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2-Azetidinone Cholesterol Absorption Inhibitors: Increased Potency by Substitution of the C-4 Phenyl Ring

Wayne D. Vaccaro,* Rosy Sher and Harry R. Davis, Jr.

Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033-0539, USA

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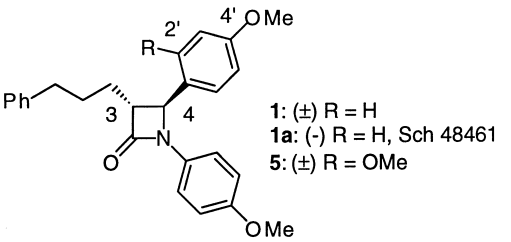
Abstract—SAR studies directed towards the optimization of 2-azetidinone cholesterol absorption inhibitors led to the discovery of **11a**, the most potent cholesterol absorption inhibitor yet identified.

Introduction

The 2-azetidinone **1a** (Sch 48461) was identified as a potent cholesterol absorption inhibitor in the cholesterol-fed hamster assay.[1] Subsequently, **1a** was shown to reduce serum cholesterol in human trials.[2] Compound **1a** demonstrated a synergistic effect with HMG-CoA reductase inhibitors in reducing plasma lipoprotein levels in chow fed dogs and rhesus monkeys.[3] Although the mechanism of cholesterol absorption inhibition of **1a** has yet to be determined, studies suggest that the site of action is the intestinal wall.[4]

Previous SAR studies found that an alkoxy group at the 4′-position of 2-azetidinones such as **1** is crucial for in vivo activity.[1] Attempts to change the position of the 4′-alkoxy group, introduce additional substituents on to the 4′-alkoxy substituted phenyl ring or replace the 4′-alkoxy group with other functional groups generally resulted in a loss of potency.[5,6] However, the 2′,4′-dimethoxy substituted analogue **5** was determined to be equipotent with **1**. The biological activity of compound **5** demanded further investigation of the effect of 2′,4′-substitution on cholesterol absorption inhibition. The results of this investigation are reported below.



Chemistry

The 2-azetidinones reported in Table 1 were prepared with high *trans* diastereoselectivity by modification of the ketene-imine reaction as previously reported (Scheme 1).[7a,b] Compounds displaying significant biological activity were resolved by chiral HPLC on either Chiracel® OD or Chiralpak® AS columns and retested as single enantiomers.[8] The biologically most active enantiomer of each pair was assigned the 3*R*,4*S*-absolute stereochemistry in analogy to **1a**.[9]

Compounds reported in Table 2 were prepared as shown in Scheme 2. The *trans* stereochemistry of **12** was established by the ketene–imine reaction. Hydrolysis of ester **12** affords the acid **13**. Conversion of **13** to the corresponding acid chloride and subsequent palladium mediated coupling with an arylzinc reagent provided ketone **14**. Ketone **14** was resolved into its enantiomers **14a** and **14b** by HPLC on a Chiralpak® AS column.

*Corresponding author.

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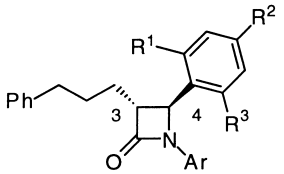
Compounds **14a** and **14b** were independently reduced with a chiral oxazaborolidine catalyst derived from (*S*)-diphenyl-2-pyrrolidinemethanol and borane dimethylsulfide to set the stereochemistry at the 3′-positions of **15a** and **15b**.[10a,b] Subsequent hydrogenation afforded the desired bisphenols **11a** and **11b**. The absolute stereochemistry was assigned by analogy to compound **10** (Sch 58235).[11]

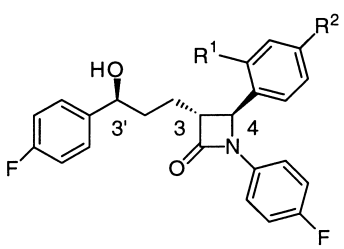
Table 1. Cholesterol absorption activity of analogues of **1**



					Cholesterol-fed Hamster[12]			
Compd	R^1	R^2	R^3	Ar	SC[a]	LCE[b]	Dose (mpk)[c]	ED_{50} (mpk)[c]
1(±)	H	MeO	H	4-MeOPh	−29	−78	50	
1a	H	MeO	H	4-MeOPh	−43	−93	10	2.2
1b	H	MeO	H	4-MeOPh	0	0	50	
2(±)	H	MeO	H	Ph	−41	−90	10	1.5
3(±)	H	MeO	H	4-FPh	−24	−77	10	3.9
4a	H	HO	H	4-MeOPh	−10	−70	10	5.0
5(±)	MeO	MeO	H	4-MeOPh	−26	−78	50	
6(±)	MeO	MeO	MeO	4-MeOPh	−13	0	50	
7(±)	HO	MeO	H	4-MeOPh	−30	−95	10	
7a	HO	MeO	H	4-MeOPh	−50	−97	3	0.22
7b	HO	MeO	H	4-MeOPh	0	−31	3	
8a	HO	HO	H	4-FPh	−34	−95	10	0.37
8b	HO	HO	H	4-FPh	0	0	10	
9a	HO	HO	H	Ph	−45	−94	10	0.08
9b	HO	HO	H	Ph	−14	−69	10	

[a]% Reduction serum cholesterol.
[b]% Reduction liver cholesterol esters.
[c]mpk = mg/Kg/day.

Table 2. Cholesterol absorption activity of analogues of **10**



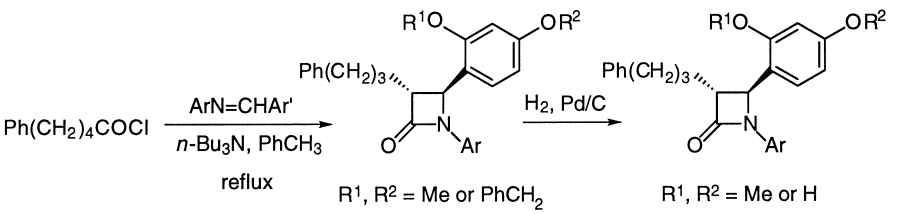
						Cholesterol-fed Hamster[12]		
Compd	Stereo	R^1	R^2	SC[a]	LCE[b]	Dose (mpk)[c]	ED_{50} (mpk)[c]
10	3′(*S*),3(*R*),4(*S*)	H	OH	−59	−95	1	0.04
11a	3′(*S*),3(*R*),4(*S*)	OH	OH	−65	−96	1	0.005
11b	3′(*S*),3(*S*),4(*R*)	OH	OH	−33	−42	1	

[a]% Reduction serum cholesterol.
[b]% Reduction liver cholesterol esters.
[c]mpk = mg/Kg/day.

