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Design, Synthesis, and Structure–Activity Relationship of a Novel Series of GluN2C-Selective Potentiators

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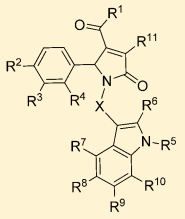
Supporting Information

ABSTRACT: NMDA receptors are tetrameric complexes composed of GluN1 and GluN2A–D subunits that mediate a slow Ca^{2+}-permeable component of excitatory synaptic transmission. NMDA receptors have been implicated in a wide range of neurological diseases and thus represent an important therapeutic target. We herein describe a novel series of pyrrolidinones that selectively potentiate only NMDA receptors that contain the GluN2C subunit. The most active analogues tested were over 100-fold selective for recombinant GluN2C-containing receptors over GluN2A/B/D-containing NMDA receptors as well as AMPA and kainate receptors. This series represents the first class of allosteric potentiators that are selective for diheteromeric GluN2C-containing NMDA receptors.



INTRODUCTION

N-Methyl-D-aspartate (NMDA) receptors are members of the family of ionotropic glutamate receptors that mediate excitatory neurotransmission. NMDA receptors are tetrameric assemblies of two GluN1 subunits, which bind the coagonist glycine, and two GluN2 subunits, which bind glutamate.[1] Both GluN1 and GluN2 subunits share a similar architecture, comprised of an extracellular amino-terminal domain (ATD), an extracellular ligand-binding domain (LBD), a transmembrane domain (TMD), and an intracellular carboxyl-terminal domain (CTD).[2] The GluN2 subunit is encoded by four distinct gene products (GluN2A-D), which have temporally and spatially distinct expression patterns in the brain.[3] The GluN2 subunit controls pharmacological characteristics such as agonist sensitivity, deactivation time course, mean open time, and open probability.[2,3b,4]

The distinct anatomical locations of the GluN2 subunits could allow subunit-selective modulators (either potentiators or inhibitors) to target specific brain regions for therapeutic gain. NMDA receptors are thought to play a role in neuronal development, learning, and memory formation,[5] as well as being implicated in ischemia,[6] dementia,[7] schizophrenia,[8] treatment resistant depression,[9] and Parkinson's disease.[10] Recently discovered modulators have demonstrated selectivity for GluN2A, 3-chloro-4-fluoro-*N*-[4-[[2-(phenylcarbonyl)hydrazino]carbonyl]benzyl]-benzenesulfonamide (TCN201); GluN2A/GluN2B, 9-cyclopropylphenanthrene-3-carboxylic acid (UBP710); and GluN2C/GluN2D, (3-chlorophenyl) [3,4-dihydro-6,7-dimethoxy-1-[(4-methoxyphenoxy)methyl]-2(1*H*)-isoquinolinyl]methanone (CIQ), 4-[6-methoxy-2-[(1*E*)-2-(3-nitrophen yl)ethenyl]-4-oxo-3(4*H*)quinazolinyl]benzoic acid (QNZ46), 5-(4-bromophenyl)-3-(1,2-dihydro-6- methyl-2-oxo-4-phenyl-3-quinolinyl)-4,5-dihydro-g-oxo-1*H*-pyrazole-1-butanoic acid (DQP1105), and (2*R*,3*S*)-1-(phenanthrenyl-3-carbonyl)piperazine-2,3-dicarboxylic acid (UBP141).[11] Here, we describe the development of the first class of positive allosteric modulators that are selective for GluN2C-containing NMDA receptors over GluN2A-, GluN2B-, and GluN2D-containing receptors.

To identify this class of ligands, a GluN1/GluN2C cell line and multiwell fluorescence-based assay were developed to enable screening of compound libraries for NMDA receptor modulators. We screened two commercial diversity libraries to identify several compounds that modulate GluN2C-containing NMDA receptors. One of these screening hits established a novel class of subunit-selective potentiators for recombinant GluN1/GluN2C NMDA receptors, exemplified by compound **1** (Figure 1). Optimization of the initial lead pyrrolidinone scaffold involved the development of a structure–activity relationship, which led to the identification of a novel series of compounds with potency in the low micromolar range and high selectivity for recombinant GluN2C-containing receptors over GluN2A/B/D-containing NMDA receptors. In addition, no detectable potentiation was observed at recombinant AMPA, kainate, GABA, glycine, serotonin, nicotinic, or purinergic receptors (data not shown).

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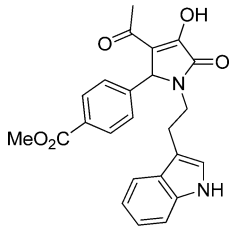

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Figure 1. Structure of screening hit. Chemical structure of methyl 4-(1-(2-(1*H*-indol-3-yl)ethyl)-3-acetyl-4-hydroxy-5-oxo-2,5-dihydro-1*H*-pyrrol-2-yl)benzoate (compound **1**) that was identified as a positive modulator using a fluorescence-based screen of compound libraries in a cell line expressing diheteromeric GluN1/GluN2C NMDA receptors.

These analogues represent a novel class of NMDA receptor modulators that are highly selective for diheteromeric GluN1/GluN2C receptor subtypes and provide a useful tool with which to evaluate the physiological role of GluN2C in normal and neuropathological conditions.

RESULTS

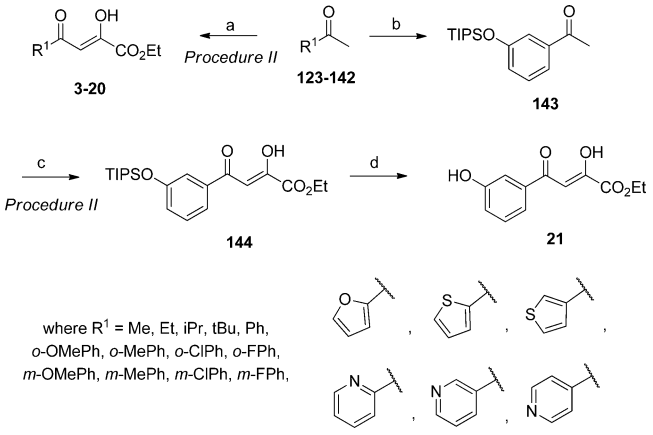
Chemistry. We used bioinformatic searches and medicinal chemistry to obtain analogues for our initial screening hit, compound **1** (see below). Both commercially available analogues and compounds synthesized via a mi-component Biginelli-like reaction (Scheme 1) were assessed at 30 μM. We determined the EC_{50} and maximal potentiation from concentration–effect curves for compounds that showed potentiation of more than 120% of control at 30 μM. No compounds in this class potentiated GluN2A-, GluN2B-, or GluN2D-containing receptors, suggesting remarkable selectivity for this class (see below). Modifications were made at either R^1, the A-ring, or the B-ring using alternative methodologies to access the appropriate precursor.

Addition of diethyl oxalate and sodium ethoxide to a methyl ketone generated a series of pyruvate analogues (**3**–**20**) containing modifications at R^1 (Scheme 2). Only when R^1 was a phenol was it necessary to first protect the hydroxyl group with triisopropyl chloride (TIPSCl) before the addition of diethyl oxalate. Standard deprotection afforded the target pyruvate (**21**).

Analogues containing disubstituted A-rings were synthesized using several procedures based on the commercially available precursors (Scheme 3). Benzaldehydes **32**–**41** were prepared from methyl esters **145**–**154**. Dibromination and hydrolysis afforded analogues **32** and **33**.[12] Suzuki coupling between dibutyl vinylboronate and the appropriately substituted methyl 4-iodobenzoate, followed by ozonolysis, gave phenols **34** and **35**. Alternatively, addition of a Grignard reagent and *N*,*N*-dimethylformamide (DMF) led to isolation of benzaldehyde **36**. A palladium-catalyzed formylation was used to access benzaldehydes **37**–**40**.[13] Finally, anisole **41** was prepared via a dialkylation of both the hydroxyl and carboxylic acid functional groups.

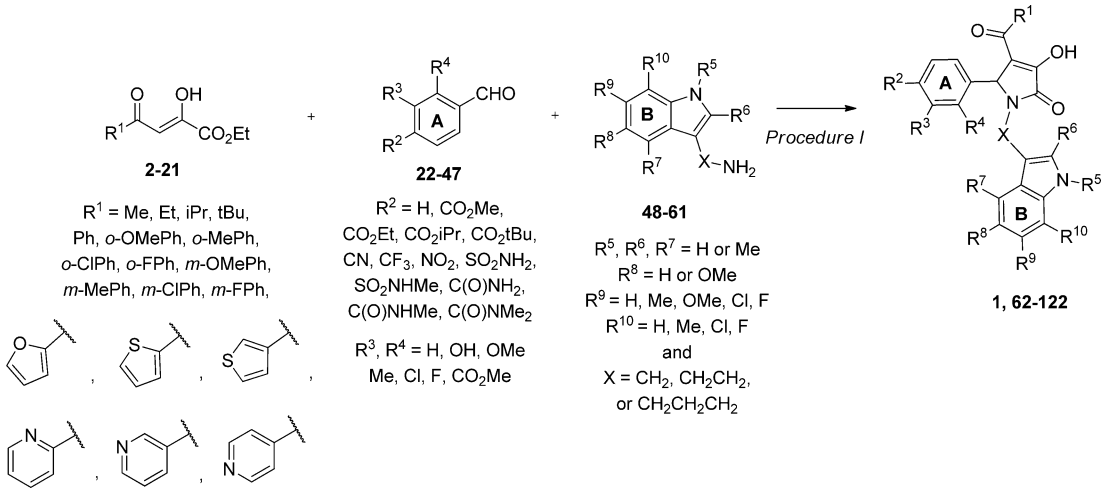
Benzaldehydes containing a *para*-amide (**42**–**44**) or *para*-ester (**45**–**47**) substituent were synthesized as illustrated in Scheme 4. Primary amide **42** was synthesized from carboxylic acid **155** by generating the acid chloride in situ. Standard amide

Scheme 2. Route for the Synthesis of Pyruvate Derivatives[a]



[a]Reaction conditions: (a) diethyl oxalate, NaOEt, EtOH, 0 °C to rt, 4 h, 15% to >99% (procedure II); (b) TIPSCl, imidazole, rt, 6 h, >99%; (c) diethyl oxalate, NaOEt, EtOH, 0 °C to rt, 4 h, 28% (procedure II); (d) TBAF, 0 °C to rt, 1 h, 43%.

Scheme 1. Synthesis of 1*H*-Pyrrol-2(5*H*)-ones[a]



[a]Reaction conditions: PPTS, rt, 1–24 h, 2% to >99% (procedure I). Final compounds **161**–**180**, in which either the A or B ring is replaced, were also prepared using these conditions.

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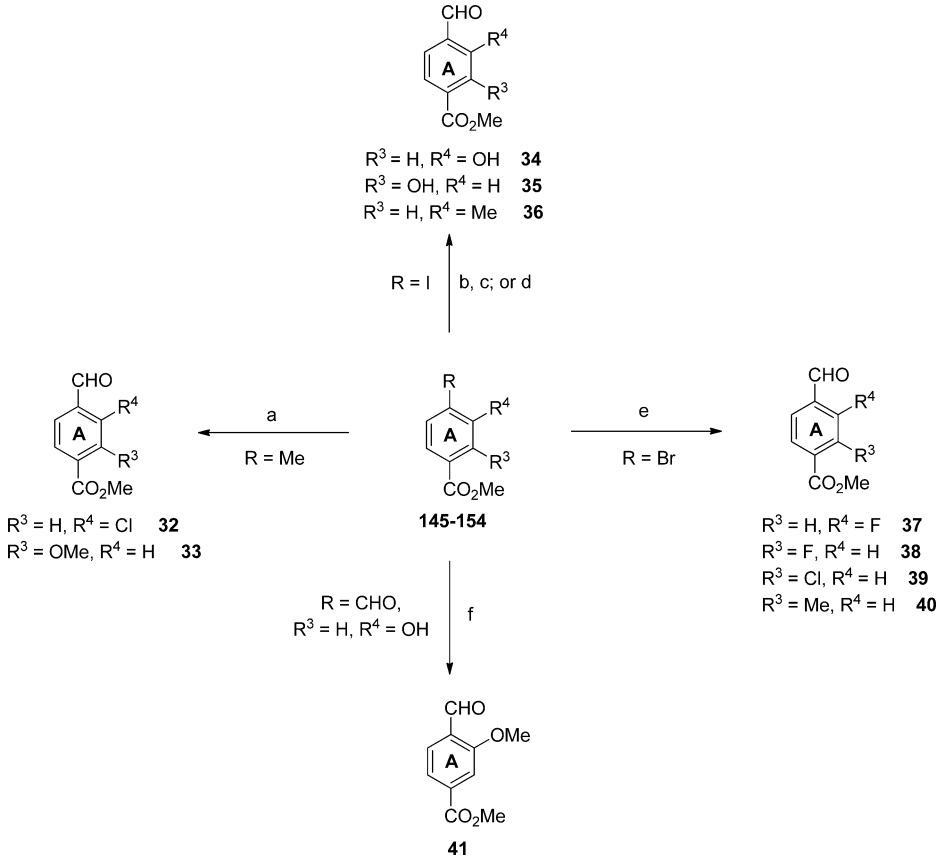
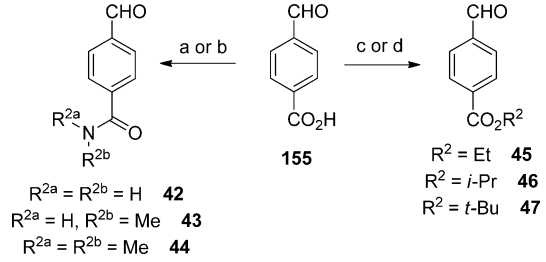
Scheme 3. Synthetic Routes to Access Substituted Benzaldehydes 32−41[a]



[a]Reaction conditions: (a) 2.0 equiv NBS, $(PhCOO)_2$, reflux, 4 h, then $AgNO_3$, rt, 3 h, 38−63%; (b) dibutyl vinylboronate, 5 mol % $(PPh_3)_2PdCl_2$, $NaCO_3$, reflux, 2 h, 68−80%; (c) O_3; then $(CH_3)_2S$, −78 °C to rt, 12 h, 60−87%; (d) *i*-PrMgCl, DMF, −15 °C to rt, 3 h, 70%; (e) $CO_{(g)}$, $(PPh_3)_2PdCl_2$, $NaCO_3$, 110 °C, 8−24% (procedure IV); (f) CH_3I, K_2CO_3, rt, 3 h, 58%.

Scheme 4. Routes for the Synthesis of Amides 42−44 and Esters 45−47[a]



[a]Reaction conditions: (a) Vilsmeier reagent, aq NH_3, 0 °C, 16 h, 30%; (b) $R^{2a}R^{2b}N$ where R^{2a} = H and R^{2b} = Me or where R^{2a} = R^{2b} = Me, DMAP, EDCI, 0 °C to rt, 24 h, 14−51%; (c) R^2I where R^2 = Et or R^2 = *i*-Pr, K_2CO_3, rt, 4 h, 24−87%; (d) $(CH_3)_2NCH(Ot\text{-}Bu)_2$, reflux, $1^1/_2$ h, 81%.

coupling conditions were employed for the preparation of amides **43** and **44**. Alkylation of carboxylic acid **155** with the appropriate alkyl iodide afforded esters **45** and **46**, while *t*-butyl ester **47** was prepared using a method previously described.[14]

An alternative strategy was used to synthesize analogues containing a modification at R^{11} starting from pyrrolidinones **1** and **106** (Scheme 5). Protection of analogue **1** with trimethylsilyl diazomethane afforded methoxy **156**. Amine **157** was generated by reaction with ammonium formate. Esterification of **1** with acetic anhydride gave acetate **158**. Alternatively, esters **159** and **160** were synthesized from enol **106** using the appropriate acyl chloride and triethylamine.

Pyrrolidinones Selectively Potentiate GluN2C-Containing Receptors. A fluorescence-based screen of 57504 compounds obtained from Asinex and ChemDiv libraries was performed in BHK cells with inducible expression of GluN1/GluN2C receptors. Hits were defined as compounds that produced changes that were 2.5 standard deviations away from the average response to maximally effective agonist (i.e., glutamate and glycine) application. In this primary screen, 1% of the compounds met these criteria. Compounds that showed potentiation were further evaluated for their ability to produce responses in cells with no NMDA receptor expression (in uninduced cells) in order to identify false positive hits. False positive results can occur when the compounds directly release Ca^{2+} from intracellular stores, enhance Ca^{2+} channel function, possess fluorescent properties in the excitation/emission range of Fluo-4, or otherwise produce an increase in intracellular Ca^{2+} signal independent of NMDA receptor activation. Compounds that showed potentiation of glutamate responses in induced cells and did not produce responses in uninduced cells were subsequently studied by two-electrode voltage-clamp recording of NMDA receptor responses.

A single compound was found to selectively potentiate the GluN1/GluN2C receptors and did not show any activity at GluN2A/B/D-containing NMDA receptors expressed in *Xenopus laevis* oocytes (Figure 2A). Compound **1**, which contains a pyrrolidinone core motif, potentiated GluN1/GluN2C

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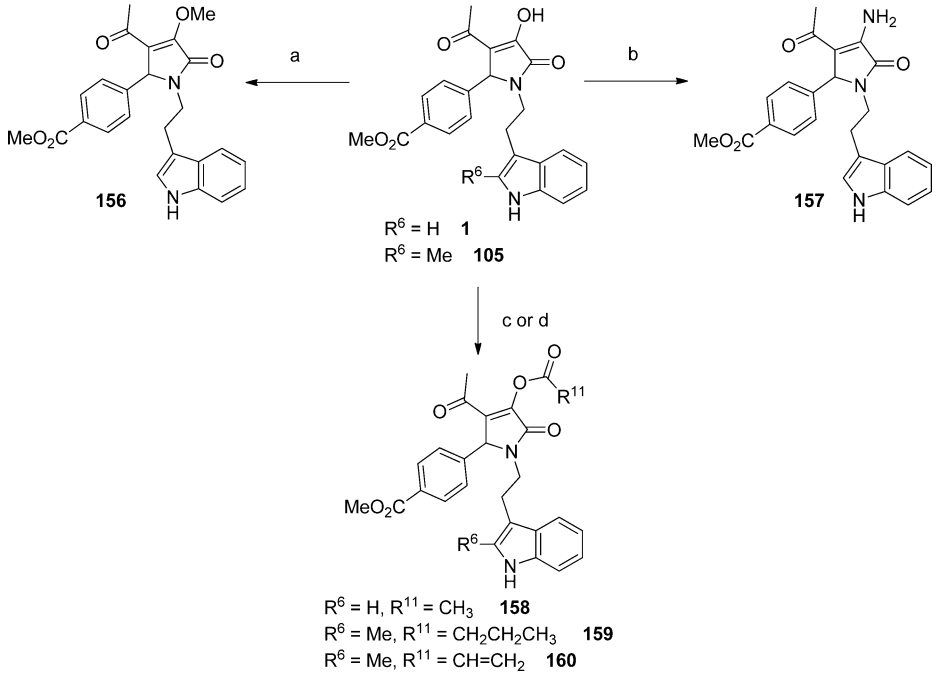
Scheme 5. Route to Modifications at R^{11}[a]



[a]Reaction conditions: (a) $TMSCH_2N_2$, rt, 5 h, 46%; (b) NH_4HCO_2, reflux, 3 h, 14%; (c) Ac_2O, pyridine, rt, $6^1/_2$ h, 7%; (d) $R^{11}C(O)Cl$ where R^{11} = $CH_2CH_2CH_3$ or R^{11} = $CH{=}CH_2$, TEA, −30 °C, 2 h, 20−35%.

responses to 238 ± 8.2% of control at 100 μM with an EC_{50} of 24 ± 2.4 μM (n = 12) (Figure 2B). Compound **1** had no agonist activity on its own in that it did not induce current responses in oocytes expressing GluN1/GluN2C in the absence of glutamate and glycine (n = 4). In addition, 30 μM of compound **1** did not potentiate homomeric recombinant GluA1 AMPA receptor responses (97 ± 1.1% control, n = 16). In addition, 120 μM of compound **1** did not potentiate homomeric GluK2 recombinant kainate receptors (95 ± 2.3% of control, n = 5).

Compound **1** (68 μM) did not detectably alter the EC_{50} of glycine or glutamate (n = 4−6; Figure 2C). Additionally, the reversal potential of glutamate and glycine induced current responses was unchanged in the presence (−5.0 + 1.2 mV, n = 6) or absence (−5.1 + 0.8 mV, n = 6) of compound **1**. Potentiation was not significantly different at −40 mV (202 ± 11%) compared to +30 mV (180 ± 12%; p = 0.2679; paired t test), indicating that potentiation of GluN2C-containing receptors by compound **1** at 20 μM was voltage-independent (n = 6; Figure 2D).

Effect of Modifications to R^1 on Potency at GluN2C-Containing Receptors. We subsequently evaluated the response to 30 μM of all pyrrolidinone analogues at GluN1/GluN2A, GluN1/GluN2B, GluN1/GluN2C, and GluN1/GluN2D and proceeded to determine the concentration−effect curve when potentiation exceeded 120% of control. Exploration of the effects of keto-linked R^1 (Scheme 1; see Chemistry section) substitutions on potentiation of GluN2C-containing receptors in oocytes revealed that additional steric bulk was tolerated, with only minimal improvements in potency (Table 1, **62**−**65**). For example, replacement of R^1 with a phenyl group, as in **65**, produced a small increase in potency (EC_{50} = 17 ± 2.3) accompanied by a modest decrease in maximal potentiation compared to compound **1** (Table 1). Analogues containing *m*-substituted phenyl rings (**66**−**70**) offered variable potentiation, while analogues with *o*- and *p*-substituted phenyl rings were inactive (data not shown). Notably, **66**, with a *meta*-hydroxyl group, displayed a considerably higher potency at GluN2C-containing receptors (7.0 ± 0.9 μM) but caused significant inhibition of GluN2A-, GluN2B-, and GluN2D-containing receptors at 100 μM (responses were 76 ± 2.0%, 42 ± 1.6%, and 48 ± 2.4% of control, respectively, normalized to agonist activated current). Such mixed-action modulators that potentiate one subunit while inhibiting another are intriguing but of little utility as pharmacological probes. Two compounds containing a pyridine ring at R^1 potentiated responses up to ∼200% with EC_{50} values of 12 ± 1.9 μM (**72**) and 8.9 ± 1.3 μM (**73**). Interestingly, **71**, which contains a 2-substituted pyridine ring, was inactive at all receptor subunits. These initial experiments confirmed the ability of derivatives within this class to selectively potentiate GluN2C-containing receptors compared to other NMDA receptor subtypes.

Effect of A-Ring Modifications. Next, we evaluated the effects of various A-ring substituents (Table 2) utilizing R^1 substitutions shown to offer the desired activity. Positional isomer analogues **81** and **82** were inactive at GluN1/GluN2C. One compound, **84**, which contains an ethyl ester at ring position R^2, displayed comparable potency compared to screening hit **1**. Analogues containing bulkier ester substituents (e.g., **85** with an *iso*-propyl ester and **86** with a *tert*-butyl ester) led to inactivity. A series of compounds containing ester isosteres including a nitrile (**87**), nitro (**88**), amide (**89**−**91**), and sulfonamide (**92** and **93**) were also evaluated for their ability to potentiate GluN2C-containing NMDA receptors. Unfortunately, none of these analogues exhibited any activity.

