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Conversion of α-Amino Acids into Bioactive *o*-Aminoalkyl Resorcylates and Related Dihydroxyisoindolinones

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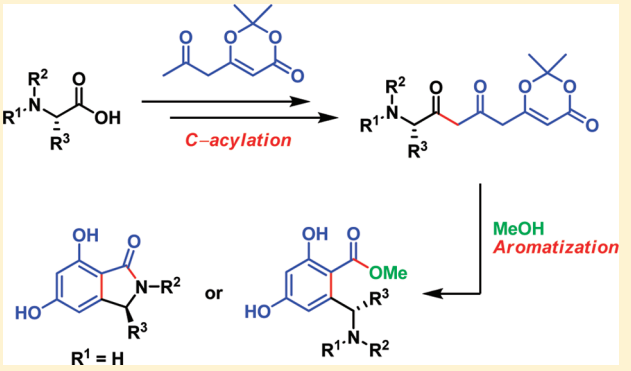
Supporting Information

ABSTRACT: The synthesis of biologically active *o*-aminoalkyl resorcylates and related dihydroxyisoindolinones from functionalized α-amino acids without the use of phenolic protection is described. The key aminoalkyl-diketo-dioxinone intermediates were prepared utilizing a crossed Claisen condensation reaction in the presence of diethylzinc. The aromatic unit was constructed via late stage cyclization and aromatization, and subsequent modification provided the novel resorcylates which showed activity against a selection of receptors and kinases, including 5-HT and CDK.



INTRODUCTION

The resorcylic acid lactone (RAL) family of natural products consists of a diverse variety of biologically active compounds bearing the resorcylate unit **1** (Figure 1).[1] Within this family are the 14-membered resorcylic macrolides (*S*)-zearalenone (**2**), an estrogen agonist,[2] radicicol (**3**), a HSP-90 inhibitor (20 nM),[3] aigialomycin D (**4**), a CDK (cyclin-dependent kinase) 1 and 5 inhibitor (6 μM)[4] and antimalarial (18 μM),[5] and LL-Z1640−2 (**5**), a TAK-1 kinase inhibitor (8.1 nM).[6]

Small differences in macrocyclic ring functionality have resulted in diverse biological effects, and in consequence of this, we sought to synthesize additional classes of resorcylates from readily available building blocks, as novel, potentially active drug-like templates. Having recently published the biomimetic syntheses of several macrocyclic resorcylate natural products by late stage aromatization reactions from triketo-ester precursors,[7] we sought to employ this methodology,[8] to generate resorcylate amino acid derivatives as potentially novel pharmacophoric classes. Herein, we report the conversion of simple α-amino acids into resorcylates bearing *o*-1-aminoalkyl residues both as potential biologically active hit structures and as templates for the synthesis of new classes of potential pharmaceuticals.

We considered that the amino acid-derived resorcylates **6** (Scheme 1) with variable functionality (R^1, R^2, R^3) at C-6, should be available from the C-acylation of the dianion derived from dioxinone **9**, with the Weinreb amides **8**, and aromatization of the resultant diketo-dioxinones **7**. In turn, amides **8** should be available from amino acid derivatives **10**. Clearly such precursor

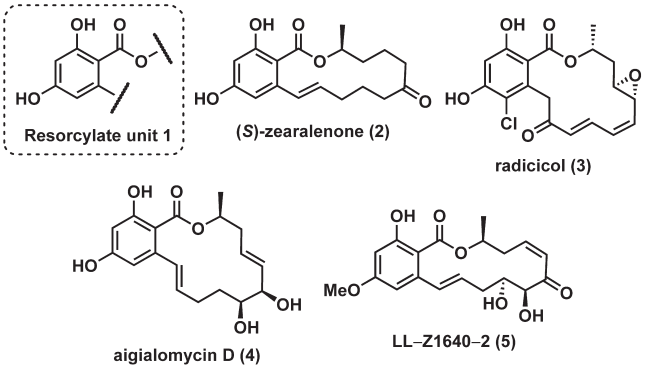


Figure 1. Resorcylate unit and related natural products.

acids **10** would include derivatives of the common α-amino acids of either antipodal series.

RESULTS AND DISCUSSION

The *N*-Boc protected α-amino acids **11a**−**f**, and freshly prepared (*S*)-1-(*tert*-butyldimethylsilyl)-4-oxoazetidine-2-carboxylic acid (**11g**)[9] and (±)-*cis*-5-(ethoxycarbonyl)-1-benzylpyrrolidine-2-carboxylic acid (**11h**)[10] (both in two steps from commercially available precursors), were subjected to amide

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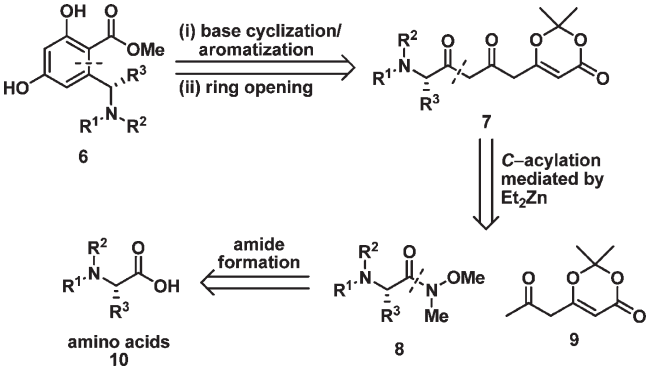
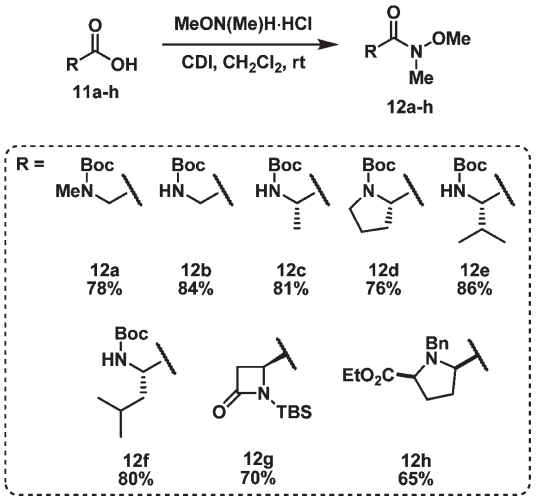
Scheme 1. Retrosynthesis of *o*-Aminoalkyl-Functionalized Resorcylates



Scheme 2. Synthesis of α-Amino Acid-Related Weinreb Amides

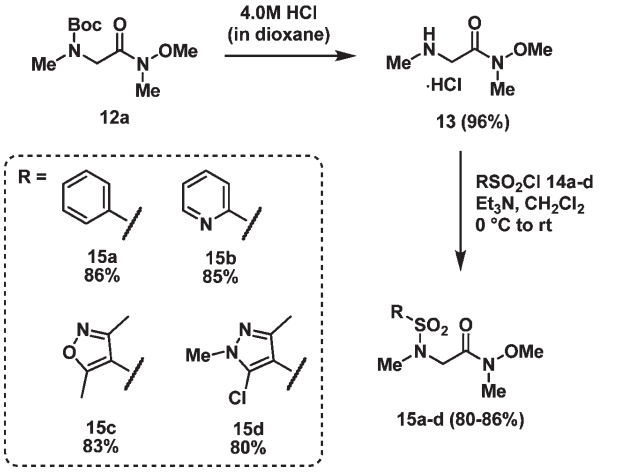


coupling with *N*,*O*-dimethylhydroxylammonium chloride under mild conditions using carbonyl diimidazole (CDI),[11] to give the sarcosine **12a**, glycine **12b**, L-alanine **12c**, L-proline **12d**, L-valine **12e**, L-leucine **12f**, (*S*)-1-(*tert*-butyldimethylsilyl) *β*-lactam **12g**, and cis-2,5-substituted pyrrolidine **12h**-derived Weinreb amides in 65−86% yield (Scheme 2).[12]

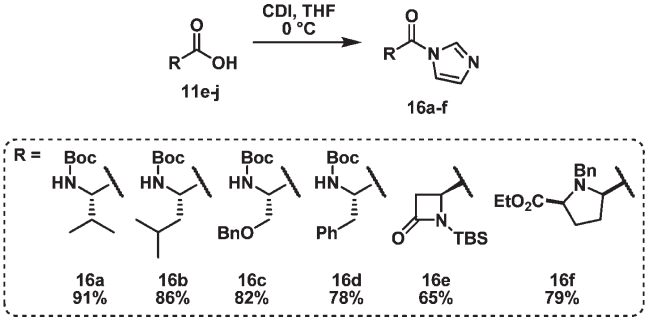
Alternative resorcylate precursors containing an aromatic or heteroaromatic sulfonamide unit were also synthesized from Weinreb amide **13** (Scheme 3). Carbamate **12a** was *N*-Boc deprotected under acidic conditions to give hydrochloride salt **13** in 96% yield. Subsequent reaction with the appropriate arene or heteroarene sulfonyl chloride **14a**−**d** using triethylamine as base gave the Weinreb amide sulfonamides with phenyl- **15a**, 2-pyridyl- **15b**, 3,5-dimethyl-4-isoxazolyl- **15c**, and 1,3-dimethyl-5-chloro-4-pyrazoyl- **15d** substituents in 80−86% yield (Scheme 3).