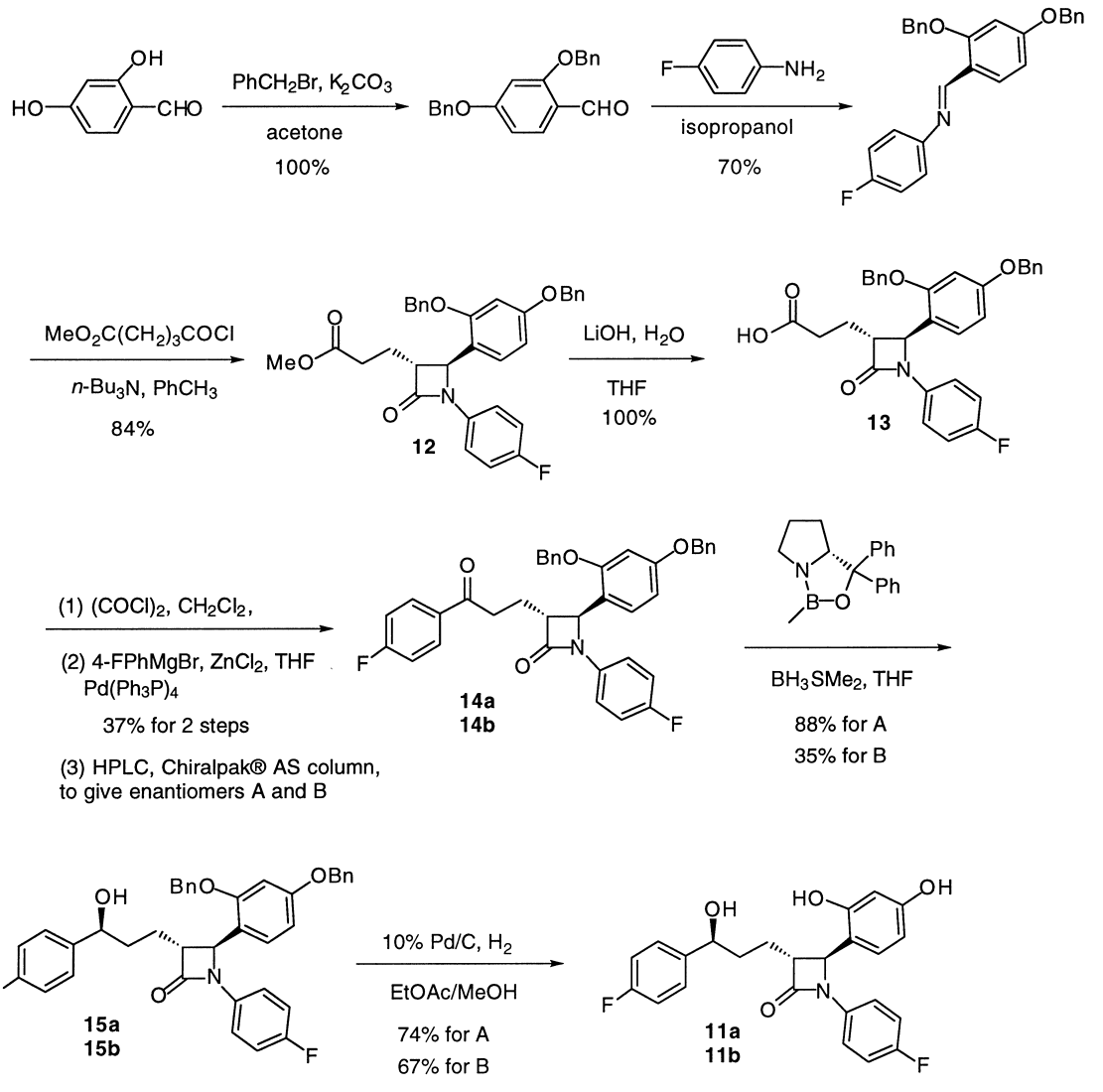
Biological Results

Cholesterol absorption inhibition was assessed in orally dosed, cholesterol-fed hamsters as previously described.[1] Both serum cholesterol and liver cholesterol ester levels were determined. ED_{50}s, the dose required to achieve a 50% reduction in liver cholesterol ester levels, were determined for select compounds.

In Table 1, the phenylpropyl substitution at C-3 was held constant while the N-1 and C-4 substituents were varied. Whereas the 2′,4′-dimethoxy substituted analogue



Scheme 1. Preparation of *trans*-2-azetidinones.



Scheme 2. Preparation of **11a** and **11b**.

5 was determined to be equipotent with **1**, the sterically congested 2′,4′,6′-trimethoxy substituted compound **6** was inactive. Substitution of hydroxy for the 2′-methoxy group of **5** as in compound **7** resulted in an increase in potency. In general, we found that incorporation of a 2′-hydroxy group significantly increased potency. 2-Hydroxy substituted analogues **7a**, **8a** and **9a** are almost an order of magnitude more potent than compounds **1a**, **2**, **3**, and **4a** which lack a 2′-hydroxy group.

