.22 (d, *J* = 15.1 Hz, 1H), 6.09 (dd, *J* = 15.1, 5.2 Hz, 1H), 4.40-4.31 (m, 1H), 3.85 (s, 6 H), 3.73-3.65 (m, 4H), 3.64-3.55 (br s, 4H), 2.76-2.70 (m, 2H), 0.85 (s, 9H), -0.08 (s, 3H), -0.16 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 165.9, 148.4, 147.4, 143.9, 140.4, 138.1, 130.5, 128.5,127.6, 127.2, 126.8, 123.2, 121.7, 113.2, 111.0, 73.9, 55.7, 55.6, 44.3, 43.5, 25.7, 18.0, -4.8, -5.2; EIMS: 484 [M+Na]$^+$.

(*R*,2*E*,4*E*)-7-(3,4-dimethoxyphenyl)-6-hydroxy-1-morpholinohepta-2,4-dien-1-one (14): Pale yellow oil, 89% yield; $[\alpha]_D^{25}$: –12.9 (*c* 0.24, CHCl$_3$); IR (KBr): 3410, 2922, 2854, 1649, 1620, 1592, 1514, 1441, 1263, 1238, 1114, 1028, 850, 760; ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.29 (dd, *J* = 14.7, 11.1 Hz, 1H), 6.81 (d, *J* = 7.9 Hz, 1H), 6.78-6.70 (m, 2H), 6.38 (dd, *J* = 15.2, 10.9 Hz, 1H), 6.28 (d, *J* = 14.7 Hz, 1H), 6.14 (dd, *J* = 15.2, 5.0 Hz, 1H), 4.49-4.39 (m, 1H), 3.86 (s, 6H), 3.68 (br s, 4H), 3.61 (br s, 4H), 2.87 (dd, *J* = 13.7, 5.0 Hz, 1H), 2.73 (dd, *J* = 13.7, 7.9 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 165.4, 148.7, 147.6, 142.7, 142.4, 129.5, 127.7, 121.4, 119.5, 112.4, 111.1, 72.4, 66.6, 55.7, 45.9, 43.2, 42.2; HRMS (ESI) (*m/z*): calcd. for $C_{19}H_{26}O_5N$ [M+H]$^+$ 348.1805; found 348.1809.

(*R*,2*E*,4*E*)-6-((*tert*-butyldimethylsilyl)oxy)-7-(3,4-dimethoxyphenyl)-1-thiomorpholinohepta-2,4-dien-1-one (15a): Pale yellow oil, 79% yield; $[\alpha]_D^{25}$: –17 (*c* 0.2, CHCl$_3$); IR (KBr): 2929, 2855, 1649, 1625, 1514, 1461, 1259, 1146, 1028, 834, 774; ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.25 (dd, *J* = 14.8, 11.1 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 1H), 6.70-6.66 (m, 2H), 6.26 (dd, *J* = 15.1, 10.9 Hz, 1H), 6.23 (d, *J* = 14.8 Hz, 1H), 6.07 (dd, *J* = 15.1, 5.3 Hz, 1H), 4.37-4.32 (m, 1H), 3.88 (br s, 2H), 3.84 (s, 6H), 3.80 (br s, 2H), 2.74-2.70 (m, 2H), 2.65-2.59 (m, 4H), 0.84 (s, 9H), -0.09 (s, 3H), -0.17 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 165.4, 148.3, 147.4, 144.0, 142.6, 130.3, 127.0, 121.7, 119.3, 113.0, 110.8, 73.8, 55.7, 55.5, 48.3, 44.6, 44.2, 27.8, 27.1, 25.6, 17.9, -4.9, -5.3; EIMS: 500 [M+Na]$^+$.

