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SYNTHESIS OF NOVEL β -LACTAM HYBRIDS OF PHENSTATIN AND OTHER SUBSTITUTED AROMATICS AS NEW BIOACTIVES

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Abstract – Novel β -lactam hybrids have been synthesized as new chemical entities in the development of new antibiotic antineoplastic agents.

A persistent challenge in today's society is the pressing need to develop new anticancer and antimicrobial agents in response to constantly emerging reports of drug resistance phenomena.¹ Accordingly, investigative efforts have been refocused toward developing more potent systems, and with the evolving strategy of covalently linking two biologically significant species, new hybrids with very promising pharmacological properties have been developed and evaluated.² Among these are new antibacterial, anti-malarial, anti-Alzheimer, and antitumor agents. In this context, our team recently reported on the synthesis and evaluation of new phenstatin-fatty acid conjugates as potential tubulin-binding agents.³ Kamal et al. similarly reported on the anticancer activities of hybrids possessing a cinnamide subunit linked to benzophenones.⁴ Furthermore, and in separate studies, D'hooghe et al. investigated the biological properties of novel purine- β -lactam and purine-aminopropanol hybrids,⁵ while the Tripodi team focused on developing 1,4-diaryl-2-azetidinones as specific anticancer agents.⁶ In the latter study, select systems were shown to induce inhibition of tubulin polymerization accompanied by activation of adenosine monophosphate activated protein kinase and apoptosis induction.

To further extend our work on hybridized systems, we embarked on the synthesis of some novel β -lactam hybrids of combretastatin-A4 (CA-4) and phenstatin (both tubulin polymerization inhibitors), and of estrone, in the hope of developing new potent antibiotic antineoplastic agents.⁷ By structurally incorporating the element fluorine, we envision these new entities to possess enhanced lipophilicity and metabolic stability.⁸ Herein we report on the synthesis of the hybrids represented in Figure 1.

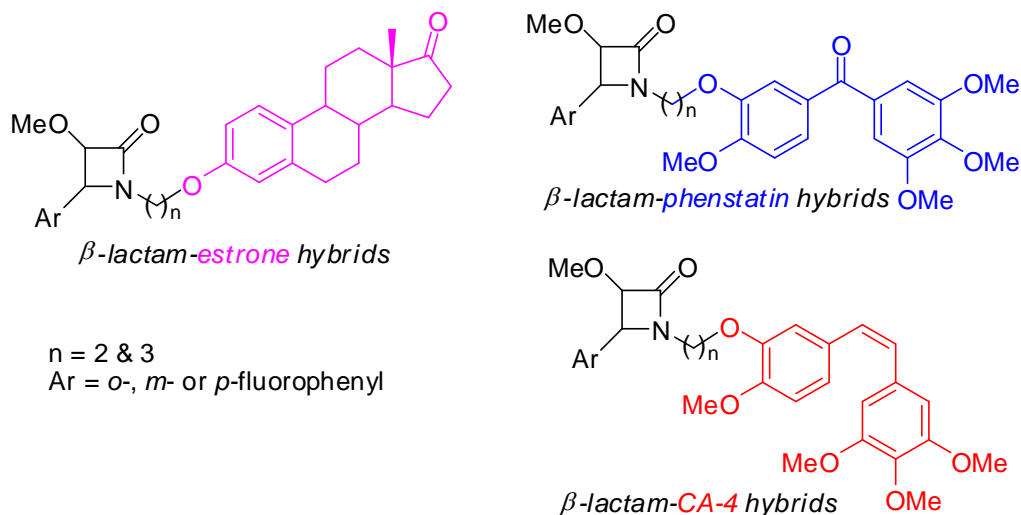
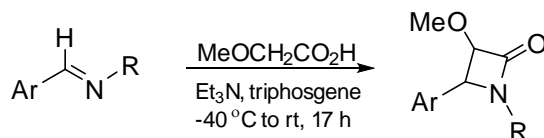


Figure 1. Targeted β -lactam hybrids

All β -lactams were prepared either by the traditional Staudinger method or by the modified protocol mediated by triphosgene, Scheme 1, and obtained as racemates.⁹



Scheme 1. Triphosgene-mediated β -lactam synthesis

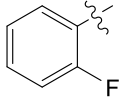
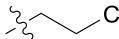
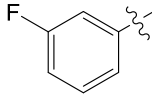
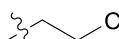
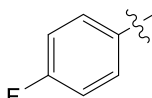
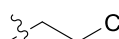
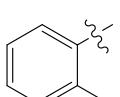
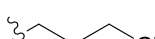
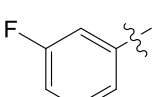