During the course of these studies the potent cholesterol absorption inhibitor compound **10** (Sch 58235) was discovered (Table 2).[11] We were delighted to find that the addition of a 2′-hydroxy group to compound **10** (Sch 58235) as in compound **11a** increased potency eightfold.[11]

Conclusion

The addition of a 2′-hydroxy group to the C-4 phenyl ring of 2-azetidinone cholesterol absorption inhibitors increases potency, typically by an order of magnitude. This study suggests that 2′,4′-dihydroxyphenyl is the preferred C-4 substituent of 2-azetidinone cholesterol absorption inhibitors as evidenced by compounds **9a** and **11a**. We were gratified that the investigation of 2′,4′-substitution led to the discovery of **11a**, the most potent 2-azetidinone cholesterol absorption inhibitor yet identified. **11a** is 440-fold more potent in the cholesterol-fed hamster model than our initial lead compound **1a** (Sch 48461). However, since we are presently restricted to an in vivo assay, interpretation of the cholesterol absorption activity of the compounds in the tables may not be straight forward. The observed cholesterol absorption inhibition may be due to a compound's bioavailability and/or ease of conversion to active metabolites and not its intrinsic cholesterol absorption inhibition activity.

Experimental

Reagents were used as received unless stated otherwise. Anhydrous solvents were purchased from Aldrich Chemical Company. Melting points were taken on a Thomas Hoover Capillary Melting Point apparatus and are uncorrected. ^{1}H NMR spectra were taken on Varian 200, 300, 400 and 500 spectrometers and are reported in ppm downfield from internal tetramethylsilane. Elemental analyses were carried out on Leemann Labs CE440 elemental analyzer or a Fissions EA 1108 CHNS. IR Spectra were obtained on Perkin–Elmer 1320 or Nicolet MA-1 FT infrared spectrophotometers. TLC was performed on Merck silica plates (60F F_{254}, 250 μm) and are reported as R_f, (solvent system used to develop plate), method of visualization UV, Ce stain (dipping TLC plate into a mixture of $CeSO_4$ (4 g) concd H_2SO_4 (10 mL), H_2O (190 mL) and heating on a hot plate). Chromatography was performed on Selecto Scientific 40 Micron Flash silica gel (32–63). SGFC: Silica gel flash chromataography.

***trans*-1-(4-Methoxyphenyl)-3-(phenylpropyl)-4-(4-methoxyphenyl)-2-azetidinones[1,7] (1,1a,1b), *trans* 1-(4-methoxyphenyl)-3-(phenylpropyl)-4-(4-hydroxy-phenyl)-2-azetidinones[13] (4a) and *trans*-1-(4-fluorophenyl)-3(*S*)-[3(*S*)-hydroxy-3-(4-fluoro-phenyl)propyl]-4(*R*)-(4-hydroxyphenyl)-2-azetidinone[11] (10).** These compounds were prepared as previously described.

Method 1: Preparation of aldehydes

2,4-Dibenzyloxybenzaldehyde (16). Benzylbromide (45.2 mL, 380 mmol) was added to a mixture of 2,4-dihydroxy benzaldehyde (25 g, 181 mmol) and potassium carbonate (75 g, 543 mmol) in acetone (300 mL). The mixture was refluxed overnight. TLC (25% EtOAc/hexanes) indicated consumption of starting material. The mixture was filtered through Celite and the filter cake was well washed with acetone. The filtrate was concentrated. The resulting residue was redissolved in ethyl acetate, transferred to a separatory funnel, washed with sodium carbonate (satd), HCl (3 N) and brine, dried over anhydrous sodium sulfate and concentrated to give 60.5 g, (~100%) of the title compound as a solid of sufficient purity to be used in the subsequent step. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.10 (2H, s), 5.13 (2H, s), 6.59 (1H, d, J=2 Hz), 6.64 (1H, dd, J=2, 9 Hz), 7.39 (10H, m), 7.84 (1H, d, J=9 Hz), 10.4 (1H, s). MS (CI): M^+H, 319 (11), 89 (100).

In a similar fashion the following compounds were prepared

2-Methoxy-4-benzyloxybenzaldehyde (17). Prepared from 2-methoxy-4-hydroxybenzaldehyde. Yield: 88%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.89 (3H, s), 5.14 (2H, s), 6.54 (1H, s), 6.62 (1H, dd, J=2, 9 Hz), 7.41 (5H, m), 7.82 (1H, d, J=9 Hz), 10.3 (1H, s). MS (CI): M^+H, 243 (100). Purification: SGFC: 25% EtOAc/hexane TLC:(25% EtOAc/hexane, R_f=0.43), UV.

2-Benzyloxy-4-methoxybenzaldehyde (18). Prepared from 2-hydroxy-4-methoxybenzaldehyde. Yield: 88%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.85 (3H, s), 5.17 (2H, s), 6.51 (1H, s), 6.57 (1H, dd, J=2, 9 Hz), 7.41 (5H, m), 7.85 (1H, d, J=9 Hz), 10.4 (1H, s). MS (CI): M^+H, 243 (29), 91 (100). Purification: SGFC: 20% EtOAc/hexane TLC:(25% EtOAc/hexane, R_f=0.36), UV.

Method 2: Preparation of imines

***N*-(2-Methoxy-4-benzyloxybenzylidene)-4-fluoroaniline (19).** A mixture of 2-methoxy-4-benzyloxybenzaldehyde

17 (10.12 g, 41.8 mmol) and 4-fluoroaniline (3.96 mL, 41.8 mmol) in toluene (300 mL) was refluxed with azeotropic removal of water via a Dean–Strark trap for 40 h. NMR analysis of a small aliqout indicated imine formation was ~90% complete. The mixture was cooled to room temperature and concentrated in vacuo to give a brown–yellow solid. Recrystallizaion from ethyl acetate:hexane provide 10.5 g (75%) of the title compound as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.86 (3H, s), 5.13 (2H, s), 6.56 (1H, d, J = 2 Hz), 6.68 (1H, d, J = 9 Hz), 7.06 (2H, m), 7.20 (2H, m), 7.42 (5H, m), 8.19 (1H, d, J = 9 Hz), 8.80 (1H, s). MS (CI): M^+H, 336 (27), 257 (68), 75 (100).

In a similar fashion the following imines were prepared.