(*R*,2*E*,4*E*)-7-(3,4-dimethoxyphenyl)-6-hydroxy-1-thiomorpholinohepta-2,4-dien-1-one (15): Pale yellow oil, 86% yield; $[\alpha]_D^{25}$: –21.6 (*c* 0.24, CHCl$_3$); IR (KBr): 3359, 2925, 2840, 1643, 1612, 1567, 1514, 1461, 1252, 1148, 1028, 807, 765; ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.28 (dd, *J* = 15.1, 11.1 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.77-6.72 (m, 2H), 6.39 (dd, *J* =

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15.1, 11.1 Hz, 1H), 6.29 (d, *J* = 14.6 Hz, 1H), 6.14 (dd, *J* = 15.1, 5.3 Hz, 1H), 4.47-4.42 (m, 1H), 3.94 (br s, 2H), 3.87 (s, 6H), 3.83 (br s, 2H), 2.87 (dd, *J* = 13.7, 5.0 Hz, 1H), 2.74 (dd, *J* = 13.7, 7.9 Hz, 1H), 2.64 (br s, 4H), 1.74 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 165.2, 148.5, 147.4, 142.1, 141.5, 129.7, 127.9, 121.3, 120.5, 112.4, 111.0, 72.4, 55.6, 46.7, 43.2, 43.0, 26.4, 25.4; EIMS: 386 $[M+Na]^+$.

(*R*,2*E*,4*E*)-6-((*tert*-butyldimethylsilyl)oxy)-7-(3,4-dimethoxyphenyl)-1-(4-methylpiperazin-1-yl)hepta-2,4-dien-1-one (16a): Thick liquid, 84% yield; $[\alpha]_D^{25}$: –12.3 (*c* 0.12, $CHCl_3$); IR (KBr): 2928, 2854, 1650, 1624, 1598, 1513, 1457, 1259, 1142, 1032, 833, 773; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.25 (dd, *J* = 14.6, 11.2 Hz, 1H), 6.78 (d, *J* = 8.6 Hz, 1H), 6.70 (s, 2H), 6.30-6.24 (m, 2H), 6.07 (dd, *J* =15.0, 5.2 Hz, 1H), 4.39-4.33 (m, 1H), 3.85 (s, 6H), 3.72 (br s, 2H), 3.58 (br s, 2H), 2.76-2.70 (m, 2H), 2.43 (br s, 4H), 2.32 (s, 3H), 0.86 (s, 9H), -0.07 (s, 3H), -0.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 165.2, 148.2, 147.3, 143.7, 142.2, 130.3, 127.0, 121.6,119.3, 113.0, 110.8, 73.8, 55.6, 55.5, 54.8, 54.3, 45.5, 45.1, 44.2, 41.5,25.6, 17.9, -4.9, -5.3; EIMS: 497 $[M+Na]^+$.

(*R*,2*E*,4*E*)-7-(3,4-dimethoxyphenyl)-6-hydroxy-1-(4-methylpiperazin-1-yl)hepta-2,4-dien-1-one (16): Pale yellow oil, 88% yield; $[\alpha]_D^{25}$: –18.1 (*c* 0.22, $CHCl_3$); IR (KBr): 3405, 2933, 2851, 1649, 1619, 1591, 1513, 1446, 1259, 1139, 1000, 771; ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 7.26 (dd, *J* = 14.8, 11.1 Hz, 1H), 6.82 (d, *J* = 7.9 Hz, 1H), 6.75 (d, *J* = 8.5 Hz, 1H), 6.73 (s, 1H), 6.37 (dd, *J* = 15.1, 11.2 Hz, 1H), 6.30 (d, *J* = 14.8 Hz, 1H), 6.12 (dd, *J* = 15.1, 5.4 Hz, 1H), 4.46-4.39 (m, 1H), 3.86 (s, 6H), 3.71 (br s, 2H), 3.56 (br s, 2H), 2.85 (dd, *J* = 13.5, 5.1 Hz, 1H), 2.75 (dd, *J* = 13.5, 7.7 Hz, 1H), 2.42 (br s, 4H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 165.2, 148.6, 147.5, 142.7, 142.1, 129.8, 127.7, 121.3, 119.9, 112.5, 111.1, 72.3, 55.8, 54.8, 54.3, 45.6, 43.2, 41.5; HRMS (ESI) (*m/z*): calcd. for $C_{20}H_{29}O_4N_2$ $[M+H]^+$ 361.2121; found 361.2122.