A variety of substituents at A-ring positions R^3 and R^4 were systematically tested while holding the *para*-methyl ester constant at R^2 (Table 3). Substitution at the *meta* position (R^3) revealed either a reduction in potency (**95**) or complete inactivity (**96**−**99**). Evaluation of a series of *ortho* (R^4) ring substituents demonstrated a preference for electron donating groups. For example, analogues containing an *ortho*-hydroxyl

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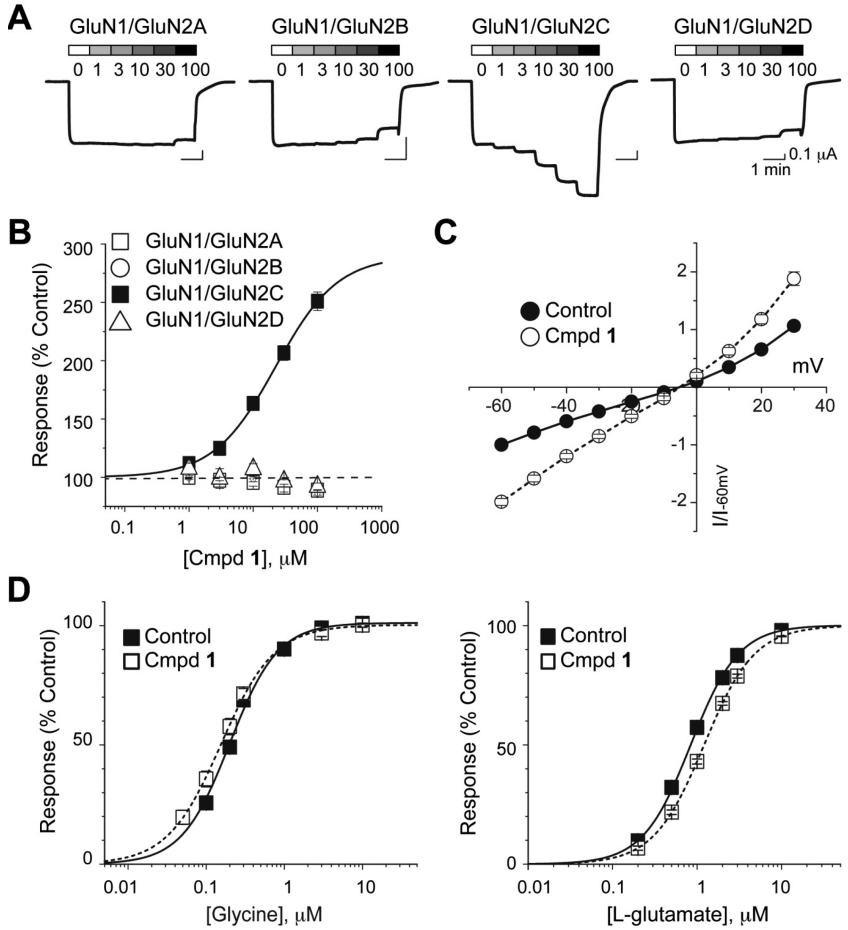

Figure 2. Compound **1** selectively potentiates the GluN1/GluN2C response. (A) Current traces for **1** at the GluN1/GluN2A, GluN1/GluN2B, GluN1/GluN2C, and the GluN1/GluN2D receptors. (B) Compound **1** selectively potentiates the GluN1/GluN2C receptor to a fitted maximum of 275 ± 10% with an EC_{50} of 24 ± 2.4, n = 12. (C) The EC_{50} for glycine in the absence and presence of **1** is 0.20 ± 0.01 μM (n = 6) and 0.16 ± 0.02 μM (n = 4), respectively. The EC_{50} for glutamate in the absence and presence of **1** is 0.8 ± 0.07 μM (n = 8) and 1.2 ± 0.04 μM (n = 6), respectively. The presence of **1** did not shift the glycine or glutamate EC_{50} values significantly. (D) The reversal potential is −5.1 ± 0.8 mV when activated by coagonists (100 μM glutamate and 30 μM glycine) and is −5.0 ± 1.2 mV (n = 6) when the GluN1/GluN2C receptor is potentiated by **1**. The reversal potential was not significantly shifted in the presence of **1**, suggesting that potentiation is independent of membrane potential.

(**100**) exhibited potentiation with a modest increase in potency, whereas *ortho*-chloro (**103**) or -fluoro (**104**) substituents were slightly less active.

Effect of B-Ring Modifications. Replacement of the B-ring with an assortment of acyclic, cyclic, and heterocyclic systems generated a series of compounds that were evaluated for potency and subunit selectivity while retaining optimal R^1 and A-ring substitutions (Table 4). Interestingly, substitution with a napthyl derivative, as in **162**, led to strong inhibition at all four subunits. Replacement of the indole NH with an oxygen atom led only to weak activity (**163**), suggesting the presence of a hydrogen bond in the binding pocket. In all other instances, removal of the indole led to complete inactivity (i.e., **164** and **165**). These data suggest that the indole functionality is preferred for activity.

This led us to examine B-ring substituents as an alternative strategy to access increased potency. The data describing these compounds is summarized in Table 5. Methylation of the indole nitrogen led to inactivity (**105**), further suggesting the importance of a hydrogen atom at this position in the binding pocket. The best potency was obtained for analogues with substitutions at B-ring position R^9. Compound **111** demonstrated an ability to selectively potentiate GluN2C-containing NMDA receptors up to 218% with an EC_{50} value of 4.3 ± 0.3 μM. It is unclear whether the increase in potency observed for **111** can be ascribed to a steric effect or, alternatively, to a mildly electropositive effect. Consistent with a steric effect, analogues which contain larger R^9 substituents such as R^9 = OMe (**112**) revealed a loss of potency compared to **111**. Analogues containing strongly electron withdrawing R^9 substituents such as R^9 = F (**109**) also decreased the observed activity.

Effect of Combinatorial Modifications on Potency at GluN2C-Containing Receptors. We subsequently evaluated the effect of combining modifications at R^1, the A-ring and the B-ring that had previously demonstrated an improvement in potency (Table 6). Substitution with either a *meta*- or *para*-substituted pyridine ring at R^1 and a *para*-ethyl ester at R^2 revealed potentiation of GluN1/GluN2C responses with EC_{50} values of 8.2 ± 0.9 μM (**116**) and 9.7 ± 0.6 μM (**117**), respectively. Modification of the B-ring and either R^1 (R^1 = *m*-pyridine) or R^2 (R^2 = *p*-CO_2Et) exhibited a similar increase in on-target potency. For example, substitution with a methyl group at R^6 and a *para*-ethyl ester at R^2, as in analogue **119**, resulted in a 2-fold potency enhancement.

Effect of Linker Modifications on Potency of 1616-Series. The original screening hit, **1**, contains a two carbon region linking the B-ring with the core pyrrolidinone. The linker

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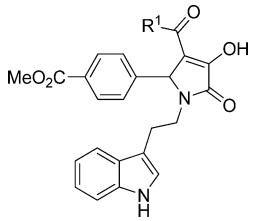
Table 1. Optimization of Potency through Evaluation of Keto-Linked Substituents



		$I_{30\ \mu M}$ / $I_{control}$ (mean ± SEM %)				EC_{50} (max.) μM (%)[a]
#	R^1	GluN2A	GluN2B	GluN2C	GluN2D	GluN2C
1	Me	95 ± 4.4	96 ± 4.1	196 ± 7.4	96 ± 3.0	24 ± 2.4 (275)
62	Et	85 ± 2.8	77 ± 2.4	160 ± 3.0	78 ± 2.0	24 ± 2.5 (204)
63[b]	*i*-Pr	95 ± 0.2	87 ± 1.8	119 ± 1.1[b]	89 ± 2.0	61 ± 10 (170)[b]
64	*t*-Bu	87 ± 4.8	93 ± 3.6	129 ± 5.8	79 ± 2.0	52 ± 6.4 (187)
65	Ph	116 ± 5.4	85 ± 2.3	143 ± 2.7	79 ± 1.4	17 ± 2.3 (161)
66	*m*-OH-Ph	89 ± 1.3	65 ± 2.4	169 ± 8.9	69 ± 2.2	7.0 ± 0.92 (176)
67	*m*-OMe-Ph	92 ± 1.1	90 ± 1.5	109 ± 2.3	80 ± 4.0	--
68	*m*-Me-Ph	97 ± 2.1	90 ± 2.8	122 ± 3.2	84 ± 0.7	16 ± 1.9 (131)
69	*m*-Cl-Ph	107 ± 6.4	83 ± 3.1	145 ± 3.4	83 ± 2.1	8.7 ± 0.3 (145)
70	*m*-F-Ph	98 ± 6.5	83 ± 2.4	133 ± 3.5	78 ± 2.4	11 ± 1.1 (136)
71		106 ± 3.5	78 ± 4.4	97 ± 3.0	75 ± 3.9	--
72		97 ± 1.7	76 ± 3.0	180 ± 7.1	78 ± 1.2	12 ± 1.9 (201)
73		92 ± 5.9	87 ± 2.9	186 ± 3.7	84 ± 1.6	8.9 ± 1.3 (196)

[a]Fitted EC_{50} values are shown for GluN1/GluN2C to two significant figures when potentiation at 30 μM of the test compound exceeded 120% of control; values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) response. Hill slopes varied between 1.2 and 2.0. Data for active compounds at GluN1/GluN2C are from between 6 and 12 oocytes from 2−3 frogs for each compound. When no effect was found (n = 3−15 oocytes), the lack of effect was confirmed by testing at 100 μM (data not shown, $n \geq 3$ oocytes all compounds). For all tables, GluN2 subunits were coexpressed with GluN1 in *Xenopus* oocytes and evaluated using two-electrode voltage-clamp recordings. [b]The response to 100 μM of test compound was greater than 140% of control.

modifications explored are illustrated in Table 7. Both shortening (**121**) and extending (**122**) the linker eliminated all activity, suggesting that the potency of pyrrolidinone analogues is highly dependent on the length of the carbon linkage.

Effect of Modifications to R^{11} on Potency at GluN2C-Containing Receptors. Several modifications were made at R^{11} to determine the significance of the enol in controlling potency and selectivity (Table 8). Replacement with an amine, as in **157**, led to a complete loss of potentiation at concentrations up to 100 μM. In most instances, compounds containing a protected alcohol led to less potent analogues. For example, a 2-fold decrease in potency was observed for acetate **158**. In contrast, propyl ester **159** maintained activity comparable to lead analogue **1**, with an EC_{50} of 17 ± 1.8 μM. These data suggest that enhancements in potency cannot be gained though modifications of the enol.

Effect of Absolute Configuration on Potency at GluN2C-Containing Receptors. To enable evaluation of potential stereoselectivity for pyrrolidinone analogues at GluN1/GluN2C, we separated the enantiomers of **106** using a semipreparatory

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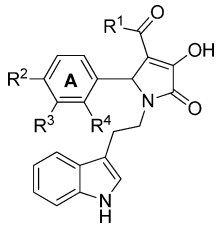
Table 2. Optimization of A-Ring Substituents



					$I_{30\ \mu M}/I_{control}$ (mean ± SEM %)				EC_{50} (max.) μM (%) [a]
#	R^1	R^2	R^3	R^4	GluN2A	GluN2B	GluN2C	GluN2D	GluN2C
81	Me	H	CO_2Me	H	99 ± 2.6	88 ± 0.91	94 ± 1.2	94 ± 1.5	--
82	Me	H	H	CO_2Me	88 ± 3.1	78 ± 0.6	99 ± 4.5	93 ± 7.0	--
83	Me	CO_2H	H	H	100 ± 8.5	94 ± 3.2	93 ± 1.0	88 ± 0.7	--
84	Me	CO_2Et	H	H	104 ± 5.8	83 ± 2.0	201 ± 4.5	91 ± 2.2	15 ± 1.1 (237)
85	Me	CO_2i-Pr	H	H	96 ± 0.9	95 ± 3.2	102 ± 2.0	83 ± 4.9	--
86	Me	CO_2t-Bu	H	H	99 ± 4.1	81 ± 4.3	85 ± 2.8	66 ± 2.8	--
87		CN	H	H	98 ± 6.8	89 ± 0.8	100 ± 2.7	94 ± 1.8	--
88	Me	NO_2	H	H	106 ± 3.4	83 ± 2.0	94 ± 0.3	77 ± 1.1	--
89		$C(O)NH_2$	H	H	101 ± 4.2	92 ± 4.5	90 ± 2.7	91 ± 0.8	--
90		C(O)NHMe	H	H	96 ± 1.3	105 ± 5.7	93 ± 2.8	89 ± 2.4	--
91		$C(O)NMe_2$	H	H	118 ± 3.2	86 ± 1.2	101 ± 1.8	89 ± 0.8	--
92		SO_2NH_2	H	H	86 ± 2.0	82 ± 1.9	123 ± 2.2	83 ± 1.5	16 ± 0.76 (130)
93		SO_2NHMe	H	H	74 ± 2.9	88 ± 1.6	114 ± 3.8	73 ± 0.6	--

[a]Fitted EC_{50} values are shown for GluN1/GluN2C to two significant figures when potentiation at 30 μM of the test compound exceeded 120% of control; values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) response. Hill slopes varied between 1.3 and 1.7. Data for active compounds at GluN1/GluN2C are from between 8 and 12 oocytes from 2−3 frogs for each compound. When no effect was found (n = 3−11 oocytes), the lack of effect was confirmed by testing at 100 μM (data not shown, $n \geq 3$ oocytes all compounds).

OD-RH chiral HPLC column (see Chemistry Experimentals). Each enantiomer was subjected to two-electrode voltage clamp analysis in *Xenopus laevis* oocytes. The results, illustrated in Figure 3, indicate that only one enantiomer (**106a**) is active and may account for the activity of **106**. Compound **106a** potentiated GluN2C response by 259 ± 7.8% with an estimated EC_{50} value of 18 ± 0.6 μM (n = 6). In contrast, no activity was observed for the other enantiomer (**106b**) (n = 6). The active analogue

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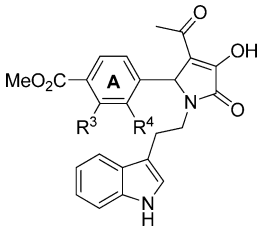
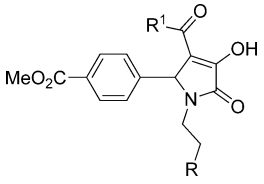
Table 3. Evaluation of Combinations of A-Ring Substituents

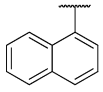
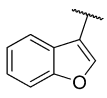
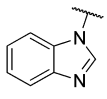


			$I_{30\ \mu M}/I_{control}$ (mean ± SEM %)				EC_{50} (max) μM (%)[a]
#	R^3	R^4	GluN2A	GluN2B	GluN2C	GluN2D	GluN2C
95	OH	H	81 ± 1.7	79 ± 1.2	123 ± 2.5	90 ± 3.0	29 ± 2.8 (151)
96	OMe	H	98 ± 3.3	80 ± 1.8	92 ± 2.4	86 ± 1.4	
97	Me	H	108 ± 3.4	91 ± 2.5	88 ± 2.1	86 ± 0.4	
98	Cl	H	88 ± 4.3	95 ± 5.1	113 ± 4.2	83 ± 1.5	
99	F	H	99 ± 4.1	83 ± 2.2	114 ± 3.3	93 ± 5.3	
100	H	OH	107 ± 3.9	86 ± 3.8	173 ± 3.0	88 ± 1.9	15 ± 0.6 (202)
101	H	OMe	102 ± 6.1	83 ± 0.3	132 ± 3.3	100 ± 3.1	46 ± 19 (183)
102	H	Me	101 ± 1.8	95 ± 4.2	129 ± 3.6	85 ± 1.9	35 ± 1.4 (165)
103	H	Cl	103 ± 3.9	87 ± 1.7	139 ± 2.8	90 ± 0.6	36 ± 3.0 (191)
104	H	F	93 ± 2.5	96 ± 2.0	123 ± 3.4	91 ± 1.1	37 ± 2.6 (155)

[a]Fitted EC_{50} values are shown for GluN1/GluN2C to two significant digits when potentiation at 30 μM of the test compound exceeded 120% of control; values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) response; Hill slopes ranged between 1.3 and 1.8. Data for active compounds at GluN1/GluN2C are from between 3 and 12 oocytes from 2−3 frogs for each compound. When no effect was found (n = 3−15 oocytes), the lack of effect was confirmed by testing at 100 μM (data not shown, $n \geq 5$ oocytes for all compounds).

Table 4. Effect of Replacing the B-Ring



			$I_{30\ \mu M}/I_{control}$ (mean ± SEM %)				**EC_{50} (max.) μM (%)[a]**
#	**R_1**	**R**	**GluN2A**	**GluN2B**	**GluN2C**	**GluN2D**	**GluN2C**
161	Me	Ph	108 ± 1.7	117 ± 4.9	95 ± 2.8	99 ± 3.7	--
162[b]	Me		44 ± 2.6[b]	20 ± 1.6[b]	34 ± 2.5[b]	18 ± 1.7[b]	--
163			96 ± 1.1	83 ± 2.6	113 ± 3.8	80 ± 2.7	--
164			104 ± 5.8	107 ± 2.7	84 ± 4.1	89 ± 3.0	--
165			101 ± 2.6	95 ± 1.0	89 ± 6.1	94 ± 2.0	--

[a]Fitted EC_{50} values are shown for GluN1/GluN2C to two significant digits when potentiation at 30 μM of the test compound exceeded 120% of control; values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) response. All data are from 3−14 oocytes from 2−3 frogs. When no effect was found, the lack of effect was confirmed by testing at 100 μM (data not shown, $n \geq 3$ oocytes for all compounds). [b]Inhibited at GluN1/GluN2A with an IC_{50} of 18 μM, at GluN1/GluN2B with an IC_{50} of 7.2 μM, at GluN1/GluN2C with an IC_{50} of 11 μM, and GluN1/GluN2D with an IC_{50} of 5.7 μM.

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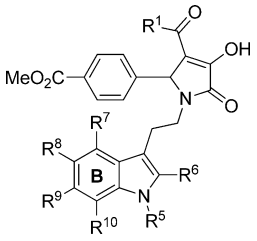
Table 5. Optimization of B-Ring Substituents



								$I_{30\ \mu M}/I_{control}$ (mean ± SEM %)				EC_{50} (max.) μM (%) [a]
#	R^1	R^5	R^6	R^7	R^8	R^9	R^{10}	GluN2A	GluN2B	GluN2C	GluN2D	GluN2C
105		Me	H	H	H	H	H	111 ± 5.4	87 ± 2.5	106 ± 3.3	85 ± 1.9	--
106	Me	H	Me	H	H	H	H	97 ± 3.8	88 ± 1.6	179 ± 3.4	95 ± 2.5	16 ± 0.5 (217)
107		H	H	Me	H	H	H	112 ± 0.8	70 ± 3.7	85 ± 2.7	74 ± 1.4	--
108		H	H	H	OMe	H	H	112 ± 1.6	90 ± 3.7	94 ± 2.6	91 ± 4.3	--
109		H	H	H	H	F	H	94 ± 4.3	64 ± 3.3	163 ± 11	82 ± 1.7	13 ± 1.8 (167)
110		H	H	H	H	Cl	H	93 ± 8.1	66 ± 1.4	170 ± 9.2	86 ± 3.0	8.5 ± 1.0 (204)
111		H	H	H	H	Me	H	103 ± 1.1	82 ± 1.5	219 ± 5.4	86 ± 1.7	4.3 ± 0.3 (218)
112		H	H	H	H	OMe	H	84 ± 1.8	98 ± 7.6	194 ± 2.8	85. ± 0.7	8 ± 1.3 (204)
113		H	H	H	H	H	F	105 ± 2.4	84 ± 1.2	161 ± 3.2	86 ± 4.7	18 ± 1.8 (191)
114		H	H	H	H	H	Cl	90 ± 3.4	85 ± 3.7	127 ± 2.3	78 ± 1.5	7 ± 2.1 (128)
115	Me	H	H	H	H	H	Me	98 ± 5.1	81 ± 2.4	121 ± 3.7	92 ± 1.1	25 ± 2.9 (139)

[a]Fitted EC_{50} values are shown for GluN1/GluN2C to two significant digits when potentiation at 30 μM of the test compound exceeded 120% of control; values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) response. Hill slopes were between 1.3 and 1.9. Data for active compounds at GluN1/GluN2C are from between 6 and 27 oocytes from 2−3 frogs for each compound. When no effect was found (n = 4−11 oocytes), the lack of effect was confirmed by testing at 100 μM (data not shown, $n \geq 4$ oocytes for all compounds).

demonstrated weak inhibition at GluN2D-containing receptors and had no effect at GluN2A- or GluN2B-containing receptors. Compound **106b** was inactive at all other subunits. These data suggest that the activity of pyrrolidinone analogues may rely on a single enantiomer and that the binding pocket can distinguish between the enantiomers.

CONCLUSION

The incorporation of a methyl group at the C-7 position of the indole of initial screening hit **1** afforded **111**, which selectively potentiates GluN2C-containing NMDA receptors with a potency of 4.3 ± 0.3 μM. In addition, the activity of this series appears to originate from one enantiomer. These compounds

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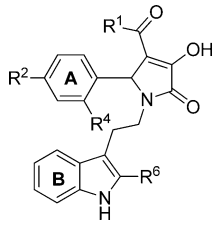
Table 6. Optimization of Potency though Additional Modifications



					$I_{30\ \mu M}/I_{control}$ (mean ± SEM %)				EC_{50} (max.) μM (%)[a]
#	R^1	R^2	R^4	R^6	GluN2A	GluN2B	GluN2C	GluN2D	GluN2C
116		CO_2Et	H	H	97 ± 6.5	71 ± 4.7	201 ± 4.4	83 ± 1.9	8.2 ± 0.9 (207)
117		CO_2Et	H	H	109 ± 0.4	91 ± 1.7	223 ± 4.4	86 ± 2.0	9.7 ± 0.6 (245)
118		CO_2Me	H	Me	82 ± 5.2	77 ± 1.4	174 ± 3.7	82 ± 0.1	13 ± 2.6 (204)
119	Me	CO_2Et	H	Me	108 ± 4.8	99 ± 5.5	220 ± 6.8	85 ± 2.4	13 ± 0.9 (265)
120	Me	CO_2Et	OH	H	110 ± 6.4	100 ± 3.4	145 ± 8.9	88 ± 0.8	40 ± 2.8 (194)

[a]Fitted EC_{50} values are shown for GluN1/GluN2C to two significant digits when potentiation at 30 μM of the test compound exceeded 120% of control; values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) response. Data for active compounds at GluN1/GluN2C are from between 8 and 14 oocytes from 2 frogs for each compound; the Hill slope varied between 1.2 and 1.5. When no effect was found at 30 μM (n = 3−6 oocytes), the lack of effect was confirmed by testing at 100 μM (data not shown, $n \geq 7$ oocytes for all compounds).

represent the first class of allosteric potentiators selective for diheteromeric GluN1/GluN2C receptors over receptors containing GluN2A-, GluN2B-, and GluN2D subunits. Future studies will address the activity of this series of modulators on triheteromeric GluN2C-containing NMDA receptors containing two different GluN2 subunits (e.g., GluN1/GluN2A/GluN2C). This series of molecules may serve as a pharmacological tool to evaluate the role of the GluN2C subunit in normal and neuropathological function.

EXPERIMENTAL METHODS

Biology Experimentals. All protocols involving *Xenopus laevis* were approved by the Emory University Institutional Animal Care and Use Committee. Two-electrode voltage-clamp recordings were made from *Xenopus laevis* oocytes expressing recombinant GluN1/GluN2A, GluN1/GluN2B, GluN1/GluN2C, GluN1/GluN2D, GluA1, or GluK2 receptors following injection of cRNA. cDNAs for rat GluN1−1a (GenBank accession numbers U11418 and U08261; hereafter GluN1), GluN2A (D13211), GluN2B (U11419), GluN2C (M91563), GluN2D (L31611), GluA1 (X17184), and GluK2 (Z11548) were provided by Drs. S. Heinemann (Salk Institute), S. Nakanishi (Kyoto University), and P. Seeburg (University of Heidelberg). Oocyte isolation, cRNA synthesis, and cRNA injection have been previously described;[15] some experiments were performed with oocytes obtained from Ecocyte (Austin, TX). Voltage-clamp recordings from oocytes were made during perfusion with recording solution containing 90 mM NaCl, 1.0 mM KCl, 0.5 mM $BaCl_2$, 0.005 mM EDTA, and 10 mM HEPES at pH 7.4 (23 °C). Glass microelectrodes had resistances of 0.3−1.0 MΩ and were filled with 0.3−3.0 M KCl; the membrane potential was held at −40 mV for all recordings. Compounds were made as 20 mM stock solutions in DMSO and diluted to the final concentration in recording solution; final DMSO content was 0.05−0.5% (v/v). Oocytes expressing GluK2 receptors were pretreated with 10 μM concanavalin A for 10 min. NMDA receptors were activated by 100 μM glutamate plus 30 μM glycine; GluA1 and GluK2 receptors were activated by 100 μM glutamate. To prevent a gradual increase in current response over the course of the experiment of GluN1/GluN2A receptor responses in oocytes, some oocytes expressing GluN1/GluN2A were injected with 20−50 nL of 2 mM K-BAPTA (potassium 1,2-bis(*o*-aminophenoxy)ethane-*N*,*N*,*N*′,*N*′-tetraacetic acid). When the response to agonist in the presence of 30 μM of a test compound exceeded 120% of control, the response to glutamate and glycine in the absence and presence of 5−7 concentrations of active analogues were recorded in multiple oocytes obtained from two or more different frogs for all experiments. The EC_{50} (half-maximally effective concentration of potentiator) was determined by fitting the equation

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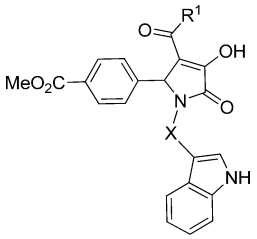
Table 7. Optimization of Potency though Linker Modifications



			$I_{30\ \mu M}/I_{control}$ (mean ± SEM %)				EC_{50} (max.) μM (%)[a]
#	R^1	X	GluN2A	GluN2B	GluN2C	GluN2D	GluN2C
121		$-CH_2-$	106 ± 1.1	101 ± 1.1	84 ± 1.9	87 ± 1.7	--
122		$-CH_2CH_2CH_2-$	96 ± 1.3	93 ± 3.1	84 ± 2.1	98 ± 1.9	--

[a]Fitted EC_{50} values are shown for GluN1/GluN2C to two significant digits when potentiation at 30 μM of the test compound exceeded 120%; values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) response. Data for active compounds at GluN1/GluN2C are from between 7 and 8 oocytes from 2 frogs for each compound tested; the Hill slope varied between 1.3 and 1.4. When no effect was found at 30 μM (n = 3−11 oocytes), the lack of effect was confirmed by testing at 100 μM (data not shown, $n \geq 4$ oocytes for all compounds).

$$\text{response} = (100 - \textit{maximum})/(1 + ([\text{concentration}]/EC_{50})^{N}) + \textit{maximum} \quad (1)$$

to the concentration−response data normalized to the current in the absence of potentiator (100%) for each oocyte, and the mean (±SEM) presented. N is the Hill slope, which ranged between 1 and 2 and is not reported; *maximum* is the fitted maximal response expressed as a percent of control to a saturating concentration of potentiator. When responses were inhibited by test compound at 30 μM to less than 60% of control, the IC_{50} value was determined by fitting the equation

$$\text{response} = 100/(1 + ([\text{concentration}]/IC_{50})^{N}) \quad (2)$$

to the concentration−response data normalized to the current. For some compounds, visual detection of precipitation led to inclusion of 1−10 mM 2-hydroxypropyl-β-cyclodextrin in the recording solution to enhance solubility and enable generation of the full concentration−response data.