For the more elaborately functionalized amino acids previously mentioned (**11e**−**j**, Scheme 2), an alternative process was employed because of the somewhat low reactivity of the Weinreb amides in subsequent C-acylation reactions, relative to *N*-acyl imidazoles (Scheme 4). N-Protected-amino acids **11e**−**j** were allowed to react with carbonyl diimidazole at 0 °C,[13] to directly provide the corresponding acyl imidazoles **16a**−**f** in 65−91% yield (Scheme 4).[14]

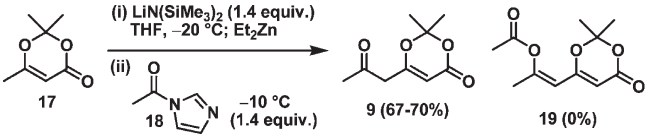
Scheme 3. Synthesis of Functionalized α-Sulfonamido Weinreb Amides via Key Coupling Intermediate 13



Scheme 4. Synthesis of Functionalized Imidazole Derivatives



Scheme 5. Improved Synthesis of Keto-dioxinone 9



An improved synthesis of key intermediate keto-dioxinone **9** has been developed. Dioxinone **17** was allowed to react with an excess of lithium hexamethyldisilazide followed by diethylzinc at −20 °C. Subsequent reaction with *N*-acetylimidazole **18** at −10 °C gave **9** in 67−70% yield (Scheme 5). The use of diethylzinc was employed to minimize further reaction of **9** via proton transfer with the lithium enolate of **17**. This leads to the formation of the double acylated byproduct **19** which was a major limitation of the previous syntheses of this key building block.[7b,15] Consequently, this procedure was much preferred for large scale synthesis, giving rise to no significant byproduct.[16]

A generalized route for the Claisen condensation−cyclization−aromatization−ring-opening sequence is shown in Scheme 6. The dilithium enolate of keto-dioxinone **9**, which was generated using lithium diisopropylamide, was consecutively allowed to react with diethylzinc[17] and the Weinreb amides **12a**−**d**, **15a**−**d**, or acyl imidazoles **16a**−**f** at −30 or −78 °C

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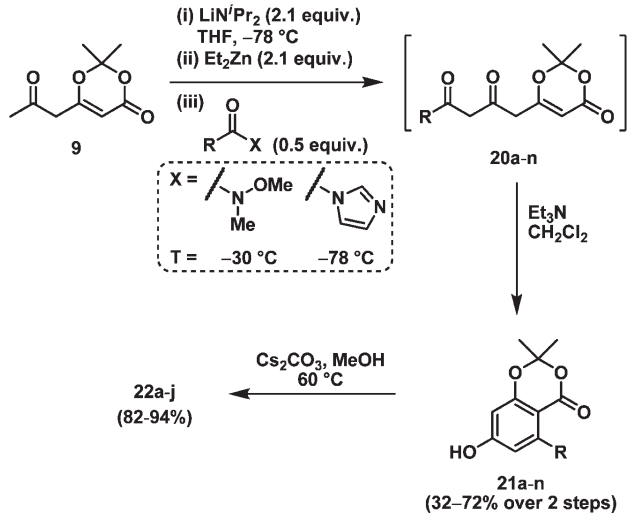
respectively, to give the functionalized diketo-dioxinones **20a**−**n** (Scheme 6).[18] Reaction of the valine-derived Weinreb amide **12e** failed to give the desired diketo-dioxinone in sufficient yield (<5% conversion to **21e**), presumably due to the added steric bulk close to the reactive sites. Furthermore, an extension of the isopropyl group by one carbon atom (leucine-derived amide **12f**) resulted in a 60% conversion to diketo-dioxinone **20f**, signifying that steric congestion was still an issue. In both cases, the more reactive imidazole derivatives **16a**,**b** gave complete conversion.[19]

Scheme 6. Synthesis of Novel Amino Resorcylates 22a−**j**



Subsequent cyclization and aromatization of crude diketo-dioxinones **20a**−**n** using triethylamine[20] gave the corresponding isopropylidene-protected resorcylates **21a**−**n** in 32−72% yield over the two steps.[21] Without the use of diethylzinc in the crossed Claisen coupling step, the overall two-step yields decreased significantly to 0−25%. Presumably higher yielding C-acylation was due to the reduced basicity of the zinc dienolates relative to the lithium systems.

Transesterification with ring-opening of several dioxinone-resorcylates using methanol at 60 °C in the presence of cesium carbonate (Scheme 6)[22] gave the aminoalkyl resorcylates or dihydroxyisoindolinones **22a**−**j** in 82−94% yield, all the structures of which are shown in Figure 2.

The synthesis of *N*-alkyl dihydroxyisoindolinones such as **24** (Scheme 7, alkyl = Me) has not been reported in the literature; however, related structures are known.[23] Herein we report the use of this methodology to form isoindolinone **24** without the use of phenolic protection (Scheme 7), which could be applied to obtain specific isoindolinones dependent upon the precursor α-amino acid.

Methanolysis of resorcylate precursor **21a** in the presence of cesium carbonate gave resorcylate **22a**, which was subjected directly to acidic *N*-Boc deprotection to give hydrochloride salt **23**,[24] followed by base-mediated lactamization,[25] to give functionalized isoindolinone **24** in 86% over the three steps.

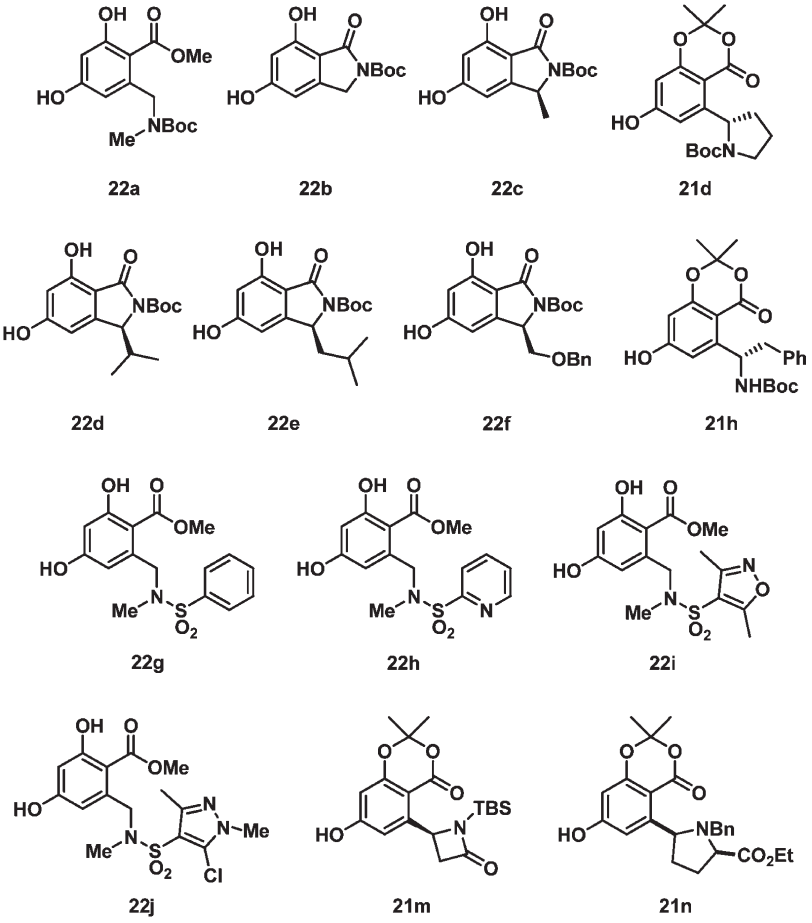


Figure 2. Structures of the α-amino acid-related resorcylate derivatives synthesized.

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Scheme 7. Facile Synthesis of Dihydroxyisoindolinone 24

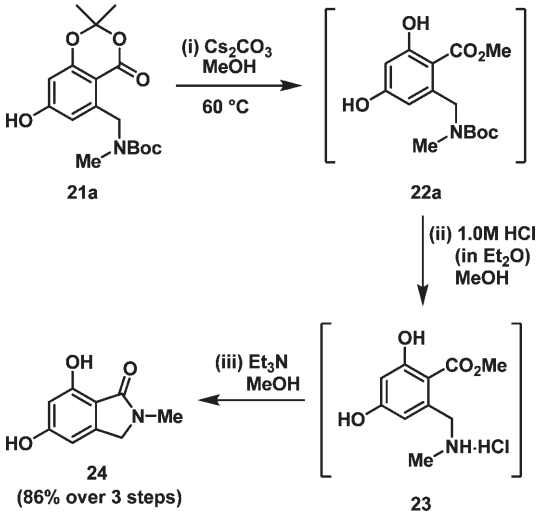

Table 1. CDK2 and CDK7 Cellular Inhibition by Resorcylates 22a,b,d−j

entry	resorcylate	GI_{50}[a] (μM)	CDK2 IC_{50}[a] (μM)	CDK7 IC_{50}[a] (μM)
1	**22a**	48.6	0.64	0.68
2	**22b**	49.0	0.61	0.28
3	**22d**	>100	>1.00	>1.00
4	**22e**	83.7	0.45	0.39
5	**22f**	20.3	0.34	0.43
6	**22g**	58.3	0.37	1.29
7	**22h**	53.0	0.58	0.41
8	**22i**	75.9	0.44	0.35
9	**22j**	2.71	0.52	1.44

[a] GI_{50}: concentration that inhibits 50% of cell growth; IC_{50}: concentration that inhibits 50% of enzyme activity.

A selection of the novel amino resorcylates (**22a,b,d−j**, Figure 2) were initially screened in MCF7 breast cancer cell lines against the cyclin dependent kinases CDK2 and CDK7 to evaluate their biological activities. We hoped to see CDK inhibition due to the previously observed activities of several resorcylate macrolactone natural products and related analogues toward CDK,[4,26] and other kinases.[27] Table 1 shows the inhibition data of the resorcylates tested.

Micromolar activity was recorded for all nine examples screened. Significant selectivity for CDK2 over CDK7 was shown for compounds **22g** (Table 1, entry 6) and **22j** (Table 1, entry 9), with the latter inhibiting cell growth the most.

Following on from these promising activities against CDK, we further screened resorcylates **22a,b,g−j** (Figure 2) in a series of biological assays to determine any significant bioactivity due to the varied activities displayed by known resorcylate macrolactones.[1] These assays included inhibition of alpha 1 nicotinic acetylcholine receptor (α1 nAChR), 5-hydroxytryptamine (5-HT) receptors, and glycogen synthase kinase 3 beta (GSK3B). The data are shown in Table 2.

All six resorcylates tested displayed micromolar activity against α1 nAChR and some micromolar activity toward 5-HT receptors. Furthermore, two of the sulfonamide-alkyl resorcylates **22i,j** (Table 2, entries 5 and 6) showed micromolar inhibition of GSK3B.

In summary, we have shown the synthesis of a new series of *o*-aminoalkyl resorcylate derivatives and isoindolinones of novel structural classes. This efficient synthesis produced compounds displaying promising biological activities, at least toward CDKs 2 and 7, α1 nAChR, and 5-HT receptors. We have highlighted that this methodology is amenable to the inclusion of diverse functional groups and can potentially lead to many varied resorcylate compounds. Further studies will be reported in due course.