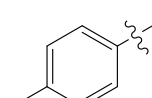
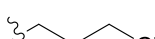
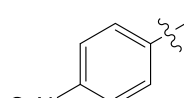
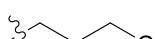
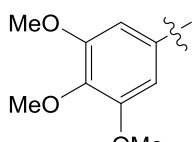
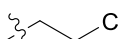
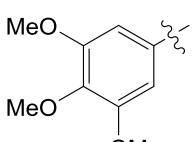
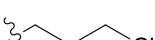
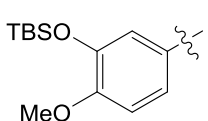

For the two approaches, we found the product yields and purity to be comparable, affording the *cis* β -lactams exclusively; the proton NMR spectra revealing coupling constants of $J = 4.5$ Hz from the doublets of the two protons of the 2-azetidinone ring.¹⁰ Product yields for these systems range from 65% to 95%, Table 1, and all β -lactams were sufficiently stable under ambient conditions and accordingly were amenable to flash chromatographic purification on silica gel.

Combretastatin-A4 was prepared by the Wittig olefination approach reported in the literature.¹¹ Likewise, phenstatin was synthesized according to the modified approach outlined in our previously published work.³

Generation of the β -lactam hybrids was accomplished by standard nucleophilic coupling in acetonitrile (MeCN), or by phase transfer catalysis in aqueous dichloromethane (DCM).¹² In the former approach, a mixture of the phenol (0.500 g, 1.00 equiv), cesium carbonate (1.50 equiv), and the β -lactam (1.05 equiv) in MeCN (~40 mL) was stirred at room temperature before work-up. The biphasic approach involved

combining a solution of the phenol (1.00 equiv in 5 mL DCM) with a stirred aqueous solution of KOH (1.50 equiv) and tetrabutylammonium hydrogensulfate (TBAHSO₄, 0.250 equiv) in ~10 mL water.

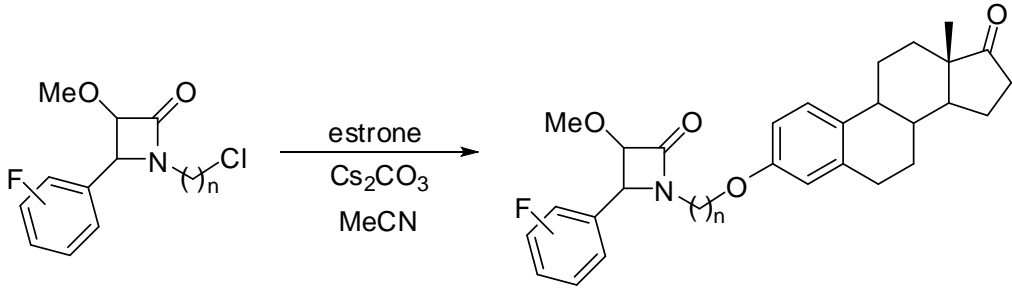
Table 1. *N*-Chloroalkyl-substituted β-lactams

entry	(±)-β-lactam		yield(%)	mp (°C)
	Ar	R		
1			80	55 - 57
2			78	63 - 65
3			95	87 - 88
4			88	40 - 41
5			90	62 - 64
6			95	56 - 58
7			82	66 - 68
8			65	57 - 59
9			70	54 - 56
10			68	56 - 58

A solution of the β -lactam (1.05 equiv) dissolved in 5 mL DCM was added portion-wise to this vigorously stirred solution at room temperature, with the reaction progress being monitored by TLC.

Shown in Table 2 are the hybrids of estrone with select β -lactam systems.

Table 2. β -Lactam-estrone hybrids



entry	β -lactam	n	hybrid	yield (%)
1	(+/-)-cis-3	2	11	46 ^a
2	(+/-)-cis-4	3	12	68
3	(+/-)-cis-5	3	13	72
4	(+/-)-cis-6	3	14	77

^a Product yield by the phase transfer catalysis approach

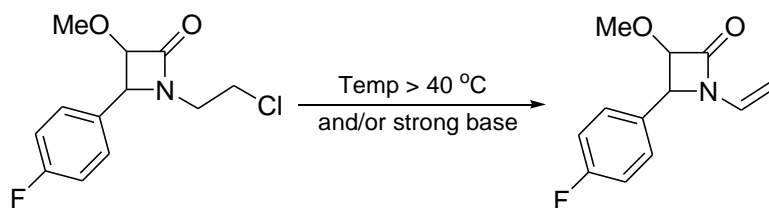
As expected, a 1:1 diastereomeric mixture was obtained in all instances from the coupling of the racemic β -lactams with enantiopure estrone.

Hybrids of phenstatin and CA-4 with representative β -lactams were similarly prepared with results summarized in Table 3. All hybrids were obtained as viscous oils, and in comparable yields for compounds **16**, **17**, **18**, and **19** by either of the two coupling methods. Formation of compound **15** however, was somewhat sluggish yielding at best about 40% by the phase transfer catalytic approach, and 20 – 25% by the alternative method mediated by cesium carbonate. All attempts to improve on the intended reaction outcome proved unsuccessful. The use of stronger bases and/or elevated temperatures on these 2-chloroethyl systems resulted in competing eliminations to the *N*-vinyl substituted derivative (identified by proton NMR of the crude reaction mixture), Scheme 2.