To generate a cell line with inducible NMDA receptor expression, we used a previously described Tet-On (tetracycline-inducible promoter; Clontech, Mountain View, CA) baby hamster kidney (BHK-21, ATCC CCL-10) cell line.[16] The BHK-21 Tet-On cell line was maintained at 37 °C, 5% CO_2, and 95% relative humidity in culture medium com posed of Dulbecco's Modified Eagle Medium (DMEM) containing GlutaMAX-I, 4500 mg/L glucose, and 110 mg/L sodium pyruvate (Invitrogen, Carlsbad, CA) supplemented with penicillin (100 units/mL), streptomycin (100 μg/mL), (Invitrogen, Carlsbad, CA), 10% dialyzed fetal bovine serum (Invitrogen, Carlsbad, CA), and 1 mg/mL G418 (Invitrogen, Carlsbad, CA). The selection marker G418 was always included to provide continuous selection of Tet-On-compatible BHK-21 cells. The cells were cotransfected with rat GluN1-1a (GenBank accession no. U11418) in the inducible pTRE2 vector and rat GluN2C (GenBank accession no. D13212) in the pCI-IRES-bla vector (see ref 16 for details on this vector) using Fugene 6 transfection reagent (Promega, Madison, WI). The ratio of GluN1 and GluN2C DNA used for transfection was 10:1. The NMDA receptor antagonists DL-2-amino-5-phosphonopentanoate (AP5) (200 μM; Abcam, Cambridge, MA) and 7-chloro-kynurenate (7-CKA) (200 μM; Abcam, Cambridge, MA) were added to the culture medium to prevent NMDA receptor-mediated cell death. The following day, the cells were diluted 1:1000 and 1:10,000 and seeded in 144 mm dishes. The next day (e.g., two days after transfection), 10 μg/mL blasticidin S (Invivogen, San Diego, CA) was added to the culture medium to select for transfected cells. Unless otherwise stated, the culture medium for the cell lines always contained 1 mg/mL G418 and 10 μg/mL blasticidin S for selection as well as 200 μM AP5 and 200 μM DCKA to prevent NMDA receptor-mediated cell death. The media was changed every 2−3 days, and blasticidin S-resistant clones were isolated 10−20 days after transfection and evaluated for their response properties. Fluorescence-based assays were conducted as previously described,[17] and test compounds were screened at 10 μM.

Chemistry Experimentals. Compounds for which synthesis is not described were purchased from commercial vendors. Purity of purchased compounds was greater than 90%, as determined by the suppliers, via HPLC or NMR.

All dry solvents were obtained from a Glass Contour System. Reagents used were acquired from commercial suppliers and utilized without additional purification. Precoated glass plates (silica gel 60 F254, 0.25 mm) were used to monitor the progress of reactions by thin layer chromatography (TLC). Purification by flash column chromatography was performed on a Teledyne ISCO Combiflash Companion using prepackaged Teledyne RediSep disposable normal phase silica columns. Melting temperatures were determined on a Mel-Temp apparatus and are uncorrected. ^1H and ^{13}C NMR experiments were each carried out on an INOVA-400 (400 MHz), VNMR 400 (400 MHz), INOVA-600 (600 MHz), Unity-600 (600 MHz), or Mercury 300 Vx (300 MHz). All chemical shifts are reported in parts per million and referenced to the residual solvent peak. All coupling

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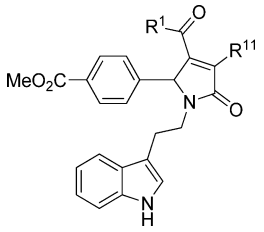
Table 8. Optimization of Potency though Evaluation of Vinyl Substituents



#	R^1	R^{11}	$I_{30\ \mu M}/I_{control}$ (mean ± SEM %) GluN2 A	GluN2 B	GluN2 C	GluN2 D	EC_{50} (max.) μM (%)[a] GluN2C
156	Me	OMe	109 ± 4.1	91 ± 3.5	127 ± 3.0	82 ± 2.8	37 ± 2.2 (163)
157	Me	NH_2	93 ± 4.4	85 ± 5.8	102 ± 1.2	75 ± 1.1	--
158	Me	OAc	95 ± 1.7	90 ± 1.2	120 ± 3.2	92 ± 1.3	52 ± 5.8 (173)
159		$OC(O)(CH_2)_2CH_3$	112 ± 3.2	93 ± 5.0	186 ± 11	93 ± 2.3	14 ± 1.9 (184)
160		$OC(O)CH{=}CH_2$	106 ± 6.0	104 ± 2.5	125 ± 5.0	100 ± 4.5	105 ± 25 (208)

[a]Fitted EC_{50} values are shown for GluN1/GluN2C to two significant digits when potentiation at 30 μM of the test compound exceeded 120% of control; values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) response. Data for active compounds at GluN1/GluN2C are from between 5 and 9 oocytes from 2−3 frogs for each compound. The Hill slope varied between 1.2 and 1.8 and was fixed to be 1.5 for less potent analogues (**157**, **159**). When no effect was found (n = 3−9 oocytes), the lack of effect was confirmed by testing at 100 μM (data not shown, $n \geq 4$ oocytes for all compounds).

constants are reported in hertz (Hz). The IR spectra were acquired with a Nicolet Avatar 370 DTGS. Mass spectra were performed by the Emory University Mass Spectrometry Center on a VG 70-S Nier Johnson or JEOL instrument. Purity of all final compounds was found to be ≥95% by LC/MS analysis unless otherwise noted.

Separation of Enantiomers. The separation of the enantiomers of **106** was obtained using a ChiralPak OD-RH 30 mm × 250 mm, 5 μm column with the following conditions: flow rate 10 mL/min, injection volume 1−2 mL (5 mg/mL), 44% ACN/66% water with 0.1% formic acid; **106a** t_R = 121.3 min; **106b** t_R = 129.3 min. Enantiomeric excess (*ee*) of both enantiomers **106a** and **106b** was determined using a ChiralPak OD-RH 4.6 mm × 150 mm, 5 μm column with the following conditions: flow rate 0.5 mL/min, injection volume 10 μL, 44% ACN/66% water with 0.1% formic acid; **106a** $[\alpha]_D^{20}$ −18 (c = 0.10, methanol), t_R = 26.1 min, 98% *ee*; **106b** $[\alpha]_D^{20}$ + 9 (c = 0.10, methanol), t_R = 29.1 min, 96% *ee*. A Perkin-Elmer 314 instrument was used to obtain optical rotation data.

*General Procedure for Synthesis of Pyrrolidinone Compounds (Procedure I: **1**, **62**−**82**, **84**−**122**, **161**−**180**).* To a stirred solution of aldehyde (1.0 mmol) in dioxane (1.0 M) was added tryptamine (1.0 equiv) and 10 mol % pyridinium 4-methylbenzenesulfonate. Upon the formation of a slurry, methyl acetopyruvate (1.0 equiv) was added. The resulting mixture was allowed to stir at rt for up to 12 h. In most instances, a precipitate was visible, which was collected via filtration and washed with Et_2O. The solid was dissolved in an appropriate solvent and washed with saturated ammonium chloride and brine before being dried over $MgSO_4$, filtered, and concentrated in vacuo. If a precipitate did not form, the mixture was concentrated in vacuo before being subjected to the workup as described above. Purification was achieved via flash column chromatography on SiO_2 (MeOH/DCM) to afford the desired pyrrolidinone. Additional purification was obtained by HPLC (85% ACN/15% water with 0.1% formic acid) as needed.

*General Preparation of Pyruvate Compounds (Procedure II: **3**−**20**, **144**).* To a solution of sodium ethanolate (1.0 equiv) in EtOH (0.72 M) at 0 °C was added a mixture of diethyl oxalate (1.0 equiv) and ethanone (1.0 mmol) over 20 min. The mixture was allowed to stir at rt for 4 h. In most instances, a precipitate had formed which was collected via filtration and washed with absolute EtOH. If no precipitate was evident, a minimal amount of water was added and the mixture was concentrated in vacuo. The residue was dissolved in water, neutralized with acetic acid,

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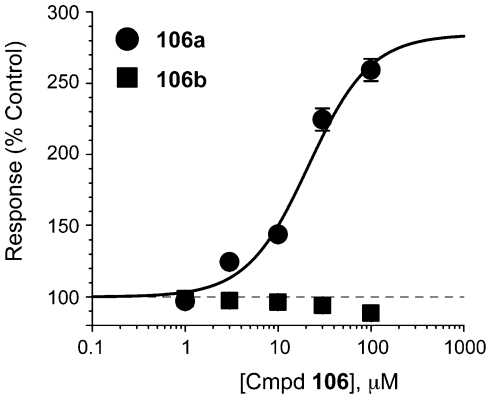

Figure 3. Composite concentration−effect curves for **106** enantiomers. Concentration−effect curves for the enantiomers of **106** demonstrate that only one enantiomer, **106a**, is active, potentiating the GluN1/GluN2C receptor to a fitted maximum of 259 ± 8% of control with an EC_{50} of 18 ± 0.6 μM (n = 6).

and extracted with Et_2O (3×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification was achieved as needed via flash column chromatography on SiO_2 (hexanes/EtOAc: 4/1) to obtain the product.

*General Preparation of Methyl Benzoate Compounds (Procedure III: **184**−**186**).* To a solution of 4-bromobenzoic acid (1.0 mmol) in THF:MeOH (4:1, 0.3 M) at 0 °C was added (diazomethyl)-trimethylsilane (2.4 equiv). The reaction was allowed to warm to rt over the period of 1 h. At this time, the mixture was concentrated in vacuo and 1.0 M HCl was added. The mixture was extracted with EtOAc (2×), dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the product.

*General Preparation of Methyl 4-Formylbenzoate Compounds (Procedure IV: **37**−**40**).* To a solution of methyl 4-bromobenzoate (1.0 mmol) in DMF (0.6 M) was added 17 mol % bis(triphenylphosphine)-palladium(II) dichloride and sodium formate (1.5 equiv). The reaction mixture was stirred at 110 °C under a steady stream of $CO_{(g)}$ for 2 h. At this time, the mixture was cooled to rt, diluted with saturated sodium carbonate, and extracted with EtOAc (2×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification was achieved via flash column chromatography on SiO_2 (hexanes/EtOAc: 3/1) to yield the desired product, which was taken on without further purification.

*Methyl 4-(1-(2-(1H-Indol-3-yl)ethyl)-3-acetyl-4-hydroxy-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**1**).* Compound **1** was prepared via procedure I from methyl 4-formylbenzoate (3.0 g, 18 mmol), tryptamine (2.9 g, 18 mmol), and methyl acetopyruvate (2.6 g, 18 mmol) to yield a cream-colored solid (5.5 g, 72%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.83 (s, 1H), 7.88 (d, J = 8.0 Hz, 2H), 7.33−7.24 (m, 4H), 7.12−7.03 (m, 2H), 6.91 (t, J = 7.6 Hz, 1H), 5.17 (s, 1H), 3.83 (s, 3H), 3.83−3.77 (m, 1H), 3.00−2.90 (m, 1H), 2.87−2.80 (m, 1H), 2.74−2.67 (m, 1H), 2.27 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 165.6, 165.1, 142.5, 136.3, 129.3, 128.1, 126.9, 125.5, 122.9, 121.2, 121.1, 118.4, 118.3, 118.1, 111.6, 111.5, 110.8, 66.4, 59.8, 52.2, 40.8, 23.6; mp 99−105 °C. HMS (APCI) calcd for $C_{24}H_{22}N_2O_5$ 419.1607; found 419.1606 $[M + H]^+$.

*Methyl 4-(1-(2-(1H-Indol-3-yl)ethyl)-4-hydroxy-5-oxo-3-propionyl-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**62**).* Compound **62** was prepared via procedure I from methyl 4-formylbenzoate (0.095 g, 0.58 mmol), tryptamine (0.93 g, 0.58 mmol), and **3** (0.10 g, 0.58 mmol) to yield a cream-colored solid (0.16 g, 64%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.84 (s, 1H), 7.87 (d, J = 8.4 Hz, 2H), 7.33−7.23 (m, 4H), 7.09 (d, J = 2.4 Hz, 1H), 7.05 (t, J = 8.0 Hz, 1H), 6.91 (t, J = 6.8 Hz, 1H), 5.17 (s, 1H), 3.83−3.76 (m, 4H), 2.96−2.89 (m, 1H), 2.86−2.79 (m, 1H), 2.75−2.57 (m, 3H), 0.85 (t, J = 7.6 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 165.9, 165.1, 142.5, 136.2, 129.7, 129.3, 128.1, 126.9, 125.5, 122.9, 121.0, 118.2, 118.1, 111.5, 110.7, 59.8, 54.9, 52.2, 40.8, 40.0, 23.6 (note: carbons 1 and 2 are absent); mp 175−180 °C. HMS (APCI) calcd $C_{25}H_{24}N_2O_5$ 433.1758; found 433.1756 $[M + H]^+$.

*Methyl 4-(1-(2-(1H-Indol-3-yl)ethyl)-4-hydroxy-3-isobutyryl-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**63**).* Compound **63** was prepared via procedure I from methyl 4-formylbenzoate (0.088 g, 0.54 mmol), tryptamine (0.086 g, 0.54 mmol), and **4** (0.10 g, 0.54 mmol) to yield a light-brown, amorphous solid (0.067 g, 28%). ^{1}H NMR (600 MHz, DMSO-d_6, 70 °C) δ 10.65 (s, 1H), 7.84 (d, J = 7.8 Hz, 2H), 7.32 (d, J = 7.8 Hz, 2H), 7.28 (d, J = 7.8 Hz, 2H), 7.06−7.03 (m, 2H), 6.92 (t, J = 8.4 Hz, 1H), 5.18 (s, 1H), 3.83 (s, 3H), 3.79−3.75 (m, 1H), 3.40−3.20 (m, 2H), 2.98−2.93 (m, 1H), 2.91−2.86 (m, 1H), 2.72−2.67 (m, 1H), 0.86 (d, J = 4.8 Hz, 6H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 182.1, 166.0, 136.2, 129.2, 128.1, 128.0, 126.9, 125.5, 123.4, 122.8, 121.1, 121.0, 118.5, 118.2, 118.1, 111.6, 111.5, 110.9, 109.5, 60.0, 52.1, 40.9, 23.7, 23.2, 18.5, 17.7. HMS (APCI) calcd for $C_{26}H_{26}N_2O_5$ 447.1915; found 447.1916 $[M + H]^+$.

*Methyl 4-(1-(2-(1H-Indol-3-yl)ethyl)-4-hydroxy-5-oxo-3-pivaloyl-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**64**).* Compound **64** was prepared via procedure I from methyl 4-formylbenzoate (0.082 g, 0.50 mmol), tryptamine (0.080 g, 0.50 mmol), and **5** (0.10 g, 0.50 mmol) to yield an orange oil (0.092 g, 40%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.17 (br s, 1H), 7.93 (d, J = 7.8 Hz, 2H), 7.40−7.35 (m, 2H), 7.20 (t, J = 7.2 Hz, 1H), 7.09 (t, J = 7.2 Hz, 1H), 7.04 (dd, J = 1.2 Hz, J = 7.8 Hz, 2H), 6.96 (s, 1H), 5.04 (s, 1H), 4.02−3.99 (m, 1H), 3.91 (s, 3H), 3.09−3.00 (m, 2H), 2.95−2.91 (m, 1H), 1.06 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.2, 181.2, 166.7, 141.2, 136.5, 130.6, 130.2, 128.0, 127.2, 122.5, 122.2, 119.8, 118.8, 118.7, 111.6, 111.4, 63.0, 52.4, 41.7, 27.7, 25.3, 24.5 (note: either carbon 1 or 2 is absent). HMS (APCI) calcd for $C_{27}H_{28}N_2O_5$ 461.2071; found 461.2077 $[M + H]^+$.

*Methyl 4-(1-(2-(1H-Indol-3-yl)ethyl)-3-benzoyl-4-hydroxy-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**65**).* Compound **65** was prepared via procedure I from **6** (0.15 g, 0.68 mmol), tryptamine (0.11 g, 0.68 mmol), and methyl 4-formylbenzoate (0.11 g, 0.68 mmol) to yield a cream-colored solid (0.031 g, 9%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.83 (s, 1H), 7.79 (d, J = 7.2 Hz, 2H), 7.59−7.48 (m, 2H), 7.40−7.28 (m, 3H), 7.24−7.21 (m, 3H), 7.11−7.04 (m, 2H), 6.92 (t, J = 7.6 Hz, 1H), 6.74 (s, 1H), 5.25 (s, 1H), 3.80−3.74 (m, 4H), 3.00−2.90 (m, 1H), 2.82−2.67 (m, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 190.1, 188.9, 165.9, 165.4, 142.1, 138.2, 136.4, 132.4, 129.6, 129.5, 128.7, 128.3, 128.1, 127.0, 123.0, 121.1, 118.9, 118.4, 118.2, 111.6, 110.9, 60.8, 52.1, 41.2, 23.8; mp 200−205 °C. HMS (APCI) calcd for $C_{29}H_{24}N_2O_5$ 481.1771; found 481.1765 $[M + H]^+$.

*Methyl 4-(1-(2-(1H-Indol-3-yl)ethyl)-4-hydroxy-3-(3-hydroxybenzoyl)-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**66**).* Compound **66** was prepared via procedure I from methyl 4-formylbenzoate (0.35 g, 2.1 mmol), tryptamine (0.34 g, 2.1 mmol), and **21** (0.50 g, 2.1 mmol) to yield a cream-colored solid (1.0 g, 96%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.77 (s, 1H), 7.83 (d, J = 7.8 Hz, 2H), 7.37−7.29 (m, 6H), 7.13−7.12 (m, 1H), 7.07−7.03 (m, 3H), 6.91 (t, J = 7.8 Hz, 1H), 5.36 (s, 1H), 3.87−3.81 (m, 4H), 3.00−2.93 (m, 2H), 2.78−2.73 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 198.0, 166.0, 157.1, 136.40, 136.3, 129.4, 128.4, 128.2, 125.6, 123.4, 122.9, 121.2, 121.1, 119.5, 118.6, 118.4, 118.25, 118.19, 115.2, 111.7, 111.6, 110.9, 109.7, 66.5, 52.2, 41.2, 23.8; mp 78−80 °C. HMS (APCI) calcd for $C_{29}H_{24}N_2O_6$ 497.1707; found 497.1707 $[M + H]^+$.

*Methyl 4-(1-(2-(1H-Indol-3-yl)ethyl)-4-hydroxy-3-(3-methoxybenzoyl)-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**67**).* Compound **67** was prepared via procedure I from methyl 4-formylbenzoate (0.066 g, 0.40 mmol), tryptamine (0.064 g, 0.40 mmol), and **7** (0.10 g, 0.40 mmol) to yield a pale-yellow, amorphous solid (0.046 g, 23%). ^{1}H NMR (600 MHz, DMSO-d_6, 80 °C) δ 10.64 (s, 1H), 7.89−7.82 (m, 3H), 7.35−7.22 (m, 6H), 7.07−7.05 (m, 2H), 6.98−6.91 (m, 2H), 5.34 (s, 1H), 4.26 (m, 1H), 3.82 (s, 3H), 3.74 (s, 3H), 3.01−2.90 (m, 2H), 2.78−2.75 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 188.6, 165.9, 165.1, 158.9, 141.9, 139.3, 136.3, 129.6, 129.4, 129.3, 128.3, 128.1, 126.9, 125.5, 122.9, 121.2, 121.1, 119.0, 118.3, 118.1, 113.5, 111.5, 110.8, 60.7, 55.3, 52.2, 41.1, 23.8. HMS (APCI) calcd for $C_{30}H_{26}N_2O_6$ 511.1877; found 511.1871 $[M + H]^+$.

*Methyl 4-(1-(2-(1H-Indol-3-yl)ethyl)-4-hydroxy-3-(3-methylbenzoyl)-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**68**).* Compound **68** was prepared via procedure I from methyl 4-formylbenzoate (0.17 g, 1.0 mmol), tryptamine (0.17 g, 1.0 mmol), and **8** (0.24 g, 1.0 mmol) to yield a pale-yellow, amorphous solid (0.029 g, 6%). ^{1}H NMR (600 MHz,

DMSO-d_6, 80 °C) δ 10.67 (s, 1H), 7.72 (m, 2H), 7.36−7.33 (m, 2H), 7.28−7.21 (m, 2H), 7.11−7.04 (m, 6H), 6.93 (t, J = 7.2 Hz, 1H), 5.29 (s, 1H), 3.86−3.78 (m, 4H), 3.01−2.96 (m, 1H), 2.91−2.86 (m, 1H), 2.76−2.72 (m, 1H), 2.23 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 190.2, 190.0, 182.1, 182.0, 166.0, 145.4, 144.7, 136.2, 128.8, 127.9, 126.9, 122.9, 122.8, 121.0, 118.3, 118.1, 111.5, 111.1, 109.2, 52.0, 48.6, 41.1, 23.6, 20.9 (note: carbons 1, 2, 3, and 4 are absent). HMS (APCI) calcd for $C_{30}H_{26}N_2O_5$ 493.1769; found 493.1768 $[M - H]^-$.

*Methyl 4-(1-(2-(1H-Indol-3-yl)ethyl)-3-(3-chlorobenzoyl)-4-hydroxy-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**69**).* Compound **69** was prepared via procedure I from methyl 4-formylbenzoate (0.064 g, 0.39 mmol), tryptamine (0.063 g, 0.39 mmol), and **9** (0.10 g, 0.39 mmol) to yield a pale-yellow, amorphous solid (0.045 g, 22%). ^{1}H NMR (600 MHz, DMSO-d_6, 80 °C) δ 10.69 (s, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.69 (s, 1H), 7.58 (d, J = 6.0 Hz, 1H), 7.35−7.32 (m, 3H), 7.29−7.26 (m, 3H), 7.07−7.05 (m, 2H), 6.93 (t, J = 7.2 Hz, 1H), 5.28 (s, 1H), 3.82−3.79 (m, 4H), 2.98−2.94 (m, 1H), 2.88−2.84 (m, 1H), 2.74−2.68 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 182.1, 166.1, 145.4, 137.9, 136.4, 136.3, 129.2, 128.2, 127.0, 126.8, 125.5, 123.44, 123.43, 122.8, 121.2, 121.0, 118.5, 118.3, 118.1, 111.6, 111.5, 111.0, 109.5, 60.5, 52.1, 23.2, 20.8. HMS (APCI) calcd for $C_{29}H_{23}ClN_2O_5$ 513.1223; found 513.1219 $[M - H]^-$.