(*R*,2*E*,4*E*)-6-((*tert*-butyldimethylsilyl)oxy)-7-(3,4-dimethoxyphenyl)-1-(4-ethylpiperazin-1-yl)hepta-2,4-dien-1-one (17a): Pale yellow oil, 81% yield; $[\alpha]_D^{25}$: –16.5 (*c* 0.28, $CHCl_3$); IR (KBr): 2929, 2855, 1652, 1625, 1514, 1439, 1262, 1155, 1027, 834, 775; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.26 (dd, *J* = 14.9, 11.2 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 1H), 6.70-6.67 (m, 2H), 6.26 (dd, *J* = 15.1, 11.1 Hz, 1H), 6.24 (d, *J* = 14.9 Hz, 1H), 6.08 (dd, *J* = 15.1, 5.4 Hz, 1H), 4.38-4.32 (m, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.80 (br s, 2H), 3.68 (br s, 2H), 2.74-2.70 (m, 2H), 2.63-2.52 (m, 6H), 1.16 (t, *J* = 7.1 Hz, 3H), 0.85 (s, 9H), -0.09 (s, 3H), -0.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 165.4, 148.3, 147.4, 143.9, 142.5, 130.5, 127.2, 121.8, 119.4, 113.1, 110.9, 73.9, 55.8, 55.7, 52.7, 52.0, 45.1, 44.3, 41.5, 29.2, 25.7, 18.1, 11.4, -4.8, -5.1. EIMS: 511 $[M+Na]^+$.

(*R*,2*E*,4*E*)-7-(3,4-dimethoxyphenyl)-1-(4-ethylpiperazin-1-yl)-6-hydroxyhepta-2,4-dien-1-one (17): Pale yellow oil, 87% yield; $[\alpha]_D^{25}$: –21.3 (*c* 0.3, $CHCl_3$); IR (KBr): 3410, 2924, 2850, 1649, 1619, 1592, 1513, 1449, 1261, 1146, 1026, 762; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.27 (dd, *J* = 15.1, 10.5 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 6.79-6.71 (m, 2H), 6.38 (dd, *J* = 15.1, 11.1 Hz, 1H), 6.31 (d, *J* = 14.3 Hz, 1H), 6.12 (dd, *J* = 15.1, 5.2 Hz, 1H), 4.48-4.38 (m, 1H), 3.87 (s, 6H), 3.73 (br s, 2H), 3.59 (br s, 2H), 2.86 (dd, *J* = 13.5, 5.2 Hz, 1H), 2.75 (dd, *J* = 13.5, 7.5 Hz, 1H), 2.57-2.40 (m, 6H), 1.11 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 165.2, 148.6, 147.5, 142.7, 142.1, 129.9, 127.7, 121.3, 119.9, 112.5, 111.0, 72.3, 55.6, 52.7, 51.9, 45.2, 43.2 41.6, 11.5; HRMS (ESI) (*m/z*): calcd. for $C_{21}H_{31}O_4N_2$ $[M+H]^+$ 375.2278; found 375.2283.

(*R*,2*E*,4*E*)-6-((*tert*-butyldimethylsilyl)oxy)-7-(3,4-dimethoxyphenyl)-1-(4-phenylpiperazin-1-yl)hepta-2,4-dien-1-one (18a): Colorless oil, 89% yield; $[\alpha]_D^{25}$: –14.1 (*c* 0.22, $CHCl_3$); IR (KBr): 2927, 2855, 1599, 1510, 1456, 1229, 1151, 1032, 833, 770; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.42-7.22 (m 6H), 6.83-6.65 (m, 3H), 6.38-6.23 (m, 2H), 6.10 (dd, *J* = 15.1, 4.5 Hz, 1H), 4.44 (m, 1H), 3.86 (s, 6H), 3.85 (br s, 2H), 3.24 (br s, 4H), 2.74 (br s, 2H), 2.56-2.44 (m, 1H), 2.34-2.22 (m, 1H), 0.87 (s, 9H), -0.07 (s, 3H), -0.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 165.3, 150.7, 148.4, 147.4, 143.9, 142.4, 130.4, 129.0, 127.1, 121.7, 120.3, 119.3, 116.4, 113.1, 111.0, 73.8, 55.7, 55.6, 49.5, 49.3, 45.4, 44.2, 41.7, 25.7, 18.0, -4.8, -5.2. EIMS: 559 $[M+Na]^+$.