Table 3. Phenstatin and CA-4 β -lactam hybrids

entry	β -lactam	nucleophile	hybrid	yield (%)
1	(+/-)-cis-2	Phenstatin	15	43 ^b
2	(+/-)-cis-4	Phenstatin	16	62
3	(+/-)-cis-5	Phenstatin	17	66
4	(+/-)-cis-6	Phenstatin	18	68
5	(+/-)-cis-6	CA-4	19	68

^b Product yield by the phase transfer catalysis approach

**Scheme 2.** Competing elimination reaction

As detailed below, all new compounds gave conclusive analytical data in support of their respective structures with the new hybrids currently being screened against various cell lines for their antiproliferative properties. The results of these investigations will be reported in a forthcoming manuscript.

EXPERIMENTAL

Infrared (IR) spectra were obtained on a Perkin-Elmer Spectrum 2 FT-IR spectrometer with the aid of a PIKE MIRacle ATR (Attenuated Total Reflectance) accessory. ¹H NMR and ¹³C NMR spectra were recorded using a Bruker DPX 400 MHz spectrometer, with chemical shifts reported as parts per million (δ ppm) downfield of the internal standard TMS. Mass Spectrometry (GC/MS) analyses were performed using the Shimadzu GCMS-QP5050A system equipped with a direct insertion (DI) port. Elemental

analyses were performed by Atlantic Microlab Inc., Norcross, GA. All required compounds for the outlined syntheses were obtained from Aldrich Chemical Company. Dichloromethane (DCM) and acetonitrile (MeCN) were distilled from CaH₂ and stored over 4 angstrom molecular sieves under nitrogen. Flash chromatographic purification was performed using silica gel, 200 – 400 mesh, purchased from Aldrich.

(+/-)-cis-1-(2-Chloroethyl)-4-(2-fluorophenyl)-3-methoxyazetid-2-one (1).

¹H NMR (400 MHz, CDCl₃): δ 3.20 (3H, s), 3.25 (1H, m), 3.55 (1H, m), 3.65 (1H, m), 3.88 (1H, m), 4.82 (1H, d, *J* = 4.5 Hz), 5.29 (1H, d, *J* = 4.5 Hz), 7.10 (1H, m), 7.21 (1H, m), 7.35 (2H, m). ¹³C NMR (100 MHz, CDCl₃): δ 41.2, 42.2, 56.0, 58.5, 85.9, 115.5, 120.9, 124.2, 129.3, 130.1, 160.1, 167.4. IR (cm⁻¹): 755, 1208, 1494, 1581, 1748, 2841, 2928, 2940, 2958, 3011. MS (EI, *m/z*): 257 (M⁺), 226, 186, 152 (100%), 137, 109, 95, 83, 72, 44, 41. *Anal.* Calcd for C₁₂H₁₃ClFNO₂ (257.7): C, 55.93; H, 5.08; Cl, 13.76; F, 7.37; N, 5.44; O, 12.42. Found: C, 55.90; H, 5.04.

(+/-)-cis-1-(2-Chloroethyl)-4-(3-fluorophenyl)-3-methoxyazetid-2-one (2).

¹H NMR (400 MHz, CDCl₃): δ 3.19 (3H, s), 3.23 (1H, m), 3.57 (1H, m), 3.65 (1H, m), 3.84 (1H, m), 4.84 (1H, d, *J* = 4.5 Hz), 5.26 (1H, d, *J* = 4.5 Hz), 7.08 (1H, m), 7.25 (1H, m), 7.35 (2H, m). ¹³C NMR (100 MHz, CDCl₃): δ 41.1, 42.2, 56.1, 58.5, 85.9, 115.4, 120.9, 124.3, 129.2, 130.3, 160.0, 167.3. IR (cm⁻¹): 753, 1206, 1494, 1581, 1747, 2839, 2927, 2959, 3012. MS (EI, *m/z*): 257 (M⁺), 226, 186, 152 (100%), 137, 109, 95, 83, 72, 44, 41. *Anal.* Calcd for C₁₂H₁₃ClFNO₂ (257.7): C, 55.93; H, 5.08; Cl, 13.76; F, 7.37; N, 5.44; O, 12.42. Found: C, 55.92; H, 5.10.

(+/-)-cis-1-(2-Chloroethyl)-4-(4-fluorophenyl)-3-methoxyazetid-2-one (3).