*Methyl 4-(1-(2-(1H-Indol-3-yl)ethyl)-3-(3-fluorobenzoyl)-4-hydroxy-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**70**).* Compound **70** was prepared via procedure I from methyl 4-formylbenzoate (0.069 g, 0.42 mmol), tryptamine (0.067 g, 0.42 mmol), and **10** (0.10 g, 0.42 mmol) to yield a yellow, amorphous solid (0.028 g, 14%). ^{1}H NMR (600 MHz, DMSO-d_6, 80 °C) δ 10.66 (s, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.53−7.45 (m, 2H), 7.34 (dd, J = 3.0 Hz, J = 8.4 Hz, 2H), 7.29−7.26 (m, 1H), 7.22 (d, J = 7.8 Hz, 2H), 7.13−7.10 (m, 1H), 7.07−7.04 (m, 2H), 6.93 (t, J = 7.8 Hz, 1H), 5.32 (s, 1H), 3.84−3.79 (m, 4H), 3.01−2.96 (m, 1H), 2.92−2.88 (m, 1H), 2.76−2.71 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 191.7, 167.0, 161.5 (d, J = 241.7 Hz), 143.0, 137.6, 136.2, 129.3, 128.9, 128.6, 128.1, 127.9, 126.9, 125.5, 124.1, 122.8, 121.0, 118.3, 118.1, 116.6, 116.5, 111.5, 110.9, 61.0, 52.0, 41.2, 23.5 (note: carbon 3 is absent). HMS (APCI) calcd for $C_{29}H_{23}FN_2O_5$ 497.1510; found 497.1513 $[M - H]^-$.

*Methyl 4-(1-(2-(1H-Indol-3-yl)ethyl)-4-hydroxy-5-oxo-3-picolinoyl-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**71**).* Compound **71** was prepared via procedure I from methyl 4-formylbenzoate (0.074 g, 0.45 mmol), tryptamine (0.072 g, 0.45 mmol), and **18** (0.10 g, 0.45 mmol) to yield a yellow, amorphous solid (0.037 g, 17%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.66 (d, J = 4.2 Hz, 1H), 8.21 (s, 1H), 8.14 (d, J = 7.8 Hz, 1H), 8.07 (dt, J = 1.2 Hz, J = 7.8 Hz, 1H), 7.94 (d, J = 8.4 Hz, 2H), 7.71 (dt, J = 0.6 Hz, J = 6.0 Hz, 1H), 7.39 (d, J = 7.2 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.21−7.17 (m, 3H), 7.07 (t, J = 8.4 Hz, 1H), 7.01 (d, J = 1.8 Hz, 1H), 5.14 (s, 1H), 4.15−4.10 (m, 1H), 3.89 (s, 3H), 3.11−2.95 (m, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 181.8, 173.2, 166.8, 165.7, 151.7, 145.3, 142.5, 140.6, 136.5, 130.3, 130.0, 128.3, 128.1, 127.3, 125.2, 122.3, 119.6, 118.7, 112.5, 111.5, 109.6, 61.6, 41.4, 29.9, 24.3 (note: carbon 3 is absent). HMS (APCI) calcd for $C_{28}H_{23}N_3O_5$ 482.1710; found 482.1708 $[M + H]^+$.

*Methyl 4-(1-(2-(1H-Indol-3-yl)ethyl)-4-hydroxy-3-nicotinoyl-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**72**).* Compound **72** was prepared via procedure I from methyl 4-formylbenzoate (0.079 g, 0.48 mmol), tryptamine (0.077 g, 0.45 mmol), and **19** (0.10 g, 0.48 mmol) to yield a yellow solid (0.11 g, 49%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.89 (s, 1H), 8.80 (s, 1H), 8.69 (d, J = 4.4 Hz, 1H), 8.00 (d, J = 7.6 Hz, 1H), 7.88 (d, J = 7.2 Hz, 2H), 7.43−7.42 (m, 2H), 7.34−7.29 (m, 2H), 7.14 (d, J = 8.0 Hz, 2H), 7.06 (t, J = 6.8 Hz, 1H), 6.92 (t, J = 7.2 Hz, 1H), 5.42 (s, 1H), 3.87−3.82 (m, 4H), 3.02−2.89 (m, 2H), 2.79−2.74 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 186.8, 165.9, 165.0, 152.1, 149.1, 142.1, 136.3, 133.9, 129.5, 129.4, 128.3, 128.1, 126.9, 125.5, 123.5, 122.9, 121.0, 118.3, 118.1, 111.5, 110.7, 109.5, 60.4, 52.2, 41.1, 23.7; mp 199−205 °C. HMS (APCI) calcd for $C_{28}H_{23}N_3O_5$ 482.1711; found 482.1707 $[M + H]^+$.

*Methyl 4-(1-(2-(1H-Indol-3-yl)ethyl)-4-hydroxy-3-isonicotinoyl-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**73**).* Compound **73** was prepared via procedure I from methyl 4-formylbenzoate (0.15 g, 0.9 mmol), tryptamine (0.15 g, 0.9 mmol), and **20** (0.20 g, 0.9 mmol) to yield a yellow solid (0.13 g, 30%). ^{1}H NMR (600 MHz, DMSO-d_6, 80 °C) δ 10.63 (s, 1H), 8.47 (d, J = 2.8 Hz, 1H), 7.76−6.92 (m, 12H), 5.27 (s, 1H), 3.82−3.78 (m, 4H), 3.00−2.95 (m, 1H), 2.91−2.86 (m, 1H), 2.74−2.72 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 191.3, 166.0, 149.5, 149.0, 146.6, 136.3, 128.9, 128.5, 128.0, 127.0, 122.8, 122.3, 121.1, 120.7, 118.3, 118.1, 111.5, 111.0, 52.0, 48.6, 41.1, 23.5 (note: carbons 1 and 2 are absent); mp >250 °C. HMS (APCI) calcd for $C_{28}H_{23}N_3O_5$ 480.1570; found 480.1568 $[M - H]^-$.

*Methyl 4-(1-(2-(1H-Indol-3-yl)ethyl)-4-hydroxy-3-(2-methoxybenzoyl)-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**74**).* Compound **74** was prepared via procedure I from methyl 4-formylbenzoate (0.13 g, 0.80 mmol), tryptamine (0.13 g, 0.80 mmol), and **11** (0.20 g, 0.80 mmol) to yield a pink, amorphous solid (0.028 g, 7%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.83 (s, 1H), 7.89 (s, 1H), 7.50 (d, J = 6.0 Hz, 1H), 7.34−7.18 (m, 5H), 7.09−7.04 (m, 3H), 6.96−6.88 (m, 3H), 5.27 (s, 1H), 3.83−3.74 (m, 6H), 2.99−2.87 (m, 2H), 2.73−2.65 (m, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 190.1, 182.1, 166.2, 156.0, 146.1, 137.3, 132.7, 129.1, 128.8, 128.4, 128.1, 128.0, 127.7, 127.0, 125.6, 122.8, 121.0, 119.7, 118.2, 118.1, 111.5, 111.1, 111.0, 60.3, 56.1, 55.2, 52.1, 40.9, 23.6, 18.6. HMS (APCI) calcd for $C_{30}H_{26}N_2O_6$ 509.1710; found 509.1711 $[M - H]^-$.

*Methyl 4-(1-(2-(1H-Indol-3-yl)ethyl)-4-hydroxy-3-(2-methylbenzoyl)-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**75**).* Compound **75** was prepared via procedure I from methyl 4-formylbenzoate (0.14 g, 0.85 mmol), tryptamine (0.14 g, 0.85 mmol), and **12** (0.20 g, 0.85 mmol) to yield a pale-yellow, amorphous solid (0.040 g, 9%). ^{1}H NMR (600 MHz, DMSO-d_6, 70 °C) δ 10.71 (br s, 1H), 7.67 (d, J = 7.2 Hz, 2H), 7.37 (d, J = 9.0 Hz, 1H), 7.30 (d, J = 7.8 Hz, 1H), 7.13−6.99 (m, 4H), 6.94−6.91 (m, 2H), 6.84−6.74 (m, 3H), 4.96 (s, 1H), 3.82−3.76 (m, 4H), 2.97−2.92 (m, 1H), 2.82−2.71 (m, 2H), 1.78 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 190.1, 182.1, 182.03, 182.01, 165.9, 144.4, 139.4, 136.3, 134.2, 129.3, 128.8, 128.3, 127.9, 127.0, 124.7, 123.0, 122.7, 121.1, 118.3, 118.1, 111.6, 111.2, 108.9, 60.3, 52.0, 48.6, 41.1, 23.6. HMS (APCI) calcd for $C_{30}H_{26}N_2O_5$ 493.1761; found 493.1763 $[M - H]^-$.

*Methyl 4-(1-(2-(1H-Indol-3-yl)ethyl)-3-(2-chlorobenzoyl)-4-hydroxy-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**76**).* Compound **76** was prepared via procedure I from methyl 4-formylbenzoate (0.13 g, 0.79 mmol), tryptamine (0.13 g, 0.79 mmol), and **13** (0.20 g, 0.79 mmol) to yield a cream-colored solid (0.27 g, 66%). ^{1}H NMR (600 MHz, DMSO-d_6, 80 °C) δ 10.64 (s,1H), 7.67 (m, 2H), 7.35 (d, J = 8.4 Hz, 1H), 7.30 (d, J = 7.8 Hz, 1H), 7.24−7.18 (m, 2H), 7.10−7.03 (m, 4H), 6.92 (t, J = 7.2 Hz, 2H), 6.78 (m, 1H), 5.04 (s, 1H), 3.86−3.75 (m, 4H), 2.97−2.92 (m, 1H), 2.85−2.83 (m, 1H), 2.73−2.68 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 185.2, 165.9, 144.1, 136.3, 130.0, 129.5, 129.1, 128.8, 128.7, 128.6, 128.1, 128.0, 126.9, 126.5, 123.0, 121.0, 118.3, 118.1, 111.5, 111.0, 67.1, 52.1, 40.0, 25.2 (note: carbons 1, 2, and 3 are absent); mp 248−253 °C. HMS (APCI) calcd for $C_{29}H_{23}ClN_2O_5$ 513.1214; found 513.1215 $[M - H]^-$.

*Methyl 4-(1-(2-(1H-Indol-3-yl)ethyl)-3-(2-fluorobenzoyl)-4-hydroxy-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**77**).* Compound **77** was prepared via procedure I from methyl 4-formylbenzoate (0.19 g, 0.84 mmol), tryptamine (0.14 g, 0.84 mmol), and **14** (0.20 g, 0.84 mmol) to yield a brown, amorphous solid (0.070 g, 17%). ^{1}H NMR (600 MHz, DMSO-d_6, 70 °C) δ 10.68 (s, 1H), 7.80−7.54 (m, 2H), 7.35−7.30 (m, 4H), 7.11−6.78 (m, 7H), 5.07 (s, 1H), 3.81−3.74 (m, 4H), 2.97−2.92 (m, 1H), 2.87−2.82 (m, 1H), 2.72−2.67 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 172.6, 165.9, 161.2, 156.0, 155.1, 139.5, 136.3, 135.0, 130.0, 129.6, 128.6, 126.8, 126.7, 126.3, 125.3, 124.8, 123.1, 121.1, 119.3, 118.3, 118.0, 111.5, 110.6, 59.1, 52.3, 41.2, 23.8. HMS (APCI) calcd for $C_{29}H_{23}FN_2O_5$ 497.1510; found 497.1513 $[M - H]^-$.

*Methyl 4-(1-(2-(1H-Indol-3-yl)ethyl)-3-(furan-2-carbonyl)-4-hydroxy-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**78**).* Compound **78** was prepared via procedure I from methyl 4-formylbenzoate (0.42 g, 2.6 mmol), tryptamine (0.41 g, 2.6 mmol), and **15** (0.50 g, 2.6 mmol) to yield an orange solid (0.079 g, 7%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.32 (s, 1H), 8.05 (s, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.43−7.41 (m, 2H), 7.32 (d, J = 8.4 Hz, 1H), 7.25 (d, J = 8.4 Hz, 2H), 7.16 (t, J = 7.2 Hz, 1H), 7.06 (t, J = 7.2 Hz, 1H), 6.94 (s, 1H), 6.39 (dd, J = 1.8 Hz, J = 3.6 Hz, 1H), 5.39 (s, 1H), 4.04−3.99 (m, 1H), 3.88 (s, 3H), 3.07−2.96 (m, 2H), 2.93−2.89 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.9, 167.1, 153.1, 145.1, 136.5, 129.8, 129.7, 129.2, 128.4, 128.2, 127.4, 122.3, 122.2, 119.5, 118.9, 117.1, 114.2, 112.7, 111.7, 111.4, 111.3, 61.3, 52.2, 41.3, 24.3;

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mp 60−65 °C. HMS (APCI) calcd for $C_{27}H_{22}N_2O_6$ 471.1551; found 471.1547 $[M + H]^+$.

*Methyl 4-(1-(2-(1H-Indol-3-yl)ethyl)-4-hydroxy-5-oxo-3-(thiophene-2-carbonyl)-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**79**).* Compound **79** was prepared via procedure I from methyl 4-formylbenzoate (0.073 g, 0.44 mmol), tryptamine (0.071 g, 0.44 mmol), and **16** (0.10 g, 0.44 mmol) to yield a yellow, amorphous solid (0.043 g, 20%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.80 (s, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 4.0 Hz, 1H), 7.34−7.29 (m, 4H), 7.06−7.02 (m, 3H), 6.92 (t, J = 7.2 Hz, 1H), 5.80−5.70 (m, 1H), 5.28 (s, 1H), 3.86−3.74 (m, 4H), 3.00−2.89 (m, 1H), 2.85−2.78 (m, 1H), 2.73−2.67 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 165.8, 144.7, 136.2, 129.0, 128.2, 126.9, 126.8, 123.4, 122.9, 121.2, 121.0, 118.5, 118.3, 118.1, 111.6, 111.5, 111.1, 109.5, 52.0, 48.6, 40.0, 23.5 (note: carbons 1, 2, and 4 are absent); mp 190−195 °C. HMS (APCI) calcd for $C_{27}H_{22}N_2O_5S$ 485.1177; found 485.1173 $[M - H]^-$.

*Methyl 4-(1-(2-(1H-Indol-3-yl)ethyl)-4-hydroxy-5-oxo-3-(thiophene-3-carbonyl)-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**80**).* Compound **80** was prepared via procedure I from methyl 4-formylbenzoate (0.36 g, 2.2 mmol), tryptamine (0.35 g, 2.2 mmol), and **17** (0.50 g, 2.2 mmol) to yield a cream-colored solid (0.70 g, 65%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.86 (s, 1H), 8.38 (d, J = 2.8 Hz, 1H), 7.85 (d, J = 7.6 Hz, 2H), 7.49 (t, J = 4.0 Hz, 1H), 7.37−7.31 (m, 4H), 7.13 (s, 1H), 7.07 (t, J = 7.6 Hz, 1H), 6.93 (t, J = 6.8 Hz, 1H), 5.76 (d, J = 1.2 Hz, 1H), 5.44 (s, 1H), 3.89−3.81 (m, 4H), 3.02−2.90 (m, 2H), 2.80−2.74 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 181.8, 165.9, 142.1, 141.6, 136.3, 134.2, 129.5, 129.4, 128.3, 128.1, 127.3, 126.9, 126.3, 125.5, 122.9, 121.1, 118.3, 118.1, 111.5, 110.8, 60.7, 52.1, 41.1, 23.8; mp 189−192 °C. HMS (APCI) calcd for $C_{27}H_{22}N_2O_5S$ 487.1336; found 487.1335 $[M + H]^+$.

*Methyl 3-(1−2-(1H-Indol-3-yl)ethyl)-3-acetyl-4-hydroxy-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**81**).* Compound **81** was prepared via procedure I from methyl 3-formylbenzoate (0.50 g, 3.1 mmol), tryptamine (0.49 g, 3.1 mmol), and methyl acetopyruvate (0.44 g, 3.1 mmol) to yield a pale-pink solid (0.77 g, 60%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.82 (s, 1H), 7.87 (d, J = 7.6 Hz, 1H), 7.73 (s, 1H), 7.45 (t, J = 7.2 Hz, 1H), 7.39−7.26 (m, 3H), 7.10 (d, J = 2.0 Hz, 1H), 7.05 (t, J = 7.2 Hz, 1H), 6.89 (t, J = 8.0 Hz, 1H), 5.24 (s, 1H), 3.85−3.76 (m, 4H), 2.98−2.91 (m, 1H), 2.87−2.80 (m, 1H), 2.72−2.65 (m, 1H), 2.72 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.5, 166.0, 165.1, 154.8, 137.8, 136.3, 132.5, 129.9, 129.1, 129.0, 128.4, 126.9, 122.9, 121.1, 119.8, 118.3, 118.1, 111.5, 110.8, 59.8, 52.3, 40.8, 29.8, 23.7; mp 218−220 °C. HMS (APCI) calcd for $C_{24}H_{22}N_2O_5$ 419.1593; found 419.1596 $[M + H]^+$.

*Methyl 2-(1-(2-(1H-Indol-3-yl)ethyl)-3-acetyl-4-hydroxy-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**82**).* Compound **82** was prepared via procedure I from methyl 2-formylbenzoate (0.10 g, 0.61 mmol), tryptamine (0.098 g, 0.61 mmol), and methyl acetopyruvate (0.088 g, 0.61 mmol) to yield a white solid (0.18 g, 72%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.82 (s, 1H), 7.87 (d, J = 7.6 Hz, 1H), 7.72 (s, 1H), 7.46 (t, J = 7.6 Hz, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.32−7.25 (m, 2H), 7.10 (d, J = 1.6 Hz, 1H), 7.02 (t, J = 7.6 Hz, 1H), 6.89 (t, J = 7.6 Hz, 1H), 5.24 (s, 1H), 3.86 (s, 3H), 3.82−3.75 (m, 1H), 2.97−2.90 (m, 1H), 2.86−2.79 (m, 1H), 2.71−2.66 (m, 1H), 2.27 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 191.6, 166.0, 165.0, 154.5, 137.8, 136.2, 132.5, 129.8, 129.0, 128.9, 128.3, 126.8, 122.9, 121.0, 119.9, 118.2, 118.0, 111.4, 110.7, 59.7, 52.2, 40.8, 29.8, 23.6; mp 210−218 °C. HMS (APCI) calcd for $C_{24}H_{22}N_2O_5$ 419.1602; found 419.1599 $[M + H]^+$.

*4-(1-(2-(1H-Indol-3-yl)ethyl)-3-acetyl-4-hydroxy-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoic Acid (**83**).* To a suspension of **1** (0.10 g, 0.24 mmol) in EtOH (3.5 mL) was added a 2N aq sodium hydroxide solution (0.8 mL). The reaction was heated at reflux for 2 h. The solution was then cooled to 0 °C, and concentrated HCl was added carefully. The precipitate was filtered off, rinsed with cold water, and dried under vacuum for 12 h to afford a white powder (0.090 g, 93%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.89 (br s, 1H), 10.79 (br s, 1H), 8.09 (d, J = 8.0 Hz, 2H), 7.30−7.28 (m, 2H), 7.23 (d, J = 8.0 Hz, 2H), 7.03−7.01 (m, 2H), 6.90 (app t, J = 8.0 Hz, 1H), 5.56 (s, 1H), 3.77−3.74 (m, 1H), 2.89−2.71 (m, 1H), 2.71−2.61 (m, 2H), 2.10 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 196.5, 179.9, 169.3, 164.3, 146.9, 136.5, 130.1 (×2), 128.5, 127.8 (×2), 127.4, 123.0, 119.1, 121.7, 119.8, 118.8, 113.0, 111.1, 54.7, 49.1, 26.6, 24.3; mp >250 °C. HMS (ESI$^+$) calcd For $C_{23}H_{20}N_2NaO_5$ 427.1270; found 427.1263 $[M + Na]^+$.

*Ethyl 4-(1-(2-(1H-Indol-3-yl)ethyl)-3-acetyl-4-hydroxy-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**84**).* Compound **84** was prepared via procedure I from **45** (0.20 g, 1.1 mmol), tryptamine (0.18 g, 1.1 mmol), and methyl acetopyruvate (0.16 g, 1.1 mmol) to yield a pale-pink solid (0.20 g, 42%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.48 (br s, 1H), 10.82 (s, 1H), 7.87 (d, J = 8.4 Hz, 2H), 7.33−7.24 (m, 4H), 7.09 (d, J = 2.4 Hz, 1H), 7.05 (t, J = 7.2 Hz, 1H), 6.91 (t, J = 7.6 Hz, 1H), 5.18 (s, 1H), 4.30 (q, J = 7.2 Hz, 2H), 3.83−3.76 (m, 1H), 2.97−2.89 (m, 1H), 2.87−2.80 (m, 1H), 2.74−2.67 (m, 1H), 2.26 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 191.6, 165.4, 165.1, 142.4, 136.2, 129.6, 129.3, 128.1, 126.9, 122.9, 121.0, 118.3, 118.1, 111.5, 110.7, 60.7, 59.8, 40.8, 39.9, 23.6, 14.2 (note: carbon 3 and either carbon 1 or 2 are absent); mp 180−183 °C. HMS (APCI) calcd for $C_{25}H_{24}N_2O_5$ 433.1771; found 433.1765 $[M + H]^+$.

*Isopropyl 4-(1-(2-(1H-Indol-3-yl)ethyl)-3-acetyl-4-hydroxy-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**85**).* Compound **85** was prepared via procedure I from **46** (0.20 g, 1.0 mmol), tryptamine (0.17 g, 1.0 mmol), and methyl acetopyruvate (0.15 g, 1.0 mmol) to yield an orange, amorphous solid (0.028 g, 6%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.70 (s, 1H), 7.86 (d, J = 8.4 Hz, 2H), 7.33−7.23 (m, 3H), 7.11−7.00 (m, 3H), 6.91 (t, J = 7.6 Hz, 1H), 5.16−5.11 (m, 2H), 3.82−3.77 (m, 1H), 3.02−2.85 (m, 2H), 2.76−2.71 (m, 1H), 2.26 (s, 3H), 1.32 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 190.0, 164.9, 136.2, 129.2, 128.1, 126.8, 125.5, 123.5, 122.8, 121.2, 121.0, 118.5, 118.3, 118.1, 111.5, 110.8, 68.1, 59.8, 40.9, 39.9, 23.6, 21.6 (note: carbons 1 and 2 are absent). HMS (APCI) calcd for $C_{26}H_{26}N_2O_5$ 447.1928; found 447.1922 $[M + H]^+$.

*tert-Butyl 4-(1-(2-(1H-Indol-3-yl)ethyl)-3-acetyl-4-hydroxy-5-oxo-2, 5-dihydro-1H-pyrrol-2-yl) benzoate (**86**).* Compound **86** was prepared via procedure I from **47** (0.50 g, 2.4 mmol), tryptamine (0.39 g, 2.4 mmol), and methyl acetopyruvate (0.35 g, 2.4 mmol) to yield a pale-yellow solid (0.92 g, 83%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.83 (s, 1H), 7.81 (d, J = 8.4 Hz, 2H), 7.33−7.22 (m, 4H), 7.10 (d, J = 2.0 Hz, 1H), 7.05 (t, J = 7.2 Hz, 1H), 6.91 (t, J = 7.6 Hz, 1H), 5.17 (s, 1H), 3.83−3.76 (m, 1H), 2.96−2.89 (m, 1H), 2.86−2.81 (m, 1H), 2.79−2.67 (m, 1H), 2.26 (s, 3H), 1.53 (s, 9H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 191.5, 165.1, 164.6, 154.4, 142.0, 131.1, 129.1, 127.9, 126.9, 126.2, 122.8, 121.0, 119.8, 118.2, 118.1, 111.4, 110.7, 80.7, 59.8, 40.8, 29.7, 27.8, 23.6; mp 145−150 °C. HMS (APCI) calcd for $C_{27}H_{28}N_2O_5$ 461.2063; found 461.2065 $[M + H]^+$.

*4-(1-(2-(1H-Indol-3-yl)ethyl)-4-hydroxy-3-nicotinoyl-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzonitrile (**87**).* Compound **87** was prepared via procedure I from 4-formylbenzonitrile (0.15 g, 1.1 mmol), tryptamine (0.18 g, 1.1 mmol), and **19** (0.25 g, 1.1 mmol) to yield a yellow solid (0.084 g, 17%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.84 (s, 1H), 8.81 (s, 1H), 8.69 (d, J = 3.6 Hz, 1H), 8.01 (d, J = 7.8 Hz, 1H), 7.75 (d, J = 7.8 Hz, 2H), 7.50−7.47 (m, 3H), 7.33 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 7.8 Hz, 1H), 7.13 (s, 1H), 7.07 (t, J = 7.8 Hz, 1H), 6.94 (t, J = 7.2 Hz, 1H), 5.44 (s, 1H), 3.88−3.83 (m, 1H), 3.01−2.90 (m, 2H), 2.79−2.75 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 189.3, 165.1, 152.1, 150.2, 149.2, 142.5, 136.3, 133.9, 132.4, 129.0, 126.9, 123.9, 123.4, 122.9, 121.1, 118.6, 118.3, 118.1, 117.7, 111.5, 111.0, 110.7, 60.3, 41.2, 23.7; mp >250 °C. HMS (APCI) calcd for $C_{27}H_{20}N_4O_3$ 449.1608; found 449.1607 $[M + H]^+$.