EXPERIMENTAL SECTION

General Methods. All reactions were carried out in oven-dried glassware under N_2, using commercially supplied solvents and reagents unless otherwise stated. THF, CH_2Cl_2, Et_3N, and MeOH were redistilled from Na-Ph_2CO, CaH_2, CaH_2, and Mg turnings−I_2, respectively. Hexanes refers to BDH AnalaR petroleum spirit 40−60 °C. Column chromatography was carried out on silica gel, using flash techniques (eluants are given in parentheses). Analytical thin layer chromatography was performed on precoated silica gel F_{254} aluminum plates with visualization under UV light or by staining using either acidic vanillin, anisaldehyde, or ninhydrin spray reagents. Melting points were obtained using a melting point apparatus and are uncorrected. Infrared data were carried out neat unless otherwise stated. Indicative features of each spectrum are given with adsorptions reported in wavenumbers (cm^{-1}). ^1H NMR spectra were recorded at 400 MHz with chemical shifts (δ) quoted in parts per million (ppm) and coupling constants (J) recorded in hertz (Hz). ^{13}C NMR spectra were recorded at 100 MHz with chemical shifts (δ) quoted in ppm.

General Procedure for the Synthesis of Weinreb Amides 12a−h. Carbonyl diimidazole (0.72 g, 4.4 mmol) was added to the N-protected amino acid **11a−h** (4.0 mmol) in CH_2Cl_2 (8 mL) at room temperature. After 1.5 h, *N,O*-dimethylhydroxylammonium chloride (0.43 g, 4.4 mmol) was added, and, after 16 h, the mixture was diluted with EtOAc (25 mL), washed consecutively with 1 M aqueous HCl (20 mL), saturated aqueous $NaHCO_3$ (20 mL), and brine (20 mL), dried ($MgSO_4$), and rotary evaporated to give the desired Weinreb amide **12a−h**, which was used in the next step without further purification.

*tert-Butyl 2-(Methoxy(methyl)amino)-2-oxoethyl(methyl) Carbamate (**12a**).* 78%; colorless oil; R_f 0.35 (hexanes:EtOAc 1:1); ^1H NMR ($CDCl_3$, 400 MHz) δ 4.15 (s, 1.2H, rotamer 1), 4.07 (s, 0.8H, rotamer 2), 3.71−3.69 (2s, 3H, rotamer 1 and 2), 3.19−3.18 (2s, 3H, rotamer 1 and 2), 2.93−2.92 (2s, 3H, rotamer 1 and 2), 1.47 (s, 5.4H, rotamer 1), 1.43 (s, 3.6H, rotamer 2).

*tert-Butyl 2-(Methoxy(methyl)amino)-2-oxoethyl Carbamate (**12b**).* 84%; white solid; R_f 0.30 (hexanes:EtOAc 1:1); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.37−4.96 (br m, 1H), 4.08 (d, J = 4.0 Hz, 2H), 3.71 (s, 3H), 3.20 (s, 3H), 1.45 (s, 9H).

*(S)-tert-Butyl 1-(Methoxy(methyl)amino)-1-oxopropan-2-yl Carbamate (**12c**).* 81%; white solid, R_f 0.28 (hexanes:EtOAc 1:1); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.53−4.90 (br m, 1H), 4.79−4.43 (br m, 1H), 3.76 (s, 3H), 3.20 (s, 3H), 1.43 (s, 9H), 1.30 (d, J = 6.8 Hz, 3H).

*(S)-tert-Butyl 2-(Methoxy(methyl)carbamoyl)pyrrolidine-1-carboxylate (**12d**).* 76%; pale yellow oil; R_f 0.40 (hexanes:EtOAc 1:1); ^1H NMR ($CDCl_3$, 400 MHz) δ 4.69 (br m, 0.47H, rotamer 1), 4.59 (br m, 0.53H, rotamer 2), 3.77 (s, 1.4H, rotamer 1), 3.71 (s, 1.6H, rotamer 2), 3.61−3.36 (br m, 2H, rotamer 1 and 2), 3.19 (s, 3H, rotamer 1 and 2), 2.26−2.10 (br m, 1H, rotamer 1 and 2), 2.03−1.78 (br m, 3H, rotamer 1 and 2), 1.45 (s, 4.2H, rotamer 1), 1.40 (s, 4.8H, rotamer 2).

*(S)-tert-Butyl 1-(Methoxy(methyl)amino)-3-methyl-1-oxobutan-2-yl Carbamate (**12e**).* 86%; colorless oil; R_f 0.32 (hexanes:EtOAc 1:1); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.12 (br d, J = 8.4 Hz, 1H), 4.57 (br m,

Table 2. IC_{50} Values for Resorcylates 22a,b,d−j against 5-HT2A, 5-HT2C, 5-HT3, α1 nAChR, and GSK3B

entry	resorcylate	5-HT2A[a] IC_{50} (μM)	5-HT2C[a] IC_{50} (μM)	5-HT3[a] IC_{50} (μM)	α1 nAChR[a] IC_{50} (μM)	GSK3B[b] IC_{50} (μM)
1	**22a**	na	20.0	5.01	3.16	na
2	**22b**	25.1	na	na	31.6	na
3	**22g**	7.94	12.6	3.98	3.98	na
4	**22h**	20.0	na	na	12.6	na
5	**22i**	na	7.94	na	3.16	7.94
6	**22j**	31.6	na	na	3.98	7.94

[a] Human antagonist. [b] Human inhibitor; na: no activity <100 μM.

1H), 3.77 (s, 3H), 3.21 (s, 3H), 2.02−1.94 (br m, 1H), 1.43 (s, 9H), 0.95 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H).

*(S)-tert-Butyl 1-(Methoxy(methyl)amino)-4-methyl-1-oxopentan-2-yl Carbamate (**12f**).* 80%; colorless gum, R_f 0.60 (hexanes:EtOAc 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.17 (br d, J = 9.2 Hz, 0.8H, rotamer 1), 4.98 (br d, J = 9.2 Hz, 0.2H, rotamer 2), 4.69 (br m, 0.8H, rotamer 1), 4.30 (br m, 0.2H, rotamer 2), 3.77 (br s, 3H, rotamer 1 and 2), 3.17 (s, 3H, rotamer 1 and 2), 1.76−1.62 (br m, 1.6H, rotamer 1), 1.57−1.47 (br m, 0.4H, rotamer 2), 1.41−1.40 (br m, 9H + 1H, rotamer 1 and 2), 0.93 (d, J = 6.4 Hz, 3H, rotamer 1 and 2), 0.90 (d, J = 6.8 Hz, 3H, rotamer 1 and 2).

*(S)-1-(tert-Butyldimethylsilyl)-N-methoxy-N-methyl-4-oxoazetidine-2-carboxamide (**12g**).* 70%; white gum; R_f 0.10 (hexanes:EtOAc 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.45 (br dd, J = 5.6, 2.8 Hz, 1H), 3.71 (s, 3H), 3.31 (dd, J = 14.8, 6.0 Hz, 1H, 3.21 (s, 3H), 2.98 (dd, J = 15.2, 3.2 Hz, 1H), 0.98 (s, 9H), 0.32 (s, 3H), 0.11 (s, 3H); HRMS (ESI) calcd $C_{12}H_{24}N_2O_3Si$:- $[M + H]^+$ 273.1634; found $[M + H]^+$ 273.1627.

*(±)-cis-Ethyl 5-(Methoxy(methyl)carbamoyl)-1-benzylpyrrolidine-2-carboxylate (**12h**).* 65%; pale yellow gum; R_f 0.15 (hexanes:EtOAc 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36−7.20 (m, 5H), 4.04 (q, J = 7.0 Hz, 2H), 3.94−3.84 (br m, 2H), 3.74 (br m, 1H), 3.54 (s, 3H), 3.41 (br m, 1H), 3.12 (br s, 3H), 2.22−1.93 (br m, 4H), 1.20 (t, J = 7.0 Hz, 3H); HRMS (ESI) calcd $C_{17}H_{24}N_2O_4$: $[M + H]^+$ 321.1814; found $[M + H]^+$ 321.1809.

*N-Methoxy-N-methyl-2-(methylamino)acetamide Hydrochloride (**13**).* Amide **12a** (5.0 g, 21.5 mmol) was dissolved in HCl in dioxane (4.0 M; 30 mL) at room temperature. After 6 h, rotary evaporation gave the desired hydrochloride salt **13** (3.48 g, 96%) as a white solid: R_f 0.08 (hexanes:EtOAc 1:1); mp 156−158 °C (Et_2O:MeOH 2:1); IR 3007, 2966, 2752, 2690, 2414, 1668, 1467, 1383, 954 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.95 (br s, 2H), 4.05 (s, 2H), 3.72 (s, 3H), 3.16 (s, 3H), 2.58 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 165.9, 61.4, 47.6, 32.5, 31.7; HRMS (ESI) calcd $C_5H_{13}ClN_2O_2$: $[M - Cl]^+$ 133.0977; found $[M - Cl]^+$ 133.0968.

General Procedure for the Synthesis of Weinreb Amides 15a−d. Hydrochloride **13** (0.42 g, 2.5 mmol) in CH_2Cl_2 (15 mL) was cooled to 0 °C, and Et_3N (0.70 mL, 5.0 mmol) was added with stirring. After 10 min, RSO_2Cl (2.5 mmol) in CH_2Cl_2 (3 mL) was added slowly and the mixture allowed to warm up to room temperature. After 16 h, H_2O (25 mL) was added and the product extracted with EtOAc (2 × 25 mL). The combined organic extracts were washed with 1 M aqueous HCl (30 mL) and brine (30 mL), dried ($MgSO_4$), and rotary evaporated to give the desired sulfonamides **15a−d**.

*N-Methoxy-N-methyl-2-(N-methylphenylsulfonamido)acetamide (**15a**).* 86%; pale yellow solid; R_f 0.24 (hexanes:EtOAc 1:1); mp 73−75 °C (Et_2O: hexanes 1:1); IR 2973, 2938, 1664, 1448, 1331, 1162, 1152 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86−7.84 (m, 2H), 7.60−7.50 (m, 3H), 4.17 (s, 2H), 3.73 (s, 3H), 3.15 (s, 3H), 2.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.7, 138.3, 132.6, 128.9 (2C), 127.4 (2C), 61.5, 50.2, 35.8, 32.3; HRMS (ESI) calcd $C_{11}H_{16}N_2O_4S$: $[M + H]^+$ 273.0909; found $[M + H]^+$ 273.0914. Anal. Calcd for $C_{11}H_{16}N_2O_4S$: C, 48.52; H, 5.92; N, 10.29; S, 11.77. Found: C, 48.49; H, 6.00; N, 10.23; S, 11.68.