¹H NMR (400 MHz, CDCl₃): δ 3.09 (3H, s), 3.27 (1H, ddd, *J* = 5.2, 6.9, 14.7 Hz), 3.58 (2H, m), 3.80 (1H, ddd, *J* = 5.4, 6.5, 14.6 Hz), 4.78 (1H, d, *J* = 4.4 Hz), 4.96 (1H, d, *J* = 4.4 Hz), 7.10 (2H, t, *J* = 8.7 Hz), 7.40 (2H, dd, *J* = 5.4, 8.7 Hz). ¹³C NMR (100 MHz, CDCl₃): δ 41.3, 41.9, 57.9, 61.8, 85.7, 115.2, 129.5, 130.2, 161.6, 164.0, 167.1. IR (cm⁻¹): 913, 1032, 1225, 1462, 1764, 2850, 2921. MS (EI, *m/z*): 257 (M⁺), 228, 206, 186, 169, 152, 137, 109, 85, 71, 57(100%), 43, 41. *Anal.* Calcd for C₁₂H₁₃ClFNO₂ (257.7): C, 55.93; H, 5.08; Cl, 13.76; F, 7.37; N, 5.44; O, 12.42. Found: C, 55.97; H, 5.11.

(+/-)-cis-1-(3-Chloropropyl)-4-(2-fluorophenyl)-3-methoxyazetid-2-one (4).

¹H NMR (400 MHz, CDCl₃): δ 2.02 (2H, m), 3.12 (1H, dt, *J* = 6.4, 14.0 Hz), 3.17 (3H, s), 3.55 (2H, t, *J* = 6.3 Hz), 3.62 (1H, dt, *J* = 7.1, 14.3 Hz), 4.76 (1H, d, *J* = 4.5 Hz), 5.16 (1H, d, *J* = 4.5 Hz), 7.10 (1H, dt, *J* = 1.3, 9.8 Hz), 7.21 (1H, dt, *J* = 0.8, 8.3 Hz), 7.35 (2H, m). ¹³C NMR (100 MHz, CDCl₃): δ 30.2, 38.3,

42.1, 58.2, 61.8, 85.7, 115.4, 115.9, 124.1, 130.2, 136.4, 164.1, 167.2. IR (cm⁻¹): 1212, 1463, 1761, 2850, 2922. MS: (EI, *m/z*): 271 (M⁺), 228, 205, 176, 152(100%), 149, 120, 109, 87, 73, 57. *Anal.* Calcd for C₁₃H₁₅ClFNO₂ (271.72): C, 57.46; H, 5.56; Cl, 13.05; F, 6.99; N, 5.15; O, 11.78. Found: C, 57.38; H, 5.73; Cl, 12.86; N, 5.20.

(+/-)-cis-1-(3-Chloropropyl)-4-(3-fluorophenyl)-3-methoxyazetid-2-one (5).

¹H NMR (400 MHz, CDCl₃): δ 2.00 (2H, m), 3.12 (1H, dt, *J* = 6.5, 14.0 Hz), 3.14 (3H, s), 3.53 (2H, t, *J* = 6.3 Hz), 3.60 (1H, dt, *J* = 7.1, 14.3 Hz), 4.72 (1H, d, *J* = 4.4 Hz), 4.77 (1H, d, *J* = 4.4 Hz), 7.07 (2H, m), 7.15 (1H, d, *J* = 7.7 Hz), 7.38 (1H, m). ¹³C NMR (100 MHz, CDCl₃): δ 30.3, 38.3, 42.1, 58.3, 61.8, 85.6, 115.4, 115.9, 124.1, 130.2, 136.5, 164.0, 167.1. IR (cm⁻¹): 1212, 1462, 1761, 2850, 2920. MS: (EI, *m/z*): 271 (M⁺), 228, 205, 176, 152(100%), 149, 120, 109, 87, 73, 57, 44. *Anal.* Calcd for C₁₃H₁₅ClFNO₂ (271.72): C, 57.46; H, 5.56; Cl, 13.05; F, 6.99; N, 5.15; O, 11.78. Found: C, 57.55; H, 5.62.

(+/-)-cis-1-(3-Chloropropyl)-4-(4-fluorophenyl)-3-methoxyazetid-2-one (6).

¹H NMR (400 MHz, CDCl₃): δ 1.98 (2H, m), 3.08 (1H, m), 3.13 (3H, s), 3.51 (3H, m), 4.69 (1H, d, *J* = 4.3 Hz), 4.74 (1H, d, *J* = 4.3 Hz), 7.10 (2H, t, *J* = 8.6 Hz), 7.34 (2H, dd, *J* = 5.3, 8.6 Hz). ¹³C NMR (100 MHz, CDCl₃): δ 30.5, 38.4, 42.3, 58.4, 61.9, 85.7, 115.7, 115.9, 129.5, 130.3, 130.4, 164.5, 167.4. IR (cm⁻¹): 550, 843, 1008, 1100, 1159, 1223, 1355, 1400, 1511, 1605, 1760, 2319, 2922. MS: (EI, *m/z*): 271 (M⁺), 256, 240, 200, 177, 152(100%), 137, 122, 109, 95, 83, 72, 56, 51. *Anal.* Calcd for C₁₃H₁₅ClFNO₂ (271.72): C, 57.46; H, 5.56; Cl, 13.05; F, 6.99; N, 5.15; O, 11.78. Found: C, 57.38; H, 5.73; F, 6.84; N, 5.23.