***N*-(2-Benzyloxy-4-methoxybenzylidene)-4-fluoroaniline (20).** Prepared from 2-benzyloxy-4-methoxybenzaldehyde **18** and 4-fluoroaniline. Yield: 100%, light-brown solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.85 (3H, s), 5.15 (2H, s), 6.53 (1H, d, J = 2 Hz), 6.62 (1H, d, J = 9 Hz), 7.05 (2H, m), 7.22 (4H, m), 7.40 (3H, m), 8.18 (1H, bs), 8.84 (1H, s). MS (CI): M^+H, 336 (39), 257 (96), 91 (100).

***N*-(2-Benzyloxy-4-methoxybenzylidene)-aniline (21).** Prepared from 2-benzyloxy-4-methoxybenzaldehyde **18** and aniline. Yield: 85%, light-brown solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.85 (3H, s), 5.15 (2H, s), 6.54 (1H, d, J = 2 Hz), 6.62 (1H, d, J = 9 Hz), 7.21 (2H, m), 7.39 (8H, m), 8.22 (1H, bs), 8.87 (1H, s). MS (CI): M^+H, 336 (39), 257 (96), 91 (100).

***N*-(2,4-Dibenzyloxybenzylidene)-aniline (22).** Prepared from 2,4-dibenzyloxybenzaldehyde **16** and aniline. Yield: 83%, yellow solid. 1H NMR ($CDCl_3$, 400 MHz) δ 5.11 (2H, s), 5.12 (2H, s), 6.62 (1H, d, J = 2 Hz), 6.70 (1H, dd, J = 2, 9 Hz), 7.20 (3H, m), 7.39 (12H, m), 8.19 (1H, bs), 8.87 (1H, s). Purification: recrystallized from ethyl acetate/hexanes.

***N*-(2-benzyloxy-4-methoxybenzylidene)-4-methoxyaniline (23).** Prepared from 2-benzyloxy-4-methoxybenzaldehye **18** and 4-methoxyaniline. Yield: 100%, yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.82 (3H, s), 3.85 (3H, s), 5.15 (2H, s), 6.53 (1H, d, J = 2 Hz), 6.63 (1H, d, J = 2, 9 Hz), 6.91 (2H, d, J = 9 Hz), 7.22 (2H, d, J = 9 Hz), 7.41 (5H, m), 8.21 (1H, bs), 8.90 (1H, s). Used without further purification.

***N*-(2,4,6-trimethoxybenzylidene)-4-methoxyaniline (24).** Prepared from 2,4,6-trimethoxybenzaldehyde and 4-methoxyaniline. Yield: 100%, yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.88 (3H, s), 3.92 (3H, s), 3.94 (6H, s), 6.22 (2H, s), 6.97 (2H, d, J = 9 Hz), 7.28 (2H, d, J = 9 Hz), 8.83 (1H, s). Used without further purification.

***N*-(2,4-dimethoxybenzylidene)-4-methoxyaniline (25).** Prepared from 2,4-dimethoxybenzaldehyde and 4-methoxyaniline. Yield: 100%, yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.88 (3H, s), 3.93 (3H, s), 3.94 (3H, s), 6.54 (2H, d, J = 2 Hz), 6.67 (1H, m), 6.98 (2H, d, J = 9 Hz), 7.30 (2H, d, J = 9 Hz), 8.20 (1H, d, J = 9 Hz), 8.90 (1H, s). Used without further purification.

Method 3: Preparation of imines

***N*-(2,4-Dibenzyloxybenzylidene)-4-fluoroaniline (26).** A mixture of 2,4-dibenzyloxybenzaldehyde **16** (57.6 g, 181 mmol) and 4-fluoroaniline (17.2 mL, 181 mmol) in isopropanol (400 mL) was heated to reflux, cooled to room temperature, and diluted with hexanes and allowed to stand overnight. The resulting precipitate was collected via vacuum filtration, washed with cold hexanes and dried under vacuum to give 70.4 g (95%) of a gray/white solid. ^{1}H NMR indicates the solid contained ~20% isopropanol. The solid was recrystallized from ethyl acetate/hexanes to provide 52 g (70%) of the title compound free of isopropanol. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.10 (2H, s), 5.11 (2H, s), 6.61 (1H, d, J = 2 Hz), 6.68 (1H, dd, J = 2, 9 Hz), 7.04 (2H, m), 7.16 (2H, m), 7.38 (10H, m), 8.13 (1H, m), 8.83 (1H, s). MS (CI): M^+H, 412 (100).

Method 4: Preparation of β-lactams via the ketene–imine condensation

***trans*-1-(4-Fluorophenyl)-3-(phenylpropyl)-4-(4-methoxy-2-benzyloxyphenyl)-2-azetidinone (27).** 5-Phenylvaleryl chloride (5.5 mL, 5.5 mmol, 1 M in toluene,) was added to a room temperature solution of *N*-(2-methoxy-4-benzyloxybenzylidene)-4-fluoroaniline **19** (1.23 g, 3.67 mmol), *n*-tributylamine (1.75 mL, 7.33 mmol) and anhydrous toluene (50 mL). The mixture was heated to reflux overnight. TLC (25% ethyl acetate/hexanes) indicated consumption of starting materials. The mixture was cooled to room temperature, 1 M HCl was added, the resulting mixture was stirred for 15 min, transferred to a separatory funnel, diluted with ethyl acetate, washed with 1 M HCl, $NaHCO_3$ (satd), water and brine, dried over anhydrous sodium sulfate, and concentrated to an oil. The residue was redissolved in 50% THF/MeOH, cooled to 0 °C and treated with sodium borohydride (0.28 g, 7.5 mmol) to remove any aldehyde liberated upon workup of unreacted imine. The aldehydes tend to have R_fs similar to 2-azetidinones, reduction to the alcohol usually simplifies purification. After 30 min, NH_4Cl (satd) was added. The mixture was transferred to a separatory funnel and extracted with ethyl acetate. The extracts were combined, washed with water and brine, dried over anhydrous sodium sulfate and concentrated onto enough silica gel such that a free flowing powder was obtained. The resulting powder was loaded

onto a chromatography column prepacked with silica gel and 20% ethyl acetate/hexane. Elution with the same solvent provided 1.5 g (83%) of the title compound. TLC: (25% EtOAc/hexane, $R_f = 0.45$), UV. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.86 (3H, m), 1.95 (1H, m), 2.65 (2H, t, $J = 7.0$ Hz), 3.09 (1H, m), 3.80 (3H, s), 4.95 (1H, d, $J = 2$ Hz), 5.03 (2H, s), 6.50 (1H, dd, $J = 2$, 9 Hz), 6.57 (1H, d, $J = 2$ Hz), 6.94 (2H, m), 7.06 (1H, d, $J = 9$ Hz), 7.19 (3H, m), 7.27 (5H, m), 7.39 (4H, m). MS (CI): M^+H, 496 (100).