*N-Methoxy-N-methyl-2-(N-methylpyridine-2-sulfonamido)acetamide (**15b**).* 85%; off-white solid; R_f 0.20 (hexanes:EtOAc 1:1); mp 88−90 °C (Et_2O:hexanes 1:1); IR 2941, 1669, 1577, 1424, 1337, 1176, 1113 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.70−8.69 (m, 1H), 7.96−7.87 (m, 2H), 7.49−7.46 (m, 1H), 4.35 (s, 2H), 3.73 (s, 3H), 3.14 (s, 3H), 3.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 168.7, 156.9, 149.6, 137.9, 126.5, 122.4, 61.4, 51.1, 36.4, 32.2; HRMS (ESI) calcd $C_{10}H_{15}N_3O_4S$: $[M + H]^+$ 274.0862; found $[M + H]^+$ 274.0857. Anal. Calcd for $C_{10}H_{15}N_3O_4S$: C, 43.95; H, 5.53; N, 15.37; S, 11.73. Found: C, 44.05; H, 5.60; N, 15.29; S, 11.67.

*N-Methoxy-N-methyl-2-(N,3,5-trimethylisoxazole-4-sulfonamido)-acetamide (**15c**).* 83%; white gum; R_f 0.16 (hexanes:EtOAc 1:1); IR 2940, 1677, 1591, 1407, 1338, 1176, 1115, 988, 938 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.24 (s, 2H), 3.71 (s, 3H), 3.15 (s, 3H), 2.96 (s, 3H), 2.63 (s, 3H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 173.2, 168.6, 157.9, 115.7, 61.5, 50.0, 35.4, 32.4, 12.8, 11.1; HRMS (ESI) calcd $C_{10}H_{17}N_3O_5S$: $[M + H]^+$ 292.0967; found $[M + H]^+$ 292.0950.

*2-(5-Chloro-N,1,3-trimethyl-1H-pyrazole-4-sulfonamido)-N-methoxy-N-methylacetamide (**15d**).* 80%; white gum; R_f 0.20 (hexanes: EtOAc 1:1); IR 2939, 1679, 1502, 1437, 1364, 1340, 1175, 1122, 989, 938 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.23 (s, 2H), 3.81 (s, 3H), 3.72 (s, 3H), 3.15 (s, 3H), 2.97 (s, 3H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 168.9, 148.9, 129.5, 115.0, 61.5, 50.4, 36.6, 35.6, 32.4, 14.0; HRMS (ESI) calcd $C_{10}H_{17}ClN_4O_4S$: $[M + H]^+$ 325.0706; found $[M + H]^+$ 325.0721.

General Procedure for the Synthesis of Imidazoles 16a−f. N-Protected amino acid **11e−j** (2.0 mmol) in THF (4 mL) was cooled to 0 °C, and carbonyl diimidazole (0.36 g, 2.2 mmol) was added portionwise over 5 min. After 2 h, the mixture was diluted with Et_2O (25 mL), and H_2O (10 mL) was added carefully. The organic layer was washed with H_2O (2 × 10 mL) and brine (10 mL), dried ($MgSO_4$), and rotary evaporated to give the desired product **16a−f**, which was used in the next step without further purification.

*(S)-tert-Butyl 1-(1H-Imidazol-1-yl)-3-methyl-1-oxobutan-2-yl Carbamate (**16a**).* 91%; white gum; R_f 0.12 (hexanes:EtOAc 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.26 (s, 1H), 7.52 (s, 1H), 7.12 (s, 1H), 5.27 (br d, J = 8.8 Hz, 1H), 4.78 (br dd, J = 9.2, 5.6 Hz, 1H), 2.21−2.12 (br m, 1H), 1.43 (s, 9H), 1.03 (br d, J = 6.4 Hz, 3H), 0.94 (br d, J = 6.8 Hz, 3H).

*(S)-tert-Butyl 1-(1H-Imidazol-1-yl)-4-methyl-1-oxopentan-2-yl Carbamate (**16b**).* 86%; off-white gum; R_f 0.15 (hexanes:EtOAc 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.28 (s, 1H), 7.52 (s, 1H), 7.13 (s, 1H), 5.12 (br d, J = 8.8 Hz, 1H), 5.01−4.91 (br m, 1H), 1.84−1.74 (br m, 1H), 1.66−1.59 (br m, 2H), 1.43 (s, 9H), 1.03 (br d, J = 6.8 Hz, 3H), 0.95 (br d, J = 6.8 Hz, 3H).

*(S)-tert-Butyl 3-(Benzyloxy)-1-(1H-imidazol-1-yl)-1-oxopropan-2-yl Carbamate (**16c**).* 82%; white gum, R_f 0.10 (hexanes:EtOAc 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.23 (s, 1H), 7.50 (s, 1H), 7.33−7.27 (m, 3H), 7.18−7.16 (m, 2H), 7.10 (s, 1H), 5.47 (br d, J = 8.4 Hz, 1H), 5.10−5.06 (br m, 1H), 4.54−4.46 (m, 2H), 3.83−3.73 (br m, 2H), 1.44 (s, 9H).

*(S)-tert-Butyl 1-(1H-Imidazol-1-yl)-1-oxo-3-phenylpropan-2-yl Carbamate (**16d**).* 78%; white gum; R_f 0.20 (hexanes:EtOAc 1:1); ^{1}H

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NMR ($CDCl_3$, 400 MHz) δ 8.14 (s, 1H), 7.44 (s, 1H), 7.31−7.24 (m, 3H), 7.12−7.11 (m, 2H), 7.06 (s, 1H), 5.24−5.09 (br m, 2H), 3.21 (dd, J = 13.6, 6.0 Hz, 1H), 3.08 (dd, J = 13.6, 6.4 Hz, 1H), 1.44 (s, 9H).

*(S)-1-(tert-Butyldimethylsilyl)-4-(1H-imidazole-1-carbonyl)azetidin-2-one (**16e**).* 65%; white gum; R_f 0.10 (hexanes:EtOAc 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.17 (s, 1H), 7.45 (s, 1H), 7.17 (s, 1H), 4.67 (br dd, J = 6.4, 3.2 Hz, 1H), 3.61 (dd, J = 15.2, 6.4 Hz, 1H), 3.17 (dd, J = 15.2, 3.2 Hz, 1H), 1.00 (s, 9H), 0.34 (s, 3H), 0.13 (s, 3H).

*(±)-cis-Ethyl 5-(1H-Imidazole-1-carbonyl)-1-benzylpyrrolidine-2-carboxylate (**16f**).* 79%; off-white gum; R_f 0.16 (hexanes:EtOAc 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.83 (s, 1H), 7.81 (s, 1H), 7.19−7.13 (m, 5H), 6.99 (s, 1H), 4.13 (q, J = 7.2 Hz, 2H), 3.93−3.86 (m, 1H), 3.90 (d, J = 12.8 Hz, 1H), 3.72 (d, J = 12.8 Hz, 1H), 3.57−3.53 (m, 1H), 2.38−2.12 (m, 4H), 1.28 (t, J = 7.2 Hz, 3H).

*2,2-Dimethyl-6-(2-oxopropyl)-4H-1,3-dioxin-4-one (**9**).* Dioxinone **17** (50 g, 352 mmol) in THF (150 mL) was added dropwise to lithium hexamethyldisilazide in THF (1.0M; 500 mL, 500 mmol) and THF (330 mL) at −20 °C, and after 45 min, diethylzinc in hexanes (1.0M; 500 mL, 500 mmol) was added over 2 h. After a further 30 min, the reaction mixture was allowed to warm up to −10 °C and *N*-acetylimidazole (55 g, 500 mmol) was added portionwise over 15 min. After 3.5 h, H_2O:THF (1:9; 150 mL) was added dropwise, followed by 2 M aqueous HCl (250 mL) and EtOAc (500 mL). The pH was adjusted to pH 1−2 using aqueous HCl (25%; 265 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (250 mL), and the combined organic extracts wer washed with brine (500 mL), dried ($MgSO_4$), rotary evaporated, and chromatographed (heptane:EtOAc 3:2) to give **9** (40−42 g, 67−70%) as pale yellow crystals: R_f 0.40 (hexanes:EtOAc 1:1); mp 48−51 °C (hexanes:Et_2O 2:1); IR 1726, 1636, 1374, 1275, 1206, 1013 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.29 (s, 1H), 3.31 (s, 2H), 2.19 (s, 3H), 1.66 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.8, 164.3, 160.5, 107.0, 96.5, 47.7, 30.0, 24.8; HRMS (CI) calcd $C_9H_{12}O_4$: $[M + H]^+$ 185.0814; found: $[M + H]^+$ 185.0812. Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57; found: C, 58.75; H, 6.62.

General Procedure for the C-Acylation−Cyclization−Aromatization Sequence. *n*-BuLi in hexanes (1.6 M; 1.35 mL, 2.16 mmol) was added dropwise with stirring to iso-Pr_2NH (0.31 mL, 2.16 mmol) in THF (10 mL) at −78 °C. After 20 min, keto-dioxinone **9** (0.19 g, 1.03 mmol) in THF (1.5 mL) was added dropwise with stirring at −78 °C. After 40 min, Et_2Zn in hexanes (1.0 M; 2.16 mL, 2.16 mmol) was added slowly, and after a further 20 min, the mixture was allowed to warm up to −30 °C.[28] The Weinreb amide (0.52 mmol) in THF (1.5 mL) was added and the mixture stirred for 3 h. The reaction was quenched with saturated aqueous NH_4Cl (15 mL) and 1 M aqueous HCl (5 mL), and the aqueous layer was acidified to pH 1−2 using 1 M aqueous HCl. The product was extracted twice with EtOAc (50 mL, 25 mL), the combined organic extracts were dried ($MgSO_4$) and rotary evaporated to give the crude acylation product **20a**−**n**, which was dissolved in CH_2Cl_2 (15 mL), Et_3N (2 mL) was added, and the mixture was stirred at room temperature. After 16 h, saturated aqueous NH_4Cl (40 mL) and EtOAc (80 mL) were added, and the aqueous layer was acidified to pH 1−2 using 1 M aqueous HCl. The layers were separated, and the aqueous layer was further extracted with EtOAc (40 mL). The combined organic extracts were dried ($MgSO_4$), rotary evaporated, and chromatographed (hexanes:EtOAc 5:1 to 1:1) to give the isopropylidene-protected resorcylate **21a**-**n**.