(+/-)-cis-1-(3-Chloropropyl)-3-methoxy-4-(4-nitrophenyl)azetid-2-one (7).

¹H NMR (400 MHz, CDCl₃): δ 2.02 (2H, m), 3.12 (1H, dt, *J* = 6.9, 13.9 Hz), 3.17 (3H, s), 3.55 (2H, t, *J* = 6.3 Hz), 3.59 (1H, dt, *J* = 7.0, 14.1 Hz), 4.77 (1H, d, *J* = 4.5 Hz), 4.88 (1H, d, *J* = 4.5 Hz), 7.54 (2H, d, *J* = 8.6 Hz), 8.28 (2H, d, *J* = 8.7 Hz). IR (cm⁻¹): 1033, 1462, 1763, 2850, 2920. MS: (EI, *m/z*): 299 (M⁺), 268, 236, 204, 179, 164, 152(100%), 137, 109, 85, 71, 57, 43. *Anal.* Calcd for C₁₃H₁₅ClN₂O₄ (298.7): C, 52.27; H, 5.06; Cl, 11.87; N, 9.38; O, 21.42. Found: C, 52.36; H, 5.11; Cl, 11.72; N, 9.37.

(+/-)-cis-1-(2-Chloroethyl)-3-methoxy-4-(3,4,5-trimethoxyphenyl)azetid-2-one (8).

¹H NMR (400 MHz, CDCl₃): δ 3.18 (3H, s), 3.35 (1H, ddd, *J* = 5.3, 5.8, 14.4 Hz), 3.57 (2H, m), 3.78 (1H, ddd, *J* = 5.7, 5.7, 14.5 Hz); 3.86 (3H, s), 3.88 (6H, s); 4.76 (1H, d, *J* = 4.4 Hz), 4.83 (1H, d, *J* = 4.4 Hz), 6.60 (2H, s). ¹³C NMR (100 MHz, CDCl₃): δ 41.2, 42.1, 56.0 (2C's), 58.2, 60.6, 62.7, 88.7, 105.1

(2C's), 128.9, 138.0, 153.1(2C's), 167.2. IR (cm⁻¹): 743, 913, 1005, 1129, 1239, 1328, 1427, 1464, 1508, 1591, 1757, 2838, 2929. MS: (EI, *m/z*): 329 (M⁺), 224, 209, 72, 63(100%), 45. Anal. Calcd for C₁₅H₂₀ClNO₅ (329.8): C, 54.63; H, 6.11; Cl, 10.75; N, 4.25; O, 24.26. Found: C, 54.60; H, 6.14; N, 4.27.

(+/-)-cis-4-(3-(tert-Butyldimethylsilyloxy)-4-methoxyphenyl)-1-(2-chloroethyl)-3-methoxyazetid-2-one (10).

¹H NMR (400 MHz, CDCl₃): δ 0.13 (6H, s); 0.97 (9H, s); 3.07 (3H, s); 3.57 (4H, m); 3.79 (3H, s); 4.32 (1H, s); 4.51 (1H, d, *J* = 1.0 Hz); 6.87 (3H, m). ¹³C NMR (100 MHz, CDCl₃): δ -4.67, 18.42, 25.68, 41.22, 41.34, 55.38, 55.43, 62.20, 85.70, 111.7 (2 C's), 118.8 (2 C's), 120.9 (2 C's), 125.6, 144.9, 151.5, 167.2. IR (cm⁻¹): 663, 784, 840, 1002, 1137, 1281, 1444, 1513, 1585, 1606, 1764, 2856, 2928. Anal. Calcd for C₁₉H₃₀ClNO₄Si (257.7): C, 57.05; H, 7.56; Cl, 8.86; N, 3.50; O, 16.00; Si, 7.02. Found: C, 57.12; H, 7.49; Cl, 8.91.

Estrone Conjugate 11, diastereomer with R_f = 0.39: silica gel, hexanes:EtOAc, 2:1.