*1-(2-(1H-Indol-3-yl)ethyl)-4-acetyl-3-hydroxy-5-(4-nitrophenyl)-1H-pyrrol-2(5H)-one (**88**).* Compound **88** was prepared via procedure I from 4-nitrobenzaldehyde (0.50 g, 3.3 mmol), tryptamine (0.53 g, 3.3 mmol), and methyl acetopyruvate (0.48 g, 3.3 mmol) to yield a pale-yellow solid (1.0 g, 75%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.62 (br s, 1H), 10.82 (s, 1H), 8.10 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.8 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 1.6 Hz, 1H), 7.04 (t, J = 8.0 Hz, 1H), 6.91 (t, J = 7.6 Hz, 1H), 5.26 (s, 1H), 3.85−3.78 (m, 1H), 2.97−2.84 (m, 2H), 2.80−2.77 (m, 1H), 2.27 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 191.6, 165.2, 154.7, 147.1, 144.9, 136.2, 129.0, 126.8, 123.5, 122.9, 121.0, 118.2, 118.0, 111.4, 110.7, 59.4, 41.0, 29.8, 23.5 (note: carbon 3 is absent); mp 142−150 °C. HMS (APCI) calcd for $C_{22}H_{19}N_3O_5$ 406.1398; found 406.1395 $[M + H]^+$.

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*4-(1-(2-(1H-Indol-3-yl)ethyl)-4-hydroxy-3-nicotinoyl-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzamide (**89**).* Compound **89** was prepared via procedure I from **42** (0.29 g, 2.0 mmol), tryptamine (0.32 g, 2.0 mmol), and **19** (0.44 g, 2.0 mmol) to yield a yellow solid (0.70 g, 76%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.65 (s, 1H), 8.81 (s, 1H), 8.66 (s, 1H), 7.99 (d, J = 7.8 Hz, 1H), 7.81 (d, J = 8.4 Hz, 2H), 7.45−7.32 (m, 6H), 7.12−7.06 (m, 3H), 6.95 (t, J = 7.2 Hz, 1H), 5.39 (s, 1H), 3.91−3.86 (m, 1H), 3.04−2.98 (m, 2H), 2.83−2.79 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 186.1, 175.4, 167.3, 165.0, 148.7, 139.8, 136.1, 135.7, 135.3, 134.0, 133.9, 127.4, 127.2, 126.7, 122.8, 122.7, 122.4, 120.6, 117.7, 111.1, 110.7, 108.5, 60.2, 39.9, 13.7; mp 175−180 °C. HMS (APCI) calcd for $C_{27}H_{22}N_4O_4$ 467.17138; found 467.17160 $[M + H]^+$.

*4-(1-(2-(1H-Indol-3-yl)ethyl)-4-hydroxy-3-nicotinoyl-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)-N-methylbenzamide (**90**).* Compound **90** was prepared via procedure I from **43** (0.15 g, 0.93 mmol), tryptamine (0.15 g, 0.93 mmol), and **19** (0.21 g, 0.93 mmol) to yield a yellow solid (0.33 g, 73%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.72 (s, 1H), 8.79 (s, 1H), 8.67 (d, J = 4.8 Hz, 1H), 8.24 (d, J = 3.6 Hz, 1H), 7.99 (d, J = 7.8 Hz, 1H), 7.75 (d, J = 7.8 Hz, 2H), 7.45 (t, J = 5.4 Hz, 1H), 7.39−7.34 (m, 4H), 7.11−7.05 (m, 2H), 6.94 (t, J = 7.2 Hz, 1H), 5.38 (s, 1H), 3.88−3.84 (m, 1H), 3.11−3.09 (m, 1H), 3.02−2.94 (m, 2H), 2.76 (d, J = 4.8 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 166.3, 165.0, 152.3, 149.3, 136.3, 136.1, 134.5, 128.1, 127.9, 127.3, 125.5, 123.4, 122.4, 122.9, 121.0, 118.5, 118.3, 118.14, 118.1, 111.6, 110.8, 60.4, 41.0, 26.2, 23.7 (note: carbon 4 is absent); mp 240−245 °C. HMS (APCI) calcd for $C_{28}H_{24}N_4O_4$ 481.1876; found 481.1879 $[M + H]^+$.

*4-(1-(2-(1H-Indol-3-yl)ethyl)-4-hydroxy-3-nicotinoyl-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)-N,N-dimethylbenzamide (**91**).* Compound **91** was prepared via procedure I from **19** (0.38 g, 1.7 mmol), tryptamine (0.27 g, 1.7 mmol), and **44** (0.30 g, 1.7 mmol) to yield a yellow solid (0.33 g, 39%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.85 (s, 1H), 8.81 (s, 1H), 8.69 (d, J = 4.8 Hz, 1H), 8.01 (d, J = 7.8 Hz, 1H), 7.49−7.47 (m, 2H), 7.36−7.29 (m, 4H), 7.14−7.10 (m, 2H), 7.06 (t, J = 7.8 Hz, 1H), 6.92 (t, J = 7.2 Hz, 1H), 5.42 (s, 1H), 3.88−3.82 (m, 1H), 3.02−2.95 (m, 5H), 2.84 (s, 3H), 2.77−2.71 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 169.71, 164.9, 152.3, 149.3, 136.4, 136.3, 136.2, 128.1, 127.8, 127.2, 125.5, 123.4, 122.9, 121.2, 121.0, 118.5, 118.3, 118.1, 111.6, 111.5, 110.8, 60.5, 41.0, 40.0, 23.8, 23.2 (note: carbon 4 is absent); mp 210−212 °C. HMS (APCI) calcd for $C_{29}H_{26}N_4O_4$ 495.2040; found 495.2036 $[M + H]^+$.

*4-(1-(2-(1H-Indol-3-yl)ethyl)-4-hydroxy-3-nicotinoyl-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzenesulfonamide (**92**).* Compound **92** was prepared via procedure I from 4-formylbenzenesulfonamide (0.19 g, 1.0 mmol), **19** (0.22 g, 1.0 mmol), and tryptamine (0.16 g, 1.0 mmol) to yield a pale-orange solid (0.024 g, 5%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.86 (s, 1H), 8.81 (s, 1H), 8.69 (d, J = 4.2 Hz, 1H), 8.01 (d, J = 7.8 Hz, 1H), 7.76 (d, J = 9.0 Hz, 2H), 7.50−7.47 (m, 3H), 7.34 (d, J = 7.8 Hz, 2H), 7.32 (s, 2H), 7.14 (d, J = 1.8 Hz, 1H), 7.07 (t, J = 8.4 Hz, 1H), 6.96 (t, J = 7.2 Hz, 1H), 5.41 (s, 1H), 3.91−3.86 (m, 1H), 3.03−2.98 (m, 1H), 2.92−2.88 (m, 1H), 2.81−2.76 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 181.3, 165.0, 149.3, 149.1, 143.9, 140.6, 136.3, 133.9, 131.8, 128.6, 126.9, 125.9, 123.4, 122.9, 121.1, 118.4, 118.2, 111.5, 110.8, 60.1, 41.0, 23.7 (note: two of either carbons 1, 2, or 3 are absent); mp >250 °C. HMS (APCI) calcd for $C_{26}H_{22}N_4O_5S$ 503.1384; found 503.1381 $[M + H]^+$.

*4-(1-(2-(1H-Indol-3-yl)ethyl)-4-hydroxy-3-nicotinoyl-5-oxo-2,5-dihydro-3-nicotinoyl-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)-N-methylbenzenesulfonamide (**93**).* Compound **93** was prepared via procedure I from 4-formyl-*N*-methylbenzenesulfonamide (0.20 g, 1.0 mmol), **19** (0.22 g, 1.0 mmol), and tryptamine (0.16 g, 1.0 mmol) to yield an orange-yellow solid (0.11 g, 21%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.84 (s, 1H), 8.80 (s, 1H), 8.50 (d, J = 4.8 Hz, 1H), 8.02−8.00 (m, 2H), 7.71 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 7.8 Hz, 2H), 7.40 (d, J = 4.8 Hz, 1H), 7.34−7.29 (m, 3H), 7.09−7.05 (m, 2H), 6.94 (t, J = 7.8 Hz, 1H), 3.84−3.79 (m, 1H), 3.01−2.95 (m, 1H), 2.89−2.85 (m, 1H), 2.70−2.65 (m, 1H), 2.39 (d, J = 4.8 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 169.7, 149.9, 149.6, 149.5, 146.1, 138.0, 136.4, 136.3, 135.9, 128.5, 128.1, 127.0, 126.5, 125.6, 123.4, 122.7, 122.5, 121.0, 118.5, 118.3, 118.1, 111.5, 111.1, 60.3, 41.1, 28.7, 23.6; mp >220 °C. HMS (APCI) calcd for $C_{27}H_{24}N_4O_5S$ 517.1540; found 517.1545 $[M + H]^+$.

*1-(2-(1H-Indol-3-yl)ethyl)-3-hydroxy-4-nicotinoyl-5-(4-(trifluoromethyl)phenyl)-1H-pyrrol-2(5H)-one (**94**).* Compound **94** was prepared via procedure I from 4-(trifluoromethyl)benzaldehyde (0.17 g, 1.0 mmol), **19** (0.22 g, 1.0 mmol), and tryptamine (0.16 g, 1.0 mmol) to yield a yellow solid (0.24 g, 49%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.94 (s, 1H), 8.83 (d, J = 1.2 Hz, 1H), 8.70 (dd, J = 1.8 Hz, J = 4.8 Hz, 1H), 8.20 (br s, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 7.8 Hz, 2H), 7.54−7.48 (m, 3H), 7.34 (d, J = 8.4 Hz, 1H), 7.24 (d, J = 7.8 Hz, 1H), 7.13 (s, 1H), 7.05 (t, J = 7.8 Hz, 1H), 6.91 (t, J = 7.2 Hz, 1H), 5.46 (s, 1H), 3.88−3.83 (m, 1H), 3.02−2.92 (m, 2H), 2.78−2.73 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 181.2, 165.3, 151.8, 149.0, 141.9, 136.6, 136.3, 134.2, 128.9, 128.2, 126.9, 125.5, 125.4, 123.5, 122.9, 121.2, 121.1, 118.2, 118.0, 111.5, 110.7, 60.3, 41.2, 23.7 (note: either carbon 1 or 2 is absent); mp 235−240 °C. HMS (APCI) calcd for $C_{27}H_{20}F_3N_3O_3$ 492.1535; found 492.1532 $[M + H]^+$.

*Methyl 4-(1-(2-(1H-Indol-3-yl)ethyl)-3-acetyl-4-hydroxy-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)-2-hydroxybenzoate (**95**).* Compound **95** was prepared via procedure I from **35** (0.15 g, 0.83 mmol), tryptamine (0.13 g, 0.83 mmol), and methyl acetopyruvate (0.12 g, 0.83 mmol) to yield a brown solid (0.10 g, 27%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.82 (s, 1H), 10.49 (s, 1H), 7.68 (dd, J = 8.0 Hz, J = 2.4 Hz, 1H), 7.34−7.30 (m, 2H), 7.10 (s, 1H), 7.05 (t, J = 6.8 Hz, 1H), 6.92 (t, J = 6.8 Hz, 1H), 6.84 (s, 1H), 6.64 (d, J = 8.0 Hz, 1H), 5.12 (s, 1H), 3.86 (s, 3H), 3.83−3.76 (m, 1H), 2.98−2.83 (m, 2H), 2.75−2.68 (m, 1H), 2.27 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 191.7, 168.8, 165.0, 159.8, 154.4, 154.1, 136.0, 130.3, 126.9, 122.8, 121.0, 119.6, 118.3, 118.2, 118.1, 117.0, 112.8, 111.4, 110.7, 59.6, 52.4, 40.9, 29.8, 23.5; mp 188−190 °C. HMS (APCI) calcd for $C_{24}H_{22}N_2O_6$ 435.1551; found 435.1549 $[M + H]^+$.

*Methyl 4-(1-(2-(1H-Indol-3-yl)ethyl)-3-acetyl-4-hydroxy-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)-2-methoxybenzoate (**96**).* Compound **96** was prepared via procedure I from **33** (0.1 g, 0.52 mmol), tryptamine (0.083 g, 0.52 mmol), and methyl acetopyruvate (0.074 g, 0.52 mmol) to yield a cream-colored solid (0.17 g, 74%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.83 (s, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.34−7.31 (m, 2H), 7.11 (s, 1H), 7.06 (t, J = 6.8 Hz, 1H), 6.94−6.91 (m, 2H), 6.70 (d, J = 8.0 Hz, 1H), 5.14 (s, 1H), 3.83−3.76 (m, 7H), 2.99−2.84 (m, 2H), 2.75−2.69 (m, 1H), 2.28 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 165.9, 165.0, 158.1, 136.2, 130.9, 128.1, 126.9, 125.5, 125.0, 122.9, 121.0, 119.6, 118.6, 118.3, 118.1, 111.5, 110.8, 60.0, 55.9, 51.9, 40.9, 40.0, 23.6 (note: carbons 3 and 4 are absent); mp 130−135 °C. HMS (APCI) calcd for $C_{25}H_{24}N_2O_6$ 449.1707; found 449.1709 $[M + H]^+$.

*Methyl 4-(1-(2-(1H-Indol-3-yl)ethyl)-3-acetyl-4-hydroxy-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)-2-methylbenzoate (**97**).* Compound **97** was prepared via procedure I from **40** (0.10 g, 0.56 mmol), tryptamine (0.090 g, 0.56 mmol), and methyl acetopyruvate (0.081 g, 0.56 mmol) to yield a pale-orange solid (0.13 g, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.40−7.36 (m, 2H), 7.23 (t, J = 7.6 Hz, 1H), 7.11 (t, J = 7.6 Hz, 1H), 7.00 (s, 1H), 6.83 (d, J = 7.6 Hz, 1H), 6.74 (s, 1H), 4.76 (s, 1H), 4.07−4.02 (m, 1H), 3.90 (s, 3H), 3.11−2.93 (m, 3H), 2.51 (s, 3H), 1.98 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 194.6, 167.6, 164.6, 159.8, 141.4, 139.0, 136.5, 131.5, 131.3, 130.5, 127.2, 125.2, 122.6, 122.3, 119.8, 119.5, 118.7, 112.4, 111.6, 61.4, 52.2, 41.3, 28.2, 24.4, 21.9; mp 40−43 °C. HMS (APCI) calcd for $C_{25}H_{24}N_2O_5$ 433.1745; found 433.1745 $[M + H]^+$.

*Methyl 4-(1-(2-(1H-Indol-3-yl)ethyl)-3-acetyl-4-hydroxy-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)-2-chlorobenzoate (**98**).* Compound **98** was prepared via procedure I from **39** (0.09 g, 0.45 mmol), tryptamine (0.073 g, 0.45 mmol), and methyl acetopyruvate (0.065 g, 0.45 mmol) to yield a pale-orange, amorphous solid (0.14 g, 68%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.85 (s, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.40−7.23 (m, 4H), 7.14−7.03 (m, 2H), 6.93 (t, J = 7.6 Hz, 1H), 5.13 (s, 1H), 3.83−3.78 (m, 4H), 2.98−2.82 (m, 2H), 2.75−2.68 (m, 1H), 2.27 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 190.8, 165.2, 142.8, 136.2, 131.8, 131.2, 130.5, 129.4, 128.0, 126.8, 126.0, 122.9, 121.0, 118.3, 118.0, 111.4, 110.7, 59.1, 52.5, 48.6, 40.8, 23.6 (note: carbons 1 and 2 are absent). HMS (APCI) calcd for 453.1225; found 453.1219 $[M + H]^+$.

*Methyl 4-(1-(2-(1H-Indol-3-yl)ethyl)-3-acetyl-4-hydroxy-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)-2-fluorobenzoate (**99**).* Compound **99** was prepared via procedure I from **38** (0.08 g, 0.44 mmol), tryptamine

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(0.070 g, 0.44 mmol), and methyl acetopyruvate (0.063 g, 0.44 mmol) to yield a pale-orange solid (0.096 g, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.81 (t, J = 7.6 Hz, 1H), 7.40−7.27 (m, 2H), 7.20 (t, J = 7.2 Hz, 1H), 7.14−7.06 (m, 1H), 6.95 (d, J = 1.2 Hz, 1H), 6.78 (dd, J = 1.2 Hz, J = 7.6 Hz, 1H), 6.70 (dd, J = 1.2 Hz, J = 10.8 Hz, 1H), 4.80 (s, 1H), 4.09−4.03 (m, 1H), 3.92 (s, 3H), 3.10−2.96 (m, 3H), 2.19 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 193.6, 165.5, 162.0 (d, J = 260.4 Hz), 142.8 (d, J = 7.4 Hz), 136.5, 132.8, 127.0, 123.5, 123.4 (d, J = 26.0 Hz), 122.5, 122.3, 122.1, 120.1, 119.7, 118.7, 118.5, 111.9, 111.7, 61.2, 52.6, 41.6, 29.2, 24.4; mp 40−45 °C. HMS (APCI) calcd for $C_{24}H_{21}FN_2O_5$ 437.1512; found 437.1512 $[M + H]^+$.

*Methyl 4-(1-(2-(1H-Indol-3-yl) ethyl)-3-acetyl-4-hydroxy-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)-3-hydroxybenzoate (**100**).* Compound **100** was prepared via procedure I from **34** (0.1 g, 0.56 mmol), tryptamine (0.089 g, 0.52 mmol), and methyl acetopyruvate (0.080 g, 0.56 mmol) to yield an off-white solid (0.020 g, 8%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.68 (s, 1H), 10.07 (br s, 1H), 7.47 (s, 1H), 7.35−7.29 (m, 3H), 7.05−7.02 (m, 3H), 6.91 (t, J = 10.8 Hz, 1H), 5.58 (s, 1H), 3.83 (s, 3H), 3.80−3.74 (m, 1H), 3.02−2.88 (m, 2H), 2.76−2.68 (m, 1H), 2.27 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 196.6, 190.2, 163.6, 151.5, 136.4, 136.2, 127.0, 126.9, 123.5, 123.0, 122.5, 121.0, 118.32, 118.25, 118.0, 111.4, 111.2, 110.4, 94.5, 52.7, 52.2, 44.8, 29.3, 26.7; mp 194−197 °C. HMS (APCI) calcd for $C_{24}H_{22}N_2O_6$ 435.1551; found 435.1552 $[M + H]^+$.

*Methyl 4-(1-(2-(1H-Indol-3-yl)ethyl)-3-acetyl-4-hydroxy-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)-3-methoxybenzoate (**101**).* Compound **101** was prepared via procedure I from **41** (0.20 g, 1.0 mmol), tryptamine (0.17 g, 1.0 mmol), and methyl acetopyruvate (0.15 g, 1.0 mmol) to yield an off-white solid (0.16 g, 36%). ^{1}H NMR (600 MHz, DMSO-d_6, 56 °C) δ 10.68 (s, 1H), 7.53 (s, 1H), 7.48 (dd, J = 1.6 Hz, J = 8.0 Hz, 1H), 7.32−7.28 (m, 2H), 7.06−7.02 (m, 3H), 6.92 (td, J = 7.2 Hz, J = 0.8 Hz, 1H), 5.59 (s, 1H), 3.86 (s, 6H), 3.81−3.72 (m, 1H), 2.97−2.85 (m, 2H), 2.84−2.69 (m, 1H), 2.27 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 191.5, 165.9, 165.2, 157.9, 154.8, 136.2, 130.6, 126.9, 126.6, 122.7, 121.9, 121.0, 118.3, 117.8, 111.7, 111.5, 110.7, 56.0, 52.3, 41.0, 40.1, 29.7, 23.4 (note: carbon 3 and either carbon 1 or 2 are absent); mp 103−107 °C. HMS (APCI) calcd for $C_{25}H_{24}N_2O_6$ 449.1707; found 449.1704 $[M + H]^+$.

*Methyl 4-(1-(2-(1H-Indol-3-yl)ethyl)-3-acetyl-4-hydroxy-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)-3-methylbenzoate (**102**).* Compound **102** was prepared via procedure I from **36** (0.10 g, 0.56 mmol), tryptamine (0.090 g, 0.56 mmol), and methyl acetopyruvate (0.081 g, 0.56 mmol) to yield an orange solid (0.12 g, 50%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.83 (s, 1H), 7.75 (s, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 7.09 (d, J = 1.8 Hz, 1H), 7.04 (t, J = 7.2 Hz, 1H), 6.90 (t, J = 7.8 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 5.27 (s, 1H), 3.81 (s, 3H), 3.75 (dt, J = 8.4 Hz, J = 13.8 Hz, 1H), 2.94−2.89 (m, 1H), 2.76−2.69 (m, 2H), 2.31 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 166.0, 165.5, 140.6, 138.2, 136.3, 131.0, 128.8, 127.0, 126.8, 125.4, 122.9, 121.1, 118.3, 117.7, 111.5, 110.7, 55.6, 41.5, 40.1, 23.6, 18.5, 14.1 (note: carbons 3 and 4, and either carbons 1 or 2 are absent); mp 60−70 °C. HMS (APCI) calcd for $C_{25}H_{24}N_2O_5$ 433.1763; found 433.1764 $[M + H]^+$.

*Methyl 4-(1-(2-(1H-Indol-3-yl)ethyl)-3-acetyl-4-hydroxy-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)-3-chlorobenzoate (**103**).* Compound **103** was prepared via procedure I from **32** (0.10 g, 0.50 mmol), tryptamine (0.081 g, 0.50 mmol), and methyl acetopyruvate (0.073 g, 0.50 mmol) to yield a pale-yellow solid (0.080 g, 35%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.50 (br s, 1H), 10.81 (s, 1H), 7.95 (d, J = 1.6 Hz, 1H), 7.76 (dd, J = 1.2 Hz, J = 8.0 Hz, 1H), 7.29 (d, J = 8.4 Hz, 2H), 7.09−7.01 (m, 3H), 6.91 (t, J = 7.6 Hz, 1H), 5.68 (s, 1H), 3.85 (s, 3H), 3.80−3.73 (m, 1H), 2.97−2.84 (m, 2H), 2.77−2.72 (m, 1H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 192.5, 170.4, 165.5, 164.8, 139.8, 136.2, 134.7, 130.8, 129.8, 128.2, 127.8, 126.9, 122.8, 121.0, 118.3, 117.7, 111.5, 110.4, 59.8, 55.6, 52.6, 41.5, 23.5 (note: carbon 3 is absent); mp 55−60 °C. HMS (APCI) calcd for $C_{24}H_{21}ClN_2O_5$ 453.1225; found 453.1222 $[M + H]^+$.

*Methyl 4-(1-(2-(1H-Indol-3-yl)ethyl)-3-acetyl-4-hydroxy-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)-3-fluorobenzoate (**104**).* Compound **104** was prepared via procedure I from **37** (0.12 g, 0.67 mmol), tryptamine (0.11 g, 0.67 mmol), and methyl acetopyruvate (0.097 g, 0.67 mmol) to yield an orange, amorphous solid (0.033 g, 11%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 7.65 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 7.6 Hz, 1H), 7.31−7.27 (m, 2H), 7.11 (t, J = 7.2 Hz, 1H), 7.20 (t, J = 7.6 Hz, 1H), 6.93 (s, 1H), 5.52 (s, 1H), 4.02−3.97 (m, 1H), 3.88 (s, 3H), 3.02−2.87 (m, 3H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 191.4, 171.1, 167.1 (d, J = 186.7 Hz), 162.7, 136.4, 132.6, 130.9, 127.4, 125.4, 122.3, 121.9, 119.2, 118.7, 116.9 (d, J = 23.8), 114.0, 112.5, 111.3, 102.3, 52.4, 45.9, 41.3, 28.4, 24.1. HMS (APCI) calcd for $C_{24}H_{21}FN_2O_5$ 437.1507; found 437.1509 $[M + H]^+$.