*tert-Butyl (7-Hydroxy-2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-5-yl)methyl(methyl) Carbamate (**21a**).* 72%; pale yellow solid; R_f 0.62 (hexanes:EtOAc 1:1); mp 139−143 °C (Et_2O:EtOAc 10:1); IR 3260, 2984, 1718, 1670, 1617, 1449, 1269, 1250, 1167, 1145 cm^{-1}; ^{1}H NMR (acetone-d_6, 400 MHz) δ 9.61 (br s, 1H, rotamer 1 and 2), 6.47−6.44 (br m, 1H, rotamer 1 and 2), 6.35 (br s, 1H, rotamer 1 and 2), 4.82−4.79 (2br s, 2H, rotamer 1 and 2), 2.91 (s, 3H, rotamer 1 and 2), 1.66 (s, 6H, rotamer 1 and 2), 1.48 (s, 4.15H, rotamer 1), 1.36 (s, 4.85H, rotamer 2); ^{13}C NMR (acetone-d_6, 100 MHz) δ 165.8, 161.3, 161.1, 157.2, 147.9, 147.6, 110.4, 110.2, 106.7, 105.1, 103.4, 80.7, 80.6, 53.2, 52.5, 36.4, 36.1, 29.6 (3C, rotamer 1), 29.4 (3C, rotamer 2), 26.6 (2C) (contains rotamers); HRMS (ESI) calcd $C_{17}H_{23}NO_6$: $[M + Na]^+$ 360.1423; found $[M + Na]^+$ 360.1414. Anal. Calcd for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87; N, 4.15. Found: C, 60.58; H, 6.75; N, 4.07.

*tert-Butyl (7-Hydroxy-2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-5-yl)methyl Carbamate (**21b**).* 68%; off-white solid; R_f 0.56 (hexanes:EtOAc 1:1); mp 185−189 °C (Et_2O:EtOAc 10:1); IR 3454, 3184, 2982, 1714, 1666, 1617, 1504, 1451, 1287, 1270, 1250, 1164, 1138 cm^{-1}; ^{1}H NMR (acetone-d_6, 400 MHz) δ 9.66 (s, 1H), 6.71 (d, J = 2.0 Hz, 1H), 6.36−6.33 (m, 1H + 1H), 4.56 (d, J = 6.4 Hz, 2H), 1.66 (s, 6H), 1.42 (s, 9H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 165.7, 161.7, 161.0, 157.6, 148.4, 112.7, 106.8, 105.0, 103.6, 80.0, 44.7, 29.6 (3C), 26.6 (2C); HRMS (ESI) calcd $C_{16}H_{21}NO_6$: $[M + Na]^+$ 346.1267; found $[M + Na]^+$ 346.1265. Anal. Calcd: C, 59.43; H, 6.55; N, 4.33. Found: C, 59.49; H, 6.43; N, 4.24.

*(S)-tert-Butyl 1-(7-Hydroxy-2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-5-yl)ethyl Carbamate (**21c**).* 57%; yellow solid; R_f 0.52 (hexanes:EtOAc 1:1); mp 166−170 °C (Et_2O:EtOAc 4:1); IR 3346, 2932, 1716, 1696, 1612, 1586, 1336, 1270, 1246, 1165, 1112 cm^{-1}; ^{1}H NMR (acetone-d_6, 400 MHz) δ 9.57 (s, 1H), 6.81 (d, J = 2.0 Hz, 1H), 6.59 (br d, J = 6.4 Hz, 1H), 6.33 (d, J = 2.4 Hz, 1H), 5.70 (br m, 1H), 1.68 (s, 3H), 1.65 (s, 3H), 1.40−1.23 (br m, 9H + 3H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 165.7, 165.6, 161.2, 160.8, 156.6, 155.4, 110.5, 110.5, 106.4, 105.0, 103.4, 79.7, 29.6 (3C), 27.0, 26.2, 23.6 (contains rotamers); HRMS (ESI) calcd $C_{17}H_{23}NO_6$: $[M + Na]^+$ 360.1423; found $[M + Na]^+$ 360.1422. Anal. Calcd for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87; N, 4.15. Found: C, 60.62; H, 6.76; N, 4.22.

*(S)-tert-Butyl 2-(7-Hydroxy-2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-5-yl)pyrrolidine-1-carboxylate (**21d**).* 47%; pale yellow solid; R_f 0.68 (hexanes:EtOAc 1:1); mp 197−200 °C (Et_2O:EtOAc 5:1); IR 3161, 2975, 1719, 1661, 1612, 1430, 1365, 1304, 1160, 1136 cm^{-1}; ^{1}H NMR (acetone-d_6, 400 MHz) δ 9.47 (s, 1H, rotamer 1 and 2), 6.50 (br s, 1H, rotamer 1 and 2), 6.33−6.32 (br m, 1H, rotamer 1 and 2), 5.77 (br d, J = 8.0 Hz, 0.35 H, rotamer 1), 5.68 (br d, J = 10.4 Hz, 0.65 H, rotamer 2), 3.63−3.47 (m, 2H, rotamer 1 and 2), 2.51−2.33 (br m, 1H, rotamer 1 and 2), 1.86−1.78 (m, 2H, rotamer 1 and 2), 1.70 (s, 3.2H, rotamer 2), 1.64 (s, 2.8H, rotamer 1), 1.43 (s, 3.2H, rotamer 2), 1.21 (s, 5.8H, rotamer 1); ^{13}C NMR (acetone-d_6, 100 MHz) δ 165.5, 161.1, 161.0, 155.5, 154.5, 154.5, 153.8, 110.1, 110.0, 106.5, 104.5, 103.3, 80.0, 60.6, 49.3, 49.0, 36.5, 35.7, 29.7 (3C, rotamer 1), 29.5 (3C, rotamer 2), 27.5, 26.9, 26.5, 25.8, 24.7, 24.1 (contains rotamers); HRMS (ESI) calcd $C_{19}H_{25}NO_6$: $[M + H]^+$ 364.1761; found $[M + H]^+$ 364.1766. Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.80; H, 6.93; N, 3.85. Found: C, 62.89; H, 6.85; N, 3.82.

*(S)-tert-Butyl 1-(7-Hydroxy-2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-5-yl)-2-methylpropyl Carbamate (**21e**).* 56%; white solid; R_f 0.62 (hexanes:EtOAc 1:1); mp 161−163 °C (Et_2O:EtOAc 10:1); IR 3237, 2971, 1711, 1615, 1587, 1391, 1368, 1290, 1169 cm^{-1}; ^{1}H NMR (acetone-d_6, 400 MHz) δ 9.36 (br s, 1H), 6.73 (d, J = 2.0 Hz, 1H), 6.37 (d, J = 2.0 Hz, 1H), 6.34 (br m, 1H), 5.34 (br m, 1H), 2.12 (br m, 1H), 1.68 (s, 3H), 1.66 (s, 3H), 1.37 (br s, 9H), 0.96 (d, J = 5.2 Hz, 3H), 0.87 (d, J = 5.6 Hz, 3H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 165.5, 161.9, 161.2, 157.4, 152.4, 113.9, 106.5, 106.0, 104.0, 79.8, 60.1, 34.4, 29.8 (3C), 27.2, 26.3, 21.6, 19.8; HRMS (ESI) calcd $C_{19}H_{27}NO_6$: $[M + H]^+$ 366.1917; found $[M + H]^+$ 366.1907.

*(S)-tert-Butyl 1-(7-Hydroxy-2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-5-yl)-3-methylbutyl Carbamate (**21f**).* 51%; pale yellow solid; R_f 0.62 (hexanes:EtOAc 1:1); mp 121−123 °C (Et_2O:EtOAc 10:1); IR 3223, 2958, 2871, 1691, 1613, 1585, 1287, 1269, 1166 cm^{-1}; ^{1}H NMR (acetone-d_6, 400 MHz) δ 9.32 (br s, 1H), 6.79 (d, J = 1.6 Hz, 1H), 6.37 (br m, 1H), 6.34 (d, J = 2.0 Hz, 1H), 5.69 (br m, 1H), 1.85−1.77 (br m, 1H), 1.67 (2s, 6H, rotamer 1 and 2), 1.64−1.57 (br m, 1H),

1.54−1.46 (br m, 1H), 1.37 (br s, 9H), 1.01 (br d, J = 5.2 Hz, 3H), 0.92 (br d, J = 5.6 Hz, 3H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 165.7, 161.1, 157.1, 112.0, 106.5, 105.4, 103.7, 79.8, 52.9, 47.1, 27.4 (3C, rotamer 1), 27.2 (3C, rotamer 2), 26.4 (2C), 24.8 (2C), 22.8 (contains rotamers); HRMS (ESI) calcd $C_{20}H_{29}NO_6$: $[M + H]^+$ 380.2073; found $[M + H]^+$ 380.2059.

(S)-tert-Butyl 2-(Benzyloxy)-1-(7-hydroxy-2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-5-yl)ethyl Carbamate (**21g**). 54%; white solid; R_f 0.48 (hexanes:EtOAc 1:1); mp 133−136 °C (Et_2O:EtOAc 10:1); IR 3300, 2980, 2932, 1719, 1691, 1615, 1588, 1292, 1168 cm^{-1}; ^{1}H NMR (acetone-d_6, 400 MHz) δ 9.38 (br s, 1H), 7.44−7.42 (br m, 2H), 7.31−7.28 (m, 4H), 7.27−7.22 (m, 1H), 6.86 (d, J = 2.0 Hz, 1H), 6.37 (d, J = 1.6 Hz, 1H), 6.28 (br s, 1H), 5.99 (br m, 1H), 4.61 (d, J = 9.6 Hz, 1H), 4.49 (d, J = 9.6 Hz, 1H), 3.77 (br dd, J = 8.0, 3.6 Hz, 1H), 3.61 (br dd, J = 8.0, 5.2 Hz, 1H), 1.66 (2s, 6H, rotamer 1 and 2), 1.38 (br s, 9H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 165.6, 161.5, 161.0, 157.1, 140.8, 130.1 (2C), 129.5 (2C), 129.2, 112.8, 106.7, 105.6, 104.1, 80.3, 80.1, 80.1, 79.8, 74.5, 74.3, 54.0, 53.9, 29.7 (3C), 27.1 (2C, rotamer 1), 26.5 (2C, rotamer 2) (contains rotamers); HRMS (ESI) calcd $C_{24}H_{29}NO_7$: $[M + H]^+$ 444.2022; found $[M + H]^+$ 444.2021. Anal. Calcd for $C_{24}H_{29}NO_7$: C, 65.00; H, 6.59; N, 3.16. Found: C, 65.13; H, 6.52; N, 3.04.