¹H NMR (400 MHz, CDCl₃): δ 0.91 (3H, s), 1.46 (5H, m), 2.05 (5H, m), 2.25 (1H, m), 2.38 (1H, d, *J* = 9.5 Hz), 2.51 (1H, dd, *J* = 8.8, 19.1 Hz), 2.87 (2H, m), 3.12 (3H, s), 3.29 (1H, ddd, *J* = 3.5, 7.8, 14.7 Hz), 3.80 (1H, m), 4.00 (2H, m), 4.68 (1H, d, *J* = 4.4 Hz), 4.87 (1H, d, *J* = 4.4 Hz), 6.50 (1H, s), 6.59 (1H, dd, *J* = 2.5, 8.5 Hz), 7.07 (2H, t, *J* = 8.6 Hz), 7.18 (1H, d, *J* = 8.6 Hz), 7.34 (2H, dd, *J* = 5.5, 8.5 Hz). ¹³C NMR (100 MHz, CDCl₃): δ 13.9, 21.6, 25.9, 26.5, 29.6, 31.6, 35.9, 38.3, 39.6, 44.0, 48.0, 50.4, 58.2, 62.4, 85.8, 112.0, 114.4, 115.3 (2C's), 115.5, 126.4, 129.6 (2C's), 130.1, 130.2, 132.7, 137.9, 156.0 (2C's), 167.2. IR (cm⁻¹): 1247, 1382, 1469, 1608, 1753, 1793, 2838, 2948, 3155. MS: (EI, *m/z*): 491 (M⁺), 460, 421, 390, 340, 324, 296, 253, 214, 186, 152(100%), 131, 109, 67, 40. Anal. Calcd for C₃₀H₃₄FNO₄ (491.6): C, 73.30; H, 6.91; F, 3.85; N, 2.85; O, 13.02. Found: C, 73.16; H, 7.06.

Estrone Conjugate 12, diastereomer with R_f = 0.43: silica gel, hexanes:EtOAc, 2:1.

¹H NMR (400 MHz, CDCl₃): δ 0.91 (3H, s), 1.53 (5H, m), 2.05 (8H, m), 2.40 (1H, m), 2.50 (1H, dd, *J* = 8.3, 18.6 Hz), 2.87 (2H, m), 3.13 (1H, dt, *J* = 6.7, 13.9 Hz), 3.17 (3H, s), 3.69 (1H, dt, *J* = 7.4, 14.5 Hz), 3.94 (2H, m), 4.73 (1H, d, *J* = 4.5 Hz), 5.18 (1H, d, *J* = 4.5 Hz), 6.58 (1H, d, *J* = 1.9 Hz), 6.65 (1H, dd, *J* = 2.3, 8.6 Hz), 7.09 (1H, dd, *J* = 8.5, 10.0 Hz), 7.17 (1H, d, *J* = 8.1 Hz), 7.19 (1H, d, *J* = 6.7 Hz), 7.34 (2H, m). ¹³C NMR (100 MHz, CDCl₃): δ 13.9, 21.6, 25.9, 26.5, 27.3, 29.6, 31.6, 35.9, 38.1, 38.3, 44.0, 48.0, 50.4, 55.2, 58.4, 65.3, 85.5, 112.1, 114.5, 115.3, 121.2, 124.2, 126.4, 129.3, 129.9, 132.3, 137.8, 156.6, 160.0, 162.5, 167.3. IR (cm⁻¹): 710, 1096, 1201, 1512, 1608, 1758, 1892, 2834, 2930, 3145.

MS: (EI, m/z): 505 (M^+), 474, 434, 419, 377, 353, 325, 298, 268, 255, 238, 204, 164, 152(100%), 136, 109, 72, 58. *Anal.* Calcd for $C_{31}H_{36}FNO_4$ (505.6): C, 73.64; H, 7.18; F, 3.76; N, 2.77; O, 12.66. Found: C, 73.51; H, 7.21; N, 2.68.

Estrone Conjugate 13, diastereomer with $R_f = 0.37$: silica gel, hexanes:EtOAc, 2:1.

1H NMR (400 MHz, $CDCl_3$): δ 0.91 (3H, s), 1.55 (4H, m), 2.08 (8H, m), 2.38 (1H, m), 2.50 (2H, dd, $J = 8.8, 18.6$ Hz), 2.87 (2H, m), 3.11 (1H, m), 3.13 (3H, s), 3.64 (1H, dt, $J = 7.2, 14.3$ Hz), 3.92 (2H, t, $J = 5.8$ Hz), 4.69 (1H, d, $J = 4.4$ Hz), 4.76 (1H, d, $J = 4.3$ Hz), 6.57 (1H, s), 6.64 (1H, dd, $J = 2.4, 8.5$ Hz), 7.06 (2H, m), 7.12 (1H, d, $J = 7.7$ Hz), 7.18 (1H, d, $J = 8.6$ Hz), 7.35 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 21.6, 25.9, 26.5, 27.4, 29.7, 31.6, 35.9, 37.9, 38.3, 44.0, 48.0, 50.4, 58.3, 61.7, 65.3, 85.6, 112.1, 114.5, 115.5, 115.6, 115.8, 124.1, 126.4, 130.1, 132.4, 136.6, 137.8, 156.6, 167.1. IR (cm^{-1}): 913, 1096, 1248, 1382, 1471, 1606, 1755, 1793, 2931, 2982, 3155. MS: (EI, m/z): 505 (M^+), 353, 268, 236, 204, 164, 152(100%), 136, 109, 97, 71, 57, 43, 41. *Anal.* Calcd for $C_{31}H_{36}FNO_4$ (505.6): C, 73.64; H, 7.18; F, 3.76; N, 2.77; O, 12.66. Found: C, 73.78; H, 7.21; F, 3.27; N, 2.69.