*Methyl 4-(4-Hydroxy-1-(2-(1-methyl-1H-Indol-3-yl)ethyl)-3-nicotinoyl-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**105**).* Compound **105** was prepared via procedure I from methyl 4-formylbenzoate (0.16 g, 1.0 mmol), **19** (0.22 g, 1.0 mmol), and 2-(1-methyl-1*H*-indol-3-yl)ethanamine (0.17 g, 1.0 mmol) to yield cream-colored solid (0.21 g, 43%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.81 (d, J = 1.8 Hz, 1H), 8.70 (dd, J = 1.8 Hz, J = 4.8, 1H), 8.01 (dt, J = 1.8 Hz, 8.4 Hz, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.50−7.46 (m, 3H), 7.36 (d, J = 9.0 Hz, 1H), 7.32 (d, J = 8.4 Hz, 1H), 7.14−7.10 (m, 2H), 6.96 (t, J = 7.8 Hz, 1H), 5.50 (s, 1H), 3.85−3.80 (m, 4H), 3.70 (s, 3H), 3.00−2.92 (m, 2H), 2.76−2.72 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 181.2, 165.9, 165.0, 153.9, 152.2, 149.1, 142.0, 136.6, 136.3, 133.9, 129.5, 129.4, 128.4, 127.3, 127.2, 123.5, 121.2, 118.4, 118.3, 110.1, 109.7, 60.4, 52.2, 41.3, 32.2, 23.5 (note: either carbon 1 or 2 is absent); mp 215−218 °C. HMS (APCI) calcd for $C_{29}H_{25}N_3O_5$ 496.1867; found 496.1872 $[M + H]^+$.

*Methyl 4-(3-Acetyl-4-hydroxy-1-(2-(2-methyl-1H-indol-3-yl)-ethyl)-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**106**).* Compound **106** was prepared via procedure I from methyl 4-formylbenzoate (0.094 g, 0.57 mmol), 2-(2-methyl-1*H*-indol-3-yl)ethanamine (0.10 g, 0.57 mmol), and methyl acetopyruvate (0.083 g, 0.57 mmol) to yield a cream-colored solid (0.18 g, 73%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.73 (s, 1H), 7.85 (d, J = 9.0 Hz, 2H), 7.21 (d, J = 7.8 Hz, 1H), 7.18−7.15 (m, 3H), 6.97 (t, J = 7.8 Hz, 1H), 6.86 (t, J = 7.8 Hz, 1H), 5.03 (s, 1H), 3.83 (s, 3H), 3.64−3.59 (m, 1H), 2.92−2.87 (m, 1H), 2.77−2.72 (m, 1H), 2.60−2.56 (m, 1H), 2.26 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 191.1, 165.9, 165.0, 142.4, 135.1, 132.2, 129.8, 129.7, 129.3, 128.1, 127.9, 125.6, 120.1, 118.2, 117.0, 110.5, 106.5, 60.1, 52.1, 40.9, 39.9, 24.5, 10.9; mp 182−187 °C. HMS (APCI) calcd for $C_{25}H_{24}N_2O_5$ 433.1758; found 433.1759 $[M + H]^+$.

*Methyl 4-(4-Hydroxy-1-(2-(4-methyl-1H-indol-3-yl)ethyl)-3-nicotinoyl-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**107**).* Compound **107** was prepared via procedure I from methyl 4-formylbenzoate (0.16 g, 1.0 mmol), **19** (0.22 g, 1.0 mmol), and 2-(4-methyl-1*H*-indol-3-yl)ethanamine (0.17 g, 1.0 mmol) to yield a pale-yellow solid (0.05 g, 11%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.84 (d, J = 1.8 Hz, 1H), 8.82 (d, J = 1.8 Hz, 1H), 8.70 (dd, J = 1.8 Hz, J = 4.8 Hz, 1H), 8.01 (dt, J = 1.8 Hz, J = 8.4 Hz, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.49−7.44 (m, 3H), 7.15 (d, J = 8.4 Hz, 1H), 7.04 (d, J = 2.4 Hz, 1H), 6.92 (t, J = 6.6 Hz, 1H), 6.67 (d, J = 7.2 Hz, 1H), 5.48 (s, 1H), 3.89−3.81 (m, 4H), 3.14−3.09 (m, 1H), 2.98−2.87 (m, 2H), 2.44 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 186.9, 165.9, 165.1, 152.3, 149.3, 142.2, 136.7, 136.2, 133.9, 129.5, 129.4, 128.3, 125.4, 123.4, 123.1, 122.9, 121.1, 120.1, 119.9, 118.2, 111.5, 109.6, 66.4, 60.4, 52.2, 25.5, 19.7; mp 170−175 °C. HMS (APCI) calcd for $C_{29}H_{25}N_3O_5$ 496.1845; found 496.1850 $[M + H]^+$.

*Methyl 4-(4-Hydroxy-1-(2-(5-methoxy-1H-indol-3-yl)ethyl)-3-nicotinoyl-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**108**).* Compound **108** was prepared via procedure I from methyl 4-formylbenzoate (0.16 g, 1.0 mmol), **19** (0.22 g, 1.0 mmol), and 2-(5-methoxy-1*H*-indol-3-yl)ethanamine (0.19 g, 1.0 mmol) to yield a yellow solid (0.35 g, 68%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.72 (s, 1H), 8.79 (d, J = 1.8 Hz, 1H), 8.68 (dd, J = 1.8 Hz, J = 4.8 Hz, 1H), 7.99 (dt, J = 1.8 Hz, J = 7.8 Hz, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.48−7.46 (m, 1H), 7.44 (d, J = 7.8 Hz, 2H), 7.22−7.21 (m, 2H), 7.09 (d, J = 2.4 Hz, 1H), 6.75 (d, J = 2.4 Hz, 1H), 6.70 (dd, J = 2.4 Hz, J = 9.0 Hz, 1H), 5.44 (s, H), 3.85−3.80 (m, 4H), 2.68 (s, 3H), 2.98−2.89 (m, 2H), 2.73−2.70 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 186.7, 181.1, 165.9, 165.2, 153.0, 152.0, 149.1, 142.4, 136.3, 134.1, 131.4, 129.5, 129.4, 128.3, 127.2, 123.6, 123.5, 117.9, 112.2, 111.3, 110.5, 99.7, 60.4, 55.2, 52.2, 41.1, 23.8; mp 222−225 °C. HMS (APCI) calcd for $C_{29}H_{25}N_3O_6$ 512.1816; found 512.1822 $[M + H]^+$.

*Methyl 4-(1-(2-(6-Fluoro-1H-indol-3-yl)ethyl)-4-hydroxy-3-nicotinoyl-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**109**).* Compound **109** was prepared via procedure I from methyl 4-formylbenzoate (0.16 g, 1.0 mmol), **19** (0.22 g, 1.0 mmol), and 3-(6-fluoro-1*H*-indol-3-yl)ethanamine (0.18 g, 1.0 mmol) to yield a pale-orange solid (0.44 g, 87%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.94 (s, 1H), 8.82 (d, J = 0.6 Hz, 1H), 8.69 (d, J = 4.8 Hz, 1H), 8.01 (d, J = 7.8 Hz, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.80 (br s, 1H), 7.49−7.47 (m, 1H), 7.43 (d, J = 7.8 Hz, 2H), 7.33−7.30 (m, 1H), 7.31−7.10 (m, 2H), 6.79 (td, J = 9.6 Hz, J = 1.8 Hz, 1H), 5.44 (s, 1H), 3.89−3.82 (m, 4H), 2.98−2.91 (m, 2H), 2.80−2.76 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 186.9, 181.1, 165.9, 165.1, 159.7, 158.1, 152.3, 142.2, 136.3, 136.1, 133.9, 129.5, 129.3, 128.3, 125.5, 123.8, 123.4, 119.1, 118.1, 111.1, 106.7, 106.6, 60.4 (d, J = 14.4 Hz), 52.1, 41.1, 23.1; mp 162−167 °C. HMS (APCI) calcd for $C_{28}H_{22}FN_3O_5$ 500.1595; found 500.1600 $[M + H]^+$.

*Methyl 4-(1-(2-(6-Chloro-1H-indol-3-yl)ethyl)-4-hydroxy-3-nicotinoyl-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**110**).* Compound **110** was prepared via procedure I from methyl 4-formylbenzoate (0.16 g, 1.0 mmol), **19** (0.22 g, 1.0 mmol), and 2-(6-chloro-1*H*-indol-3-yl)ethanamine (0.20 g, 1.0 mmol) to yield a yellow solid (0.44 g, 85%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.00 (s, 1H), 8.80 (s, 1H), 8.68 (d, J = 3.6 Hz, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 7.8 Hz, 2H), 7.77 (br s, 1H), 7.48−7.41 (m, 3H), 7.37 (d, J = 1.2 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 7.17 (s, 1H), 6.94 (dd, J = 1.2 Hz, J = 8.4 Hz, 1H), 3.87−3.82 (m, 4H), 2.97−2.89 (m, 2H), 2.79−2.76 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 181.2, 165.9, 165.3, 149.2, 136.6, 136.2, 129.44, 129.36, 128.3, 128.1, 125.8, 125.7, 125.5, 124.7, 124.1, 123.3, 119.5, 118.8, 118.6, 111.2, 111.1, 109.8, 60.3, 52.1, 41.0, 23.4; mp 184−189 °C. HMS (APCI) calcd for $C_{28}H_{22}ClN_3O_5$ 516.1321; found 516.1324 $[M + H]^+$.

*Methyl 4-(4-Hydroxy-1-(2-(6-methyl-1H-indol-3-yl)ethyl)-3-nicotinoyl-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**111**).* Compound **111** was prepared via procedure I from methyl 4-formylbenzoate (0.16 g, 1.0 mmol), **19** (0.22 g, 1.0 mmol), and 2-(6-methyl-1*H*-indol-3-yl)ethanamine (0.17 g, 1.0 mmol) to yield a cream-colored solid (0.10 g, 20%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.71 (s, 1H), 8.79 (s, 1H), 8.68 (d, J = 3.6 Hz, 1H), 7.99 (d, J = 6.6 Hz, 1H), 7.87 (d, J = 7.8 Hz, 2H), 7.47 (t, J = 6.0 Hz, 1H), 7.42 (d, J = 7.8 Hz, 2H), 7.17 (d, J = 7.8 Hz, 1H), 7.11 (s, 1H), 7.02 (s, 1H), 6.75 (d, J = 7.8 Hz, 1H), 5.40 (s, 1H), 3.90−3.82 (m, 4H), 2.99−2.89 (m, 2H), 2.74−2.71 (m, 1H), 2.37 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 186.7, 165.9, 165.1, 152.1, 149.1, 142.3, 136.7, 136.2, 134.0, 130.0, 129.5, 129.4, 128.4, 128.1, 125.5, 124.9, 123.4, 122.2, 120.0, 117.8, 111.3, 110.6, 60.4, 52.2, 41.1, 23.8, 21.4; mp 202−207 °C. HMS (APCI) calcd for $C_{29}H_{25}N_3O_5$ 496.1867; found 496.1868 $[M + H]^+$.

*Methyl 4-(4-Hydroxyl-1-(2-(6-methyoxy-1H-indol-3-yl)ethyl)-3-nicotinoyl-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**112**).* Compound **112** was prepared via procedure I from methyl 4-formylbenzoate (0.16 g, 1.0 mmol), **19** (0.22 g, 1.0 mmol), and 2-(6-methoxy-1*H*-indol-3-yl)ethanamine (0.19 g, 1.0 mmol) to yield a pale-orange solid (0.39 g, 76%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.64 (s, 1H), 8.78 (s, 1H), 8.67 (s, 1H), 8.06 (d, J = 7.8 Hz, 1H), 7.87 (d, J = 7.8 Hz, 2H), 7.55 (d, J = 7.2 Hz, 1H), 7.41 (d, J = 7.8 Hz, 2H), 7.11 (d, J = 7.8 Hz, 1H), 6.96 (s, 1H), 6.83 (s, 1H), 6.58 (d, J = 7.8 Hz, 1H), 5.39 (s, 1H), 3.82 (s, 3H), 3.75−3.70 (m, 4H), 2.94−2.90 (m, 2H), 2.71−2.69 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 165.8, 155.6, 145.7, 137.6, 137.4, 137.0, 130.8, 130.4, 129.5, 129.4, 128.3, 128.11, 128.07, 125.5, 121.3, 118.7, 110.8, 108.5, 107.5, 94.5, 60.4, 55.2, 40.9, 23.8, 20.8 (note: two of either carbon 1, 2, or 3 are absent); mp 195−200 °C. HMS (APCI) calcd for $C_{29}H_{25}N_3O_6$ 512.1816; found 512.1821 $[M + H]^+$.

*Methyl 4-(1-(2-(7-Fluoro-1H-indol-3-yl)ethyl)-4-hydroxy-3-nicotinoyl-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**113**).* To a slurry of 2-(7-fluoro-1*H*-indol-3-yl)ethanamine hydrochloride (0.05 g, 0.23 mmol) in MeOH (0.026 mL) was added triethylamine (0.039 mL, 0.28 mmol). Ether (1.3 mL) was added, and the mixture was stirred at −10 °C for 1 h. The resulting triethylamine hydrochloride salt was filtered off, and the filtrate was concentrated in vacuo to afford a white solid (0.040 g, >99%) which was carried on immediately. Compound **113** was prepared via procedure I from methyl 4-formylbenzoate (0.039 g, 0.24 mmol), **19** (0.052 g, 0.24 mmol), and 2-(7-fluoro-1*H*-indol-3-yl)ethanamine hydrochloride (0.040 g, 0.24 mmol) to yield a pale-yellow solid (0.11 g, 97%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.30 (s, 1H), 10.11 (s, 1H), 8.74 (m, 1H), 8.46 (m, 1H), 7.98−7.97 (m, 1H), 7.87−7.86 (m, 1H), 7.37−7.33 (m, 2H), 7.28 (m, 1H), 7.16−7.14 (m, 2H), 6.89−6.87 (m, 2H), 5.23 (s, 1H), 3.84−3.76 (m, 4H), 2.92 (m, 1H), 2.79 (m, 1H), 2.73−2.68 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 193.0 (d, J = 13.4 Hz), 169.4, 166.2, 165.5, 150.0, 149.5, 148.4, 147.7, 139.1, 136.6, 134.3, 131.1, 129.7, 129.0, 128.7, 128.3, 127.7, 124.0, 118.6, 114.7, 112.4, 105.8, 60.0 (d, J = 45.5 Hz), 52.0 (d, J = 41.2 Hz), 40.1 (d, J = 21.8 Hz), 23.3; mp 65−69 °C. HMS (APCI) calcd for $C_{28}H_{22}FN_3O_5$ 500.1616; found 500.1616 $[M + H]^+$.

*Methyl 4-(1-(2-(7-Chloro-1H-indol-3-yl)ethyl)-4-hydroxy-3-nicotinoyl-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**114**).* To a slurry of 2-(7-chloro-1*H*-indol-3-yl)ethanamine hydrochloride (0.15 g, 0.65 mmol) in MeOH (0.072 mL) was added triethylamine (0.11 mL, 0.78 mmol). Ether (3.62 mL) was added, and the mixture was stirred at −10 °C for 1 h. The resulting triethylamine hydrochloride salt was filtered off, and the filtrate was concentrated in vacuo to afford a white solid (0.074 g, 58%) which was carried on immediately. Compound **114** was prepared via procedure I from methyl 4-formylbenzoate (0.064 g, 0.39 mmol), **19** (0.086 g, 0.39 mmol), and 2-(7-chloro-1*H*-indol-3-yl)ethanamine hydrochloride (0.074 g, 0.39 mmol) to yield a yellow solid (0.009 g, 5%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.22 (s, 1H), 8.80 (s, 1H), 8.69 (d, J = 4.2 Hz, 1H), 8.00 (d, J = 7.8 Hz, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.49−7.44 (m, 3H), 7.31 (d, J = 7.8 Hz, 1H), 7.22 (d, J = 1.8 Hz, 1H), 7.14 (d, J = 7.2 Hz, 1H), 6.94 (t, J = 7.2 Hz, 1H), 5.49 (s, 1H), 3.89−3.82 (m, 4H), 3.00−2.91 (m, 2H), 2.83−2.78 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 181.3, 165.9, 165.0, 152.4, 149.3, 142.0, 136.2, 133.9, 133.0, 129.5, 129.4, 129.0, 128.3, 124.4, 123.5, 120.6, 119.4, 118.2, 117.3, 115.9, 112.3, 60.2, 52.2, 41.0, 23.6 (note: one of either carbon 1, 2, or 3 are absent); mp 246−249 °C. HMS (APCI) calcd for $C_{28}H_{22}ClN_3O_5$ 516.1321; found 516.1325 $[M + H]^+$.

*Methyl 4-(3-Acetyl-4-hydroxy-1-(2-(7-methyl-1H-indol-3-yl)-ethyl)-5-oxo-2, 5-dihydro-1H-pyrrol-2-yl) benzoate (**115**).* Compound **115** was prepared via procedure I from methyl 4-formylbenzoate (0.094 g, 0.57 mmol), 2-(7-methyl-1*H*-indol-3-yl) ethanamine (0.10 g, 0.57 mmol), and methyl acetopyruvate (0.083 g, 0.57 mmol) to yield a white solid (0.16 g, 66%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.50 (br s, 1H), 10.78 (s, 1H), 7.88 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 7.12−7.07 (m, 2H), 6.83−6.82 (m, 2H), 5.20 (s, 1H), 3.83−3.76 (m, 4H), 2.98−2.80 (m, 2H), 2.80−2.66 (m, 1H), 2.41 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 165.9, 165.0, 142.4, 135.7, 129.3, 128.1, 126.5, 125.5, 122.5, 121.5, 120.5, 118.5, 115.7, 111.1, 109.7, 59.7, 52.1, 40.8, 40.0, 23.7, 16.7 (note: carbons 3 and 4 are absent); mp 220−227 °C. HMS (APCI) calcd from $C_{25}H_{24}N_2O_5$ 433.1758; found 433.1758 $[M + H]^+$.

*Ethyl 4-(1-(2-(1H-Indol-3-yl)ethyl)-4-hydroxy-3-nicotinoyl-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**116**).* Compound **116** was prepared via procedure I from **19** (0.15 g, 0.68 mmol), tryptamine (0.11 g, 0.68 mmol), and **35** (0.12 g, 0.68 mmol) to yield a yellow solid (0.027 g, 8%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.84 (s, 1H), 8.75 (s, 1H), 8.48 (d, J = 3.2 Hz, 1H), 7.94 (d, J = 7.2 Hz, 1H), 7.83 (d, J = 8.0 Hz, 2H), 7.34−7.27 (m, 5H), 7.08−7.04 (m, 2H), 6.92 (t, J = 7.2 Hz, 1H), 5.33 (s, 1H), 4.28 (q, J = 7.6 Hz, 2H), 3.84−3.77 (m, 1H), 3.00−2.93 (m, 1H), 2.87−2.80 (m, 1H), 2.73−2.66 (m, 1H), 1.28 (t, J = 6.8 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 186.8, 182.1, 162.9, 155.0, 148.3, 148.1, 136.4, 136.3, 127.0, 123.8, 123.4, 123.2, 123.1, 121.5, 121.3, 120.8, 118.5, 118.2, 117.8, 111.8, 111.2, 109.5, 60.6, 45.3, 23.6, 23.3, 14.0; mp >250 °C. HMS (APCI) calcd for $C_{29}H_{25}N_3O_5$ 496.1867; found 496.1872 $[M + H]^+$.

*Ethyl 4-(1-(2-(1H-Indol-3-yl)ethyl)-4-hydroxy-3-isonicotinoyl-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**117**).* Compound **117** was prepared via procedure I from **45** (0.40 g, 2.3 mmol), tryptamine (0.36 g, 2.3 mmol), and **20** (0.50 g, 2.3 mmol) to yield a yellow solid (0.019 g, 2%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.84 (s, 1H), 8.68 (d, J = 5.4 Hz, 2H), 7.88 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 5.4 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.12 (d, J = 1.8 Hz, 1H), 7.06 (t, J = 7.8 Hz, 1H), 6.92 (t, J = 7.2 Hz, 1H), 5.40 (s, 1H), 4.29 (q, J = 7.2 Hz, 2H), 3.88−3.82 (m, 1H), 3.00−2.90 (m, 2H), 2.78−2.73 (m, 1H), 1.29 (7.2 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 189.0, 165.4, 165.0, 149.6, 145.8, 142.2, 136.2, 129.8,

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129.7, 129.3, 128.3, 126.9, 122.9, 121.8, 121.1, 118.3, 118.1, 117.35, 111.5, 110.7, 60.7, 60.3, 41.1, 23.6, 14.2; mp 169−172 °C. HMS (APCI) calcd for $C_{29}H_{25}N_3O_5$ 496.1880; found 496.1877 $[M + H]^+$.

*Methyl 4-(4-Hydroxy-1-(2-(2-methyl-1H-indol-3-yl)ethyl)-3-nicotinoyl-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**118**).* Compound **118** was prepared via procedure I from **19** (0.15 g, 0.68 mmol), 2-(2-methyl-1*H*-indol-3-yl)ethanamine (0.12 g, 0.68 mmol), and methyl 4-formylbenzoate (0.11 g, 0.68 mmol) to yield an orange solid (0.046 g, 14%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.75 (s, 1H), 8.73 (s, 1H), 8.48 (d, J = 4.4 Hz, 1H), 7.93 (s, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.30−7.17 (m, 5H), 6.97 (t, J = 6.4 Hz, 1H), 6.86 (t, J = 7.2 Hz, 1H), 5.23 (s, 1H), 3.81 (s, 3H), 3.63−3.56 (m, 1H), 2.96−2.88 (m, 1H), 2.76−2.69 (m, 1H), 2.57−2.50 (m, 1H), 2.18 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 182.6, 166.0, 150.4, 150.1, 149.2, 136.8, 136.1, 135.5, 135.2, 132.2, 129.0, 128.6, 128.0, 123.6, 122.6, 120.1, 118.2, 117.0, 110.6, 106.7, 61.2, 52.0, 41.3, 22.6, 11.0 (note: two of carbons 1, 2, 3, or 4 are absent); mp >250 °C. HMS (APCI) calcd for $C_{29}H_{25}N_3O_5$ 496.1867; found 496.1872 $[M + H]^+$.

*Ethyl 4-(3-Acetyl-4-hydroxy-1-(2-(2-methyl-1H-indol-3-yl)ethyl)-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**119**).* Compound **119** was prepared via procedure I from **45** (0.15 g, 0.84 mmol), 2-(2-methyl-1*H*-indol-3-yl)ethanamine (0.15 g, 0.84 mmol), and methyl acetopyruvate (0.12 g, 0.84 mmol) to yield a cream-colored solid (0.078 g, 21%). ^{1}H NMR (600 MHz, DMSO-d_6, 80 °C) δ 10.5 (br s, 1H), 7.83 (d, J = 7.2 Hz, 2H), 7.23−7.18 (m, 4H), 6.95 (t, J = 7.2 Hz, 1H), 6.86 (t, J = 7.2 Hz, 1H), 5.09 (s, 1H), 4.30 (q, J = 7.2 Hz, 2H), 3.61−3.56 (m, 1H), 2.92−2.87 (m, 1H), 2.80−2.75 (m, 1H), 2.57−2.53 (m, 1H), 2.19 (s, 3H), 2.05 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 191.3, 189.3, 165.5, 135.1, 132.1, 129.1, 127.9, 120.1, 118.1, 117.0, 112.1, 110.5, 108.9, 106.6, 98.5, 90.2, 54.9, 48.7, 48.6, 40.0, 29.0, 14.2, 11.0 (note: one of either carbon 1, 2, or 4 is absent); mp 190−195 °C. HMS (APCI) calcd for $C_{26}H_{26}N_2O_5$ 447.1928; found 447.30 $[M + H]^+$.

*Ethyl 4-(1-(2-(1H-Indol-3-yl)ethyl)-3-acetyl-4-hydroxy-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)-3-hydroxybenzoate (**120**).* Compound **120** was prepared via procedure I from **189** (0.15 g, 0.77 mmol), tryptamine (0.12 g, 0.77 mmol), and methyl acetopyruvate (0.11 g, 0.77 mmol) to yield a cream-colored solid (0.20 g, 57%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.81 (s, 1H), 10.42 (s, 1H), 7.59−7.46 (m, 1H), 7.34−7.23 (m, 3H), 7.12−7.02 (m, 2H), 6.97−6.89 (m, 2H), 5.76 (s, 1H), 4.28 (q, J = 7.2 Hz, 2H), 3.78−3.74 (m, 1H), 2.98−2.85 (m, 2H), 2.73−2.68 (m, 1H), 2.28 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 191.7, 165.5, 165.1, 156.2, 154.8, 136.2, 130.5, 128.1, 127.0, 126.7, 125.5, 122.7, 121.0, 120.2, 118.3, 118.0, 116.1, 111.4, 110.8, 60.7, 41.0, 40.0, 29.7, 23.4, 14.2; mp 200−205 °C. HMS (APCI) calcd for $C_{25}H_{24}N_2O_6$ 449.1721; found 449.1723 $[M + H]^+$.