Method 5: Preparation of phenols by debenzylation

***trans*-1-(4-Fluorophenyl)-3-(phenylpropyl)-4-(4-methoxy-2-hydroxyphenyl)-2-azetidinone (28).** *trans*-1-(4-Fluorophenyl)-3-(phenylpropyl)-4-(4-methoxy-2-benzyloxyphenyl)-2-azetidinone **27** (0.16 g, 0.32 mmol) was dissolved in ethyl acetate (15 mL) and diluted with methanol (15 mL) and purged with nitrogen. Ten percent palladium on carbon (0.016 g) was added, the resulting mixture was purged with hydrogen and stirred under a balloon of hydrogen overnight. TLC (25% ethyl acetate/hexanes) indicated consumption of starting material. The mixture was filtered through celite, and the filtercake was well washed with 50% THF/MeOH. The filtrate was concentrated to provide 0.121 g (92%) of the title compound as a yellow foam. TLC: (25% EtOAc/hexane, $R_f = 0.17$, UV). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.85(3H, m), 1.96 (1H, m), 2.64 (2H, t, $J = 7.2$ Hz), 3.10 (1H, m), 3.79 (3H, s), 4.94 (1H, d, $J = 2$ Hz), 6.34 (1H, dd, $J = 2$, 8 Hz), 6.45 (1H, d, $J = 2$ Hz), 6.95 (3H, m), 7.17 (3H, m), 7.26 (4H, m). HRMS (FAB): M^+H, $C_{23}H_{25}NO_3F$, calcd 406.1818, found 406.1806. The following compound were prepared by combination of the above methods as indicated.

***trans*-1-(4-Methoxyphenyl)-3-(phenylpropyl)-4-(4-methoxy-2-hydroxy-phenyl)-2-azetidinone (7, 7a, and 7b).** *trans*-1-(4-Methoxyphenyl)-3-(phenylpropyl)-4-(4-methoxy-2-benzyloxyphenyl)-2-azetidinone **29** was prepared from *N*-(2-benzyloxy-4-methoxybenzylidene)-4-methoxyaniline **23** and 5-phenylvaleryl chloride as described in method 4. Yield: 93% oil. Purification: SGFC: 30% EtOAc/hexane TLC: (30% EtOAc/hexane, $R_f = 0.3$), Ce stain, UV. Yield: 93%. ^{1}H NMR ($CDCl_3$, 400 Mhz) (1.77 (4H, m), 2.52 (2H, t, $J = 7$ Hz), 3.06 (1H, m), 3.75 (3H, s), 3.77 (3H, s), 5.01 (1H, d, $J = 2$ Hz), 5.08 (2H, dd, $J = 12$, 20 Hz), 6.43 (1H, dd, $J = 2$, 9 Hz), 6.57 (1H, d, $J = 2$ Hz), 6.78 (2H, dd, $J = 2$, 7 Hz), 7.08 (3H, m), 7.20 (5H, m), 7.38 (5H, m). HRMS (FAB): M^+, $C_{33}H_{33}NO_4$, calcd 507.241, found 507.2395. The enantiomers of **29** were resolved on a preparative Chiracel OD column (3% isopropanol/hexanes, 65 mL/min). Enantiomeric purity was verified on a analytical Chiracel AS column (5% isopropanol/hexane, 1.0 mL/min), **29a** $R_t = 39.7$ min, **29b** $R_t = 51.1$ min. Independent hydrogenation of **29**, **29a**, and **29b**, as described in method 5, respectfully provided 7: Yield:100%, yellow oil, **7a**: Yield: 100%, foam and **7b**: Yield 100%, oil. TLC: (25% EtOAc/hexane, $R_f = 0.16$, UV) ^{1}H NMR ($CDCl_3$, 400 Mhz) δ 1.85 (3H, m), 1.96 (1H, m), 2.64 (2H, t, $J = 7$ Hz), 3.16 (1H, m), 3.74 (3H, s), 3.75 (3H, s), 4.93 (1H, d, $J = 2$ Hz), 6.35 (1H, d, $J = 2$ Hz), 6.44 (1H, dd, $J = 2$, 8 Hz), 6.78 (2H, d, $J = 9$ Hz), 7.10 (1H, d, $J = 9$ Hz), 7.17 (2H, m), 7.25 (5H, m). HRMS (FAB): M^+H, $C_{26}H_{27}NO_4$, calcd 417.1940, **7** found 417.1941, **7a** found 417.1937, **7b** found 417.1933.

***trans*-1-(4-Methoxyphenyl)-3-(phenylpropyl)-4-(2,4,-dimethoxyphenyl)-2-azetidinone (5).** Prepared from *N*-(2,4-dimethoxybenzylidene)-4-methoxyaniline **25** and 5-phenylvaleryl chloride as described in method 4. Yield: 88%, yellow oil. ^{1}H NMR ($CDCl_3$, 300 Mhz) δ 1.93 (4H, m), 2.63 (2H, m), 3.18 (1H, m), 3.82 (3H, s), 3.85 (3H, s), 3.87 (3H, s), 4.94 (1H, d, $J = 2$ Hz), 6.37 (1H, d, $J = 2$ Hz), 6.45 (1H, m), 6.79 (2H, d, $J = 9$ Hz), 7.08 (1H, d, $J = 8$ Hz), 7.21 (8H, m). HRMS (EI): M^+, $C_{27}H_{30}NO_4$, calcd 431.2097, found 431.2075.