(S)-tert-Butyl 1-(7-Hydroxy-2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-5-yl)-2-phenylethyl Carbamate (**21h**). 52%; pale yellow solid; R_f 0.60 (hexanes:EtOAc 1:1); mp 95−98 °C (Et_2O:EtOAc 10:1); IR 3258, 2925, 1681, 1613, 1585, 1497, 1366, 1290, 1268, 1164 cm^{-1}; ^{1}H NMR (acetone-d_6, 400 MHz) δ 9.59 (br s, 1H), 7.44−7.42 (br m, 2H), 7.30−7.26 (br m, 2H), 7.20−7.17 (br m, 1H), 6.87 (br s, 1H), 6.54 (br d, J = 5.2 Hz, 1H), 6.38 (br s, 1H), 6.09−6.01 (br m, 1H), 3.12 (br dd, J = 14.0, 3.2 Hz, 1H), 2.77 (br m, 1H), 1.68 (s, 6H), 1.27 (s, 9H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 164.7, 160.5, 160.5, 159.9, 155.9, 140.0, 130.1 (2C), 128.9 (2C), 127.0, 125.8, 110.3, 105.6, 104.1, 102.7, 78.7, 54.5, 54.2, 42.9, 28.5 (3C), 25.9 (2C, rotamer 1), 25.4 (2C, rotamer 2) (contains rotamers); HRMS (ESI) calcd $C_{23}H_{27}NO_6$: $[M + Na]^+$ 436.1736; found $[M + Na]^+$ 436.1737. Anal. Calcd for $C_{23}H_{27}NO_6$: C, 66.81; H, 6.58; N, 3.39. Found: C, 66.86; H, 6.61; N, 3.50.

N-((7-Hydroxy-2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-5-yl)methyl)-N-methylbenzene-sulfonamide (**21i**). 64%; white solid; R_f 0.60 (hexanes:EtOAc 1:1); mp 214−217 °C (Et_2O:EtOAc 3:1); IR 3378, 2927, 1701, 1615, 1586, 1337, 1291, 1263, 1160 cm^{-1}; ^{1}H NMR (acetone-d_6, 400 MHz) δ 9.68 (br s, 1H), 7.91−7.89 (m, 2H), 7.76−7.66 (m, 3H), 6.95 (d, J = 2.0 Hz, 1H), 6.39 (d, J = 2.4 Hz, 1H), 4.67 (s, 2H), 2.80 (s, 3H), 1.65 (s, 6H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 165.9, 161.4, 161.0, 146.0, 140.1, 134.7, 131.3 (2C), 129.1 (2C), 112.0, 106.9, 105.4, 103.9, 53.8, 37.3, 26.6 (2C); HRMS (ESI) calcd $C_{18}H_{19}NO_6S$: $[M + H]^+$ 378.1012; found $[M + H]^+$ 378.1013. Anal. Calcd for $C_{18}H_{19}NO_6S$: C, 57.28; H, 5.07; N, 3.71; S, 8.50. Found: C, 57.29; H, 5.00; N, 3.80; S, 8.43.

N-((7-Hydroxy-2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-5-yl)methyl)-N-methylpyridine-2-sulfonamide (**21j**). 62%; white solid; R_f 0.30 (hexanes:EtOAc:acetone 2:1:1); mp 210−212 °C (Et_2O:EtOAc 3:1); IR 3368, 2936, 1701, 1615, 1587, 1331, 1290, 1264, 1169, 1151 cm^{-1}; ^{1}H NMR (acetone-d_6, 400 MHz) δ 9.71 (br s, 1H), 8.79−8.78 (m, 1H), 8.15−8.11 (m, 1H), 8.01−7.99 (m, 1H), 7.71−7.68 (m, 1H), 6.96 (d, J = 2.4 Hz, 1H), 6.38 (d, J = 2.0 Hz, 1H), 4.89 (s, 2H), 2.95 (s, 3H), 1.66 (s, 6H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 164.0, 159.5, 159.2, 157.4, 150.2, 144.4, 138.4, 127.0, 122.6, 109.9, 105.0, 103.5, 102.0, 52.9, 36.2, 24.8 (2C); HRMS (ESI) calcd $C_{17}H_{18}N_2O_6S$: $[M + H]^+$ 379.0965; found $[M + H]^+$ 379.0970. Anal. Calcd for $C_{17}H_{18}N_2O_6S$: C, 53.96; H, 4.79; N, 7.40; S, 8.47. Found: C, 54.02 H, 4.83; N, 7.37; S, 8.40.

N-((7-Hydroxy-2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-5-yl)methyl)-N,3,5-trimethylisoxazole-4-sulfonamide (**21k**). 54%; R_f white solid; 0.45 (hexanes:EtOAc 1:1); mp 202−205 °C (Et_2O:EtOAc 3:1); IR 3332, 2924, 1702, 1616, 1588, 1336, 1290, 1263, 1175, 1113 cm^{-1}; ^{1}H NMR (acetone-d_6, 400 MHz) δ 9.71 (br s, 1H), 6.86 (d, J = 2.4 Hz, 1H), 6.40 (d, J = 2.4 Hz, 1H), 4.79 (s, 2H), 2.89 (s, 3H), 2.70 (s, 3H), 2.43 (s, 3H), 1.66 (s, 6H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 173.7, 164.1, 159.6, 159.3, 157.5, 143.6, 114.7, 109.7, 105.1, 103.4, 102.1, 51.8, 34.9, 24.8 (2C), 12.1, 10.6; HRMS (ESI) calcd $C_{17}H_{20}N_2O_7S$: $[M + H]^+$ 397.1069; found $[M + H]^+$ 397.1072. Anal. Calcd for $C_{17}H_{20}N_2O_7S$: C, 51.51; H, 5.09; N, 7.07; S, 8.09. Found: 51.58; H, 5.11; N, 7.00; S, 8.00.

5-Chloro-N-((7-hydroxy-2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-5-yl)methyl)-N,1,3-trimethyl-1H-pyrazole-4-sulfonamide (**21l**). 59%; white solid; R_f 0.25 (hexanes:EtOAc 1:1); mp 196−199 °C (Et_2O:EtOAc 3:1); IR 3397, 2927, 1720, 1698, 1614, 1584, 1338, 1287, 1165, 1123 cm^{-1}; ^{1}H NMR (acetone-d_6, 400 MHz) δ 9.67 (br s, 1H), 6.89 (d, J = 2.0 Hz, 1H), 6.39 (d, J = 2.4 Hz, 1H), 4.77 (s, 2H), 3.86 (s, 3H), 2.84 (s, 3H), 2.40 (s, 3H), 1.66 (s, 6H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 165.9, 161.4, 161.1, 150.0, 146.0, 130.9, 115.8, 111.7, 106.9, 105.3, 103.8, 53.8, 38.1, 36.9, 26.6 (2C), 15.3; HRMS (ESI) calcd $C_{17}H_{20}ClN_3O_6S$: $[M + H]^+$ 430.0840; found $[M + H]^+$ 430.0825. Anal. Calcd for $C_{17}H_{20}ClN_3O_6S$: C, 47.50; H, 4.69; N, 9.77; S, 7.46. Found: C, 47.61; H, 4.77; N, 9.73; S, 7.41.

(S)-1-(tert-Butyldimethylsilyl)-4-(7-hydroxy-2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-5-yl)azetidin-2-one (**21m**). 36%; off-white solid; R_f 0.48 (hexanes:EtOAc 1:1); mp 142−144 °C (Et_2O:EtOAc 3:1); IR 3070, 2931, 1703, 1611, 1451, 1295, 1270, 1207, 1170, 1041, 838, 822 cm^{-1}; ^{1}H NMR (acetone-d_6, 400 MHz) δ 9.71 (br s, 1H), 6.94 (d, J = 2.4 Hz, 1H), 6.40 (d, J = 2.4 Hz, 1H), 5.68−5.66 (dd, J = 6.0, 2.8 Hz, 1H), 3.62−3.56 (dd, J = 15.2, 6.0 Hz, 1H), 2.66−2.62 (dd, J = 15.2, 2.8 Hz, 1H), 1.69 (s, 3H), 1.66 (s, 3H), 0.98 (s, 9H), 0.31 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 174.1, 165.9, 161.1, 160.9, 151.6, 110.2, 106.8, 105.3, 104.3, 50.4, 50.2, 27.8 (3C), 27.5, 25.7, 20.5, −4.01, −4.91; HRMS (ESI) calcd $C_{19}H_{27}NO_5Si$: $[M + H]^+$ 378.1737; found $[M + H]^+$ 378.1732. Anal. Calcd for $C_{19}H_{27}NO_5Si$: C, 60.45; H, 7.21; N, 3.71. Found: C, 60.51; H, 7.08; N, 3.61.

(±)-cis-Ethyl 5-(7-Hydroxy-2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-5-yl)-1-benzylpyrrolidine-2-carboxylate (**21n**). 32%; pale yellow gum; R_f 0.50 (hexanes:EtOAc 1:1); IR 2927, 1698, 1452, 1416, 1243, 1075, 1028 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.66 (s, 1H), 7.64 (d, J = 2.4 Hz, 1H), 7.34−7.13 (m, 5H), 6.27 (d, J = 2.4 Hz, 1H), 4.91 (t, J = 7.2 Hz, 1H), 4.02−3.93 (m, 2H), 3.81 (d, J = 13.2 Hz, 1H), 3.69 (d, J = 13.2 Hz, 1H), 3.52 (dd, J = 8.0, 6.4 Hz, 1H), 2.46−2.38 (m, 1H), 2.15−2.09 (m, 1H), 1.90−1.82 (m, 1H), 1.66 (s, 3H), 1.60 (s, 3H), 1.62−1.51 (m, 1H), 1.15 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.2, 163.0, 160.2, 158.8, 138.0, 129.6 (2C), 127.9 (3C), 127.1, 110.8, 104.8, 103.6, 101.9, 66.1, 65.1, 60.8, 58.7, 34.0, 30.3, 29.6, 26.3, 24.8, 14.0; HRMS (ESI) calcd $C_{24}H_{27}NO_6$: $[M + H]^+$ 426.1917; found $[M + H]^+$ 426.1927.