*Methyl 4-(1-((1H-Indol-3-yl)methyl)-4-hydroxy-3-isonicotinoyl-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**121**).* Compound **121** was prepared via procedure I from methyl 4-formylbenzoate (0.28 g, 1.7 mmol), (1*H*-indol-3-yl)methanamine (0.25 g, 1.7 mmol), and **20** (0.38 g, 1.7 mmol) to yield an orange solid (0.78 g, 98%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.08 (s, 1H), 8.66 (d, J = 5.6 Hz, 2H), 7.92 (d, J = 8.0 Hz, 2H), 7.51−7.37 (m, 6H), 7.13−7.08 (m, 2H), 6.97 (t, J = 7.2 Hz, 1H), 5.11−5.07 (m, 2H), 3.84 (s, 3H), 3.80 (d, J = 14.8 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 166.0, 165.1, 149.2, 129.45, 129.36, 128.2, 128.1, 126.2, 125.5, 125.1, 122.0, 121.7, 121.5, 119.0, 118.9, 118.6, 118.2, 111.7, 109.3, 59.2, 52.2, 35.5 (note: carbon 4 is absent); mp 240−243 °C. HMS (APCI) calcd for $C_{27}H_{21}N_3O_5$ 468.1567; found 468.1566 $[M + H]^+$.

*Methyl 4-(1-(3-(1H-Indol-3-yl)propyl)-4-hydroxy-3-nicotinoyl-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**122**).* Compound **122** was prepared via procedure I from methyl 4-formylbenzoate (0.16 g, 1.0 mmol), **19** (0.22 g, 1.0 mmol), and 3-(1*H*-indol-3-yl)propan-1-amine (0.17 g, 1.0 mmol) to yield a yellow solid (0.35 g, 71%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.75 (s, 1H), 8.82 (s, 1H), 8.69 (d, J = 4.8 Hz, 1H), 8.02 (d, J = 7.8 Hz, 1H), 7.87 (d, J = 8.4 Hz, 2H), 7.49−7.47 (m, 3H), 7.37 (d, J = 7.8 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.06−7.03 (m, 2H), 6.92 (t, J = 7.2 Hz, 1H), 5.54 (s, 1H), 3.62−3.55 (m, 4H), 2.83−2.79 (m, 1H), 2.62−2.55 (m, 2H), 1.84−1.80 (m, 1H), 1.73−1.69 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 186.9, 165.9, 165.2, 154.4, 152.1, 149.2, 142.4, 136.3, 134.0, 129.5, 128.3, 127.0, 123.5, 122.4, 122.3, 120.8, 118.3, 118.0, 113.4, 111.4, 60.4, 52.3, 40.7, 28.0, 22.1 (note: either carbon 1 or 2 and carbon 3 are absent); mp 221−226 °C. HMS (APCI) calcd for $C_{29}H_{25}N_3O_5$ 496.1845; found 496.1852 $[M + H]^+$.

*Methyl 4-(1-(2-(1H-Indol-3-yl)ethyl)-3-acetyl-4-methoxy-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**156**).* To a solution of **1** (0.50 g, 1.2 mmol) in DCM:MeOH (1:1, 0.13M) was added (diazomethyl)-trimethylsilane (0.72 mL, 1.4 mmol). The reaction mixture continued to stir at rt for 5 h before being concentrated in vacuo. The crude residue was then purified using flash column chromatography on SiO_2 (3% MeOH/DCM) to yield a pale-yellow solid (0.24 g, 46%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.82 (s, 1H), 7.88 (dd, J = 1.6 Hz, J = 8.0 Hz, 2H), 7.33−7.24 (m, 4H), 7.09−7.03 (m, 2H), 6.92 (t, J = 7.6 Hz, 1H), 5.20 (s, 1H), 4.36 (s, 3H), 3.84 (s, 3H), 3.80−3.71 (m, 1H), 2.96−2.89 (m, 1H), 2.84−2.77 (m, 1H), 2.72−2.63 (m, 1H), 2.25 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 191.9, 165.9, 164.2, 154.0, 141.7, 136.2, 129.5, 129.3, 128.2, 126.8, 126.2, 122.9, 121.0, 118.3, 118.0, 111.5, 110.7, 59.5, 59.1, 52.2, 40.9, 30.3, 23.6; mp 40−45 °C. HMS (APCI) calcd for $C_{25}H_{24}N_2O_5$ 433.1763; found 433.1761 $[M + H]^+$.

*Methyl 4-(1-(2-(1H-Indol-3-yl)ethyl)-3-acetyl-4-amino-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**157**).* To a solution of **1** (0.50 g, 1.2 mmol) in 2-methoxyethanol (8.36 mL, 0.14 M) was added ammonium formate (0.11 mL, 2.2 mmol, 1.8 equiv). The reaction mixture was refluxed for 3 h before being concentrated in vacuo, ground with a mortar and pestle, and triturated with Et_2O. Further purification was achieved via flash column chromatography on SiO_2 (10% MeOH/DCM) to yield a pale-yellow solid (0.070 g, 14%). ^{1}H NMR (400 MHz, $CDCl_3$, 56 °C) δ 10.02 (br s, 1H), 8.36 (br s, 1H), 7.92 (d, J = 8.0 Hz, 2H), 7.39−7.34 (m, 2H), 7.17 (t, J = 7.6 Hz, 1H), 7.08−7.02 (m, 3H), 6.97 (s, 1H), 6.44 (br s, 1H), 4.77 (s, 1H), 4.04−3.97 (m, 1H), 3.91 (s, 3H), 3.09−2.99 (m, 2H), 2.92−2.85 (m, 1H), 1.56 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 177.8, 165.9, 164.4, 163.2, 144.7, 136.2, 129.7, 129.5, 128.3, 126.9, 122.7, 121.0, 118.2, 118.0, 111.4, 110.8, 105.6, 58.0, 52.1, 48.6, 41.0, 23.2; mp 50−54 °C. HMS (APCI) calcd for $C_{24}H_{23}N_3O_4$ 418.1766; found 418.1766 $[M + H]^+$.

*Methyl 4-(1-(2-(1H-Indol-3-yl)ethyl)-4-acetoxy-3-acetyl-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**158**).* To a solution of **1** (0.50 g, 1.2 mmol) in DCM (11 mL, 0.11 M) was added acetic anhydride (0.14 mL, 1.4 mmol, 1.2 equiv) and pyridine (0.14 mL, 1.8 mmol, 1.5 equiv). The reaction mixture was stirred at rt for $6^1/_2$ h before being concentrated in vacuo. The crude material was then purified by flash column chromatography on SiO_2 (3% MeOH/DCM). Additional purification was achieved using HPLC (75% ACN with 0.1% formic acid) to give a yellow oil (0.038 g, 7%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.94−7.92 (m, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.21 (t, J = 8.0 Hz, 1H), 7.10−7.05 (m, 3H), 6.98 (d, J = 2.0 Hz, 1H), 4.93 (s, 1H), 4.07−4.00 (m, 1H), 3.91 (s, 3H), 3.08−2.89 (m, 3H), 2.47 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 191.5, 167.0, 166.6, 163.8, 147.7, 139.2, 137.0, 136.6, 131.0, 130.4, 128.1, 127.4, 122.6, 122.2, 119.9, 118.7, 112.6, 111.5, 62.3, 62.4, 41.5, 30.1, 24.4, 20.8. HMS (APCI) calcd for $C_{26}H_{24}N_2O_6$ 461.1721; found 461.1717 $[M + H]^+$.

*Methyl 4-(3-Acetyl-4-(butyryloxy)-1-(2-(2-methyl-1H-indol-3-yl)-ethyl)-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**159**).* To a solution of **106** (0.30 g, 0.69 mmol) and triethylamine (0.19 mL, 1.4 mmol, 2.0 equiv) in THF (0.69 mL, 1.0 M) at −30 °C was added butyryl chloride (0.072 mL, 0.69 mmol, 1.0 equiv) dropwise over 20 min. The mixture was allowed to stir at −30 °C for 2 h before being concentrated in vacuo. The crude material was dissolved in EtOAc, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification was achieved via flash column chromatography on SiO_2 (10% EtOAc:DCM) to afford a yellow, amorphous solid (0.12 g, 35%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.88 (d, J = 7.8 Hz, 2H), 7.25 (d, J = 8.4 Hz, 1H), 7.20 (d, J = 7.2 Hz, 1H), 7.11 (t, J = 7.2 Hz, 1H), 7.01 (t, J = 7.2 Hz, 1H), 6.94 (d, J = 7.8 Hz, 2H), 4.78 (s, 1H), 3.89 (s, 3H), 3.87−3.82 (m, 1H), 3.02 (dt, J = 13.8 Hz, J = 8.4 Hz, 1H), 2.91 (dt, J = 13.8 Hz, J = 7.8 Hz, 1H), 2.82−2.78 (m, 1H), 2.70 (t, J = 7.8 Hz, 2H), 2.24 (s, 3H), 2.23 (s, 3H), 1.85 (sextet, 7.8 Hz, 2H), 1.09 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 191.6, 170.0, 166.6, 163.7, 147.9, 139.1, 136.9, 135.4, 132.1, 130.8, 130.2, 128.3, 128.0, 121.5, 119.7, 117.8, 110.6, 108.0, 62.5, 52.4, 41.4, 35.9, 30.2, 23.3, 18.4, 13.7, 11.5. HMS (APCI) calcd for $C_{29}H_{30}N_2O_6$ 503.2168; found 503.2172 $[M + H]^+$.

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*Methyl 4-(3-Acetyl-4-(acryloyloxy)-1-(2-(2-methyl-1H-indol-3-yl)-ethyl)-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**160**).* To a solution of **106** (3.0 g, 6.9 mmol) and triethylamine (1.9 mL, 14 mmol, 2.0 equiv) in THF (6.9 mL, 1.0 M) at −30 °C was added acryloyl chloride (0.72 mL, 6.9 mmol, 1.0 equiv) dropwise over 20 min. The mixture was allowed to stir at −30 °C for 2 h before being concentrated in vacuo. The crude material was dissolved in EtOAc, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification was achieved via flash column chromatography on SiO_2 (10% EtOAc:DCM) to afford a yellow, amorphous solid (0.68 g, 20%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.89 (d, J = 8.7 Hz, 2H), 7.27−7.20 (m, 2H), 7.11 (t, J = 7.2 Hz, 1H), 7.03−6.94 (m, 3H), 6.71 (d, J = 0.9 Hz, 1H), 6.43 (d, J = 10.2 Hz, 1H), 6.20 (d, J = 0.6 Hz, 1H), 4.81 (s, 1H), 3.89−3.81 (m, 4H), 3.08−2.76 (m, 3H), 2.24 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.1, 191.6, 186.7, 166.6, 163.6, 162.2, 147.6, 139.0, 137.3, 135.7, 135.4, 132.1, 130.8, 130.2, 128.3, 128.0, 126.0, 121.5, 119.6, 117.7, 110.7, 107.9, 62.6, 52.4, 41.5, 30.2, 23.3, 11.5. HMS (APCI) calcd for $C_{28}H_{26}N_2O_6$ 487.1837; found 487.1860 $[M + H]^+$.

*Methyl 4-(3-Acetyl-4-hydroxy-5-oxo-1-phenethyl-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**161**).* Compound **161** was prepared via procedure I from methyl 4-formylbenzoate (0.34 g, 2.1 mmol), ethyl acetopyruvate (0.33 g, 2.1 mmol), and 2-phenylethanamine (0.25 g, 2.1 mmol) to yield a white solid (0.73 g, 93%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (d, J = 8.4 Hz, 2H), 7.31−7.24 (m, 4H), 7.19 (d, J = 7.2 Hz, 1H), 7.10 (d, J = 6.8 Hz, 2H), 5.15 (s, 1H), 3.83−3.76 (m, 4H), 2.82−2.60 (m, 3H), 2.26 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 190.9, 165.9, 165.0, 142.4, 138.5, 129.4, 129.4, 128.6, 128.5, 128.1, 126.4, 125.6, 119.7, 66.4, 59.7, 52.2, 41.5, 33.5; mp 123−128 °C. HMS (APCI) calcd for $C_{22}H_{21}NO_5$ 380.1493; found 380.1494 $[M + H]^+$.

*Methyl 4-(4-Hydroxy-3-isonicotinoyl-1-(2-(naphthalen-1-yl)-ethyl)-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**162**).* Compound **162** was prepared via procedure I from methyl 4-formylbenzoate (0.40 g, 2.4 mmol), **188** (0.41 g, 2.4 mmol), and **20** (0.53 g, 2.4 mmol) to yield a yellow solid (0.67 g, 56%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.70 (d, J = 3.6 Hz, 2H), 7.93−7.84 (m, 4H), 7.81 (d, J = 7.8 Hz, 1H), 7.57−7.40 (m, 7H), 7.30 (d, J = 6.6 Hz, 1H), 5.40 (s, 1H), 3.84−3.80 (m, 4H), 3.37−3.34 (m, 1H), 3.13−3.08 (m, 1H), 3.03−3.00 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 196.1, 165.9, 162.1, 160.1, 136.4, 136.3, 130.7, 129.5, 128.2, 128.0, 125.5, 123.4, 122.8, 121.2, 120.8, 118.48, 118.45, 118.2, 118.1, 115.2, 111.6, 111.3, 61.5, 52.2, 48.6, 26.2; mp 221−224 °C. HMS (APCI) calcd for $C_{30}H_{24}N_2O_5$ 493.1758; found 493.1756 $[M + H]^+$.

*Methyl 4-(1-(2-(Benzofuran-3-yl)ethyl)-4-hydroxy-3-nicotinoyl-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**163**).* Compound **163** was prepared via procedure I from methyl 4-formylbenzoate (0.20 g, 1.2 mmol), **19** (0.27 g, 1.2 mmol), and 2-(benzofuran-3-yl)ethanamine (0.20 g, 1.2 mmol) to yield a pale-yellow solid (0.028 g, 4.7%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.78 (s, 1H), 8.57 (s, 1H), 7.99 (d, J = 7.2 Hz, 1H), 7.86 (d, J = 7.8 Hz, 2H), 7.77 (s, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.47−7.42 (m, 3H), 7.37 (t, J = 5.4 Hz, 1H), 7.29 (t, J = 7.2 Hz, 1H), 7.20 (t, J = 7.2 Hz, 1H), 5.44 (s, 1H), 3.87−3.82 (m, 4H), 2.97−2.92 (m, 2H), 2.76−2.75 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 189.3, 181.3, 166.0, 154.6, 150.6, 149.5, 142.4, 135.9, 129.1, 128.8, 128.1, 127.5, 124.4, 122.7, 122.4, 119.6, 117.0, 115.6, 111.3, 60.2, 52.1, 40.0, 21.7 (note: carbons 1, 2, and 3 are absent); mp 225−230 °C. HMS (APCI) calcd for $C_{28}H_{22}N_2O_6$ 481.1397; found 481.1396 $[M - H]^-$.

*Methyl 4-(1-(2-(1H-Benzo[d]imidazol-1-yl)ethyl)-4-hydroxy-3-isonicotinoyl-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**164**).* Compound **164** was prepared via procedure I from methyl 4-formylbenzoate (0.19 g, 1.1 mmol), 2-(1*H*-benzo[*d*]imidazol-1-yl)ethanamine (0.18 g, 1.1 mmol), and **20** (0.25 g, 1.1 mmol) to yield a yellow solid (0.40 g, 73%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (d, J = 1.3 Hz, 2H), 8.59 (s, 1H), 7.80 (d, J = 8.4 Hz, 2H), 7.67 (t, J = 5.2 Hz, 1H), 7.61 (t, J = 5.2 Hz, 1H), 7.52 (d, J = 5.6 Hz, 2H), 7.33−7.29 (m, 4H), 5.37 (s, 1H), 4.61−4.54 (m, 1H), 4.48−4.44 (m, 1H), 4.03−3.98 (m, 1H), 3.82 (s, 3H), 3.08−3.04 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 186.2, 166.4, 165.9, 149.2, 146.4, 143.4, 142.6, 139.6, 132.9, 129.4, 128.4, 128.14, 128.06, 125.5, 123.5, 123.1, 122.1, 118.2, 111.0, 60.08, 52.2, 43.1 (note: one sp^3 carbon is under the DMSO peak); mp 135−140 °C. HMS (APCI) calcd for $C_{27}H_{22}N_4O_5$ 483.1676; found 483.1674 $[M + H]^+$.

*Methyl 4-(1-(2-(1H-Imidazol-4-yl)ethyl)-4-hydroxy-3-isonicotinoyl-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**165**).* Compound **165** was prepared via procedure I from methyl 4-formylbenzoate (0.37 g, 2.3 mmol), 2-(1*H*-imidazol-4-yl)ethanamine (0.25 g, 2.3 mmol), and **20** (0.50 g, 2.3 mmol) to yield an orange solid (0.031 g, 3%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (s, 1H), 8.50 (d, J = 5.2 Hz, 2H), 7.88 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 5.2 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 7.26 (s, 1H), 7.11 (s, 1H), 5.27 (s, 1H), 3.90−3.82 (m, 4H), 2.83−2.76 (m, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 182.5, 169.1, 166.1, 148.8, 148.0, 134.0, 131.2, 129.0, 128.5, 128.1, 127.8, 127.6, 122.4, 116.4, 111.6, 66.3, 52.0, 40.0, 22.3; mp 64−70 °C. HMS (APCI) calcd for $C_{23}H_{20}N_4O_5$ 433.1512; found 433.1513 $[M + H]^+$.

*Methyl 4-(3-Acetyl-4-hydroxy-1-(3-methylphenethyl)-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**166**).* Compound **166** was prepared via procedure I from methyl 4-formylbenzoate (0.30 g, 1.8 mmol), ethyl acetopyruvate (0.29 g, 1.8 mmol), and 2-(*m*-tolyl)ethanamine (0.25 g, 1.8 mmol) to yield a white solid (0.56 g, 76%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (d, J = 7.6 Hz, 2H), 7.28 (d, J = 7.6 Hz, 2H), 7.12 (t, J = 8.0 Hz, 1H), 6.99 (d, J = 7.6 Hz, 1H), 6.88−6.86 (m, 2H), 5.13 (s, 1H), 3.83 (s, 3H), 3.79−3.73 (m, 1H), 2.77−2.70 (m, 2H), 2.61−2.57 (m, 1H), 2.26 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.5, 166.0, 165.1, 142.4, 138.4, 137.5, 129.4, 129.2, 128.4, 128.1, 127.1, 126.9, 125.62, 125.56, 119.7, 66.4, 59.7, 52.2, 41.6, 33.4, 21.0; mp 118−123 °C. HMS (APCI) calcd for $C_{23}H_{23}NO_5$ 394.1649; found 394.1651 $[M + H]^+$.

*Methyl 4-(3-Acetyl-1-(3-chlorophenethyl)-4-hydroxy-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**167**).* Compound **167** was prepared via procedure I from methyl 4-formylbenzoate (0.26 g, 1.6 mmol), ethyl acetopyruvate (0.25 g, 1.6 mmol), and 2-(3-chlorophenyl)ethanamine (0.25 g, 1.6 mmol) to yield a pale-yellow solid (0.50 g, 76%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (d, J = 8.4 Hz, 2H), 7.32−7.20 (m, 5H), 7.08 (d, J = 7.2 Hz, 1H), 5.22 (s, 1H), 3.83−3.79 (m, 4H), 2.79−2.69 (m, 3H), 2.26 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.9, 165.1, 142.3, 141.2, 133.0, 130.5, 130.2, 129.4, 128.5, 128.1, 127.6, 127.4, 126.4, 125.5, 59.5, 52.2, 41.1, 32.9, 29.7 (note: carbon 4 is absent); mp 118−122 °C. HMS (APCI) calcd for $C_{22}H_{20}ClNO_5$ 414.1108; found 414.1109 $[M + H]^+$.

*Methyl 4-(3-Acetyl-1-(3-fluorophenethyl)-4-hydroxy-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**168**).* Compound **168** was prepared via procedure I from methyl 4-formylbenzoate (0.30 g, 1.8 mmol), ethyl acetopyruvate (0.28 g, 1.8 mmol), and 2-(3-fluorophenyl)ethanamine (0.25 g, 1.8 mmol) to yield an off-white solid (0.57 g, 79%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.29−7.25 (m, 1H), 7.00−6.94 (m, 3H), 5.22 (s, 1H), 3.83−3.79 (m, 4H), 2.81−2.69 (m, 3H), 2.26 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.9, 165.1, 162.2 (d, J = 241.8 Hz), 142.3, 141.6, 141.5, 130.3 (d, J = 8.1 Hz), 129.44, 129.40, 128.1, 125.6, 124.8, 115.3 (d, J = 20.9 Hz), 113.2 (d, J = 20.9 Hz), 59.5, 52.2, 41.1, 33.0, 15.2 (note: carbon 4 is absent); mp 114−119 °C. HMS (APCI) calcd for $C_{22}H_{20}FNO_5$ 398.1403; found 398.1404 $[M + H]^+$.

*Methyl 4-(3-Acetyl-4-hydroxy-1-(3-methoxyphenethyl)-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**169**).* Compound **169** was prepared via procedure I from methyl 4-formylbenzoate (0.27 g, 1.7 mmol), ethyl acetopyruvate (0.26 g, 1.7 mmol), and 2-(3-methoxyphenyl)-ethanamine (0.25 g, 1.7 mmol) to yield an off-white solid (0.52 g, 76%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 7.16 (t, J = 8.0 Hz, 1H), 6.75 (d, J = 7.6 Hz, 1H), 6.68−6.66 (m, 2H), 5.15 (s, 1H), 3.83−3.76 (m, 4H), 3.69 (s, 3H), 2.77−2.70 (m, 2H), 2.65−2.60 (m, 1H), 2.26 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.0, 165.0, 159.3, 145.8, 142.4, 140.1, 129.5, 129.42, 129.38, 128.1, 125.5, 120.8, 114.1, 111.9, 59.6, 54.9, 52.2, 41.4, 33.4, 29.7 (note: carbon 4 is absent); mp 150−153 °C. HMS (APCI) calcd for $C_{23}H_{23}NO_6$ 410.1603; found 410.1604 $[M + H]^+$.

*Methyl 4-(3-Acetyl-4-hydroxy-1-(3-hydroxyphenethyl)-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**170**).* Compound **170** was prepared via procedure I from methyl 4-formylbenzoate (0.55 g, 3.4 mmol), ethyl acetopyruvate (0.53 g, 3.4 mmol), and **190** (0.46 g, 3.4 mmol) to yield a cream-colored solid (1.0 g, 78%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.34 (br s, 1H), 7.93 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 8.8 Hz, 2H), 7.08 (t, J = 7.6 Hz, 1H), 6.61 (dt, J = 1.6 Hz, J = 6.8 Hz, 1H), 6.54−6.52 (m, 2H),

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5.16 (s, 1H), 3.87−3.83 (m, 4H), 2.74−2.69 (m, 2H), 2.56−2.52 (m, 1H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 193.0, 166.0, 165.0, 157.5, 142.4, 139.9, 129.9, 129.7, 129.5, 129.2, 128.1, 127.0, 119.2, 115.4, 113.5, 59.7, 52.2, 48.7, 41.6, 33.6; mp 98−104 °C. HMS (APCI) calcd for $C_{22}H_{21}NO_6$ 396.1447; found 396.1446 $[M + H]^+$.

*Methyl 4-(4-Hydroxy-3-isonicotinoyl-5-oxo-1-(2-(pyridin-4-yl)-ethyl)-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**171**).* Compound **171** was prepared via procedure I from methyl 4-formylbenzoate (0.19 g, 1.1 mmol), 2-(pyridin-4-yl)ethanamine (0.14 g, 1.1 mmol), and **20** (0.25 g, 1.1 mmol) to yield a yellow solid (0.47 g, 95%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (d, J = 6.0 Hz, 2H), 8.49−8.48 (m, 2H), 7.92 (d, J = 8.0 Hz, 2H), 7.56−7.53 (m, 2H), 7.50 (d, J = 8.0 Hz, 2H), 7.29−7.26 (m, 2H), 5.47 (s, 1H), 3.91−3.83 (m, 4H), 2.88−2.78 (m, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 190.1, 185.8, 182.0, 166.3, 166.0, 149.5, 149.2, 148.3, 146.6, 143.4, 129.4, 128.2, 124.6, 122.2, 115.6, 59.9, 52.2, 40.6, 32.7; mp 126−129 °C. HMS (APCI) calcd for $C_{25}H_{21}N_3O_5$ 444.1567; found 444.1566 $[M + H]^+$.