***trans*-1-(4-Methoxyphenyl)-3-(phenylpropyl)-4-(2,4,6-trimethoxyphenyl)-2-azetidinone (6).** Prepared from *N*-(2,4,6-trimethoxybenzylidene)-4-methoxyaniline **24** and 5-phenylvaleryl chloride as dexcribed in method 4. Yield: 30%, orange oil. ^{1}H NMR ($CDCl_3$, 300 Mhz) δ 1.85 (3H, m), 1.96 (1H, m), 2.69 (2H, t, $J = 8$ Hz), 3.78 (1H, m), 3.84 (6H, s), 3.85 (3H, s), 5.25 (1H, d, $J = 2$ Hz), 6.16 (2H, s), 6.80 (2H, d, $J = 9$ Hz), 7.27 (10H, m). HRMS (EI): M^+, $C_{28}H_{31}NO_5$, calcd 461.2202, found 461.2210.

***trans*-1-(4-Fluorophenyl)-3-(phenylpropyl)-4-(2,4-dihydroxyphenyl)-2-azetidinone (8a and 8b).** Ketene–imine condensation of *N*-(2,4-dibenzyloxybenzylidene)-4-fluoroaniline **26** and 5-phenylvaleryl chloride as described in method 4 provided *trans*-1-(4-fluorophenyl)-3-(phenylpropyl)-4-(2,4-dibenzyloxyphenyl)-2-azetidinone **30**. Yield: 56%. ^{1}H NMR ($CDCl_3$, 400 Mhz) δ 1.82 (4H, m), 2.52 (2H, m), 3.10 (1H, m), 5.07 (5H, m), 6.54 (1H, d), 6.61 (1H, s), 6.66 (1H, s), 6.95 (2H, m), 7.07 (2H, m), 7.25 (5H, m), 7.39 (10H, m). MS (CI), M + H: 572 (100). Purification: SGFC: 18% EtOAc/hexane. TLC:(25% EtOAc/hexane, $R_f = 0.47$), UV. **30** was resolved on a preparative Chiracel® OD column (10% isopropanol/hexanes, 70 mL/min). **30a** $R_t = 44.5$ min. **30b** $R_t = 52.8$ min. Subsequent idependent hydrogenation of each enantiomer as described in method 5 provided **8a**: Yield: 100%, yellow foam and **8b**: yield: 100%, oil. TLC:(25% EtOAc/hexane, $R_f = 0.10$, UV). ^{1}H NMR ($CDCl_3$, 400 Mhz) δ 1.83 (3H, m), 1.96 (1H, m), 2.62 (2H, t, $J = 7$ Hz), 3.19 (1H, m), 4.91 (1H, d, $J = 2$ Hz), 6.31 (1H, s), 6.35 (1H, dd, $J = 2$, 8 Hz), 6.91 (2H, m), 7.02 (1H, d, $J = 8$ Hz), 7.15 (3H, m), 7.26 (4H, m).

HRMS (FAB): M^+H, $C_{24}H_{23}NO_3F$, calcd 392.1662, **8a**: found 392.1661, **8b**: found 392.1657.

***trans*-1-Phenyl-3-(3-phenylpropyl)-4-(2,4-dihydroxyphenyl)-2-azetidinone (9a and 9b).** Ketene–imine condensation of *N*-(2,4-dibenzyloxybenzylidene)-aniline **22** and 5-phenylvaleryl chloride as described in method 4 provided *trans*-1-phenyl-3-(3- phenylpropyl) - 4 - (2, 4 - dibenzyloxyphenyl)-2-azetidinone **31**. Yield: 60%. ^{1}H NMR ($CDCl_3$, 400 Mhz) δ 1.81 (4H, m), 2.52 (2H, t, $J=7$ Hz), 3.09 (1H, m), 5.07 (5H, m), 6.51 (1H, dd, $J=2$, 9 Hz), 6.67 (1H, s), 7.23 (21H, m). MS (CI), M + H: 554 (100). Purification: SGFC: 18% EtOAc/hex. TLC:(25% EtOAc/hexane, $R_f=0.48$), UV. **31** was resolved on a preparative Chiracel OD column (7% isopropanol/hexanes). Enantiomeric purity was verified on an analytical Chiracel® OD column (7% isopropanol/hexanes, 1.0 mL/min) **31a** $R_t=18.49$ min. **31b** $R_t=21.65$ min. Subsequent independent hydrogenation of each enantiomer as described in method 5 provided **9a**: Yield: 100%, oil and **9b**: Yield 100%, oil. TLC: (25% EtOAc/hexane, $R_f=0.20$, UV). ^{1}H NMR ($CDCl_3$, 400 Mhz) δ 1.86 (3H, m), 1.97 (1H, m), 2.64 (2H, t, $J=7$ Hz), 3.16 (1H, m), 4.95 (1H, d, $J=2$ Hz), 6.34 (2H, m), 7.03 (2H, m), 7.17 (2H, m), 7.26 (7H, m). HRMS (FAB): M^+H, $C_{24}H_{24}NO_3$, calcd 374.1756, **9a**: found 374.1759, **9b**: found 374.1751.

***trans*-Methyl-3-(3-[2-oxo-4-(2,4-dibenzyloxyphenyl)-1-(4-fluorophenyl)-azetidinyl]propanoate (12).** Methyl glutaryl chloride (4.0 mL, 29 mmol) was added to a solution of the *N*-(2,4-dibenzyloxybenzylidene)-4-fluoroaniline **26** (7.95 g, 19.3 mmol) and *n*-tributylamine (9.2 mL, 38.6 mmol) in anhydrous toluene (200 mL) and the mixture was refluxed overnight. the mixture was cooled to room temperature, quenched with HCl (1 M), rapidly stirred for 15 min, transferred to a separatory funnel, diluted with ethyl acetate, washed with HCl (1 M), sodium bicarbonate (satd), water and brine, dried over anhydrous sodium sulfate, and concentrated to give 12.2 g of a dark oil. The oil was redissolved in ethyl acetate, concentrated onto enough flash grade silica gel such that a free flowing powder was obtained. The powder was loaded onto a chromatography column packed with silica gel and 25% ethyl acetate/hexanes. Elution with the same solvent gave 8.8 g (84%) of the title compound. ^{1}H NMR indicates the product is all *trans*. ^{1}H NMR ($CDCl_3$, 400 Mhz) δ 2.14 (2H, m), 2.49 (2H, m), 3.11 (1H, dt, $J=2$, 8 Hz), 3.61 (3H, s), 4.99 (1H, d, $J=2$ Hz), 5.01 (2H, s), 5.10 (2H, s), 6.51 (1H, dd, $J=2$, 8 Hz), 6.66 (1H, d, $J=2$ Hz), 6.93 (2H, app. t, $J=9$ Hz), 7.06 (1H, d, $J=9$ Hz), 7.23 (2H, m), 7.38 (10H, m). **MS** (FAB): M + H 540 (100).