Estrone Conjugate 14, diastereomer with $R_f = 0.46$: silica gel, hexanes:EtOAc, 2:1.

1H NMR (400 MHz, $CDCl_3$): δ 0.90 (3H, s), 1.56 (5H, m), 1.97 (5H, m), 2.23 (1H, t, $J = 9.8$ Hz), 2.37 (1H, d, $J = 9.6$ Hz), 2.48 (1H, dd, $J = 9.2, 18.9$ Hz), 2.87 (2H, m), 3.08 (3H, s), 3.11 (1H, m), 3.55 (3H, m), 3.92 (2H, t, $J = 5.8$ Hz), 4.68 (1H, d, $J = 4.3$ Hz), 4.79 (1H, d, $J = 4.1$ Hz), 6.57 (1H, s), 6.64 (1H, d, $J = 8.6$ Hz), 7.07 (2H, m), 7.17 (1H, d, $J = 8.6$ Hz), 7.35 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 21.6, 25.9, 26.5, 27.4, 29.6, 31.6, 35.8, 37.7, 38.3, 42.2, 43.9, 47.9, 50.3, 58.0, 61.5, 65.2, 85.5, 112.1, 114.5, 115.4, 115.6, 126.3, 129.7, 130.2, 132.3, 137.7, 156.6, 161.7, 164.1, 167.1. IR (cm^{-1}): 712, 1099, 1221, 1512, 1608, 1753, 1892, 2837, 2934, 3155. MS: (EI, m/z): 505 (M^+), 353, 271, 200, 164, 152(100%), 138, 120, 109, 86, 84, 68, 47. *Anal.* Calcd for $C_{31}H_{36}FNO_4$ (505.6): C, 73.64; H, 7.18; F, 3.76; N, 2.77; O, 12.66. Found: C, 73.51; H, 7.60; F, 3.22; N, 2.78.

Phenstatin- β -lactam Hybrid 15:

1H NMR (400 MHz, $CDCl_3$): δ 3.14 (3H, s), 3.35 (1H, m), 3.87 (7H, m), 3.94 (3H, s), 3.96 (3H, s), 4.13 (2H, m), 4.71 (1H, d, $J = 4.4$ Hz), 5.00 (1H, d, $J = 4.4$ Hz), 6.91 (1H, d, $J = 8.4$ Hz), 7.00 (2H, s), 7.04 (2H, m), 7.32 (1H, d, $J = 1.9$ Hz), 7.36 (2H, m), 7.42 (1H, dd, $J = 2.0, 8.4$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.4, 56.0, 56.4, 58.2, 61.0, 62.5, 66.8, 85.9, 107.5, 110.3, 114.3, 115.2, 115.4, 125.8, 129.6, 130.2, 130.3, 130.4, 133.2, 141.8, 147.6, 152.9, 153.3, 161.7, 167.2, 194.4. IR (cm^{-1}): 766, 1022, 1129, 1266, 1332, 1512, 1582, 1646, 1755, 2839, 2938, 3007. MS (EI, m/z): 539 (M^+), 387, 372, 344, 318,

303, 287, 220, 190, 152 (100%), 109, 95, 72, 44, 41. *Anal.* Calcd for C₂₉H₃₀FNO₈ (539.6): C, 64.56; H, 5.60; F, 3.52; N, 2.60; O, 23.72. Found: C, 64.58; H, 5.58.

Phenstatin- β -lactam Hybrid 16:

¹H NMR (400 MHz, CDCl₃): δ 2.12 (2H, m), 3.18 (4H, m), 3.79 (1H, m), 3.91 (6H, s), 3.93 (3H, s), 3.96 (3H, s), 4.11 (2H, t, $J = 5.2$ Hz), 4.75 (1H, d, $J = 4.5$ Hz), 5.29 (1H, d, $J = 4.5$ Hz), 6.91 (1H, d, $J = 8.8$ Hz), 7.04 (2H, s), 7.09 (1H, m), 7.20 (1H, m), 7.35 (2H, m), 7.42 (2H, m). ¹³C NMR (100 MHz, CDCl₃): δ 27.1, 38.1, 55.1, 55.9, 56.3, 58.3, 60.9, 66.8, 85.6, 107.4, 110.1, 114.0, 115.3, 121.4, 124.1, 125.4, 129.2, 129.8, 130.3, 133.3, 141.6, 148.0, 152.9, 153.3, 160.0, 167.3, 194.6. IR (cm⁻¹): 759, 1019, 1124, 1264, 1329, 1512, 1580, 1645, 1755, 2837, 2938, 3005. MS (EI, m/z): 553 (M⁺), 401 (100%), 386, 358, 318, 303, 287, 236, 195, 152, 109, 84, 72, 44, 41. *Anal.* Calcd for C₃₀H₃₂FNO₈ (553.6): C, 65.09; H, 5.83; F, 3.43; N, 2.53; O, 23.12. Found: C, 65.11; H, 5.86.