(*R*,2*E*,4*E*)-7-(3,4-dimethoxyphenyl)-6-hydroxy-1-(4-phenylpiperazin-1-yl)hepta-2,4-dien-1-one (18): Semi solid, 91% yield; $[\alpha]_D^{25}$: –19.0 (*c* 0.2, $CHCl_3$); IR (KBr): 3370, 2924, 2854, 1642, 1607, 1564, 1463, 1231, 1142, 1027, 762; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.31 (dd, *J* = 14.3, 11.4 Hz, 1H), 7.30-7.27 (m, 2H), 7.01-6.89 (m, 3H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.78-6.72 (m, 2H), 6.41 (dd, *J* = 15.2, 11.3 Hz, 1H), 6.36 (d, *J* = 15.2 Hz, 1H), 6.15 (dd, *J* = 15.2, 5.3 Hz, 1H), 4.48-4.42 (m, 1H), 3.87 (s, 6H), 3.85 (br s, 2H), 3.73 (br s, 2H), 3.20 (br s, 4H), 2.87 (dd, *J* = 13.7, 5.0 Hz, 1H), 2.75 (dd, *J* = 13.7, 5.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 165.3, 150.7, 148.8, 147.7, 142.5, 142.3, 129.5, 129.1, 127.9, 121.4, 120.5, 120.0, 116.5, 112.5, 111.1, 72.5, 55.8, 49.8, 49.3, 45.5, 43.3, 41.8. HRMS (ESI) (*m/z*): calcd. for $C_{25}H_{31}O_4N_2$ $[M+H]^+$ 423.2278; found 423.2287.

(*R*,2*E*,4*E*)-6-((*tert*-butyldimethylsilyl)oxy)-7-(3,4-dimethoxyphenyl)-1-(4-(pyridin-2-yl)piperazin-1-yl)hepta-2,4-dien-1-one (19a): Pale yellow oil, 75% yield; $[\alpha]_D^{25}$: –14.2 (*c* 0.2, $CHCl_3$); IR (KBr): 2927, 2854, 1651, 1624, 1594, 1513, 1433, 1236, 1153, 1031, 833, 773; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.13 (d, *J* = 3.3 Hz, 1H), 7.45 (t, *J* = 6.7 Hz, 1H), 7.23 (dd, *J* = 14.3, 11.0 Hz, 1H), 6.74-6.54 (m, 5H), 6.25 (d, *J* = 15.2 Hz, 1H), 6.22 (d, *J* = 14.3 Hz, 1H), 6.03 (dd, *J* = 15.2, 5.9 Hz, 1H), 4.33-4.26 (m, 1H), 3.79 (s, 6H), 3.75 (br s, 4H), 3.60 (br s, 2H), 3.47 (br s, 2H), 2.71-2.60 (m, 2H), 0.79 (s, 9H), -0.14 (s, 3H), -0.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 165.5, 158.7, 148.3, 147.6, 147.4, 144.0, 142.5, 137.6, 130.4, 127.1, 121.7, 119.3, 113.6, 113.1, 110.9, 107.0, 73.9, 55.7, 55.6, 45.0, 44.3, 41.4, 25.7, 18.0, -4.8, -5.2; EIMS: 560 $[M+Na]^+$.

(*R*,2*E*,4*E*)-7-(3,4-dimethoxyphenyl)-6-hydroxy-1-(4-(pyridin-2-yl)piperazin-1-yl)hepta-2,4-dien-1-one (19): Pale yellow oil, 81% yield; $[\alpha]_D^{25}$: –17 (*c* 0.3, $CHCl_3$); IR (KBr): 3276, 2922, 2844, 1652, 1598, 1518, 1437, 1237, 1157, 1032, 994, 770; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.20 (d, *J* = 4.8 Hz, 1H), 7.54-7.49 (m, 1H), 7.32 (dd, *J* = 14.6, 10.9 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.78-6.73 (m, 2H), 6.69-6.64 (m, 2H), 6.42 (dd, *J* = 15.2, 11.2 Hz, 1H), 6.37 (d, *J* = 14.8 Hz, 1H), 6.15 (dd, *J* =15.2, 5.4 Hz, 1H), 4.48-4.43 (m, 1H), 3.87 (s, 6H), 3.83 (br s, 2H), 3.67 (br s, 2H), 3.64 (br s, 2H),3.54 (br s, 2H), 2.88 (dd, *J* = 13.5, 5.0 Hz, 1H), 2.75 (dd, *J* = 13.5, 7.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ*

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165.4, 158.7, 148.6, 147.6, 147.5, 142.9, 142.3, 137.6, 129.7, 127.7, 121.3, 119.8, 113.7, 112.5, 111.0, 107.1, 72.4, 55.7, 44.9, 43.2, 41.4; HRMS (ESI) (*m/z*): calcd. for $C_{24}H_{30}O_4N_3$ $[M+H]^+$ 424.2230; found 424.2228.