***trans*-3-(3-[2-Oxo-4-(2,4-dibenzyloxyphenyl)-1-(4-fluorophenyl)-azetidinyl]propanoic acid (13).** Lithium hydroxide (0.82 g, 19.6 mmol) was dissolved in water (20 mL) and added to a room temperature solution of *trans*-methyl 3-(3-[2-oxo-4-(2,4-dibenzyloxyphenyl)-1-(4-fluorophenyl)-azetidinyl]propanoate **12** (8.8 g, 16.3 mmol) in THF (60 mL). TLC (30% EtOAc/hexanes) after ~6 h indicated consumption of starting material. The reaction was quenched with HCl (1 M), transferred to a separatory funnel, diluted with ethyl acetate, washed with HCl (1 M), water and brine, dried over anhydrous sodium sulfate, and concentrated to give 8.66 g of the title compound of sufficient purity to be used without further purification. ^{1}H NMR ($CDCl_3$, 400 Mhz) δ 2.13 (2H, m), 2.54 (2H, m), 3.12 (1H, dt, $J=2$, 6 Hz), 4.99 (1H, d, $J=2$ Hz), 5.01 (2H, s), 5.09 (2H, s), 6.50 (1H, dd, $J=2$, 9 Hz), 6.66 (1H, d, $J=2$ Hz), 6.94 (2H, app. t, $J=9$ Hz), 7.05 (1H, d, $J=8$ Hz), 7.24 (2H, m), 7.36 (10H, m). **MS** (FAB): M + H 526 (100).

***trans*-1-(4-Fluorophenyl)-3-[3-oxo-3-(4-fluorophenyl)propyl]-4-(2,4-dibenzyloxyphenyl)-2-azetidinone (14, 14a, and 14b).** Oxalyl chloride (1.85 mL, 21.2 mmol) was added to a 0 °C solution of the *trans*-3-(3-[2-oxo-4-(2,4-dibenzyloxyphenyl)-1-(4-fluorophenyl)-azetidinyl]propanoic acid **13** (8.57 g, 16.3 mmol) in methylene chloride (50 mL). The mixture was allowed to warm to room temperature overnight. The mixture was concentrated in vacuo and dried under vacuum. The residue was redissolved in THF (50 mL), cooled to 0 °C and transferred via cannula to a 0 °C solution prepared by the sequential addition 4-fluorophenylmagnesium bromide (24.5 mL, 24.5 mmol, 1 M in THF, Aldrich) and palladium (II) tetrakistriphenylphosphine (0.57 g, 0.49 mmol) to a solution of anhydrous zinc chloride (4.0 g, 29.3 mmol) in THF (50 mL). TLC (2.5% EtOH/0.5% HOAc/CH_2Cl_2) after 2 h indicated consumption of starting acid. The reaction was quenched with HCl (2 M), transferred to a separatory funnel, diluted with ethyl acetate, washed with HCl (2 M), water and brine, dried over anhydrous sodium sulfate, and concentrated onto enough flash grade silica gel such that a free flowing powder was obtained. The powder was loaded onto a chromatography column packed with silica gel and 20% ethyl acetate/hexanes. Elution with the same solvent gave 1.05 g (62%) of the title compound. **14** was resolved on a preparative Chiralpak® AS column (40% isopropanol/hexanes) to provide *trans*-1-(4-fluorophenyl)-3(*S*)-[3-oxo-3-(4-fluorophenyl)propyl]-4(*R*)-(2,4-dibenzyloxyphenyl)-2-azetidinone **14b** (0.46 g), further elution with 100% isopropanol failed to elute *trans*-1-(4-fluorophenyl)-3(*R*)-[3-oxo-3-(4-fluorophenyl)propyl]-4(*S*)-(2,4-dibenzyloxyphenyl)-2-azetidinone **14a**. Finally elution with 100% ethanol provided enatiomer **14a** (0.42 g). Enantiomeric purity was determined on a Chiralpak® AS analytical column (40% isopropanol/hexanes, 0.8 mL/min). Enantiomer **14b** $R_t=15.7$ min, enantiomer **14a** $R_t=49.8$ min and on an analytical Chiracel® OD column (30% isopropanol/hexanes, 1.0 mL/min).

Enantiomer **14b** $R_t = 32.8$ min, enantiomer **14a** $R_t = 23.2$ min. (Note reversal of elution of enantiomers **14a** and **14b**.) The Chiracel® OD column gave better peak shape for the determination of enantiomeric purity and the Chiralpak® AS column gave better separation of the two enantiomers. ^{1}H NMR ($CDCl_3$, 400 Mhz) δ 2.22 (1H, m), 2.32 (1H, m), 3.16 (3H, m), 5.01 (2H, s), 5.05 (1H, d, $J = 2$ Hz), 5.09 (2H, s), 6.51 (1H, dd, $J = 2$, 9 Hz), 6.66 (1H, d, $J = 2$ Hz), 6.94 (2H, app. t, $J = 9$ Hz), 7.08 (3H, m), 7.32 (12H, m), 7.90 (2H, dd, $J = 6$, 8 Hz). **MS** (FAB): M + H 604 (100).