Phenstatin- β -lactam Hybrid 17:

¹H NMR (400 MHz, CDCl₃): δ 2.06 (2H, q, $J = 6.4$ Hz), 3.14 (4H, m), 3.72 (1H, m), 3.89 (6H, s), 3.91 (3H, s), 3.94 (3H, s), 4.07 (2H, t, $J = 5.8$ Hz), 4.70 (1H, d, $J = 4.4$ Hz), 4.84 (1H, d, $J = 4.4$ Hz), 6.89 (1H, d, $J = 8.1$ Hz), 7.04 (4H, m), 7.12 (1H, d, $J = 7.7$ Hz), 7.36 (3H, m). ¹³C NMR (100 MHz, CDCl₃): δ 27.1, 37.9, 55.9, 56.3, 58.3, 61.0, 61.6, 66.7, 85.7, 107.5, 110.1, 114.0, 115.2, 115.5, 124.1, 125.4, 130.0, 130.3, 133.3, 136.7, 141.6, 148.0, 152.9, 153.3, 161.6, 167.1, 194.6. IR (cm⁻¹): 764, 1022, 1128, 1265, 1332, 1513, 1582, 1645, 1754, 2838, 2938, 3007. MS (EI, m/z): 553 (M⁺), 401 (100%), 386, 358, 318, 303, 287, 236, 195, 152, 109, 84, 72, 44, 41. *Anal.* Calcd for C₃₀H₃₂FNO₈ (553.6): C, 65.09; H, 5.83; F, 3.43; N, 2.53; O, 23.12. Found: C, 65.04; H, 5.79.

Phenstatin- β -lactam Hybrid 18:

¹H NMR (400 MHz, CDCl₃): δ 2.05 (2H, m), 3.12 (3H, s), 3.16 (1H, m), 3.67 (1H, q, $J = 7.1$ Hz), 3.89 (6H, s), 3.91 (3H, s), 3.94 (3H, s), 4.07 (2H, t, $J = 5.9$ Hz), 4.68 (1H, d, $J = 4.4$ Hz), 4.84 (1H, d, $J = 4.4$ Hz), 6.90 (1H, d, $J = 8.1$ Hz), 7.06 (4H, m), 7.32 (2H, m), 7.40 (1H, s), 7.42 (1H, d, $J = 1.9$ Hz). ¹³C NMR (100 MHz, CDCl₃): δ 27.1, 37.7, 55.9, 56.3, 58.1, 60.9, 61.3, 66.7, 85.5, 107.5, 110.1, 113.9, 115.3, 115.5, 125.4, 129.6, 130.1, 130.2, 130.3, 133.2, 141.6, 148.0, 152.8, 153.3, 161.7, 167.2, 194.5. IR (cm⁻¹): 761, 1020, 1126, 1264, 1330, 1510, 1580, 1646, 1752, 2838, 2937, 3008. MS (EI, m/z): 553 (M⁺), 401 (100%), 386, 358, 318, 303, 287, 236, 195, 152, 109, 84, 72, 44, 41. *Anal.* Calcd for C₃₀H₃₂FNO₈ (553.6): C, 65.09; H, 5.83; F, 3.43; N, 2.53; O, 23.12. Found: C, 65.07; H, 5.80.

CA4- β -Lactam Hybrid 19:

^1H NMR (400 MHz, CDCl_3): δ 1.91 (2H, q, $J = 6.3$ Hz), 3.03 (1H, dt, $J = 6.4, 14.0$ Hz), 3.11 (3H, s), 3.60 (1H, dt, $J = 7.2, 14.3$ Hz), 3.69 (6H, s), 3.79 (3H, s), 3.80 (2H, dt, $J = 6.0, 15.6$ Hz), 3.82 (3H, s), 4.66 (1H, d, $J = 4.4$ Hz), 4.77 (1H, d, $J = 4.3$ Hz), 6.45 (1H, d, $J = 12.2$ Hz), 6.49 (1H, d, $J = 12.2$ Hz), 6.51 (2H, s), 6.75 (2H, m), 6.88 (1H, dd, $J = 1.8, 8.4$ Hz), 7.05 (3H, m), 7.28 (1H, m). ^{13}C NMR (100 MHz, CDCl_3) δ 27.1, 29.7, 37.7, 52.3, 55.8, 56.0, 58.1, 60.9, 61.4, 84.0, 105.9, 111.2, 114.7, 115.6, 118.9, 122.4, 129.6, 131.4, 133.0, 135.6, 141.7, 151.2, 153.0, 160.2, 161.0, 163.3, 165.9. MS: (EI, m/z): 551 (M^+). *Anal.* Calcd for $\text{C}_{31}\text{H}_{34}\text{FNO}_7$ (551.6): C, 67.50; H, 6.21; F, 3.44; N, 2.54; O, 20.30. Found: C, 67.28; H, 6.46.

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