General Procedure for the Cesium Carbonate-Mediated Ring-Opening. Dioxinone-resorcylates **21a**−**d**,**f**,**g**,**i**−**l** (0.20 mmol) and Cs_2CO_3 (130 mg, 0.40 mmol) were suspended in MeOH (3 mL) and heated in a sealed tube at 60 °C. After 18 h, the solvent was evaporated and the mixture partitioned between 1 M aqueous HCl (15 mL) and EtOAc (25 mL). The layers were separated, and the organic layer was washed with brine (20 mL), dried ($MgSO_4$), rotary evaporated, and chromatographed (hexanes:EtOAc 2:1 to 1:1) to give the resorcylate esters or isoindolinones **22a**−**j**.

Methyl 2-((tert-Butoxycarbonyl(methyl)amino)methyl)-4,6-dihydroxybenzoate (**22a**). 89%; pale yellow solid; R_f 0.52 (hexanes:EtOAc 1:1); mp 149−152 °C (Et_2O:EtOAc 5:1); IR 3207, 2956, 1649, 1624, 1450, 1435, 1403, 1256, 1151, 1102 cm^{-1}; ^{1}H NMR (acetone-d_6, 400 MHz) δ 11.58 (s, 1H, rotamer 1 and 2), 9.27 (br s, 1H, rotamer 1 and 2), 6.32 (s, 1H, rotamer 1 and 2), 6.23 (br m, 1H, rotamer 1 and 2), 4.68 (s, 2H, rotamer 1 and 2), 3.94 (s, 3H, rotamer 1 and 2), 2.86 (s, 3H, rotamer 1 and 2), 1.48 (s, 4.85H, rotamer 1), 1.36 (s, 4.15H, rotamer 2); ^{13}C NMR (acetone-d_6, 100 MHz) δ 172.4, 172.3, 166.5, 166.3, 163.8, 156.3, 144.9, 144.5, 107.3, 106.7, 104.2, 104.0, 102.1, 79.6, 53.2, 52.8, 52.4, 35.1, 35.0, 29.8 (3C) (contains rotamers); HRMS (ESI) calcd $C_{15}H_{21}NO_6$: $[M + Na]^+$ 334.1267; found $[M + Na]^+$ 334.1264. Anal. Calcd for

$C_{15}H_{21}NO_6$: C, 57.87; H, 6.80; N, 4.50. Found: C, 57.75; H, 6.76; N, 4.44.

*tert-Butyl 5,7-Dihydroxy-1-oxoisoindoline-2-carboxylate (**22b**).* 82%; off-white solid; R_f 0.48 (hexanes:EtOAc 1:1); mp 102−105 °C (Et_2O:EtOAc 5:1); IR 3364, 2927, 1754, 1632, 1347, 1295, 1152 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 9.44 (s, 1H), 8.65 (s, 1H), 6.54 (d, J = 0.8 Hz, 1H), 6.32 (d, J = 1.2 Hz, 1H), 4.69 (s, 2H), 1.55 (s, 9H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 169.7, 166.7, 160.2, 151.6, 145.8, 110.4, 104.0, 103.3, 83.6, 51.3, 29.3 (3C); HRMS (ESI) calcd $C_{13}H_{15}NO_5$: $[M + MeCN + Na]^+$ 329.1113; found $[M + MeCN + Na]^+$ 329.1122.

*(S)-tert-Butyl 4,6-Dihydroxy-1-methyl-3-oxoisoindoline-2-carboxylate (**22c**).* 85%; white solid; R_f 0.50 (hexanes:EtOAc 1:1); mp 115−116 °C (Et_2O:EtOAc 5:1); IR 3366, 2980, 1751, 1631, 1477, 1334, 1227, 1152 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 9.41 (br s, 1H), 8.68 (br s, 1H), 6.52 (d, J = 0.8 Hz, 1H), 6.31 (d, J = 1.6 Hz, 1H), 4.99 (q, J = 2.4 Hz, 1H), 1.57−1.56 (m, 9H + 3H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 169.5, 166.8, 160.2, 151.7, 151.5, 108.9, 103.3, 83.7, 58.7, 29.3 (3C), 21.6; HRMS (ESI) calcd $C_{14}H_{17}NO_5$: $[M + MeCN + Na]^+$ 343.1270; found $[M + MeCN + Na]^+$ 343.1260.

*(S)-tert-Butyl 4,6-Dihydroxy-1-isopropyl-3-oxoisoindoline-2-carboxylate (**22d**).* 85%; off-white solid; R_f 0.56 (hexanes:EtOAc 1:1); mp 149−152 °C (Et_2O:EtOAc 4:1); IR 3351, 2974, 1747, 1626, 1350, 1310, 1284, 1228, 1135 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 9.92−8.54 (br m, 1H + 1H), 6.51 (br s, 1H), 6.34 (d, J = 1.6 Hz, 1H), 4.97 (d, J = 2.8 Hz, 1H), 2.64 (m, 1H), 1.55 (s, 9H), 1.15 (d, J = 7.2 Hz, 3H), 0.54 (d, J = 6.8 Hz, 3H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 170.1, 166.2, 160.3, 151.6, 147.8, 110.3, 104.8, 103.4, 83.9, 67.2, 32.0, 29.3 (3C), 20.0, 16.4; HRMS (ESI) calcd $C_{16}H_{21}NO_5$: $[M + MeCN + Na]^+$ 371.1583; found $[M + MeCN + Na]^+$ 371.1562. Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.65; H, 6.75; N, 4.52.

*(S)-tert-Butyl 4,6-Dihydroxy-1-isobutyl-3-oxoisoindoline-2-carboxylate (**22e**).* 86%; white solid; R_f 0.58 (hexanes:EtOAc 1:1); mp 97−100 °C (Et_2O:EtOAc 4:1); IR 3332, 2964, 2690, 1742, 1668, 1628, 1469, 1383, 1142, 1117, 953 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 9.79−8.49 (br m, 1H + 1H), 6.52 (br s, 1H), 6.33 (d, J = 1.6 Hz, 1H), 5.06 (d, J = 3.6 Hz, 1H), 1.98−1.86 (m, 2H), 1.72−1.61 (m, 1H), 1.56 (s, 9H), 0.90 (d, J = 5.2 Hz, 3H), 0.88 (d, J = 4.8 Hz, 3H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 169.9, 166.6, 160.4, 151.4, 150.5, 109.6, 103.9, 83.8, 61.6, 43.5, 29.3 (3C), 25.7, 25.2, 24.2; HRMS (ESI) calcd $C_{17}H_{23}NO_5$: $[M + MeCN + Na]^+$ 385.1739; found $[M + MeCN + Na]^+$ 385.1719. Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.67; H, 7.13; N, 4.30.

*(S)-tert-Butyl 1-(Benzyloxymethyl)-4,6-dihydroxy-3-oxoisoindoline-2-carboxylate (**22f**).* 88%; pale pink solid; R_f 0.62 (hexanes:EtOAc 1:1); mp 70−72 °C (Et_2O:EtOAc 10:1); IR 3312, 1751, 1682, 1615, 1365, 1335, 1287, 1146 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.51 (s, 1H), 7.35 (m, 3H), 7.23 (m, 2H), 6.49 (s, 1H),6.34 (s, 1H), 6.06 (br s, 1H), 5.01 (dd, J = 6.4, 2.8 Hz, 1H), 4.50 (m, 2H), 4.01 (dd, J = 9.2, 3.2 Hz, 1H), 3.72 (dd, J = 9.2, 2.4 Hz, 1H), 1.54 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.9, 163.2, 158.4, 149.7, 146.3, 137.5, 128.5 (2C), 127.8 (2C), 127. 7, 108.6, 102.6, 102.4, 83.6, 69.7, 60.2, 28.1 (3C); HRMS (ESI) calcd $C_{21}H_{23}NO_6$: $[M + Na]^+$ 408.1423; found $[M + Na]^+$ 408.1409.

*Methyl 2,4-Dihydroxy-6-((N-methylphenylsulfonamido)methyl)benzoate (**22g**).* 91%; white solid; R_f 0.36 (hexanes:EtOAc 1:1); mp: 134−137 °C (Et_2O:EtOAc 2:1); IR 3390, 2625, 1654, 1620, 1591, 1436, 1325, 1257, 1194, 1141, 1085 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 11.54 (s, 1H), 7.88−7.85 (m, 2H), 7.67−7.57 (m, 3H), 6.65 (d, J = 2.4 Hz, 1H), 6.61 (br s, 1H), 6.39 (d, J = 2.8 Hz, 1H), 4.46 (s, 2H), 3.88 (s, 3H), 2.69 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ171.0, 165.5, 161.6, 140.8, 137.1, 132.9, 129.2 (2C), 127.4 (2C), 108.5, 104.1, 102.8, 54.0, 52.1, 35.6; HRMS (ESI) calcd $C_{16}H_{17}NO_6S$: $[M + H]^+$ 352.0856; found $[M + H]^+$ 352.0863. Anal. Calcd for $C_{16}H_{17}NO_6S$: C, 54.69; H, 4.88; N, 3.99; S, 9.13. Found: C, 54.57; H, 4.67; N, 3.92; S, 9.07.

*Methyl 2,4-Dihydroxy-6-((N-methylpyridine-2-sulfonamido)methyl)benzoate (**22h**).* 94%; white solid; R_f 0.30 (hexanes:EtOAc 1:1); mp 184−186 °C (Et_2O:EtOAc 2:1); IR 3106, 2957, 1649, 1624, 1587, 1351, 1332, 1256, 1166, 1113 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 11.45 (s, 1H), 9.36 (s, 1H), 8.82−8.81 (m, 1H), 8.17−8.13 (m, 1H), 8.02−8.00 (m, 1H), 7.73−7.70 (m, 1H), 6.73 (d, J = 2.4 Hz, 1H), 6.33 (d, J = 2.4 Hz, 1H), 4.76 (s, 2H), 3.90 (s, 3H), 2.85 (s, 3H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 171.2, 165.3, 163.0, 157.3, 150.2, 142.0, 138.4, 127.0, 122.7, 108.1, 103.5, 101.9, 54.6, 51.6, 35.8; HRMS (ESI) calcd $C_{15}H_{16}N_2O_6S$: $[M + H]^+$ 353.0808; found $[M + H]^+$ 353.0805. Anal. Calcd for $C_{15}H_{16}N_2O_6S$: C, 51.13; H, 4.58; N, 7.95; S, 9.10. Found: C, 51.09; H, 4.47; N, 7.86; S, 8.97.