***trans*-1-(4-Fluorophenyl)-3(*R*)-[3(*S*)-hydroxy-3-(4-fluorophenyl)propyl]-4(*S*)-(2,4-dibenzyloxyphenyl)-2-azetidinone (15a).** Trimethylboroxine (0.2 mL, 1.4 mmol) was added to a solution of (*S*)-α,α-diphenyl-2-pyrrolidinemethanol (0.18 g, 0.71 mmol) in anhydrous toluene (3 mL). The mixture was stirred for 30 min and a white precipitate formed. A short path distillation head was added to the reaction flask, and the toluene was distilled under nitrogen. Toluene (4 mL) was added to the reaction flask and was again distilled. This process was repeated and the residue was dried under vacuum overnight. The white residue was redissolved in anhydrous toluene (8 mL) to yield a 0.09 M solution of oxazaborolidine catalyst.

The oxazaborolidine catalyst (4 mL, 0.09 M in toluene) was added to a 0 °C solution of *trans*-1-(4-fluorophenyl)-3(*R*)-[3(*S*)-hydroxy-3-(4-fluorophenyl)propyl]-4(*S*)-(2,4-dibenzyloxyphenyl)-2-azetidinone **14a** (1.37 g, 2.26 mmol) in THF (15 mL). Borane dimethylsulfide (1.19 mL, 2 M in THF) was added slowly via syringe over 40 min. Reaction color changes from a clear yellow to a clear gray/green. TLC (30% EtOAc/hexanes) after an additional 15 min indicates the reduction is complete. The reaction was quenched with methanol and allowed to stir for 30 min (gas evolution), transfered to a separatory funnel, diluted with ethyl acetate, washed with HCl (1 M), sodium bicarbonate (satd), water and brine, dried over anhydrous sodium sulfate, and concentrated onto enough flash grade silica gel such that a free flowing powder was obtained. The powder was loaded onto a chromatography column packed with silica gel and 30% ethyl acetate/hexanes. Elution with the same solvent gave 1.21 g (88%) of the title compound as a clear foam. ^{1}H NMR ($CDCl_3$, 400 Mhz) δ 1.84 (4H, m), 3.07 (1H, m), 4.57 (1H, m), 4.99 (1H, d, $J = 2$ Hz), 5.02 (2H, s), 5.08 (2H, m), 6.51 (1H, dd, $J = 2$, 8 Hz), 6.67 (1H, d, $J = 2$ Hz), 6.95 (4H, m), 7.06 (1H, d, $J = 9$ Hz), 7.18 (2H, m), 7.23 (2H, m), 7.38 (10H, m). HRMS (FAB): M^+H, $C_{38}H_{34}NO_4F_2$, calcd 606.2456, found 606.2451.

***trans*-1-(4-Fluorophenyl)-3(*S*)-[3(*S*)-hydroxy-3-(4-fluorophenyl)propyl]-4(*R*)-(2,4-dibenzyloxyphenyl)-2-azetidinone (15b).** Reduction of **14b** was carried out in a similar fashion to provide **15b** 0.52 g, (35%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.85 (4H, m), 3.11 (1H, m), 4.57 (1H, m), 5.00 (1H, d, $J = 2$ Hz), 5.02 (2H, s), 5.07 (2H, m), 6.52 (1H, dd, $J = 2$, 8 Hz), 6.67 (1H, d, $J = 2$ Hz), 6.95 (4H, m), 7.07 (1H, d, $J = 9$ Hz), 7.17 (2H, m), 7.23 (2H, m), 7.38 (10H, m).

***trans*-1-(4-Fluorophenyl)-3(*R*)-[3(*S*)-hydroxy-3-(4-fluorophenyl)propyl]-4(*S*)-(2,4-dihydroxyphenyl)-2-azetidinone (11a).** A suspension of *trans*-1-(4-fluorophenyl)-3(*R*)-[3(*S*)-hydroxy-3-(4-fluorophenyl)propyl]-4(*S*)-(2,4-dibenzyloxyphenyl)-2-azetidinone **15a** (0.75 g, 1.24 mL) and 10% Pd/C (0.08 g) in a mixture of methanol (20 mL) and ethyl acetate (20 mL) was hydrogenated on a Parr apparatus at 60 pi overnight. TLC (50% ethyl acetate/hexane's) indicated on a trace of product. The mixture was filtered through Celite, concentrated, redissolved in methanol (20 mL) and ethyl acetate (20 mL). 10% Pd/C (0.18 g) was added and the mixture was hydrogenated on a Parr apparatus at 60 psi overnight. TLC indicated consumption of **15a** and formation of one major spot. The mixture was filtered through Celite, the filter cake was well washed with 50% MeOH/CH_2Cl_2. The filtrate was concentrated onto enough flash grade silica gel such that a free flowing powder was obtained. The powder was loaded onto a chromatography column packed with silica gel and 50% ethyl acetate/hexanes. Elution with 50–75% ethyl acetate/hexanes gave 0.39 g (74%) of the title compound as a clear foam. ^{1}H NMR ($CDCl_3$/CD3OD, 400 Mhz) δ 1.92 (4H, m), 3.10 (1H, m), 4.64 (1H, m), 4.96 (1H, d, $J = 2$ Hz), 6.28 (1H, dd, $J = 2$, 8 Hz), 6.33 (1H, d, $J = 2$ Hz), 6.94 (5H, m), 7.26 (4H, m). HRMS (FAB): M + H, $C_{24}H_{22}NO_4F_2$, calcd 426.1517, found 426.1503.

***trans*-1-(4-Fluorophenyl)-3(*S*)-[3(*S*)-hydroxy-3-(4-fluorophenyl)propyl]-4(*R*)-(2,4-dihydroxyphenyl)-2-azetidinone (11b).** In a similar manner enantiomer **15b** was hydrogenated to give **11b** 0.237 g (67%) of a clear foam. ^{1}H NMR ($CDCl_3$/CD_3OD, 400 Mhz) δ 1.78 (1H, m), 1.95 (3H, m), 3.09 (1H, m), 4.62 (1H, app. t, $J = 6$ Hz), 4.94 (1H, d, $J = 2$ Hz), 6.30 (1H, dd, $J = 2$, 8 Hz), 6.33 (1H, d, $J = 2$ Hz), 6.94 (5H, m), 7.24 (4H, m). HRMS (FAB): M + H, $C_{24}H_{22}NO_4F_2$, calcd 426.1517, found 426.1516.

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