(*R*,2*E*,4*E*)-6-((*tert*-butyldimethylsilyl)oxy)-7-(3,4-dimethoxyphenyl)-1-(4-(pyrimidin-2-yl)piperazin-1-yl)hepta-2,4-dien-1-one (20a): Pale yellow oil, 72% yield; $[\alpha]_D^{25}$: –6.4 (*c* 0.26, $CHCl_3$); IR (KBr): 2927, 2856, 1623, 1586, 1506, 1435, 1258, 1148, 1032, 834, 764; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.36 (d, *J* = 4.9 Hz, 2H), 7.31 (dd, *J* = 14.7, 10.9 Hz, 1H), 6.79 (d, *J* = 8.6 Hz, 1H), 6.74-6.67 (m, 2H), 6.58 (t, *J* = 4.9 Hz, 1H), 6.37-6.24 (m, 2H), 6.10 (dd, *J* = 15.2, 5.2 Hz, 1H), 4.42-4.32 (m, 1H), 3.90 (br s, 4H), 3.86 (s, 6H), 3.78 (br s, 2H), 3.67 (br s, 2H), 2.77-2.70 (m, 2H), 0.86 (s, 9H), -0.07 (s, 3H), -0.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.5, 161.2, 157.5, 148.3, 147.4, 143.9, 142.5, 130.4, 127.1, 121.7, 119.3, 113.1, 110.9, 110.2, 73.8, 55.7, 55.6, 45.2, 44.2, 43.5, 41.6, 25.6, 18.0, -4.9, -5.2; EIMS: 561 $[M+Na]^+$.

(*R*,2*E*,4*E*)-7-(3,4-dimethoxyphenyl)-6-hydroxy-1-(4-(pyrimidin-2-yl)piperazin-1-yl)hepta-2,4-dien-1-one (20): Pale yellow oil, 83% yield; $[\alpha]_D^{25}$: –11.8 (*c* 0.28, $CHCl_3$); IR (KBr): 3418, 2924, 2854, 1651, 1591, 1513, 1443, 1236, 1154, 1030, 797, 768; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.33 (d, *J* = 4.5 Hz, 2H), 7.32 (dd, *J* = 14.6, 11.3 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 6.77-6.72 (m, 2H), 6.55 (t, *J* = 4.5 Hz, 1H), 6.42 (dd, *J* = 15.0, 11.3 Hz, 1H), 6.37 (d, *J* = 15.0 Hz, 1H), 6.15 (dd, *J* = 15.0, 5.2 Hz, 1H), 4.48-4.43 (m, 1H), 3.87 (s, 6H), 3.86 (br s, 4H), 3.77 (br s, 2H), 3.63 (br s, 2H), 2.87 (dd, *J* = 13.9, 5.2 Hz, 1H), 2.75 (dd, *J* = 13.9, 7.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.5, 157.7, 148.8, 147.7, 142.6, 142.3, 129.5, 127.9, 121.4, 120.1, 112.4, 111.1, 110.4, 72.5, 55.7, 45.4, 43.6, 43.4, 43.2, 41.7; HRMS (ESI) (*m/z*): calcd. for $C_{23}H_{29}O_4N_4$ $[M+H]^+$ 425.2183; found 425.2183.

(*R*,2*E*,4*E*)-1-(4-(benzo[d][1,3]dioxol-5-ylmethyl)piperazin-1-yl)-6-((*tert*-butyldimethylsilyl)oxy)-7-(3,4-dimethoxyphenyl)hepta-2,4-dien-1-one (21a): Colorless oil, 89% yield; $[\alpha]_D^{25}$: –11.3 (*c* 0.4, $CHCl_3$); IR (KBr): 2928, 2855, 1652, 1624, 1512, 1441, 1241, 1149, 1036, 1000, 833, 772; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (dd, *J* = 14.6, 11.2 Hz, 1H), 6.85 (s, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), 6.76-6.72 (m, 2H), 6.71-6.68 (m, 2H), 6.29-6.23 (m, 2H), 6.06 (dd, *J* =15.4, 5.6 Hz, 1H), 5.94 (s, 2H), 4.38-4.33 (m, 1H), 3.85 (s, 6H), 3.69 (br s, 2H), 3.55 (br s, 2H), 3.43 (br s, 2H), 2.78-2.67 (m, 2H), 2.43 (br s, 4H), 0.85 (s, 9H), -0.08 (s, 3H), -0.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.2, 148.4, 147.5, 147.4, 146.6, 143.6, 142.1, 131.0, 130.4, 127.2, 122.1, 121.7, 119.6, 113.1, 111.0, 109.2, 107.7, 100.7, 73.9, 62.3, 55.7, 55.6, 52.9, 52.4, 45.4, 44.3, 41.8, 25.6, 18.0, -4.8, -5.2; EIMS: 619 $[M+Na]^+$.