*Methyl 2,4-Dihydroxy-6-((N,3,5-trimethylisoxazole-4-sulfonamido)methyl)benzoate (**22i**).* 90%; white solid; R_f 0.28 (hexanes:EtOAc 1:1); mp 218−221 °C (Et_2O:EtOAc 3:1); IR 3197, 2924, 2856, 1655, 1625, 1588, 1409, 1329, 1257, 1168, 1112 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 11.43 (s, 1H), 9.37 (s, 1H), 6.65 (d, J = 2.4 Hz, 1H), 6.34 (d, J = 2.8 Hz, 1H), 4.69 (s, 2H), 3.94 (s, 3H), 2.79 (s, 3H), 2.70 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 175.5, 173.0, 167.3, 164.8, 159.4, 143.2, 116.5, 109.9, 105.4, 103.9, 55.2, 53.6, 36.3, 14.0, 12.5; HRMS (ESI) calcd $C_{15}H_{18}N_2O_7S$: $[M + H]^+$ 371.0914; found $[M + H]^+$ 371.0901. Anal. Calcd: C, 48.64; H, 4.90; N, 7.56; S, 8.66. Found: C, 48.59; H, 4.86; N, 7.48; S, 8.57.

*Methyl 2-((5-Chloro-N,1,3-trimethyl-1H-pyrazole-4-sulfonamido)-methyl)-4,6-dihydroxybenzoate (**22j**).* 90%; white solid; R_f 0.25 (hexanes:EtOAc 1:1); mp 126−130 °C (Et_2O:EtOAc 3:1); IR 3169, 2924, 1654, 1621, 1589, 1433, 1326, 1253, 1163, 1114 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 11.45 (s, 1H), 9.36 (s, 1H), 6.67 (d, J = 2.8 Hz, 1H), 6.33 (d, J = 2.4 Hz, 1H), 4.63 (s, 2H), 3.92 (s, 3H), 3.87 (s, 3H), 2.74 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 173.1, 167.3, 164.8, 150.0, 143.6, 130.9, 115.5, 109.8, 105.3, 103.7, 55.4, 53.6, 38.1, 36.6, 15.3; HRMS (ESI) calcd $C_{15}H_{18}ClN_3O_6S$: $[M + H]^+$ 404.0684; found $[M + H]^+$ 404.0671. Anal. Calcd for $C_{15}H_{18}ClN_3O_6S$: C, 44.61; H, 4.49; N, 10.41; S, 7.94. Found: C, 44.67; H, 4.56; N, 10.36; S, 7.86.

*5,7-Dihydroxy-2-methylisoindolin-1-one (**24**).* Resorcylate **21a** (0.10 g, 0.30 mmol) and Cs_2CO_3 (0.20 g, 0.60 mmol) were suspended in MeOH (3 mL) and heated at 60 °C. After 18 h, the solvent was evaporated and the mixture partitioned between 1 M aqueous HCl (10 mL) and EtOAc (20 mL). The layers were separated, and the organic layer was washed with brine (15 mL), dried ($MgSO_4$), and rotary evaporated to give crude **22a**, which was dissolved in MeOH (3 mL). To the stirred solution was added HCl in Et_2O (1.0 M; 10 mL, 10 mmol) at room temperature. After 14 h, the solvent was rotary evaporated, the crude intermediate salt **23** dissolved in MeOH (10 mL), Et_3N (1 mL) added, and the resultant mixture stirred at room temperature. After 3 h, the solvent was evaporated and the mixture partitioned between 1 M aqueous HCl (20 mL) and EtOAc (20 mL). The layers were separated, the aqueous layer was extracted further with EtOAc (20 mL), and the combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), rotary evaporated, and chromatographed (hexanes:EtOAc 1:1 to 0:1) to give isoindolinone **24** (45.5 mg, 86%) as a pale yellow solid: R_f 0.13 (hexanes:EtOAc 1:1); mp 151−153 °C (Et_2O:EtOAc 3:1); IR 3078, 1680, 1649, 1624, 1593, 1396, 1327, 1260, 1239, 1147, 1045 cm^{-1}; ^1H NMR (DMSO-d_6,[29] 400 MHz) δ 9.67 (br s, 1H + 1H), 6.35 (d, J = 1.6 Hz, 1H), 6.20 (d, J = 1.6 Hz, 1H), 4.25 (s, 2H), 2.93 (s, 3H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 171.5, 164.6, 158.4, 146.0, 111.5, 103.8, 102.6, 54.0, 29.5; HRMS (ESI) calcd $C_9H_9NO_3$: $[M + H]^+$ 180.0661; found $[M + H]^+$ 180.0661.

■ ASSOCIATED CONTENT

Supporting Information. Copies of ^1H and ^{13}C NMR spectra corresponding to all reported compounds and further

information related to the biological assay methods. This material is available free of charge via the Internet at http://pubs.acs.org.

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REFERENCES

(1) Winssinger, N.; Barluenga, S. *Chem. Commun.* **2007**, *1*, 22.
(2) Miksicek, R. J. *J. Steroid Biochem. Mol. Biol.* **1994**, *49*, 153.
(3) (a) Schulte, T. W.; Akinaga, S.; Soga, S.; Sullivan, W.; Stensgard, B.; Toft, D.; Neckers, L. M. *Cell Stress Chaperones* **1998**, *3*, 100. (b) Sharma, S. V.; Agatsuma, T.; Nakano, H. *Oncogene* **1998**, *16*, 2639.
(4) Barluenga, S.; Dakas, P.-Y.; Meijer, L.; Winssinger, N. *Angew. Chem., Int. Ed.* **2006**, *45*, 3951.
(5) Isaka, M.; Suyarnsestakorn, C.; Tanticharoen, M.; Kongsaeree, P.; Thebtaranonth, Y. *J. Org. Chem.* **2002**, *67*, 1561.
(6) Ninomiya-Tsuji, J.; Kajino, T.; Ono, K.; Ohtomo, T.; Matsumoto, M.; Shiina, M.; Mihara, M.; Tsuchiya, M.; Matsumoto, K. *J. Biol. Chem.* **2003**, *278*, 18485.
(7) (a) Navarro, I.; Basset, J.-F.; Hebbe, S.; Major, S. M.; Werner, T.; Howsham, C.; Brackow, J.; Barrett, A. G. M. *J. Am. Chem. Soc.* **2008**, *130*, 10293. (b) Calo, F.; Richardson, J.; Barrett, A. G. M. *Org. Lett.* **2009**, *11*, 4910.
(8) Harris, T. M.; Harris, C. M. *Tetrahedron* **1977**, *33*, 2159.
(9) Baldwin, J. E.; Adlington, R. M.; Gollins, D. W.; Schofield, C. J. *Tetrahedron* **1990**, *46*, 4733.
(10) Wang, P.-A.; Xu, Z.-S.; Chen, C.-F.; Gao, X.-G.; Sun, X.-L.; Zhang, S.-Y. *Chirality* **2007**, *19*, 581.
(11) Morwick, T.; Hrapchak, M.; DeTuri, M.; Campbell, S. *Org. Lett.* **2002**, *4*, 2665.
(12) The known Weinreb amides were authenticated by comparisons of their ^{1}H NMR spectra with reported data and used immediately in the following step: (a) Blaney, P.; Grigg, R.; Rankovic, Z.; Thornton-Pett, M.; Xu, J. *Tetrahedron* **2002**, *58*, 1719. (b) Sibi, M. P.; Stessman, C. C.; Schultz, J. A.; Christensen, J. W.; Lu, J.; Marvin, M. *Synth. Commun.* **1995**, *25*, 1255.
(13) Anderson, J. C.; Ford, J. G.; Whiting, M. *Org. Biomol. Chem.* **2005**, *3*, 3734.
(14) Because of their instability and unsuccessful purification by silica gel column chromatography, the structures of the imidazole derivatives were immediately verified using ^{1}H NMR spectroscopy, and the compounds were used directly in the following step.
(15) Navarro, I.; Pöverlein, C.; Schlingmann, G.; Barrett, A. G. M. *J. Org. Chem.* **2009**, *74*, 8139.
(16) Patel, B. H.; Mason, A. M.; Barrett, A. G. M. *Org. Synth.* **2011**, manuscript submitted.
(17) Morita, Y.; Masaaki, S.; Noyori, R. *J. Org. Chem.* **1989**, *54*, 1785.
(18) Other electrophiles such as the acyl chloride, acyl benzotriazole, and activated ester were attempted for C-acylation; however, further improvements in yield were not observed.
(19) Conversions determined from ^{1}H NMR spectra of crude product.
(20) (a) Basset, J.-F.; Leslie, C.; Hamprecht, D.; White, A. J. P.; Barrett, A. G. M. *Tetrahedron Lett.* **2010**, *51*, 783. (b) Patel, B. H.; Heath, S. F .A.; Mason, A. M.; Barrett, A. G. M. *Tetrahedron Lett.* **2011**, *52*, 2258.
(21) The lower yields obtained for compounds **21m** and **21n** were most likely due to side reactions occurring in the C-acylation step with the β-lactam ring and the pyrrolidine ester, respectively.
(22) Compounds **21d** and **21h** were not transesterified because several other examples of naturally occurring amino acids had been carried out successfully; compounds **21m** and **21n** were not transesterified because of the unfortunate lower yields in the preceding steps.
(23) (a) Hoarau, C.; Couture, A.; Deniau, E.; Grandclaudon, P. *Synthesis* **2000**, *5*, 655.(b) Wagenen B. V.; Ukkiramapandian R.; Clayton J.; Egle I.; Empfield J. R.; Isaac M.; Ma F.; Slassi A.; Steelman G.; Urbanek R.; Walsh S. US Patent 7,868,008, 2009.
(24) An alternative route was attempted via *N*-Boc deprotection of **21a** and subsequent intramolecular ring opening to give **24**; however, high temperature (135 °C) was required and the yield was lower (67%).
(25) Both Et_3N or NaOMe in MeOH can be used for this lactamization.
(26) Schirmer, A.; Kennedy, J.; Murli, S.; Reid, R.; Santi, D. V. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 4234.
(27) Moulin, E.; Barluenga, S.; Totzke, F.; Winssinger, N. *Chem.—Eur. J.* **2006**, *12*, 8819.
(28) For the imidazole derivatives, the reaction mixture was held at −78 °C, the imidazole (0.52 mmol) in THF (1.5 mL) was added, and the reaction mixture was stirred for 2 h.
(29) ^{1}H NMR was initially recorded in acetone-d_6; however, the OH protons were not observed and therefore the spectrum was recorded in DMSO-d_6.