*Methyl 4-(4-Hydroxy-3-isonicotinoyl-5-oxo-1-(2-(pyridin-3-yl)-ethyl)-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**172**).* Compound **172** was prepared via procedure I from methyl 4-formylbenzoate (0.19 g, 1.1 mmol), 2-(pyridin-3-yl)ethanamine (0.14 g, 1.1 mmol), and **20** (0.25 g, 1.1 mmol) to yield a yellow solid (0.47 g, 93%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (d, J = 6.0 Hz, 2H), 8.44 (dd, J = 1.2 Hz, J = 4.8 Hz, 1H), 8.41 (d, J = 1.6 Hz, 1H), 7.92 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 7.6 Hz, 1H), 7.55 (d, J = 6.0 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.35 (dd, J = 4.8 Hz, J = 7.6 Hz, 1H), 5.51 (s, 1H), 3.91−3.83 (m, 4H), 2.91−2.77 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 206.6, 186.6, 165.9, 165.6, 149.3, 148.9, 146.9, 146.1, 142.7, 137.3, 134.7, 129.5, 128.2, 128.1, 123.8, 122.0, 116.6, 59.9, 52.2, 41.3, 30.5; mp 160−163 °C. HMS (APCI) calcd for $C_{25}H_{21}N_3O_5$ 444.1567; found 444.1565 $[M + H]^+$.

*Methyl 4-(4-Hydroxy-3-isonicotinoyl-5-oxo-1-(2-(pyridin-2-yl)-ethyl)-2,5-dihydro-1H-pyrrol-2-yl)benzoate (**173**).* Compound **173** was prepared via procedure I from methyl 4-formylbenzoate (0.19 g, 1.1 mmol), 2-(pyridin-2-yl)ethanamine (0.14 g, 1.1 mmol), and **20** (0.25 g, 1.1 mmol) to yield a yellow solid (0.50 g, >99%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (d, J = 6.0 Hz, 2H), 8.48 (dd, J = 1.6 Hz, J = 5.2 Hz, 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.73 (td, J = 2.0 Hz, J = 7.6 Hz, 1H), 7.53 (dd, J = 1.2 Hz, J = 4.4 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.27 (s, 1H), 7.25 (t, J = 3.6 Hz, 1H), 5.44 (s, 1H), 4.00−3.93 (m, 1H), 3.82 (s, 3H), 3.07−2.97 (m, 2H), 2.92−2.84 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 206.6, 186.7, 165.9, 165.5, 158.1, 156.6, 149.4, 148.7, 146.1, 142.6, 137.3, 129.5, 128.2, 125.6, 123.6, 122.0, 116.9, 60.1, 52.2, 40.3, 35.4; mp 187−190 °C. HMS (APCI) calcd for $C_{25}H_{21}N_3O_5$ 444.1567; found 444.1564 $[M + H]^+$.

*1-(2-(1H-Indol-3-yl(ethyl)-3-hydroxy-4-nicotinoyl-5-(pyridine-4-yl)-1H-pyrrol-2(5H)-one (**173**).* Compound **174** was prepared via procedure I from isonicotinaldehyde (0.11 g, 1.0 mmol), **19** (0.22 g, 1.0 mmol), and tryptamine (0.16 g, 1.0 mmol) to yield a mustard-colored solid (0.32 g, 76%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.93 (s, 1H), 8.84 (d, J = 1.8 Hz, 1H), 8.67 (dd, J = 1.8 Hz, J = 4.8 Hz, 1H), 8.53 (d, J = 5.4 Hz, 2H), 8.05 (dt, J = 2.4 Hz, J = 8.4 Hz, 1H), 7.49−7.47 (m, 2H), 7.42−7.34 (m, 3H), 7.30 (br s, 1H), 7.13 (d, J = 1.8 Hz, 1H), 7.06 (t, J = 7.8 Hz, 1H), 6.94 (t, J = 8.4 Hz, 1H), 5.34 (s, 1H), 3.92−3.87 (m, 1H), 3.02−2.91 (m, 2H), 2.82−2.77 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 185.5, 166.1, 151.3, 148.9, 148.4, 136.7, 136.3, 134.5, 126.9, 125.5, 123.6, 123.4, 123.0, 121.1, 118.3, 118.1, 116.1, 111.6, 110.8, 59.7, 41.2, 23.7 (note: either carbon 1 or 2 is absent); mp 225−230 °C. HMS (APCI) calcd for $C_{25}H_{20}N_4O_3$ 425.1608; found 425.1610 $[M + H]^+$.

*1-(2-(1H-Indol-3-yl)ethyl)-3-hydroxy-4-nicotinoyl-5-(pyridine-3-yl)-1H-pyrrol-2(5H)-one (**175**).* Compound **175** was prepared via procedure I from nicotinaldehyde (0.11 g, 1.0 mmol), **19** (0.22 g, 1.0 mmol), and tryptamine (0.16 g, 1.0 mmol) to yield an orange solid (0.29 g, 67%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.90 (s, 1H), 8.83 (d, J = 2.4 Hz, 1H), 8.68 (dd, J = 1.8 Hz, J = 4.8 Hz, 1H), 8.57 (d, J = 1.8 Hz, 1H), 8.49 (dd, J = 2.4 Hz, J = 4.8 Hz, 1H), 8.04 (dt, J = 1.8 Hz, J = 7.8 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.49−7.47 (m, 1H), 7.36−7.32 (m, 3H), 7.24 (s, 1H), 7.13 (d, J = 1.8 Hz, 1H), 7.06 (t, J = 7.8 Hz, 1H), 6.94 (t, J = 8.4 Hz, 1H), 5.39 (s, 1H), 3.89−3.85 (m, 1H), 3.02−2.93 (m, 2H), 2.79−2.75 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 165.3, 151.9, 149.3, 149.1, 148.9, 136.4, 136.3, 135.7, 134.1, 128.1, 126.9, 125.5, 124.0, 123.4, 122.9, 121.1, 118.3, 118.1, 111.5, 110.7, 58.4, 41.0, 23.7 (note: carbons 1 and 2 are absent); mp 225−227 °C. HMS (APCI) calcd for $C_{25}H_{20}N_4O_3$ 425.1608; found 425.1610 $[M + H]^+$.

*1-(2-(1H-Indol-3-yl)ethyl)-3-hydroxy-4-nicotinoyl-5-(pyridine-2-yl)-1H-pyrrol-2(5H)-one (**176**).* Compound **176** was prepared via procedure I from picolinaldehyde (0.11 g, 1.0 mmol), **19** (0.22 g, 1.0 mmol), and tryptamine (0.16 g, 1.0 mmol) to yield a yellow solid (0.30 g, 71%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.91 (s, 1H), 8.80 (d, J = 1.2 Hz, 1H), 8.69 (dd, J = 1.2 Hz, J = 4.8 Hz, 8.55 (d, J = 4.2 Hz, 1H), 8.00 (d, J = 7.2 Hz, 1H), 7.77 (td, J = 1.2 Hz, J = 7.2 Hz, 1H), 7.50−7.46 (m, 2H), 7.38−7.30 (m, 4H), 7.12 (d, J = 1.8 Hz, 1H), 7.05 (t, J = 7.8 Hz, 1H), 6.95 (t, J = 7.8 Hz, 1H), 5.54 (s, 1H), 3.87−3.82 (m, 1H), 3.01−2.91 (m, 2H), 2.72−2.67 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 189.2, 165.4, 156.1, 151.9, 149.4, 149.0, 137.2, 136.3, 134.2, 128.2, 126.9, 125.5, 123.8, 123.4, 122.8, 121.0, 118.3, 118.1, 111.5, 110.8, 62.1, 41.4, 23.6 (note: either carbon 1 or 2 and carbon 3 are absent); mp 218−223 °C. HMS (APCI) calcd for $C_{25}H_{20}N_4O_3$ 425.1613; found 425.1613 $[M + H]^+$.

*1-(2-(1H-Indol-3-yl)ethyl)-5-(furan-3-yl)-3-hydroxy-4-nicotinoyl-1H-pyrrol-2(5H)-one (**177**).* Compound **177** was prepared via procedure I from furan-3-carbaldehyde (0.10 g, 1.0 mmol), **19** (0.22 g, 1.0 mmol), and tryptamine (0.16 g, 1.0 mmol) to yield an orange solid (0.12 g, 28%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.86 (s, 1H), 8.85 (d, J = 1.8 Hz, 1H), 8.71 (dd, J = 1.2 Hz, J = 4.8 Hz, 1H), 8.05 (dt, J = 1.8 Hz, J = 7.8 Hz, 1H), 7.74 (s, 1H), 7.50−7.48 (m, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.34 (d, J = 7.8 Hz, 1H), 7.18 (s, 1H), 7.15 (d, J = 1.8 Hz, 1H), 7.10 (s, 1H), 7.07 (t, J = 7.2 Hz, 1H), 6.98 (t, J = 7.8 Hz, 1H), 6.48 (d, J = 1.2 Hz, 1H), 5.40 (s, 1H), 3.89−3.84 (m, 1H), 3.12−3.00 (m, 2H), 2.84−2.80 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.4, 152.4, 149.5, 144.1, 142.7, 136.3, 133.8, 127.0, 125.5, 123.4, 122.9, 121.1, 120.8, 118.3, 118.2, 117.5, 111.5, 110.9, 108.6, 52.4, 40.7, 23.7 (note: carbon 1 and 2 are absent); mp 211−217 °C. HMS (APCI) calcd for $C_{24}H_{19}N_3O_4$ 414.1448; found 414.1449 $[M + H]^+$.

*1-(2-(1H-Indol-3-yl)ethyl)-5-(furan-2-yl)-3-hydroxy-4-nicotinoyl-1H-pyrrol-2(5H)-one (**178**).* Compound **178** was prepared via procedure I from furfural (0.10 g, 1.0 mmol), **19** (0.22 g, 1.0 mmol), and tryptamine (0.16 g, 1.0 mmol) to yield a mustard-colored solid (0.06 g, 14%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.87 (s, 1H), 8.82 (d, J = 1.2 Hz, 1H), 8.72 (dd, J = 1.8 Hz, J = 4.8 Hz, 1H), 8.03 (dt, J = 1.8 Hz, J = 5.4 Hz, 1H), 7.62 (t, J = 0.6 Hz, 1H), 7.53−7.52 (m, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.34 (d, J = 7.8 Hz, 1H), 7.18 (s, 1H), 7.15 (d, J = 2.4 Hz, 1H), 7.10−7.06 (m, 2H), 6.99 (t, J = 6.6 Hz, 1H), 6.52 (d, J = 3.0 Hz, 1H), 6.433−6.425 (m, 1H), 3.82−3.77 (m, 1H), 3.19−3.14 (m, 1H), 3.00−2.95 (m, 1H), 2.66−2.61 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 186.9, 164.5, 152.3, 149.1, 148.9, 143.4, 143.2, 136.3, 134.0, 127.0, 123.5, 122.9, 122.8, 121.0, 118.4, 118.3, 118.1, 115.0, 111.5, 110.8, 110.2, 54.5, 41.4, 23.7; mp 211−216 °C. HMS (APCI) calcd for $C_{24}H_{19}N_3O_4$ 414.1448; found 414.1452 $[M + H]^+$.

*1-(2-(1H-Indol-3-yl)ethyl)-3-hydroxy-4-nicotinoyl-5-(thiophen-2-yl)-1H-pyrrol-2(5H)-one (**179**).* Compound **179** was prepared via procedure I from thiophene-2-carbaldehyde (0.11 g, 1.0 mmol), **19** (0.22 g, 1.0 mmol), and tryptamine (0.16 g, 1.0 mmol) to yield an orange solid (0.07 g, 16%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.87 (s, 1H), 8.81 (s, 1H), 8.72 (d, J = 4.8 Hz, 1H), 8.02 (dd, J = 1.8 Hz, J = 6.0 Hz, 1H), 7.53-7.51 (m, 1H), 7.48−7.44 (m, 2H), 7.34 (d, J = 7.8, 1H), 7.20 (d, J = 3.0 Hz, 1H), 7.15 (d, J = 1.8 Hz, 1H), 7.07 (t, J = 7.8 Hz, 2H), 7.00−6.96 (m, 2H), 5.76 (s, 1H), 3.87−3.83 (m, 1H), 3.14−3.09 (m, 1H), 3.05−3.00 (m, 1H), 2.77−2.72 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.2, 152.4, 149.2, 140.2, 136.3, 133.8, 130.3, 128.7, 127.02, 126.96, 126.5, 123.6, 122.9, 121.1, 118.3, 118.2, 111.5, 110.8, 56.1, 40.9, 23.6 (note: carbons 1, 2, and 3 are absent); mp 150−155 °C. HMS (APCI) calcd for $C_{24}H_{19}N_3O_3S$ 430.1226; found 430.1223 $[M + H]^+$.

*1-(2-(1H-Indol-3-yl)ethyl)-3-hydroxy-4-nicotinoyl-5-(thiophen-3-yl)-1H-pyrrol-2(5H)-one (**180**).* Compound **180** was prepared via procedure I from thiophene-3-carbaldehyde (0.11 g, 1.0 mmol), **19** (0.22 g, 1.0 mmol), and tryptamine (0.16 g, 1.0 mmol) to yield a yellow solid (0.11 g, 25%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.87 (s, 1H), 8.86 (s, 1H), 8.71 (d, J = 4.8 Hz, 1H), 8.06 (d, J = 7.8 Hz, 1H), 7.70 (d, J = 1.8 Hz, 1H), 7.50−7.47 (m, 2H), 7.40 (d, J = 7.8 Hz, 1H), 7.34 (d, J = 7.8 Hz, 1H), 7.25 (s, 1H), 7.14 (s, 1H), 7.08−7.06 (m, 2H), 6.96 (t, J = 7.8 Hz, 1H), 5.55 (s, 1H), 3.86−3.80 (m, 1H), 3.06−2.98 (m, 2H),

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2.76−2.70 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 187.4, 181.2, 164.5, 152.5, 137.2, 136.3, 133.8, 127.05, 126.98, 126.2, 126.0, 125.4, 123.5, 122.9, 122.8, 121.1, 118.4, 118.2, 118.0, 111.5, 110.9, 55.0, 41.2, 23.9; mp 238−242 °C. HMS (APCI) calcd for $C_{24}H_{19}N_3O_3S$ 430.1198; found 430.1201 $[M + H]^+$.

■ ASSOCIATED CONTENT

Supporting Information

Experimental information and the generic formula for experimental test compounds described in Tables 1−8. This material is available free of charge via the Internet at http://pubs.acs.org.

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The manuscript was written by all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare the following competing financial interest(s): Some authors are coinventors on Emory owned IP (S.S.Z., E.G.A., S.F.T., D.C.L.), have an equity position (S.F.T, D.C.L.), are Board members (D.C.L.), or paid consultants (S.F.T., K.B.H) for companies developing NMDA receptor modulators.

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■ ABBREVIATIONS USED

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA, *N*-methyl D-aspartate; ATD, amino-terminal domain; LBD, ligand-binding domain; TMD, transmembrane domain; CTD, carboxyl-terminal domain; GABA, γ-aminobutyric acid; DMF, dimethylformamide; SEM, standard error of the mean

■ REFERENCES

(1) (a) Furukawa, H.; Gouaux, E. Mechanisms of activation, inhibition and specificity: crystal structures of the NMDA receptor NR1 ligand-binding core. *EMBO J.* **2003**, *22*, 2873−2885. (b) Furukawa, H.; Singh, S. K.; Mancusso, R.; Gouaux, E. Subunit arrangement and function in NMDA receptors. *Nature* **2005**, *438* (7065), 185−192.

(2) Traynelis, S.; Wollmuth, L.; McBain, C.; Menniti, F.; Vance, K.; Ogden, K.; Hansen, K.; Yuan, H.; Myers, S.; Dingledine, R. Glutamate Receptor Ion Channels: Structure, Regulation and Function. *Pharmacol. Rev.* **2010**, *62*, 405−496.

(3) (a) Akazawa, C.; Shigemoto, R.; Bessho, Y.; Nakanishi, S.; Mizuno, N. Differential expression of five *N*-methyl-D-aspartate receptor subunit mRNAs in the cerebellum of developing and adult rats. *J. Comp. Neurol.* **1994**, *347*, 150−160. (b) Monyer, H.; Burnashev, N.; Laurie, D. J.; Sakmann, B.; Seeburg, P. H. Developmental and regional expression in the rat brain and functional properties of four NMDA receptors. *Neuron* **1994**, *12*, 529−540.

(4) (a) Vicini, S.; Wang, J. F.; Li, J. H.; Zhu, W. J.; Wang, Y. H.; Luo, J. H.; Wolfe, B. B.; Grayson, D. R. Functional and pharmacological differences between recombinant *N*-methyl-D-aspartate receptors. *J Neurophysiol.* **1998**, *72*, 555−566. (b) Yuan, H.; Hansen, K. B.; Vance, K. M.; Ogden, K. K.; Traynelis, S. F. Control of NMDA receptor function by the NR2 subunit amino-terminal domain. *J. Neurosci.* **2009**, *29*, 12045−12058. (c) Paoletti, P.; Neyton, J. NMDA receptor subunits: function and pharmacology. *Curr. Opin. Pharmacol.* **2007**, *7*, 39−47.

(5) (a) Nakanishi, S. Molecular diversity of glutamate receptors and implications for brain function. *Science* **1992**, *258*, 597−603. (b) Nicoll, R. A.; Malenka, R. C. Expression mechanisms underlying NMDA receptor-dependent long-term potentiation. *Ann. N. Y. Acad. Sci.* **1999**, *868*, 515−525.

(6) Choi, D. W.; Rothman, S. M. The Role of Glutamate Neurotoxicity in Hypoxic-Ischemic Neuronal Death. *Annu. Rev. Neurosci.* **1990**, *13*, 171−182.

(7) Hu, N.-W.; Ondrejcak, T.; Rowan, M. J. Glutamate receptors in preclinical research on Alzheimer's disease: update on recent advances. *Pharmacol., Biochem. Behav.* **2012**, *100*, 855−862.

(8) Coyle, J. T.; Basu, A.; Benneyworth, M.; Balu, D.; Konopaske, G. Glutamatergic synaptic disregulation in schizophrenia: therapeutic implications. *Handb. Exp. Pharmacol.* **2012**, *213*, 267−295.

(9) Mathew, S. J.; Shah, A.; Lapidus, K.; Clark, C.; Jarun, N.; Ostermeyer, B.; Murrough, J. W. Ketamine for Treatment-Resistant Unipolar Depression. *CNS Drugs* **2012**, *26*, 189−204.

(10) (a) Hallett, P. J.; Spoelgen, R.; Hyman, B. T.; Standaert, D. G.; Dunah, A. W. Dopamine D1 Activation Potentiates Striatal NMDA Receptors by Tyrosine Phosphorylation-Dependent Subunit Trafficking. *J. Neurosci.* **2006**, *26*, 4690−4700. (b) Hallett, P. J.; Standaert, D. G. Rationale for and use of NMDA receptor antagonists in Parkinson's disease. *Pharmacol. Ther.* **2004**, *102*, 155−174. (c) Hallett, P. J.; Dunah, A. W.; Ravenscroft, P.; Zhou, S.; Bezard, E.; Crossman, A. R.; Brotchie, J. M.; Standaert, D. G. Alterations of striatal NMDA receptor subunits associated with the development of dyskinesia in the MPTP-lesioned primate model of Parkinson's disease. *Neuropharmacology* **2005**, *48*, 503−516. (d) Duty, S. Targeting Glutamate Receptors to Tackle the Pathogenesis, Clinical Symptoms and Levodopa-Induced Dyskinesia Associated with Parkinson's Disease. *CNS Drugs* **2012**, *26*, 1017−1032. (e) Nakamura, T.; Lipton, S. A. Excitatory amino acids, S-nitrosylation, and protein misfolding in neurodegenerative disease protection by memantine and nitromemantine at NMDA-gated channels. *Oxid. Stress Dis.* **2010**, *26* (Micronutrients and Brain Health), 59−78.

(11) (a) Mullasseril, P.; Hansen, K.; Vance, K.; Ogden, K.; Yuan, H.; Kurtkaya, N.; Santangelo, R.; Orr, A.; Le, P.; Vellano, K.; Liotta, D.; Traynelis, S. A subunit-selective potentiator of NR2C- and NR2D-containing NMDA receptors. *Nature Commun.* **2010**, *1*, 90. (b) Mosley, C. A.; Acker, T. M.; Hansen, K. B.; Mullasseril, P.; Andersen, K. T.; Le, P.; Vellano, K. M.; Bräuner-Osborne, H.; Liotta, D. C.; Traynelis, S. F. Quinazolin-4-one Derivatives: A Novel Class of Noncompetitive NR2C/D Subunit-Selective *N*-Methyl-D-aspartate Receptor Antagonists. *J. Med. Chem.* **2010**, *53*, 5476−5490. (c) Bettini, E.; Sava, A.; Griffante, C.; Carignani, C.; Buson, A.; Capelli, A. M.; Negri, M.; Andreeta, F.; Senar-Sancho, S. A.; Guiral, L.; Cardullo, F. Identification and characterization of novel NMDA receptor antagonists selective for NR2A- over NR2B-containing receptors. *J. Pharmacol. Exp. Ther.* **2010**, *335*, 636−644. (d) Costa, B. M.; Irvine, M. W.; Fang, G.; Eaves, R. J.; Mayo-Martin, M. B.; Skifter, D. A.; Jane, D. E.; Monaghan, D. T. A Novel Family of Negative and Positive Allosteric Modulators of NMDA Receptors. *J. Pharmacol. Exp. Ther.* **2010**, *335*, 614−621. (e) Acker, T. M.; Yuan, H.; Hansen, K. B.; Vance, K. M.; Ogden, K. K.; Jensen, H. S.; Burger, P. B.; Mullasseril, P.; Snyder, J. P.; Liotta, D. C.; Traynelis, S. F. Mechanism for Noncompetitive Inhibition by Novel GluN2C/D *N*-Methyl-D-aspartate Receptor Subunit-Selective Modulators. *Mol. Pharmacol.* **2011**, *80*, 782−795. (f) Santangelo Freel, R. M.; Ogden, K. K.; Strong, K. L.; Khatri, A.; Chepiga, K. M.; Jensen, H. S.; Traynelis, S. F.; Liotta, D. C. Synthesis and Structure−Activity Relationship of Tetrahydroisoquinoline-Based Potentiators of GluN2C and GluN2D Containing *N*-Methyl-D-aspartate Receptors. *J. Med. Chem.* **2013**, *56*, 5351−5381. (g) Acker, T. M.; Khatri, A.; Vance, K. M.; Slabber, C.; Bacsa, J.; Snyder, J. P.; Traynelis, S. F.; Liotta, D. C. Structure−Activity Relationships and Pharmacophore Model of a Noncompetitive Pyrazoline Containing Class of GluN2C/GluN2D Selective Antagonists. *J. Med. Chem.* **2013**, *56*, 6434−6456. (h) Hansen, B. K.; Ogden, K.

K.; Traynelis, S. F. Subunit-selective allosteric inhibition of glycine binding to NMDA receptors. *J. Neurosci.* **2012**, *32*, 6197−6208.
(12) Gauuan, P. J. F.; Trova, M. P.; Gregor-Boros, L.; Bocckino, S. B.; Crapo, J. D.; Day, B. J. Superoxide dismutase mimetics: synthesis and structure−activity relationship study of MnTBAP analogues. *Bioorg. Med. Chem.* **2002**, *10*, 3013−3021.
(13) Kelly, M. G.; Kincaid, J.; Duncton, M.; Sahasrabudhe, K.; Janagani, S.; Upasani, R. B.; Wu, G.; Fang, Y.; Weig, Z.-L. Amide derivatives as ion-channel ligands and pharmaceutical compositions and methods of using same. US 2006/0194801, 2006.
(14) Widmer, U. A convenient preparation of *t*-butyl esters. *Synthesis* **1983**, 135−136.
(15) Hansen, K. B.; Tajima, N.; Risgaard, R.; Perszyk, R. E.; Jørgensen, L.; Vance, K. M.; Ogden, K. K.; Clausen, R. P.; Furukawa, H.; Traynelis, S. F. Structural determinants of agonist efficacy at the glutamate binding site of *N*-methyl-D-aspartate receptors. *Mol. Pharmacol.* **2013**, *84*, 114−127.
(16) Hansen, K. B.; Brauner-Osborne, H.; Egebjerg, J. Pharmacological characterization of ligands at recombinant NMDA receptor subtypes by electrophysiological recordings and intracellular calcium measurements. *Comb. Chem. High Throughput Screening* **2008**, *11*, 304−315.
(17) Hansen, K. B.; Mullasseril, P.; Dawit, S.; Kurtkaya, N.; Yuan, H.; Vance, K.; Orr, A.; Kvist, T.; Ogden, K.; Le, P. Implementation of a fluorescence-based screening assay identifies histamine H3 receptor antagonists clobenpropit and iodophenpropit as subunit-selective *N*-methyl-D-aspartate receptor antagonists. *J. Pharmacol. Exp. Ther.* **2010**, *333*, 650−662.