(*R*,2*E*,4*E*)-1-(4-(benzo[d][1,3]dioxol-5-ylmethyl)piperazin-1-yl)-7-(3,4-dimethoxyphenyl)-6-hydroxyhepta-2,4-dien-1-one (21): Thick liquid, 91% yield; $[\alpha]_D^{25}$: –16.0 (*c* 0.28, $CHCl_3$); IR (KBr): 3402, 2921, 1645, 1614, 1569, 1514, 1448, 1239, 1144, 1033, 1005, 798; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.25 (dd, *J* = 14.3, 11.3 Hz, 1H), 6.86 (s, 1H), 6.81 (d, *J*= 7.9 Hz, 1H), 6.76-6.71 (m, 4H), 6.37 (dd, *J* = 15.4, 11.3 Hz, 1H), 6.30 (d, *J* = 14.3 Hz, 1H), 6.11 (dd, *J* = 15.4, 5.2 Hz, 1H), 5.94 (s, 2H), 4.45-4.40 (m, 1H), 3.86 (s, 6H), 3.70 (br s, 2H), 3.55 (br s, 2H), 3.45 (s, 2H), 2.85 (dd, *J* = 13.5, 4.8 Hz, 1H), 2.74 (dd, *J* = 13.5, 7.9 Hz, 1H), 2.44 (br s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.2, 148.6, 147.6, 147.5, 142.4, 141.9, 131.1, 129.6, 127.9, 122.1 121.4, 120.1, 112.4, 111.0, 109.2, 107.7, 100.8, 72.4, 62.3, 55.7, 52.8, 52.3, 45.5, 43.2, 41.8; EIMS: 481 $[M+H]^+$.

(*R*,2*E*,4*E*)-1-(4-benzhydrylpiperazin-1-yl)-6-((*tert*-butyldimethylsilyl)oxy)-7-(3,4-dimethoxyphenyl)hepta-2,4-dien-1-one (22a): Colorless oil, 90% yield; $[\alpha]_D^{25}$: –4.9 (*c* 0.2, $CHCl_3$); IR (KBr): 2953, 2929, 2855, 1652, 1624, 1598, 1513, 1446, 1260, 1237, 1148, 999, 834, 754; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (d, *J* = 7.4 Hz, 4H), 7.29 (d, *J* = 7.4 Hz, 4H), 7.24 (dd, *J* = 15.1, 11.3 Hz, 1H), 7.19 (t, *J* = 7.4 Hz, 2H), 6.77 (d, *J* = 8.5 Hz, 1H), 6.70-6.67 (m, 2H), 6.28-6.20 (m, 2H), 6.05 (dd, *J* = 15.1, 5.4 Hz, 1H), 4.37-4.31 (m, 1H), 4.23 (s, 1H), 3.85 (s, 3H), 3.85 (s, 3H), 3.69 (br s, 2H), 3.54 (br s, 2H), 2.76-2.67 (m, 2H), 2.39 (br s, 4H), 0.84 (s, 9H), -0.10 (s, 3H), -0.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.9, 148.4, 147.4, 143.6, 142.1, 142.0, 130.5, 128.5, 127.8, 127.3, 127.0, 121.8, 119.7, 113.1, 110.9, 75.8, 74.0, 55.8, 55.7, 52.1, 51.5, 45.8, 44.4, 42.1, 25.7, 18.1, -4.8, -5.1; EIMS: 649 $[M+Na]^+$.

(*R*,2*E*,4*E*)-1-(4-benzhydrylpiperazin-1-yl)-7-(3,4-dimethoxyphenyl)-6-hydroxyhepta-2,4-dien-1-one (22): Pale yellow oil, 86% yield; $[\alpha]_D^{25}$: –6.2 (*c* 0.45, $CHCl_3$); IR (KBr): 3386, 2924, 2853, 1648, 1618, 1591, 1513, 1450, 1236, 1146, 996, 753, 703; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 (d, *J* = 7.4 Hz, 4H), 7.29 (d, *J* = 7.4 Hz, 4H), 7.23 (dd, *J* = 14.8, 11.1 Hz, 1H), 7.19 (t, *J* = 7.3 Hz, 2H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.76-6.71 (m, 2H), 6.35 (dd, *J* = 15.2, 11.1 Hz, 1H), 6.28 (d, *J* = 14.8 Hz, 1H), 6.10 (dd, *J* = 15.2, 5.4 Hz, 1H), 4.45-4.39 (m, 1H), 4.24 (s, 1H), 3.86 (s, 6H), 3.69 (br s, 2H), 3.53 (br s, 2H), 2.85 (dd, *J* = 13.5, 5.0 Hz, 1H), 2.73 (dd, *J* = 13.5, 7.9 Hz, 1H), 2.39 (br s, 4H), 1.83 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.2, 148.5, 147.5, 142.5, 141.9, 141.8, 129.6, 128.4, 127.8, 127.6, 126.9, 121.3, 119.9, 112.4, 111.0, 75.7, 72.4, 55.6, 51.9, 51.3, 45.6, 43.1, 42.0; HRMS (ESI) (*m/z*): calcd. for $C_{32}H_{37}O_4N_2$ $[M+H]^+$ 513.2747; found 513.2743.

Biology:

Cell culture: four different human tumor cell lines from lung (A549), cervix (HeLa), breast (MCF7) and neuroblastoma (IMR32) were purchased from American Type culture collection. All the cells were maintained in Dulbecco's modified Eagle's medium (DMEM), supplemented with 10% fetal bovine serum (Gibco, USA) and 1% penicillin-streptomycin solution (Gibco, USA). Cell lines were maintained at pH- 7.2 to 7.5 and 37 ^oC in a humidified atmosphere containing 5% CO_2 in the incubator. Cellular morphology was checked using Phase Contrast Microscope (Olympus, Japan).

anti-proliferative activity assay: A549, HeLa, MCF7 and IMR32 cells were grown up to 80% confluence in T75 flasks. The cells were trypsinized and 5×10^4 cells/ml cell suspensions were prepared with complete medium. 100 µl/well cell suspensions were seeded in 96 well plates and incubated 24 h at 37 ^oC in 5% CO_2. Then the cells were treated with different doses (1, 10, 50, 100 µM) of kunstleramide derivatives for 48 h at 37 °C. After 48 h, cell monolayers were fixed by the addition of

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100 μL of 10% (wt/vol) cold trichloroacetic acid and incubated at 4 °C for 1 h. The supernatant was discarded. The plate was washed four times with tap water and was allowed to air dry. The cells were then stained with 0.057% SRB dissolved in 1% acetic acid for 30 min at room temperature. Unbound SRB was washed away with four washes of 1% acetic acid. The plate was again allowed to air dry and the bound SRB stain, representing surviving cells, was dissolved in 50 μL of Tris base (10 mm). The optical density was determined at 510 nm using a microplate reader (Enspire, Perkin Elmer, USA). And calculated for IC50 values of the compounds.

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Synthesis and biological evaluation of (-)-kunstleramide and its derivatives

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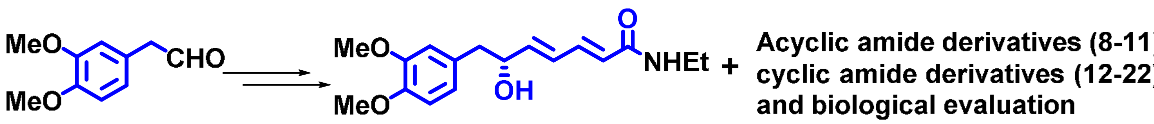
Stereoselective synthesis of (-)-kunstleramide and its amide derivatives has been achieved and evaluated their in vitro anti-proliferative activities against various cell lines.



(-)-Kunstleramide (1)